Phytochemical Research on Two *Ancistrocladus* Species, Semi-Synthesis of Dimeric Naphthylisoquinoline Alkaloids, and Structure Optimization of Antitumoral Naphthoquinones

Phytochemische Untersuchungen an zwei *Ancistrocladus*-Arten, Semi-Synthese dimerer Naphthylisochinolin-Alkaloide und Strukturoptimierung von antitumoralen Naphthochinonen

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Dedicated to my family

Contents

General Introduction

1 Introduction

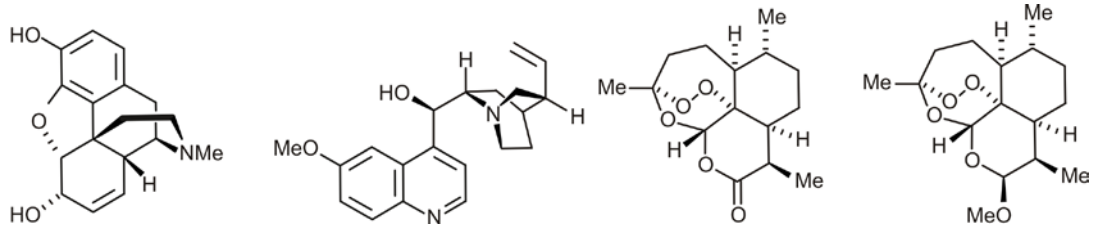
1.1 Natural Product Chemistry

Mankind has known about the benefit of drugs from the crude herbs worldwide for thousands of years.[1] In Asia, Traditional Chinese Medicine (TCM) and Ayurveda, Traditional Indian Medicine (TIM) remain the most ancient yet living traditions.[2] The earliest and most fundamental composition identified in TCM is the Yellow Emperor's Classic of Internal Medicine probably dating back to 2697 B.C.,[3] while Ayurvedic fundamental and applied principles were organized and recorded around 1500 B.C.[4] In Africa, the Egyptians in the days of pharaohs had developed great skills in the use of herbs, and the earliest medical texts, some 4000 years old, described the rich choice of plants.[5] In Europe, there is also a very long history of traditional medicine that has respectable historical and scientific dignity.[6] In fact, for most of history, herbal medicine was the only medicine.

Nowadays, herbal medicines are still used and continue to be used for therapies,[7,8] but considerable confusion remains about their exact mechanism of action. Herbalists claim that secondary metabolites (*e.g.*, alkaloids, quinones, flavonoids, terpenoids, steroids, carbohydrates, and others), produced by plants, can work together synergistically so that the effect of the whole herb is greater than the summed effects of the individual components and the toxicity of the whole herb is lower than that of isolated active ingredients.[9] This contrasts with conventional practice, where polypharmacy is generally avoided whenever possible. Conventional practitioners believe that the efficacy of herbs used to treat illness has originated from the lead compounds (or active principles) contained in herbs in a mixture of other compounds. Such compounds must be isolated and purified, and structurally identified, which provides the fundamental prerequisites for the subsequent series of validation steps.

The first example of conventional medicine derived from a plant is morphine (**1**) (Figure 1). From about 800, *Papaver somniferum* was used not only to treat pain but also to anaesthetize patients. Morphine was isolated from this plant source in 1806, and the manufacturing of this analgesic drug was realized by E. Merck, Germany in 1826.[10] Two other examples of a plant-derived drug were quinine (**2**) and artemisinin (**3**), which are used to treat malaria widespread in tropical and subtropical regions. The pure active principle quinine (**2**) was first

isolated in 1820s from the bark of the *Cinchona* tree. Artemisinin (qinghaosu) (**3**) was identified in 1972 as the bioactive principle of *Artemisia annua* (qinghao plant). Artemether (**4**), a semi-synthetic derivative of **3**, is used for the treatment of multi-drug resistant strains of *Plasmodium falciparum*.[11]



1 **2** **3** **4**

Figure 1. Three naturally occurring structures isolated from medicinal plants, morphine (**1**), quinine (**2**), and artemisinin (**3**), and one semi-synthetic derivative of **3**, artemether (**4**).

Given that natural products have historically provided many novel drugs, one would assume that they would still play a pivotal role in the drug discovery strategy in pharmaceutical company. However, most big pharmaceutical companies have terminated or significantly scaled down their natural products operations during the past 15–20 years.[12,13] This trend could be explained by two aspects: the great obstacles of natural products research and the emergence of combinatorial chemistry in combination with high-throughput screening (HTS). In the course of natural products research, considerable research time and increasingly expensive purification technologies *e.g.*, preparative HPLC, are needed to eliminate known compounds, and accumulate enough quantities of bioactive molecules for further biological evaluation. Also, the complex nature of some naturally bioactive structures impeded the further lead optimization process. By contrast, combinatorial synthesis can efficiently provide large libraries of related compounds for modern HTS.[12,14] Therefore, this rapidly growing area provides an enormous potential to accelerate drug discovery and development.

It is certainly true that biased combinatorial libraries of pure products are particularly easy and convenient to screen, while the hope of identifying interesting lead structures is often disappointed. By contrast, natural products derived from all sources or related to natural products have played and continue to play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases.[15-19] In Figure 2, the number (616, 52%) of naturally inspired agents (*i.e.*, N, ND, S/NM, S^*, S^*/NM) in the 1184 chemical entities from 1981–2006 is much higher than that of merely synthetic drugs (355, 30%) by random screening, even though most of work by the pharmaceutical industry was devoted to HTS of predominantly combinatorial chemistry.[17]

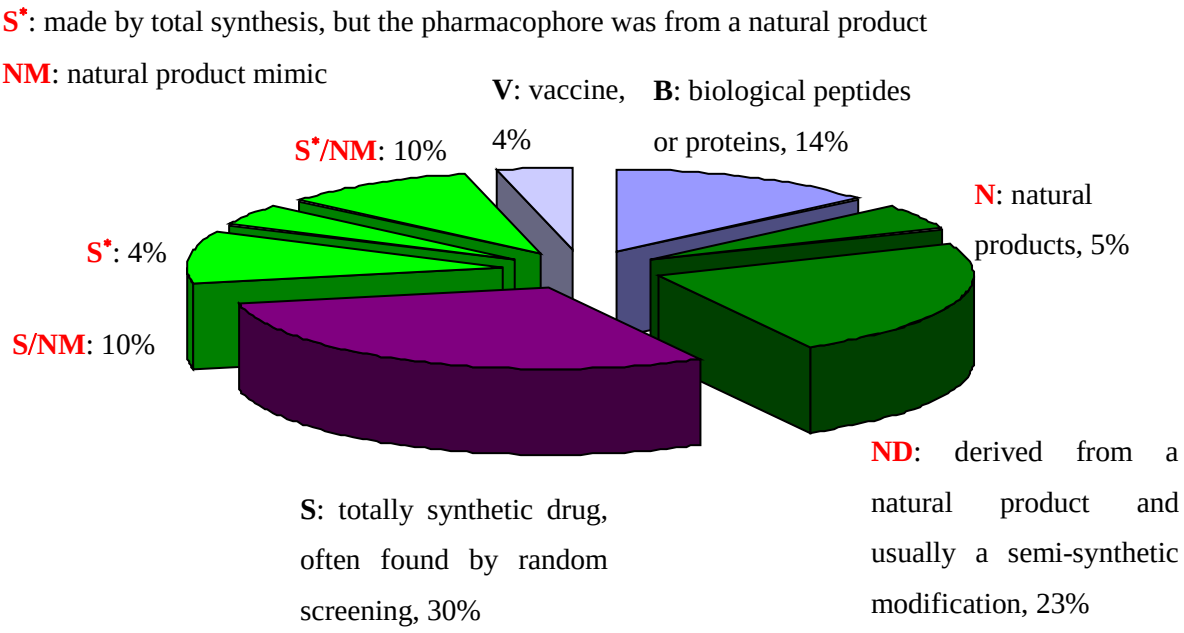


Figure 2. All new chemical entities, 01/1981–06/2006, by source (*N* = 1184) (Figure from Lit.[17]).

In conclusion, the search for natural products by isolation and their derivatives by partial or total synthesis still provides the best solution to the current productivity crisis in drug discovery and development.

1.2 Ancistrocladaceae and Dioncophyllaceae

The tropical lianas of the Ancistrocladaceae and Dioncophyllaceae families,[20] mainly occurring in Africa, Southern, and Southeastern Asia, have been widely used in the traditional medicine. Examples are *Ancistrocladus tectorius*, which has been applied to treat dysentery and malaria in Thailand,[21] and *Triphyophyllum peltatum* (Figure 3), which has been used to treat malaria, elephantiasis, and other diseases.[22]

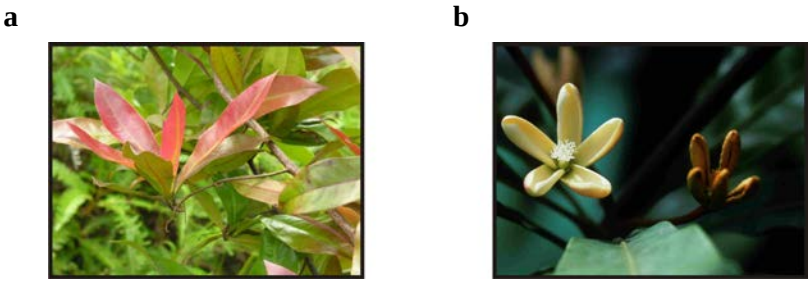


Figure 3. Pictures of *A. tectorius* (a) and *T. peltatum* (b) (pictures from AK Bringmann).

Phytochemical investigations on these plants have revealed that the bioactive principles are

due to the presence of a variety of *C*,*C*- and *N*,*C*-coupled naphthylisoquinoline alkaloids, like ancistrocladine (**5a**), dioncophylline A (**6**), and ancistrocladinium A (**7b**) (Figure 4). Their occurrence is restricted to the two small families, exclusively.

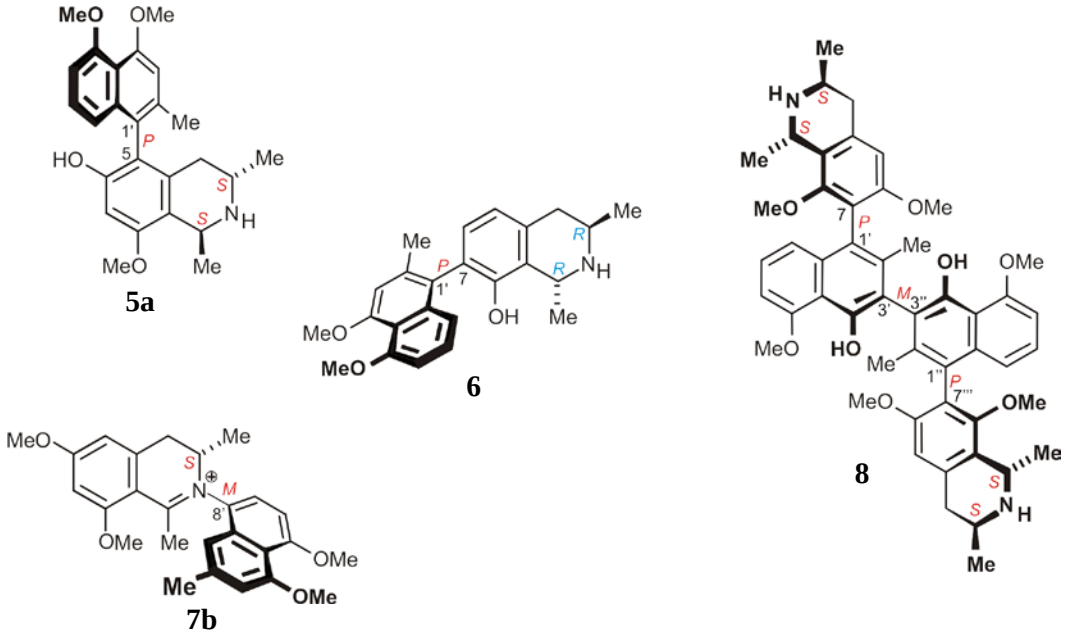


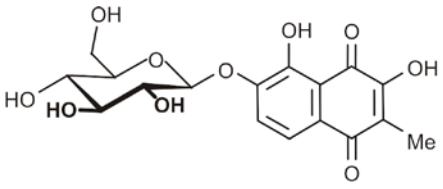
Figure 4. Structures of the naphthylisoquinoline alkaloids ancistrocladine (**5a**), dioncophylline A (**6**), ancistrocladinium A (**7b**), and shuangancistrotectorine A (**8**).

The crude extracts and many of more than 140 so far isolated alkaloids from the two families Ancistrocladaceae and Dioncophyllaceae, as well as their partial- and total-synthetic analogs exhibit promising biological activities. This class of biaryls has been described as exhibiting strong growth-inhibition activities *in vitro* against the plasmodial parasites *P. falciparum*[23-29] and *P. berghei*[30-32] and *in vivo* against *P. berghei*,[33] against the pathogens of leishmaniasis, *Leishmania donovani*,[34-37] and of trypanosomasis, *Trypanosoma cruzi*[35,38,39] and *T. brucei rhodesiense*.[40] Efficacy against HIV-1 and HIV-2,[41-44] the tropical water snail *Biomphalaria glabrata* (the vector of *Schistosoma mansoni*, which causes schistosomiasis),[45-47] and the malarial vector *Anopheles stephensi*,[48] have also been reported. These findings suggest that naphthylisoquinoline alkaloids constitute a class of pharmacologically interesting compounds.

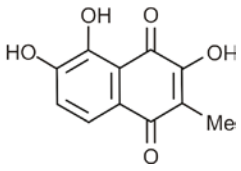
Structurally, the naphthylisoquinoline alkaloids are unique, consisting of a naphthalene ring system and an isoquinoline moiety, which are connected by a *C*,*C*-biaryl or an iminium-aryl axis (*i.e.*, *C*,*C*- or *N*,*C*-coupled), while naturally occurring dimers like shuangancistrotectorine A (**8**) (Figure 4) contain an additional *C*,*C*-biaryl axis between the two monomeric portions.[27,40,47] Most of these alkaloids display the phenomenon of atropisomerism, resulting

from hindered rotation about the biaryl axes. The large structural variety in their constitutions stems from the presence of diverse coupling patterns (i.e., 5,1′-, 5,3′-, 5,8′-, 7,1′-, 7,3′-, 7,6′-, 7,8′-, *N*,6′-, and *N*,8′-), in their oxygen substitution patterns, in their absolute configurations at C-1 and C-3, and in the unsaturation degree in the isoquinoline moieties.

Biosynthetically this class of secondary metabolites, with its broad structural variety, originates from an acetate-malonate pathway for both, the naphthalene parts and the isoquinoline moieties.[49-51] The biosynthesis of the isoquinoline unit can, however, be easily blocked by all sorts of chemical, physical or biotic stress. Then, only small quantities of naphthylisoquinoline alkaloids are produced, while enhanced quantities of naphthoquinones are formed.[52,53] Recently, phytochemical investigation on cell cultures of *T. peltatum* led to the isolation of two highly promising naphthoquinones, dioncoquinones A (**9**) and B (**10**), and nine further analogs from *A. heyneanus*.[54,55] Dioncoquinones A (**9**) and B (**10**) exhibited excellent anti-multiple myeloma properties (especially **10** with EC_{50} = 11 μM against INA-6) without any significant cytotoxicity on normal cells. In particular, these effective-concentration ranges of the compounds **9** and **10** (Figure 5) were similar to those of melphalan, a well-known DNA-alkylating agent[56] routineously used in standard chemotherapeutic regiments for multiple myeloma.[54]



dioncoquinone A (**9**)



dioncoquinone B (**10**)

Figure 5. Structures of bioactive dioncoquinones A (**9**) and B (**10**).

Despite the availability of some antimalarial drugs and co-opted chemotherapeutic treatments for multiple myeloma, an urgent need is still to discover more powerful drugs to overcome resistance of pathogens and to diminish the side effects. Therefore, the main aims of this thesis were to search for two classes of new pharmacologically promising structures, naphthylisoquinoline alkaloids and naphthoquinones, by isolation from plants and by synthesis.

In detail, the present work is divided into the following nine parts:

1) Phytochemical investigations on naphthylisoquinoline alkaloids from the stems of the

Chinese species *Ancistrocladus tectorius*.

2) Phytochemical investigations on naphthylisoquinoline alkaloids from the root bark of a novel and botanically yet undescribed Congolese *Ancistrocladus* species.

3) Semi-synthesis of the dimeric naphthylisoquinoline alkaloid jozimine A_2 and its isomers from dioncophylline A.

4) Phytochemical investigations on naphthoquinones from cell cultures of *Triphyophyllum peltatum*.

5) Phytochemical investigations on Nepenthaceae.

6) Establishment of a strategy for improved access to dioncoquinones B and C, and synthesis of dioncoquinone B analogs for the first SAR studies.

7) Synthesis of epoxides and SAR studies.

8) The first total synthesis of a new naturally occurring compound triphoquinone.

9) Phytochemical investigations on the *Streptomyces* strain RV-15 derived from a marine sponge.

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2 Multiple Myeloma and Naphthoquinones

Multiple myeloma is the second most common blood cancer after non-Hodgkin's lymphoma, accounting for approximately 10% of blood cancer and 1% of all cancers.[57] The incidence of multiple myeloma varies by gender, race, and age. The statistical data indicate an evident predominance among males, blacks, and older individuals for multiple myeloma.[58,59]

Multiple myeloma is characterized by clonal proliferation of malignant plasma cells in the bone marrow. The development of multiple myeloma is described in Figure 6. As multipotent stem cells in humans, they are able to give rise to all of the blood cell types including myeloid (monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes, platelets, and dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells). B cells are one of the lymphoid lineages. Immature B cells are produced in the bone marrow of humans. Subsequently, these immature B cells migrate to the lymph node, where there are called transitional B cells, and some of these cells differentiate into mature B cells. Most of these B cells will become plasmablasts, and eventually plasma cells, and begin producing large volumes of antibodies (immunoglobulin) upon exogenous stimulus. These plasma cells are able to go back to bone marrow and reside there as a memory pool. Therefore, plasma cells are terminally differentiated B cells, and, in normal subject plasma cells, they play an important role in the human immune system.[60]

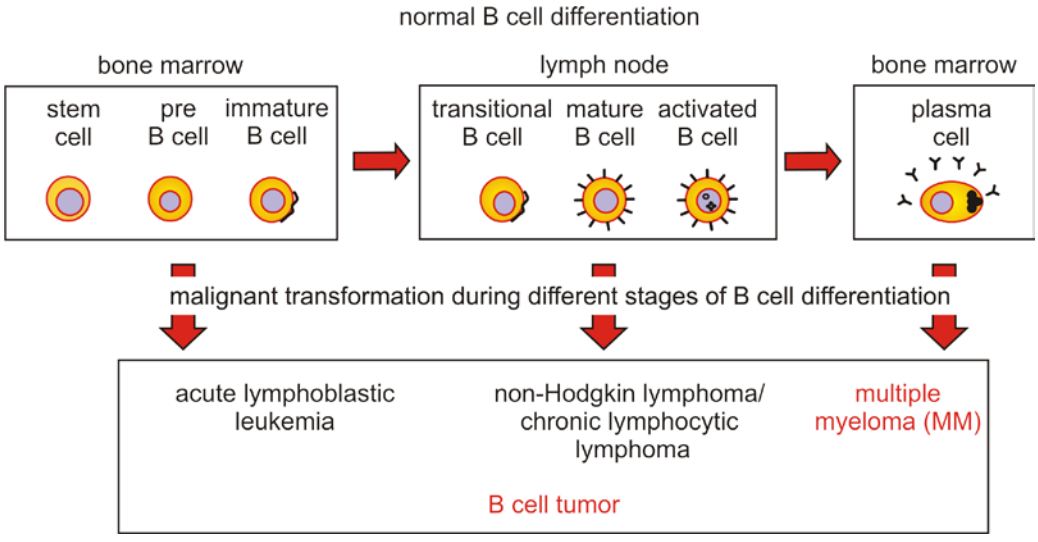


Figure 6. The development of B cell tumor.

However, in multiple myeloma, the space in the marrow will be concurred and occupied by the abnormal proliferation of cancerous plasma cells resulting in the suppression of other

normal blood cells population. As a consequence, the patients will develop anaemia because of a deficiency in red cell and platelet production. At the same time, these cancerous plasma cells will produce abnormal immunoglobulin called paraprotein, which suppresses production of other normal immunoglobulin leading to immunosuppression of the patients and causing them to become very susceptible to infection.[60]

The first successful myeloma treatment with a combination of melphalan (**11**) (Figure 7) and prednisone was introduced in the late 1960s, and was further improved by high-dose chemotherapy with hematopoietic stem-cell transplantation 1980s. The most common induction regimens used today are co-opted treatment protocols.[61] Treatment with thalidomide (**12**) plus dexamethasone, lenalidomide (**13**) plus dexamethasone, **13** plus **11** and prednisone, or bortezomib (**14**) plus **11** and prednisone, are superior to monotherapy alone, as initial therapy for patients with myeloma.[62,63]

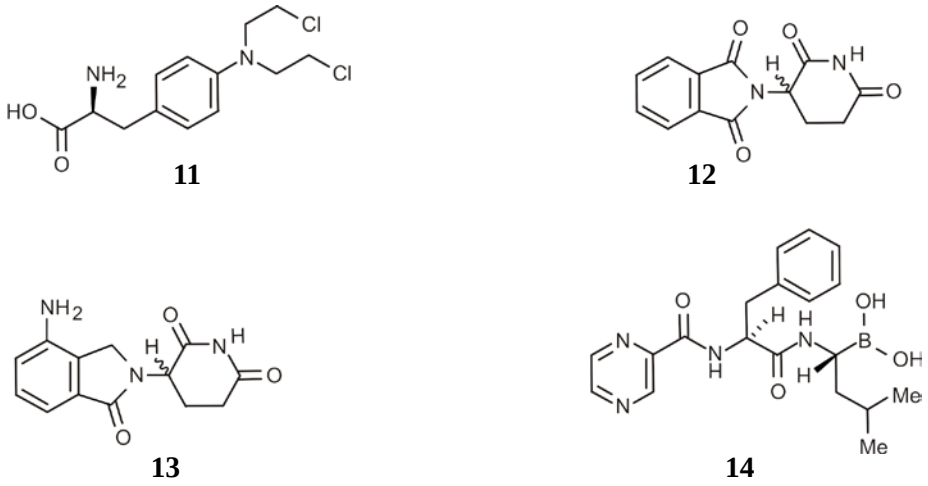


Figure 7. Structures of melphalan (**11**), thalidomide (**12**), lenalidomide (**13**), and bortezomib (**14**).

Melphalan (**11**) belongs to the class of alkylating agents containing nitrogen. It attaches the alkyl group to the guanine base of DNA. Thalidomide (**12**) was introduced into the market initially as a sedative and for treatment of morning sickness for pregnant women in the 1950s,[64] and first tested in humans as a single agent for the treatment of multiple myeloma in 1999.[65] Lenalidomide (**13**), formerly called CC-5013, belongs to a class of thalidomide analogs, termed immunomodulatory drugs. With the promising results in two large phase-3 trials, **13** was approved by the FDA in 2006 for the treatment of myeloma in patients.[66,67] Bortezomib (**14**), a boronic acid dipeptide, is the first inhibitor of the proteasome pathway that is responsible for the orderly degradation of eukaryotic cellular proteins,[68] and was approved by the FDA in 2003.

One class of compounds of potential value for the treatment of tumor diseases are naphthoquinones, which often show pronounced biological activities, such as antibiotic, cytotoxic, or allergenic actions, and they may serve the organism producing them as a weapon for defense.[69] The mechanism by which quinones cause these effects can be quite complex.[70] Quinones can be Michael acceptors; therefore, damage can occur through covalent binding with crucial cellular nucleophiles. For example, they react readily with sulfur nucleophiles, such as GSH or cysteine residues on proteins, and with nucleophilic amino groups on proteins or with DNA. Alternatively, quinones are highly redox-active molecules which can undergo enzymatic and nonenzymatic redox cycling with their semiquinone radicals, leading to formation of reactive oxygen species (ROS), including superoxide, hydrogen peroxide, and ultimately hydroxy radicals. The hydroxy radicals are powerful oxidizing agents that may be responsible for damage to essential macromolecules.[70]

Naphthoquinones have been demonstrated to possess a wide range of biological activities *e.g.*, against tumor cell lines, malarial parasites, fungi, and bacteria. Table 1 covers the representatives of naturally occurring bioactive naphthoquinones (Figure 8) during the past 15 years.

Table 1. Chemical names, origins, and biological activities of naphthoquinones.

Structure	Origin	Bioactivity	Lit.
	Antitumoral Activities		
6-methoxydihydrolindbladione (**15**)	*Lindbladia tubulina*	leukemia cells	[71]
chabrolon-naphthoquinone B (**16**)	*Nephthea chabrolii*	breast cancer cells	[72,73]
neomarinone (**17**)	actinomycete	colon carcinoma	[74]
rhinacanthin Q (**18**)	*Rhinacanthus nasutus*	a variety of tumor cells	[75]
	Antimalarial Activities		
isodiospyrin (**19**)	*Diospyros*	*T. brucei*	[76-80]
8'-hydroxyisodiospyrin (**20**)	*Diospyros*	*L. donovani*	
newbouldiaquinone A (**21**)	*Newbouldia laevis*	*P. falciparum*	[81]
sterekunthal A (**22**)	*Stereospermum*	*P. falciparum*	[82]
naphthoquinone **23**	*Cordyceps*	*P. falciparum*	[83]
	Antibacterial Activities		
alnumycin (**24**)	strain of *Streptomyces*	G-positive bacterial	[84]
juglomycin Z (**25**)	*Streptomyces tendae*	antibacterial	[85]
	Antifungal Activities		
cordiaquinone A (**26**)	*Cordia curassavica*	antifungal activities	[86]
chimaphilin (**27**)	*Chimaphila umbellata*	antifungal activities	[87]
chlorosesamone (**28**)	*Sesamum indicum*	antifungal activities	[88,89]
engelharquinone (**29**)	*Engelhardia*	*M. tuberculosis*	[90]
malvone A (**30**)	*Malva sylvestris*	*V. dahliae*	[91]

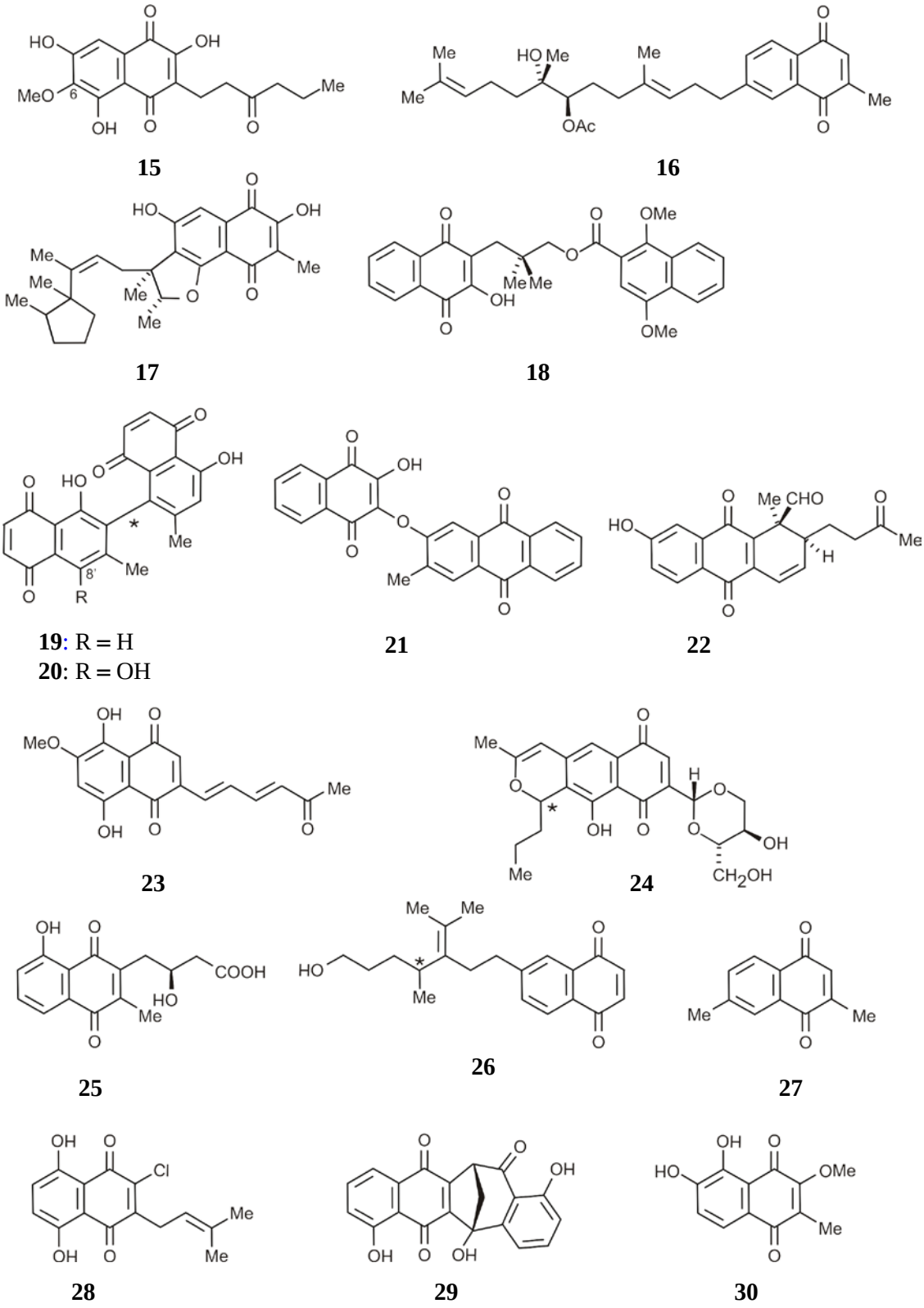


Figure 8. Structures of naturally occurring bioactive naphthoquinones (* stereogenic element of unknown absolute configuration).

The methods for synthesizing pharmacologically promising naphthoquinones include reactions like oxidative transformations,[92,93] ring-closures by condensation of benzaldehydes with succinic acid derivatives,[94-96] [4+2]-cycloadditions,[97-99] annulations of *ortho*-substituted tertiary benzamides,[100-103] annulations of phthalide anions with Michael acceptors,[104-106] Friedel-Crafts acylations,[107] syntheses from cyclobutenediones,[108-111] and reactions of Fischer-type carbene complexes with alkynes.[112,113] These eight strategies are briefly described in the following part.

Method 1: Oxidative transformations (Scheme 1)

The most general method for the preparation of naphtho-1,4-quinones **32** is the oxidation of varied naphthalenes **31**, using oxidative reagents such as metal derivatives with or without hydrogen peroxide.[92,93] This strategy has been applied to prepare naphthoquinones in the present thesis, as described in the Results and Discussion part.

Method 2: Condensation of benzaldehydes with succinic acid derivatives (Scheme 1)

Benzaldehyde (**33**) is reacted under typical Stobbe condensation conditions with derivatives of succinic acid derivatives **34** to provide the monoesters **35**, which may undergo an intramolecular Friedel-Crafts acylation, affording naphthalenecarboxylates **36** as precursors to naphthoquinones.[94-96] This strategy was used to synthesize dioncoquinone B (**10**) in A. Voskobojnik's diploma thesis.[114]

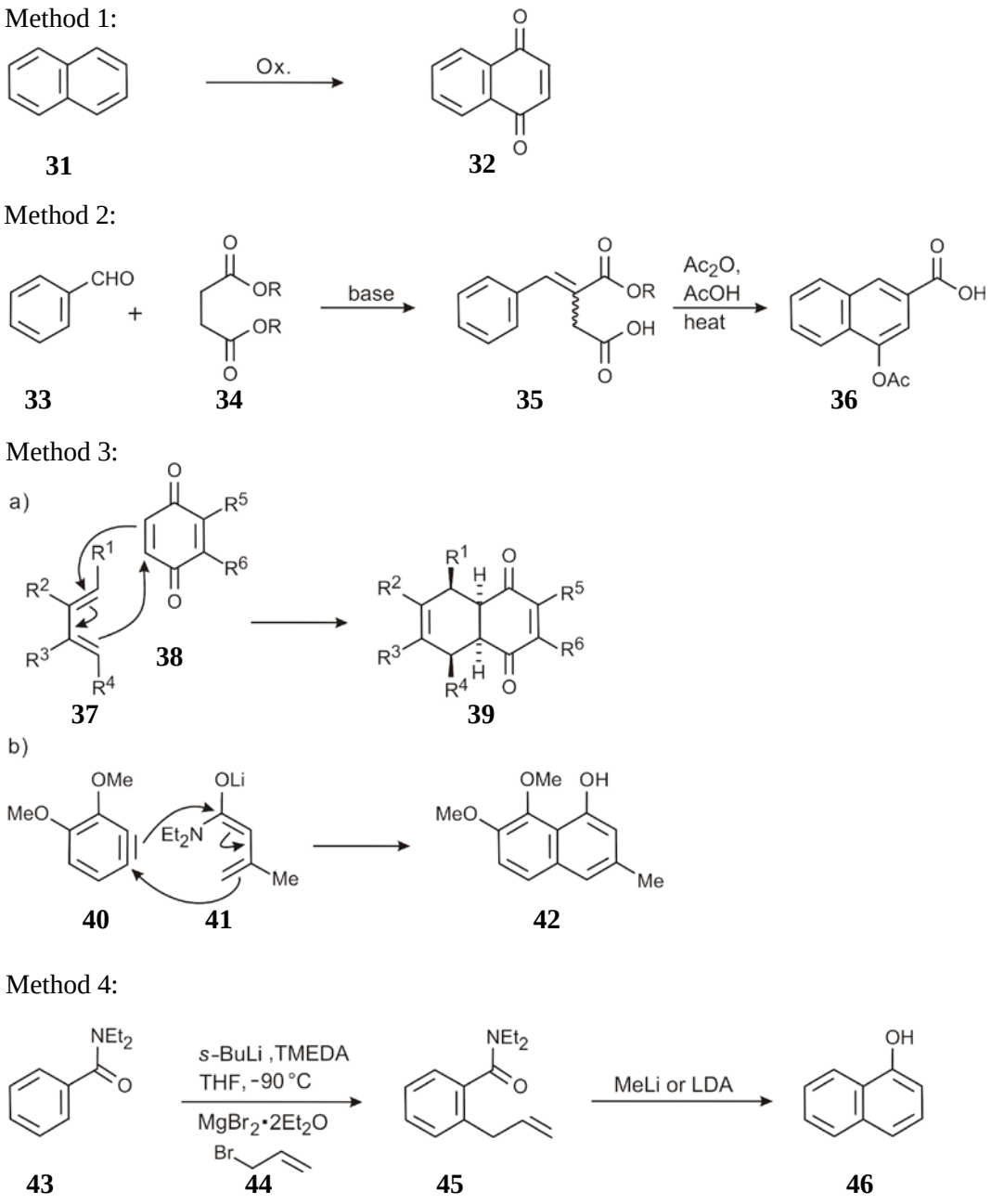
Method 3: [4+2]-Cycloaddition reactions (Scheme 1)

This reaction proceeds between dienes **37** and dienophiles **38** almost exclusively with *endo* selectivity.[97,98] Within this class, the cycloaddition process of the benzyne **40** with the diene **41** was applied to synthesize dioncoquinone B (**10**) in M. Moos' diploma thesis.[99]

Method 4: Annulation of *ortho*-substituted tertiary benzamides (Scheme 1)

Tertiary benzamides **43** are exceptional members of the family of Directed *ortho*-Metalation (DoM) groups, being good coordinating sites for alkyllithium bases but poor electrophilic sites in order to avoid attack from the base itself. These benzamides can undergo selective *ortho*-deprotonation by the action of a strong base, giving rise to *ortho*-metalated species. The latter, upon reaction with an electrophilic reagent allyl bromide (**44**), yield *ortho*-substituted products **45**, which are subject to a base-mediated anionic cyclization affording naphthol **46** as a synthetic precursor to naphthoquinones.[100-103] In the present thesis,

this strategy was used to synthesize dioncoquinone B (**10**).



Scheme 1. Strategies to synthesize precursors to naphthoquinones, as used for the synthesis of dioncoquinone B (**10**) and its analogs in our group.[115]

Method 5: Annulation of phthalide anions with Michael acceptors (Scheme 2)

The phthalide anion **47** reacts with various Michael acceptors **48** *via* intermediate **49** to dinaphthol **50**, which undergoes air oxidation to the corresponding naphthoquinones. The presence of the X group serves two purposes: Initially, it provides essential stabilization for the carbanion, and later, it becomes a good leaving group, allowing aromatization of the newly formed ring.[104-106]

Method 6: Friedel-Crafts acylation (Scheme 2)

5,8-dihydroxynaphthoquinone (**51**) is prepared by double Friedel-Crafts acylation of 1,4-dihydroxybenzene (**52**) with maleic anhydride (**53**) in a fused mixture of aluminum trichloride and sodium chloride.[107]

Method 7: Synthesis from cyclobutenediones (Scheme 2)

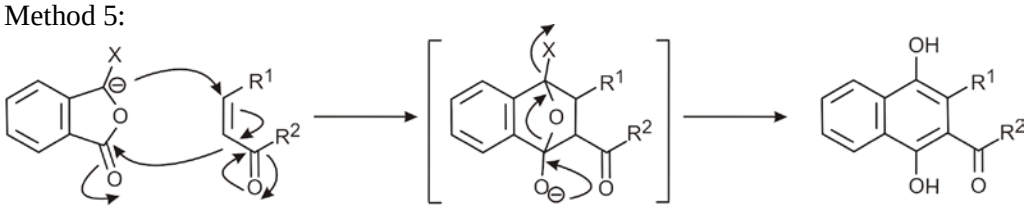
Benzocyclobutenedione (**54**) is easily transformed into phthaloyl metalate **55** by reaction with transition-metal complexes such as chlorotris(triphenylphophine)cobalt (I). The phthaloyl complexe serves as a precusor to naphthoquinone **31** by reacting with simple or functionalized alkynes.[108,109]

Cyclobutenedione **56** or substituted squaric acid ester is also used to prepare naphthoquinone **31** by nucleophilic addition with an aryllithium derivative *via* intermediate **57**, followed by ring-opening, concomitant cyclization, and oxidation on exposure to air.[109-111]

Method 8: Reaction of Fischer-type carbene complexes with alkynes (Scheme 2)

The Fischer-type metal carbene **59** can be easily prepared from the addition of an aryl organolithium nucleophile **58** to a metal carbonyl, followed by *O*-alkylation using strong alkylating reagents (such as trialkyloxonium salts). Subsequently oxidative demetalation on **59** is used to generate the corresponding quinones.[112,113]

Method 5:



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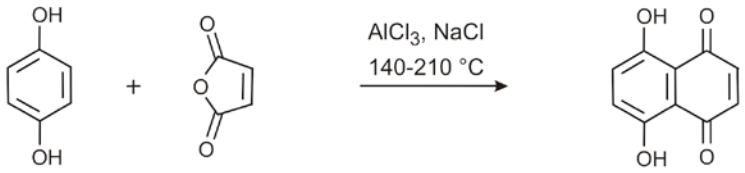

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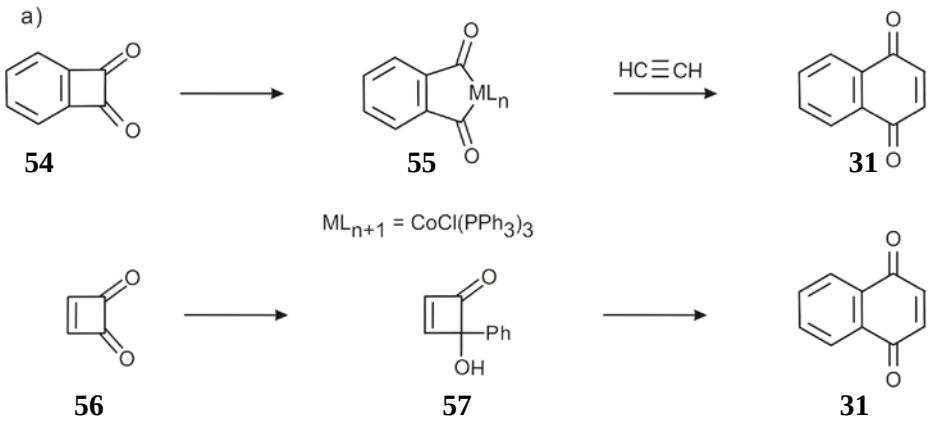
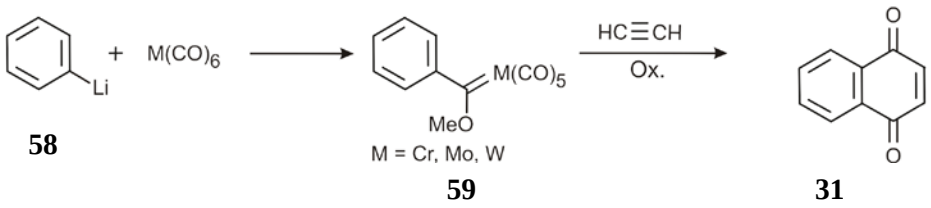


Method 8:



Scheme 2. Alternative potential strategies used to synthesize naphthoquinones (or their precursors).

In summary, multiple myeloma is a treatable but incurable blood cancer, and there is, thus, still an urgent need for new drugs. Naphthoquinones have been found to exhibit diverse pharmacological properties, including activities against a variety of tumor cells. To search such promosing compounds, some of the numerous synthetic methods for the preparation of naphthoquinones were applied in the present thesis.

Results and Discussion

3 Isolation and Characterization of Naphthylisoquinoline Alkaloids from the Chinese *Ancistrocladus tectorius* Species

3.1 Naphthylisoquinoline Alkaloids from *A. tectorius*

The crude extract of the Chinese species *Ancistrocladus tectorius* is used in traditional medicine to treat dysentery and malaria,[21] and has, additionally, been found to exhibit antiviral[116] and antitumoral[117] activity, even *in vivo*. Phytochemically, this plant has so far been investigated in several groups, giving rise to a series of structurally divergent monomeric naphthylisoquinoline alkaloids with five different coupling types (5,1', 5,8', 7,1', 7,3', and 7,6'),[117-122] naphthalene-devoid isoquinolines,[120] and five dimeric analogs with a high degree of steric hindrance at the central biaryl axes.[27] The large number and structural diversity of meanwhile ca. 30 isolated such alkaloids is in accordance with the pronounced morphological and genetic variation within the same species, *A. tectorius*, which is thus, more appropriately, addressed as an '*A. tectorius* complex'.[123]

In this thesis, the isolation, structural elucidation, and pronounced antiplasmodial activities of nine new naphthylisoquinoline alkaloids from *A. tectorius* is described, including six 5,1'-coupled structures; ancistectorine A_1 (**60**), *N*-methylancistectorine A_1 (**61**), ancistectorine A_2 (**62a**), 5-*epi*-ancistectorine A_2 (**62b**), 4'-*O*-demethylancistectorine A_2 (**63**), ancistectorine A_3 (**64**), the 7,1'-coupled ancistectorine B_1 (**65**), the 7,8'-linked ancistectorine C_1 (**66**), and the 5,8'-linked 5-*epi*-ancistrolikokine D (**67**) (Figure 9).

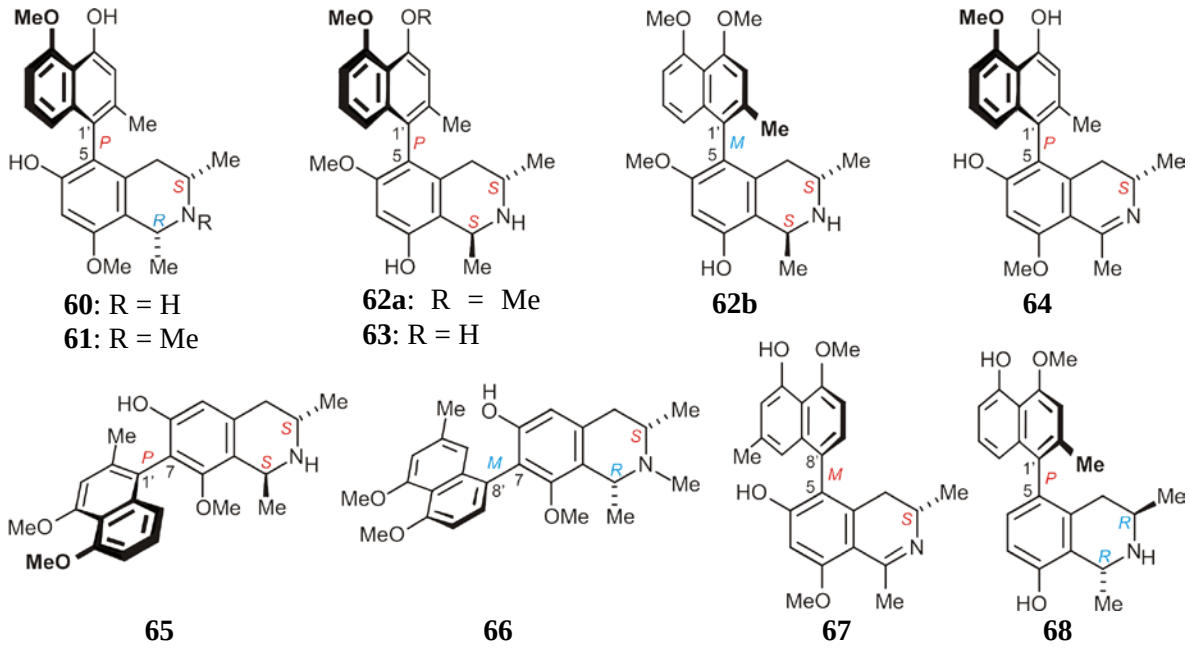


Figure 9. Nine new naphthylisoquinoline alkaloids, **60**–**67**, isolated from the Chinese *A. tectorius*, and the highly antiplasmodial known dioncophylline C (**68**).

Besides the above nine new alkaloids presented, seven known[124-127] compounds, **69**–**74** (Figure 10), were isolated for the first time from *A. tectorius*, together with fourteen other known[21,117-121] metabolites, **5**, **7**, and **75**–**83** (Figure 11), which had already been previously found in this plant.

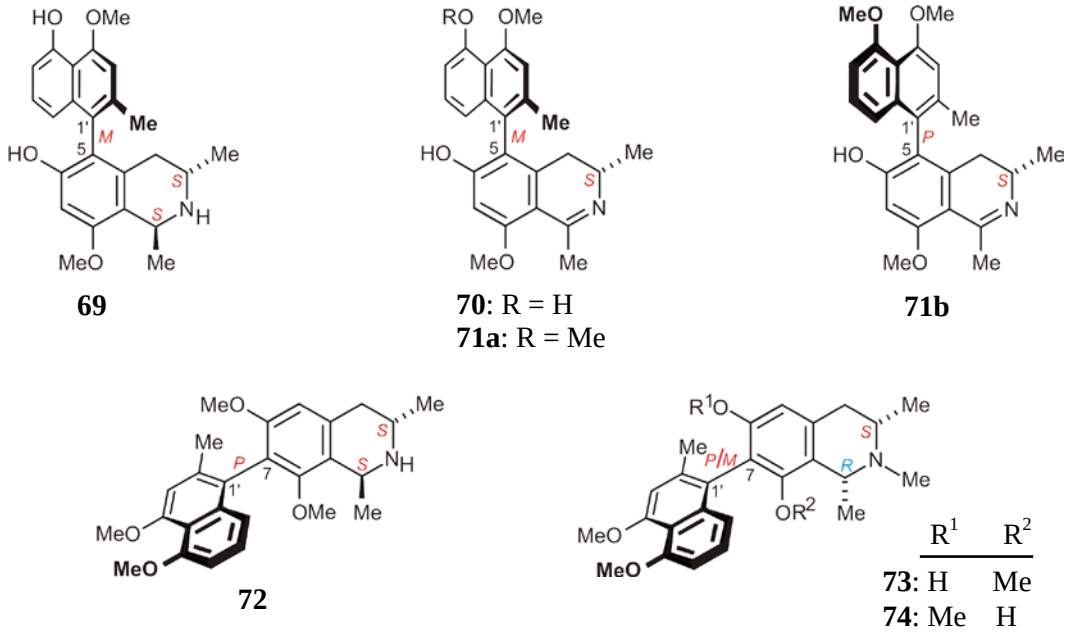


Figure 10. Seven known naphthylisoquinoline alkaloids, **69**–**74**, isolated from *A. tectorius* for the first time.

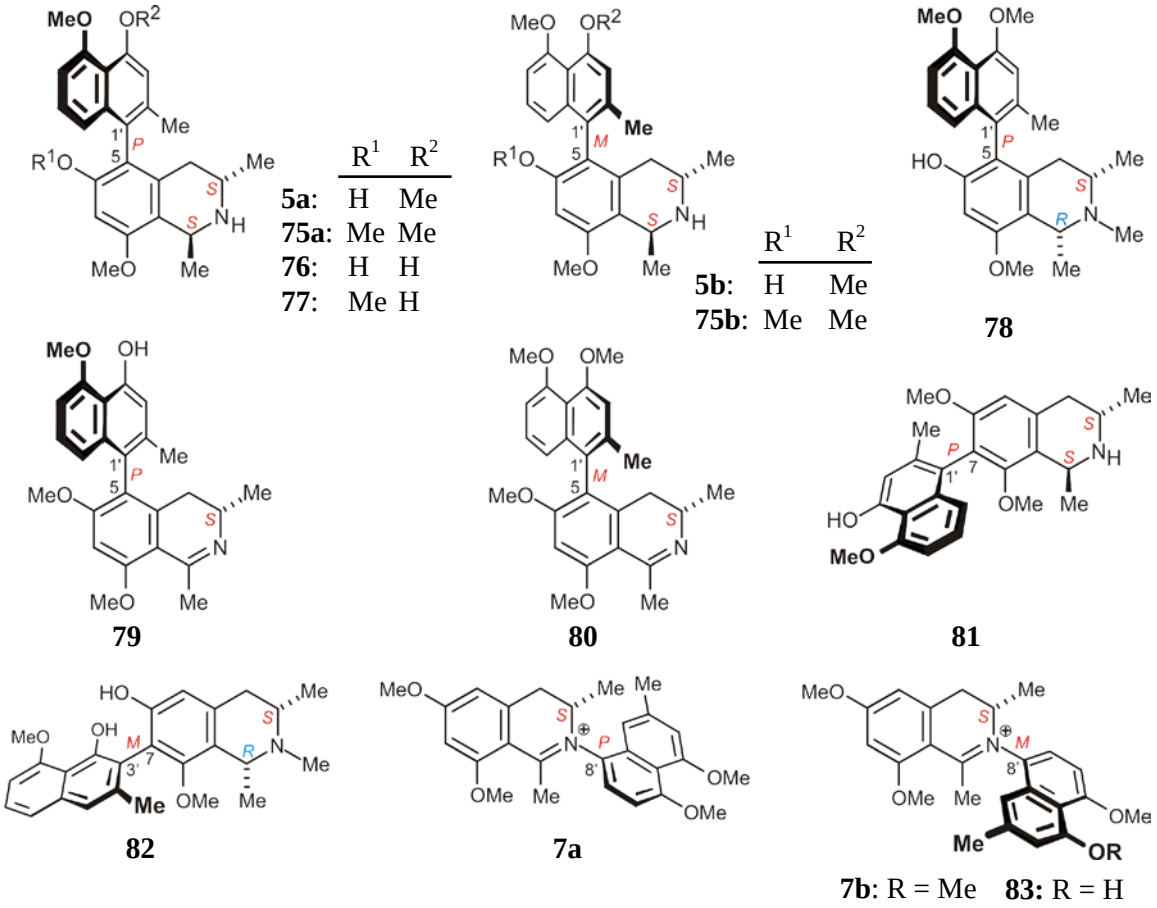


Figure 11. Fourteen further identified known naphthylisoquinoline alkaloids, **5**, **7**, and **75**–**83**, which had already been isolated from *A. tectorius* before.

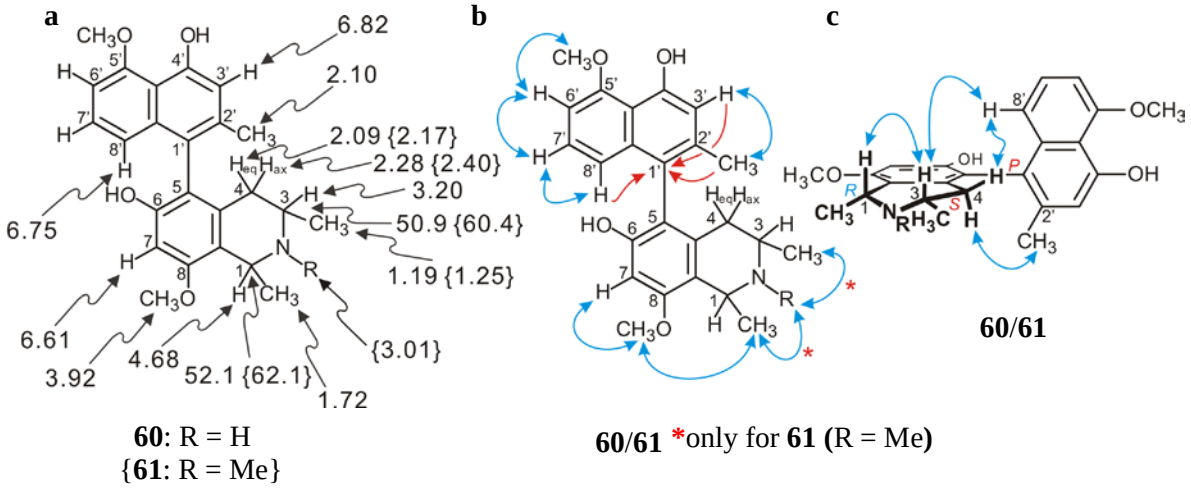
3.2 Results and Discussion

Recent investigations on the gene sequences of *A. tectorius* suggested that the species possesses a broad morphological and genetic variability and produces a pronounced structural diversity of naphthylisoquinoline alkaloids.[123] Among them are the shuangancistrotectorines, the very first naphthylisoquinoline dimers that contain three consecutive stereogenic biaryl axes due to the presence of a rotationally hindered central axis between the naphthalene moieties.[27] These dimers exhibit excellent and specific antiplasmodial activities. For all these reasons, it seemed intriguing to further investigate the secondary metabolites of *A. tectorius* from the Chinese island Hainan in more detail.

The air-dried twigs from this plant were ground and extracted with 95% EtOH at room temperature. The crude extract was submitted to liquid-liquid separation, FCPC (fast centrifugal partition chromatography), column chromatography on silica gel, and preparative

HPLC, which permitted isolation of nine new monomeric naphthylisoquinoline alkaloids, compounds **60**–**67**.

The molecular formula of compound **60** was $C_{24}H_{27}NO_4$, as evidenced from HRESIMS and from the number of signals in the ^{13}C NMR spectra. The coupling pattern of the aromatic protons (one triplett, two doublets of doublets, and two singlets) and the high-field shifted signal (Figure 12a) of the CH_3-2' protons (2.10 ppm) indicated that the axis in the naphthalene moiety was located at C-1' or C-3'. The latter could be excluded due to the HMBC long-range couplings of H-8' (6.75 ppm), H-3' (6.82 ppm), and CH_3-2' to C-1' (Figure 12b). The assignment of H-8' in turn was deduced by a NOESY interaction with equatorial H-4 (2.09 ppm) (Figure 12c) and by the NOESY series {H-8' ↔ H-7' ↔ H-6' ↔ OCH_3-5'}. Consequently, the biaryl axis in the naphthalene moiety had to be located at C-1'.



60: R = H
{**61**: R = Me}

60/61 *only for **61** (R = Me)

Figure 12. Selected ^1H and ^{13}C NMR data (δ in ppm) (a) for **60**; in {}: the values of compound **61** that are different from those of **60**. All other values of **61** and **60** are nearly identical (± 0.02 ppm in ^1H NMR and ± 0.4 ppm in ^{13}C NMR). HMBC (single red arrows) (b) and NOESY (double blue arrows) (b, c) correlations for evidencing the constitution of **60** and **61** and their relative configurations at the biaryl axis and the stereogenic centers.

The other methoxy group in compound **60**, resonating at 3.92 ppm, was assigned to be located at C-8, since its protons were observed to interact with both, H-7 (6.61 ppm) and CH_3-1 (1.72 ppm) in the NOE correlations. Therefore, the biaryl axis had to be located at C-5 in the isoquinoline moiety, and accordingly the C-4 position was in direct proximity of this axis, which was in agreement with the high-field shifts of H-4_{eq} (2.09 ppm) and H-4_{ax} (2.28 ppm) (Figure 12a). In conclusion, this alkaloid was established to be 5,1'-coupled and to possess the constitution **60**, with free hydroxy functions at C-6 and C-4'.

The relative configuration at C-1 versus C-3 in **60** was deduced to be *cis* from an NOE correlation between H-1 (4.68 ppm) and H-3 (3.20 ppm) (Figure 12c). The absolute configuration at C-3 was determined as 3*S* by GC-MSD analysis of the Mosher derivatives of (*S*)-*N*-methyl-3-aminobutyric acid and (*S*)-3-aminobutyric acid (both derived from C-3) obtained by a ruthenium-mediated oxidative degradation developed by us earlier.[128] Thus, the new alkaloid **60** was *S*-configured at C-3 and, given the relative *cis*-configuration assigned above, *R*-configured at C-1.

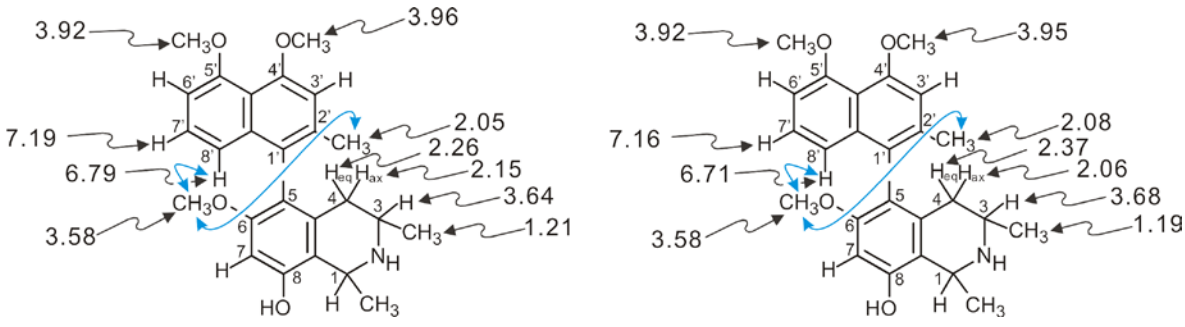
The configuration at the axis relative to the stereocenters was assigned from NOE interactions between equatorial H-4 and H-3 with H-8' (Figure 12c). This indicated that the spin systems were all on the same side of the isoquinoline plane, which, given the above-assigned 3*S*-configuration, should be the upper side, so that the stereogenic axis should be *P*-configured, as shown in Fig. 2c. This stereochemical assignment was confirmed by the complementary NOE interaction between the axial proton at C-4 and CH_3-2', which are both on the bottom side of the molecule. The axial *P*-configuration was further corroborated by the CD spectrum [λ_{max} ($\Delta\varepsilon$) = 210 nm (–7.3) and 238 nm (+7.5)], which was in accordance with that of the known,[117] likewise 5,1'-coupled and *P*-configured[118] - and co-occurring - alkaloid (+)-ancistrocline (**78**). The latter had previously been obtained both, by semi-synthesis from the naturally occurring 3,4-dihydroisoquinoline alkaloid ancistrocladinine,[118] and by total synthesis via a biaryl lactone key intermediate obtained in an intramolecular aryl coupling step.[129] The thus established full stereostructure **60**, which had not been described previously, was named ancistectorine A_1, after the name of the plant. The compound is, simultaneously, the 4'-*O*,*N*-didemethyl analog of (+)-ancistrocline (**75**).

Compound **61** was found to possess a molecular formula of $C_{25}H_{29}NO_4$ as deduced by HRESIMS, showing 14 additional mass units (corresponding to a CH_2 portion) compared to **60**. Its ^1H and ^{13}C NMR spectra were very similar to those of **61**, and specifically the 2D NMR correlations indicated that **61** was also a 5,1'-coupled type alkaloid containing two methoxy groups at C-8 and C-5'. A substantial structural difference between **61** and **60** was the presence of an additional *N*-methyl group in the isoquinoline moiety in compound **61**, which was evidenced by NOE correlations of the *N*-CH_3 protons at 3.01 ppm with the two methyl doublets of C-1 and C-3 (Figure 12b). This also explained the distinct differences between **60** and **61** in the chemical shifts of C-1 and C-3 and CH_3-3 (Figure 12a).

Oxidative degradation experiments in combination with the same specific NOE correlations as for compound **61** (Figure 12c) established **61** to be *R*-configured at C-1, *S* at

C-3, and *P* at the biaryl axis. The nearly identical CD curve of **61** as compared to that of **60** was expectedly in accordance with the axial configuration in **61**. Because the new alkaloid **61** was the *N*-methyl analog of **60**, it was named *N*-methylancistectorine A_1. The compound is, simultaneously, the 4'-*O*-demethyl analog of (+)-ancistrocline (**78**).

Two further new alkaloids, **62a** and **62b**, gave very close but baseline separated peaks on a reversed-phase HPLC column. Each compound possessed a molecular formula of $C_{25}H_{29}NO_4$, as deduced from HRESIMS. The NMR spectra and specific HMBC correlations of **62a** and **62b**, in particular the signals of CH_3-2' protons (2.05/2.08 ppm), H-4_{ax} (2.15/2.06 ppm), and H-4_{eq} (2.26/2.37 ppm), indicated that they were 5,1'-coupled, like **60** and **61**. Their sets of signals were found to be very similar to each other, with just slightly different chemical shifts, except for the protons and carbons in the region between the biaryl axis and the stereogenic center at C-3 (Figure 13) suggesting that **62a** and **62b** were diastereomers, probably atropo-diastereomers. Based on the observed NOE interactions, two methoxy groups, resonating at 3.96 and 3.92 ppm in **62a** and 3.95 and 3.92 ppm in **62b**, were attributed to be at C-4' and C-5'. The remaining methoxy group, showing a significant high-field shift (each 3.58 ppm), should be located at C-6 in the shielding zone of the naphthalene ring, which was further confirmed by the NOE correlations between MeO-6 and H-8' (6.79 ppm) and between MeO-6 and Me-2' (2.08 ppm) in both compounds (Figure 13), thus leaving the free hydroxy group at C-8.



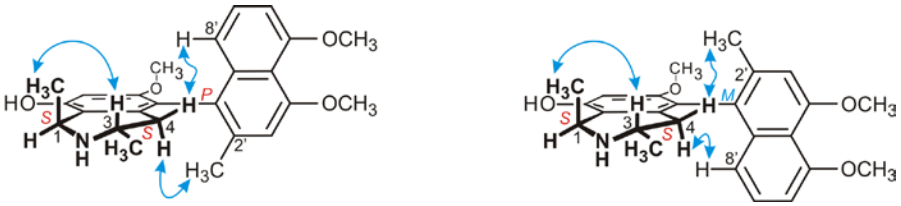
62a **62b**

Figure 13. Comparison of selected ^{1}H data and NOE interactions of compounds **62a** and **62b** indicative of the (joint) constitution. The differences of chemical shifts of the other protons in these two compounds that are ≤ 0.01 ppm, are not shown.

The relative configurations of the two methyl groups at C-1 and C-3 in **62a** and **62b** were demonstrated to be *trans* to each other in both compounds, from NOE correlations between CH_3-1 and H-3 (Figure 14). Again by oxidative degradation, the absolute configurations were determined, here evidencing *S*, both for C-1 and C-3. This, in combination with specific NOE

interactions between H-4_{eq} (2.26 ppm) and H-8', and between H-4_{ax} (2.15 ppm) and Me-2' (2.05 ppm), evidenced the biaryl axis to be *P*-configured in compound **62a** while, expectedly, compound **62b** was *M*-configured, as demonstrated by a complementary NOE interaction between H-4_{ax} (2.06 ppm) and H-8' (6.71 ppm) and an (albeit weak) NOE correlation from H-4_{eq} (2.37 ppm) to CH_3-2', which was covered by the strong interaction from H-4_{eq} to the overlapping signal of H-4_{ax} (Figure 14).

In agreement with the thus established 1*S*,3*S*,*P*-configuration for **62a** and the 1*S*,3*S*,*M*-configuration for **62b**, the equatorial proton at C-4 is upfield shifted for **62a** (2.26 ppm) as compared to the analogous signal in **62b** (2.37 ppm) and, vice versa, the axial proton at C-4 is upfield shifted for **62b** (2.06 ppm) as compared to that of **62a** (2.15 ppm), with the protons of the higher-shifted signals always being closer to the larger naphthalene portion and thus more strongly influenced by its ring-current effect.



62a **62b**

Figure 14. Selected NOE interactions indicative of the relative configurations at the biaryl axes and the stereogenic centers in **62a** and **62b**.

In agreement with the presence of opposite configurations at the biaryl axes in **62a** and **62b**, their CD spectra were fully opposite to each other (Figure 15). The CD curve of **62a** gave a positive Cotton effect at 240 nm and a negative one at 227 nm, nearly identical to that of its known[118,130] 6-*O*-demethyl-8-*O*-methyl analog ancistrocladine (**5a**), while **62b** showed a spectrum fully in accordance with that of its known[118,131,132] 6-*O*-demethyl-8-*O*-methyl analog hamatine (**5b**). Compounds **62a** and **62b** had hitherto not been described in the literature; since they had the same 5,1'-coupling type ("A") as an A_1 (**60**) and its *N*-methyl analog **61**, they were named ancistectorine A_2 (**62a**) and 5-*epi*-ancistectorine A_2 (**62b**).

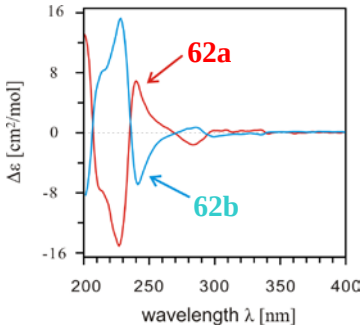
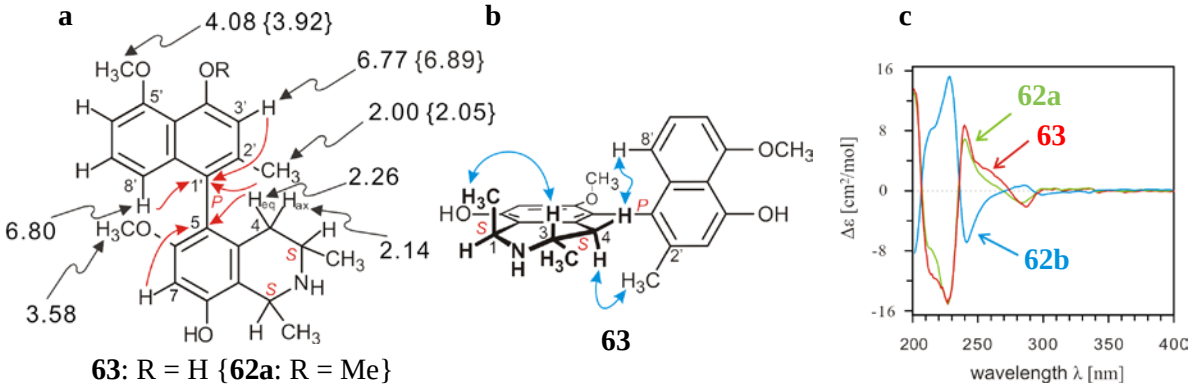


Figure 15. Comparison of the CD spectra of **62a** and its atropisomer **62b**.

The fifth new alkaloid, **63**, was found to have a molecular formula of $C_{24}H_{27}NO_4$, as established by HRESIMS and from the number of carbon signals in the ^{13}C NMR spectrum. As in the case of compounds **60**–**62**, it had a 5,1'-coupling pattern, as deduced from HMBC correlations from H-3', H-8', and CH_3-2' to C-1', from H-4 and H-7 to C-5 (Figure 16a). This was in agreement with the signals of the CH_3-2' protons (2.00 ppm), of H-4_{ax} (2.14 ppm), H-4_{eq} (2.26 ppm), and 6-OCH_3 (3.58 ppm).

The two methyl groups of **63** at C-1 and C-3 were *trans* to each other, as indicated by an NOE correlation between CH_3-1 and H-3 (Figure 16b). By application of the usual degradation procedure, the configurations at both, C-1 and C-3, were determined as *S*. This, in conjunction with the specific NOE correlations between H-4_{eq} and H-8' (6.80 ppm), and between H-4_{ax} and CH_3-2', demonstrated the biaryl axis to be *P*-configured. It was further confirmed by the nearly identical CD curve of **63** to that of **62a**, which also had a *P*-configured axis, while the spectrum of **63** was opposite to that of **62b**, which had a *M*-configured one (Figure 16c).

The comparison of the ^1H NMR spectra of compounds **63** and **62a** showed that the structures differed in the naphthalene portions, for instance, for CH_3-2' (2.00/2.05 ppm), H-3' (6.77/6.89 ppm), and 5'-OCH_3 (4.08/3.92 ppm), as shown in Figure 16a. In contrast to **62a**, H-3' in **63** did not show a NOESY interaction with any of the methoxy groups. This suggested that **63** was the 4'-*O*-demethylated analog of **62a**. It was, thus, named 4'-*O*-demethylancistectorine A_2.

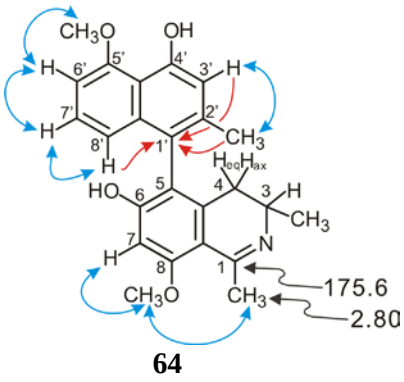


63: R = H {**62a**: R = Me}

Figure 16. Selected ^{1}H NMR data (δ in ppm) for **63** (a); in {}: the values of compound **62a** that are different from those of **63**. All other values of **62a** are nearly identical to those of **63** (± 0.02 ppm in ^{1}H NMR). HMBC correlations (single red arrows) (a) in **63**, NOESY interactions indicative of the relative configurations at C-1 and C-3 and at the biaryl axis (b), and comparison of the CD spectra of **63** and its analogs **62** (c).

The molecular formula of the sixth new alkaloid, compound **64**, was $C_{24}H_{25}NO_4$, as established by HRESIMS. Like compounds **60**–**63**, it was also 5,1'-coupled, as indicated by its NMR spectra, in particular by HMBC correlations from H-3', H-8', and CH_3-2' to C-1' and NOE interactions between H-7 and CH_3O-8 (Figure 17). However, different from the tetrahydroisoquinoline moiety contained in compounds **60**–**63**, the presence of a 3,4-dihydroisoquinoline part in compound **64** was suggested from the ^{1}H NMR shift (2.80 ppm) of CH_3-1 and its multiplicity (singlet), from the low-field shifted value (175.6 ppm) (Figure 17) of the ^{13}C NMR signal of C-1, and from the absence of an H-1 signal, which normally appears at ca. 4.60–4.80 ppm in naphthyltetrahydroisoquinoline alkaloids, like in **60**–**63**. From the NOE interactions between CH_3O-5' and H-6', and between CH_3O-8 and both, H-7 and CH_3-1, the two methoxy groups were attributed to be located at C-5' and C-8, leaving the remaining two free hydroxy groups at C-4' and C-6.

Our oxidative degradation[128] established the absolute configuration at C-3 of **64** to be *S*, and NOE interactions between H-4_{ax} and CH_3-2', and between H-4_{eq} and H-8' (not shown, similar as for **60**, **61**, **62a**, and **63**) indicated the biaryl axis to be *P*-configured. This stereochemical assignment was further confirmed by the mirror-image like CD spectrum of **64** in comparison to that of the known[124] alkaloid 5'-*O*-demethylhamatinine, which has an *M*-configured biaryl axis and has previously been isolated from a Congolese *Ancistrocladus* species related to *Ancistrocladus congolensis*. Because of its 5,1'-coupling type, compound **64** was henceforth named ancistectorine A_3; it is, simultaneously, the 4'-*O*-demethyl analog of the known[133] alkaloid ancistrocladinine.



64

Figure 17. Selected ^{1}H and ^{13}C NMR data, HMBC (single red arrows), and NOESY (double blue arrows) correlations for the constitution of **64**.

The seventh new alkaloid, compound **65**, possessed a molecular formula of $C_{25}H_{29}NO_4$ as revealed from HRESIMS and a system of three neighboring and two single aromatic protons in the ^{1}H NMR spectrum. The high-field shift of the signal of CH_3-2' (2.18 ppm) and HMBC long-range couplings from the signals of two aromatic protons of H-8' (6.89 ppm), from H-3' (6.90 ppm), and from CH_3-2' to C-1' (Figure 18a) established the biaryl axis in the naphthalene moiety in **65** to be located at C-1', as in **60**–**64**. However, different from the upfield shifted signals of H-4 ranging from 2.10 to 2.40 ppm in compounds **60**–**64**, the two diastereotopic protons of H-4 in **65** had "normal" chemical shifts (2.86 and 3.15 ppm), i.e., no shielding effect from the naphthalene moiety (Figure 18a), indicating the biaryl axis not to be linked to C-5, but to C-7 in the isoquinoline part. An additional proof for this connection site was the upfield shifted resonance (3.12 ppm) of one of the CH_3O signals, which, in turn, was deduced to be located at C-8 by a NOESY interaction to CH_3-1. Furthermore, a NOESY correlation between H-5 and H-4 evidenced C-5 to be devoid of a naphthalene substituent, which was confirmed by an HMBC interaction from H-5 to C-4. The other two methoxy groups (3.95 and 3.91 ppm) were assigned to be at C-4' and C-5' by the NOESY interactions with H-3' and H-6', respectively (Figure 18a). Thus, the alkaloid **65** was established to be of the 7,1'-linkage type, with three methoxy groups at C-8, C-4', and C-5', and with a free hydroxy group at C-6.

The relative configuration at C-1 *versus* C-3 was shown to be *trans* by a NOESY interaction between CH_3-1 and H-3 (Figure 18b), in agreement with the absolute configuration at these stereogenic centers, which was determined to be 1*S*, 3*S* by oxidative degradation. A NOESY correlation between CH_3-1 and H-8' revealed that these two spin systems were on the same side of the isoquinoline plane, which was, in combination with the above established absolute configuration at C-1, the "upper" side of the isoquinoline, thus

enabling the assignment of the stereoarray at the axis as *P*-configured (Figure 18b). This axial configuration was further corroborated by the resemblance of the CD spectrum of **65** with that of the known alkaloid ancistrotectoriline B,[121] in which the biaryl axis is also *P*-configured. Different from the above identified five structures **60**–**64**, which are based on a 5,1'-coupling type, compound **65** is 7,1'-coupled and was, thus, named ancistectorine B_1. A similar compound, ancistrocongoline D, possessing the same constitution and even the same axial configuration but opposite configurations at both of the stereogenic centers (i.e., 1*R*, 3*R*) had previously been found in *A. congolensis*.[34]

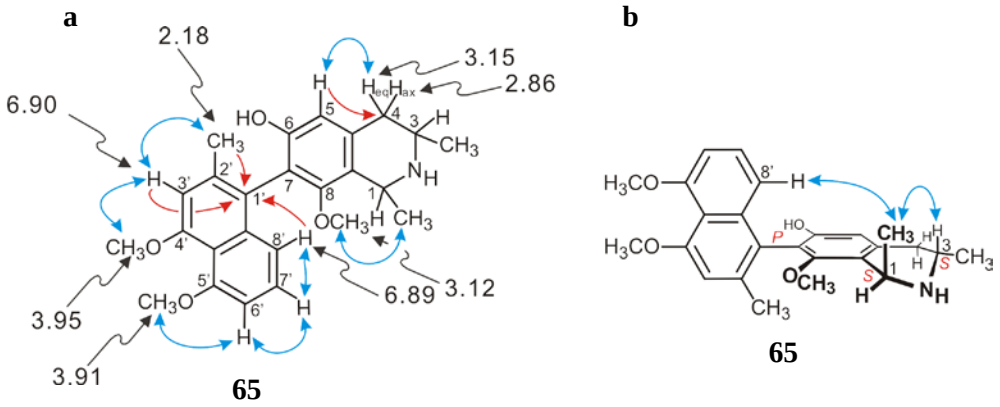


Figure 18. Selected ^{1}H NMR data, HMBC correlations (single red arrows), and NOE interactions (double blue arrows) (a) in **65**, and NOESY interactions indicative of the relative configurations at C-1 and C-3 and at the biaryl axis (b).

The eighth isolated alkaloid, compound **66**, corresponded to a molecular formula of $C_{26}H_{31}NO_4$ according to HRESIMS. Its ^{1}H NMR spectrum showed two pairs of doublets and one singlet representing the aromatic protons, instead of three neighboring and two single aromatic protons like in compounds **60**–**75**, suggesting that the coupling site of its biaryl axis should be located in the methyl-free portion of the naphthalene part, i.e., at C-6', or C-8', which was in agreement with the "normal" chemical shift measured for the signal of CH_3-2' (2.32 ppm) in the ^{1}H NMR spectrum. A linkage of the isoquinoline to C-6' in the naphthalene ring was excluded by a NOESY correlation of H-6' (6.94 ppm) to the 5'-methoxy group (3.96 ppm) (Figure 19a), and to C-1' or C-3' excluded by HMBC correlations from H-1' and H-6' to C-8' and by an NOE interaction between H-3' and the methoxy group at C-4' (3.95 ppm) (Figure 19a). Consequently, the biaryl axis in the naphthalene moiety was located at C-8'.

In the isoquinoline part of compound **66**, the biaryl axis had to be at C-7, like in compound **65**, as evidenced, i.a., from the 'normal' chemical shift of H-4 (3.02 ppm), and the upfield-shifted signal of CH_3O-8 (3.15 ppm). The positions of the three methoxy groups at

C-8, C-4', and C-5', and a methyl group at the nitrogen atom were deduced from NOE interactions (Figure 19a). Thus, structure **66** was established as one of the relatively rare *N*-methylated 7,8'-coupled naphthylisoquinolines.[134,135] This coupling type had never been found in *A. tectorius* before.

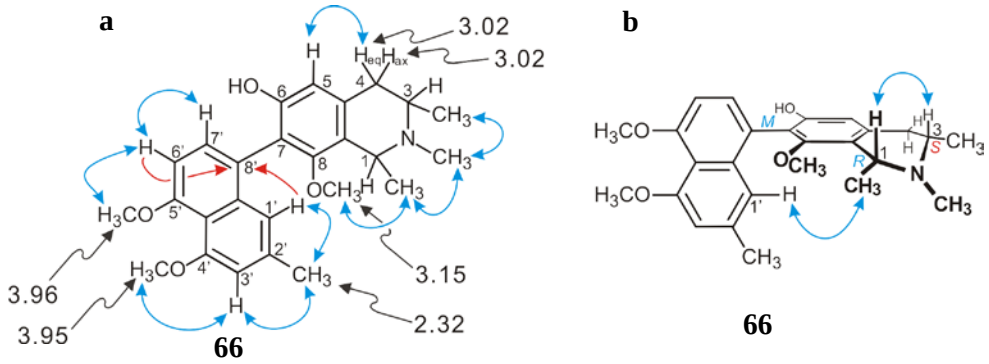


Figure 19. Selected ^{1}H NMR data and HMBC correlations (single red arrows) in **66** (a), and NOE interactions (double blue arrows) (b) indicative of the relative configuration of **66**.

By the usual oxidative degradation in combination with NOE experiments, compound **66** was determined to be 1*R*- and 3*S*-configured (Figure 19b). In conjunction with this result, the biaryl axis was evidenced to be *M*-configured by an NOE interaction between H-1' and CH_3-1 (Figure 19b). The CD spectrum exhibited a positive Cotton effect at 216 nm (Δε, +2.0) and a negative one at 236 nm (Δε, –6.3). The curve was, thus, opposite to that of its *P*-configured, and thus atropisomeric, analog 6-*O*-demethylancistrobrevine A, which had previously been isolated from the West African species *A. abbreviatus*.[135] Since being 7,8'-linked and, thus, belonging to the third coupling type described in this study, compound **66** was named ancistectorine C_1.

The last isolated new alkaloid, **67**, possessed a molecular formula of $C_{24}H_{25}NO_4$ according to HRESIMS. Like compounds **60**–**64**, the coupling site in the isoquinoline portion of **67** was C-5, as revealed from the HMBC correlations from H-4 (2.27 and 2.70 ppm) and H-7 (6.68 ppm) to C-5. The presence of a 3,4-dihydroisoquinoline part in **67**, like in **64**, was suggested from the ^{1}H NMR shift (2.79 ppm) and the multiplicity (singlet) of the signal of CH_3-1, and from the low-field shifted value (175.5 ppm) (Figure 20a) of the ^{13}C NMR signal of C-1. The coupling position in the naphthalene portion in **67** was assigned at C-8', as indicated from the NOE interactions from H-1' (6.53 ppm) and H-6' (6.95 ppm) to C-8' (Figure 20a). The two methoxy functions were located at C-5' and C-8, as evidenced from the NOE interactions from CH_3O-5' (4.12 ppm) to H-6', and from CH_3O-8 (4.04 ppm) to H-7 (6.68 ppm) and

CH_3-1.

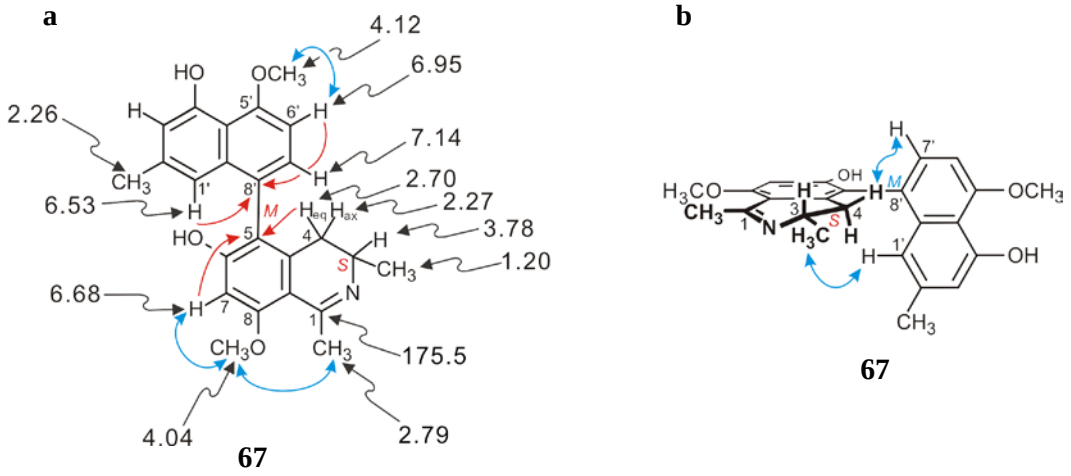


Figure 20. Selected ^{1}H and ^{13}C NMR data, HMBC correlations (single red arrows), and NOE interactions (double blue arrow) in **67** (a); and NOESY interactions indicative of the configuration at the biaryl axis relative to the stereogenic center (b).

The absolute configuration at C-3 was identified as *S*-configured by the usual oxidative degradation. The biaryl axis was deduced to be *M*-configured from the NOE interactions between H-4_{eq} and H-7' (7.14 ppm) and between 3-CH_3 (3.78 ppm) and H-1' (Figure 20b).

The comparison of the CD spectra of **67** with those of other two co-occurring compounds **71a** and **64** further corroborated the *M*-configuration in **67**. As expected, the CD curve of **67** was identical to that of compound **71a**, and opposite to that of ancistectorine A_3 (**64**) (Figure 21).

The new alkaloid **67** was named 5-*epi*-ancistrolikokine D since a similar compound, ancistrolikokine D, which had previously been found in *A. likoko*,[136] possessed the same constitution as **67** and an opposite axial configuration (*P*-configured).

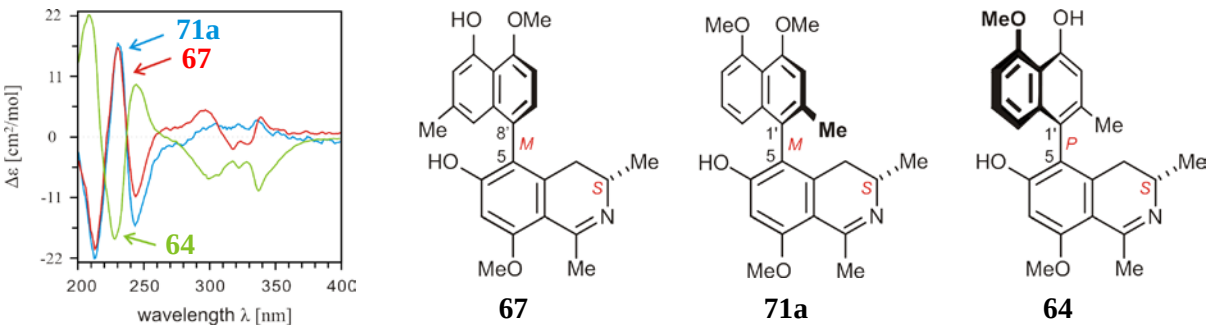


Figure 21. Comparison of CD spectra of **67** with those of the co-occurring alkaloids **64** and **71a**.

3.3 Conclusion

The nine new alkaloids described here and those known isolated from *A. tectorius* show a great structural variety of coupling sites (i.e., the location of the biaryl axis), *O*-methylation patterns, and hydroxylation degrees and stereochemical issues, and still, they have one structural feature in common: They possess an oxygen at C-6 and are *S*-configured at C-3, and can, thus, all be classified as so-called[60,137] Ancistrocladaceae-type alkaloids. The remarkable variability of naphthylisoquinoline alkaloids of *A. tectorius* is paralleled by a high genetic variability of the plant, which had already been proven by a comparative study of the ITS sequence in samples of *A. tectorius* collected from 21 locations.[123] Thus, regarding the number of isolated alkaloids, this plant is now even more intensely investigated than the as yet best-studied,[41,138] phylogenetically closely related[123] African species *A. korupensis*.

4 Isolation and Characterization of Naphthylisoquinoline Alkaloids from a Congolese *Ancistrocladus* Species

4.1 Naphthylisoquinoline Alkaloids from an African *Ancistrocladus* Species

Besides the rain forests of Southeast Asia, those of Central and West Africa are another rewarding source – for probably an even new, botanically undescribed *Ancistrocladus* species. Samples of a supposed probably new species were collected by Prof. V. Mudogo in the region of the town Ikela in the Democratic Republic of Congo, in July 2006. A voucher specimen (No. 108) has been deposited at Herb. Bringmann, University of Würzburg.

From the phytochemically and phytogenetically as yet uninvestigated Congolese *Ancistrocladus* species, the isolation of the new monomeric 6-*O*-demethylancistrobrevine C (**84**) and the unprecedented dimeric naphthylisoquinoline alkaloid jozimine A_2 (**85**) is described. Additionally, four well-known[22,130,131,135,139-141] compounds, ancistrocladine (**5a**), hamatine (**5b**), dioncophylline A (**6**), and ancistrobrevine C (**86**) (Figure 22) were isolated.

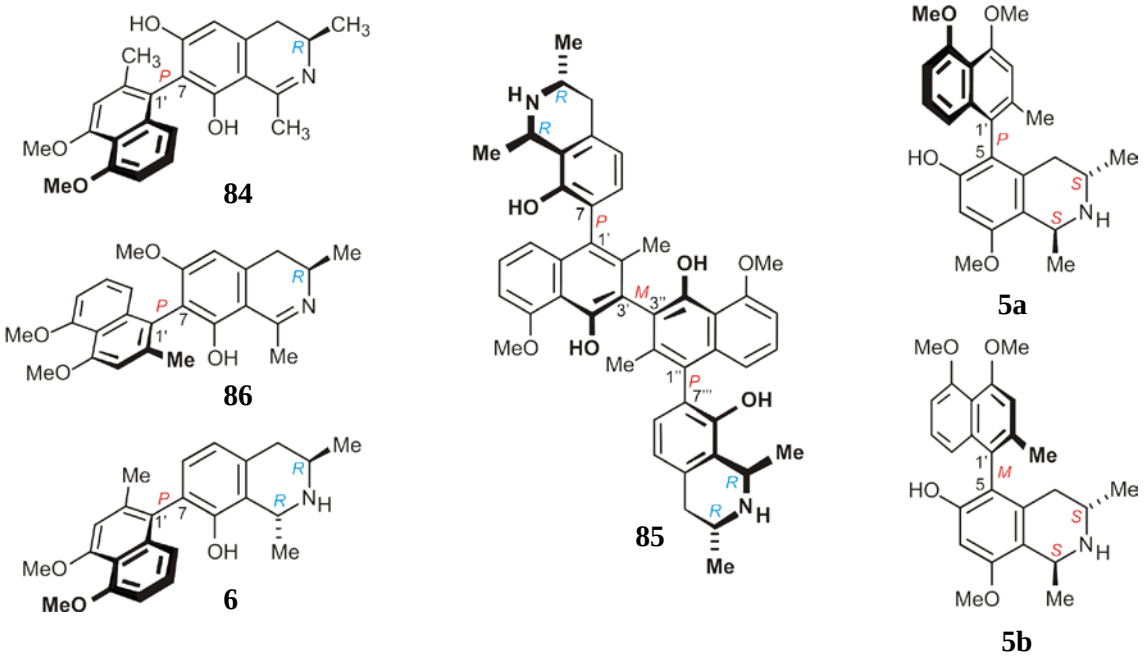


Figure 22. Structures of the naturally occurring new monomer 6-*O*-demethylancistrobrevine C (**84**), the dimer jozimine A_2 (**85**), and the known ancistrocladine (**5a**), hamatine (**5b**), dioncophylline A (**6**), and ancistrobrevine C (**86**).

4.2 Results and Discussion

The root bark of the plant was extracted with CH_3OH/CH_2Cl_2 (*v*/*v* 1:1). The crude extract was subjected to ion-exchange column chromatography for removal of non-alkaloids. From the fractions containing alkaloids six naphthylisoquinolines were isolated by preparative HPLC.

Compound **84** possessed a molecular formula of $C_{24}H_{25}NO_4$ as demonstrated by HRESIMS. The NMR signals of the alkaloid **84** for 1-CH_3 (δ 2.76 ppm, s), 3-CH_3 (δ 1.50 ppm, d, J = 6.8 Hz) and C-1 (δ 176.0 ppm) (Figure 23a) indicated the presence of a 3,4-dihydroisoquinoline. The linkage of the biaryl axis of the isoquinoline part at C-5 in **84** was be ruled out by the NOESY correlation of H-5 to H-4 and the HMBC interaction of H-5 to C-4 (Figure 23b). Thus, the coupling site in the isoquinoline moiety had to be located at C-7, which was in agreement with the typical signals of the two protons at C-4 (δ 2.91 ppm, dd, J = 18.0, 11.2 Hz, H_{ax}-4; 3.12 ppm, dd, J = 17.0, 5.1Hz, H_{eq}-4).

The HMBC long-range couplings between H-8', H-3', and CH_3-2' to C-1' (Figure 23b) established the biaryl axis of compound **84** in the naphthalene moiety to be located at C-1'. The two methoxy groups were attributed to be at C-4' (δ 3.99 ppm) and C-5' (δ 3.93 ppm), as revealed by the NOE interactions to H-3', and H-6', respectively.

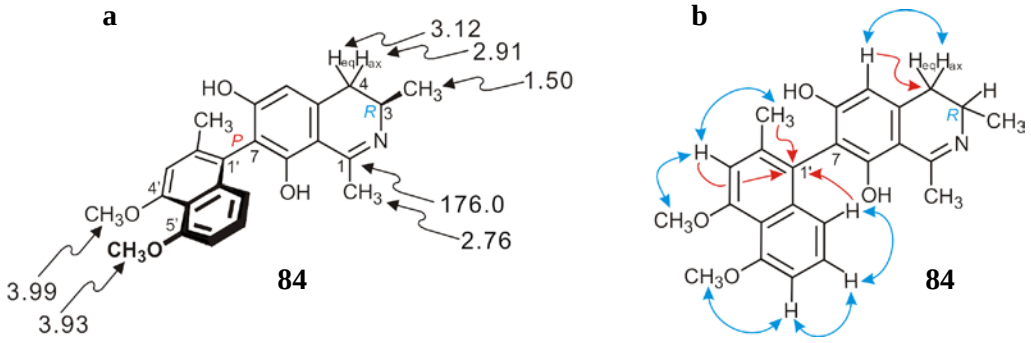


Figure 23. Selected NMR data of 6-*O*-demethylancistrobrevine C (**84**). a) Selective ^1H and ^{13}C NMR shifts (δ in ppm). b) ROESY (blue double arrows) and HMBC interactions (red single arrows) indicative of the constitution.

The ^1H NMR spectrum of compound **84** clearly showed a doubling for almost all peaks in parallel with the ^{13}C NMR displaying "doubled peaks" with a very small difference in chemical shifts (≤ 0.05 ppm). Evidently the doubled signals of CH_3-2' were of different intensity with an integration ratio of 1.7 : 1. This information suggested the presence of an inseparable diastereomeric mixture of the epimer at C-3 or the epimer at C-7.

The oxidative degradation experiment[128] gave a 4.3 : 1 mixture of 3-*R*- and 3-*S*-aminobutyric acid derivatives, which evidenced the presence of the two epimers at C-3. Although this was not in a good agreement with the ratio of the two products as determined by ^{1}H NMR spectroscopy (1.7 : 1), C-3 in the main alkaloid, **84**, was presumably determined to be *R*-configured.

The CD spectrum of **84** was nearly identical to that of ancistrocladisine (structure not shown.),[142] which suggested the biaryl axis in **84** (for the major compound) to be *P*-configured. These results could not make a conclusion that **84** was a mixture of diastereomers with epimerization at C-3 or a mixture of 7,1'-atropoisomers, thus, the isomers should have to be resolved. But the major compound, **84**, was unambiguously the 6-*O*-demethylated analog of ancistrobrevine C (**86**), hence, name 6-*O*-demethylancistrobrevine C.

In the course of the phytochemical investigation of the plant, LC-MS data hinted at the presence of a dimeric alkaloid. In detail, the combination of a monoprotonated mass at *m*/*z* 725.4 $[M+1]^+$ and a doubly protonated one at *m*/*z* 363.2 $[M+2]^{2+}$, observed within the very same peak, suggested the existence of a Dioncophyllaceae-type dimer, i.e., lacking an oxygen function at C6,[143] which was first discovered by G. Bauckmann. Subsequently, the further isolation and structural chracterization of the dimer was done in this thesis. It was found to have the molecular formular $C_{46}H_{48}N_2O_6$, as deduced from HRESIMS (725.3581 $[M+1]^+$, calcd 725.3585) and MALDI-TOF-MS (725.358 $[M+1]^+$). The ^{1}H and ^{13}C NMR data showed only a half set of signals, indicating that the dimer was symmetric, leaving open whether it was C_2-symmetric (i.e., with two homomorphous halves) or C_S-symmetric (i.e., with two enantiomorphous molecular portions). The latter, an achiral *meso*-structure, was excluded by its optical activity ($[\alpha]_D^{20} = -29.8$).

The ^{1}H NMR spectrum showed five aromatic protons, a two-proton spin system with signals at δ 6.89 ppm (d, J = 7.8 Hz, H-5) and δ 7.00 ppm (d, J = 7.8 Hz, H-6) and a three-proton spin system with signals at δ 7.01 ppm (d, J = 8.6 Hz, H-6'), δ 7.25 ppm (dd, J = 8.6, 7.8 Hz, H-7'), and δ 6.92 ppm (d, J = 7.8 Hz, H-8') (Figure 24a), which suggested a Dioncophyllaceae-type dimer with 7,1'-, 7,3'-, 5,1'-, or 5,3'-linked monomers. The coupling position in the isoquinoline moiety, located at C-7 (δ 125.9 ppm) could be deduced by the ROESY series [H-4 ↔ H-5 ↔ H-6] (Figure 24b) and by the HMBC interactions between C-7 and the 8-OH group (δ 7.44 ppm) and between C-7 and H-5. The connection position at C-1' in the naphthalene part was indicated by the ROESY signal of H-8' to the 8-OH group and the

HMBC correlations of C-1' (δ 126.3 ppm) to the 2'-CH_3 protons (s, δ 1.84 ppm), H-8', and H-6 (Figure 24b).

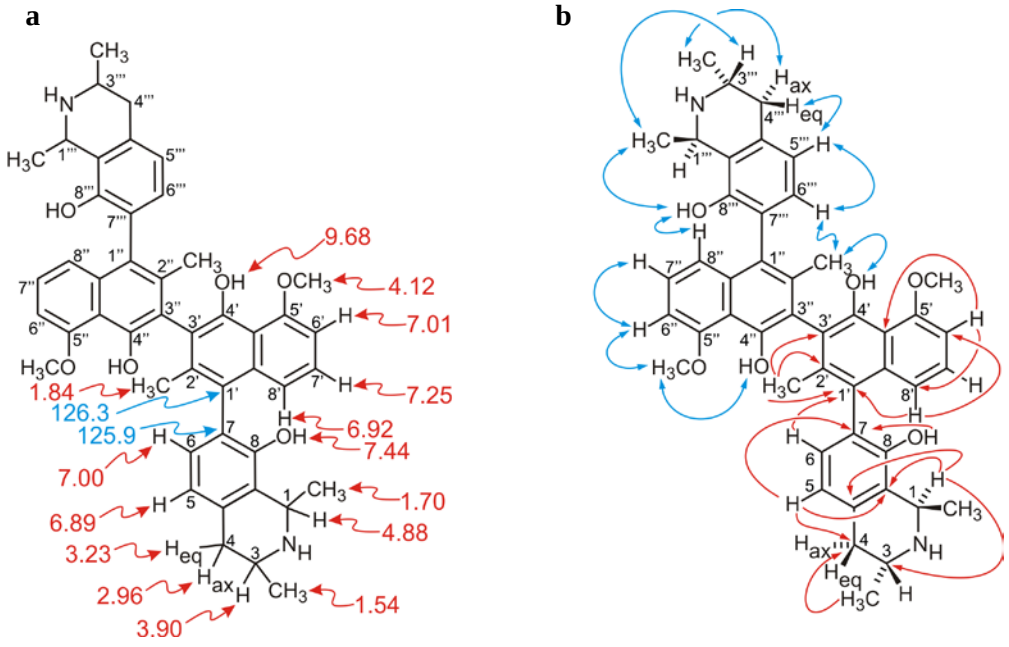


Figure 24. Selected NMR data of jozimine A_2 (**85**) in [D_4]methanol (OH signals measured in [D_6]acetone). a) ^{1}H and ^{13}C NMR shifts (δ in ppm). b) ROESY (blue double arrows) and HMBC interactions (red single arrows) indicative of the constitution (including the position of the central axis and the outer ones).

The position of the 5'-OCH_3 group at δ = 4.12 ppm was assigned by its ROESY correlations to the neighboring hydroxy function 4'-OH (δ = 9.68 ppm) in [D_6]acetone and H-6'. The extremely upfield shifted proton signal at δ = 1.84 ppm (s, 2'-CH_3) as compared to cases where the methyl group is next to one biaryl axis (ca. 2.15 ppm)[124] or not neighbored by an aryl substitution (ca. 2.37 ppm)[34] indicated that this methyl group was doubly shielded, by even two aryl substituents. This was in agreement with the assumption that the two monomeric halves of the dimer were 3',3''-coupled, which was further approved by the ROESY signal between the 2'-CH_3 group and the 4''-OH function obtained in [D_6]acetone.

The shifts of the proton signals at δ = 1.70 ppm (d, J = 6.7 Hz, 1-CH_3) and δ = 1.54 ppm (d, J = 6.4 Hz, 3-CH_3) were assigned to the methyl groups in a 1,3-dimethyltetrahydroisoquinoline and the position of the 8-OH group was confirmed by its ROESY correlation to the 1-CH_3 group.

The relative configuration of the stereocenters at C-1 and C-3 was determined to be *trans* by the ROESY correlation between the 1-CH_3 (d, δ = 4.88 ppm) group and H-3 (m, δ = 3.90

ppm) (Figure 25). From the coupling constants of the protons at C-4 ($H4_{eq}$, dd, δ = 3.23 ppm, J = 17.7, 4.7 Hz; $H4_{ax}$, dd, δ = 2.96, J = 17.7, 11.8 Hz) with H-3, H-3 was evidenced to be axial, and, thus, the 1-CH_3 group also had to be axial and hence H-1 was equatorial. The absolute configurations at C-1 and C-3 were determined by oxidative degradation,[125,128] which resulted in D-alanine and (*R*)-3-aminobutyric acid derivatives detected by GC-MSD analysis. Thus the new dimer **85** was *R*-configured both, at C-1 and C-3.

The "outer" axes of the dimer, i.e., the linkages between the naphthalene and isoquinoline portions, were assigned to be *P*-configured by the ROESY correlations between 1-CH_3 and 2'-CH_3, and between H1 (q, δ = 4.88 ppm) and H8' (Figure 24) obtained in a low-temperature NMR experiment.

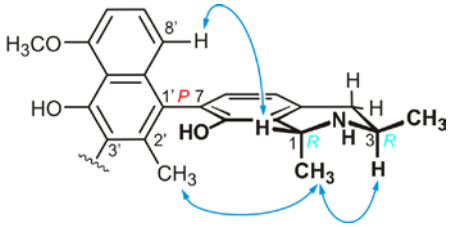


Figure 25. ROESY interactions defining the relative configurations at centers versus axes among the stereogenic axes in the monomeric halves.

The structural elucidation of two monomeric halves of the dimer was fully established by NMR experiments but still leaving the configurational situation at the central axis unresolved. The central axis, being flanked by four *ortho* substituents, like in the case of the shuangancistrotectorine A (**8**) (Figure 28), was rotationally hindered, too. The structural similarity of the inner part of new dimer with that of **7** made it possible to assign the absolute configuration at the central axis in jozimine A_2 (**85**) by comparison of its CD spectrum with that of **8**. This is based on the assumption that the CD behavior of the compounds, despite their different configurations at C-1 and C-3 and divergent substitution patterns at C-6 and C-8, is dominated by the orientation of the naphthyl portions (as the main chromophores) to each other, i.e., by the configuration at the central axis.

Indeed, the CD spectrum of the dimer **85** was virtually identical with that of **8**, giving nearly the same curve (Figure 25), evidencing that the central axis in **85** should have the same *M*-configuration like in **8**, so that **85** should be 1*R*,3*R*,7*P*,3'*M*,7'''*P*,3'''*R*,1'''*R*-configured, as shown in Figure 26.

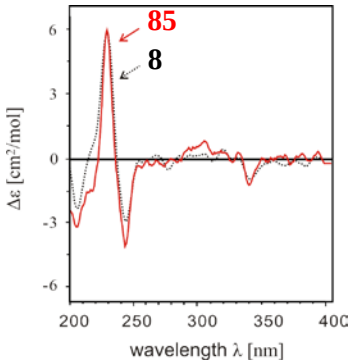


Figure 26. Assignment of the absolute configuration at the central axis of jozimine A_2 (**85**) by comparison of its CD spectrum (solid line, red) with that of shuangancistrotectorine A (**8**) (dotted line, black).

The structure of jozimine A_2 (**85**) thus established was subsequently verified in all details of its constitution and relative configuration by an X-ray diffraction analysis (Figure 27). Suitable single crystals were obtained by slow (over one week) recrystallization from acetone/cyclohexane at room temperature. Even though the data set appeared to be of adequate quality, weak scattering and the presence of at least five highly disordered acetone solvent molecules within the crystal lattice significantly hampered a reasonable structure refinement. Consequently, the results deduced form X-ray crystallography can only serve to validate the molecular composition and the relative configuration of **85** in the solid state. However, the structural characterization of **85** is unique given the fact that no X-ray diffraction data of any dimeric naphthylisoquinoline alkaloid has been reported so far.

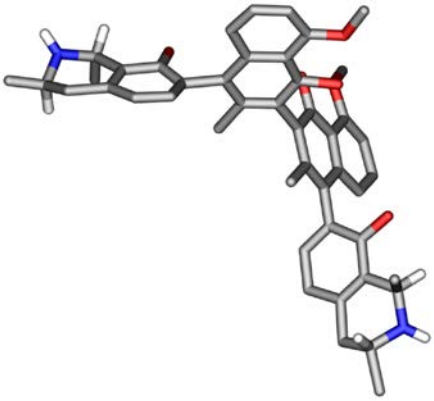


Figure 27. Molecular structure of jozimine A_2 (**85**) in the solid state. Hydrogen atoms (except for those attached to nitrogen) have been omitted for clarity (carbon: grey; nitrogen: blue; oxygen: red).

Jozimine A_2 (**85**) is the first natural dimeric Dioncophyllaceae-type naphthylisoquinoline alkaloid, consisting of two identical 4'-*O*-demethyldioncophylline A halves. It has a third

rotationally hindered biaryl axis and, thus, an additional stereogenic element as in the case of shuangancistrotectorine A (**8**) (Figure 28).[27] The structurally as yet closest known analogs of **85** are the – albeit 6'-coupled and additionally side-chain oxygenated – jozipeltine A (**87**),[144] and the – albeit 5-coupled – dimer of dioncophylline A (**6**), jozimine A (**88**),[145] and they are, both, synthetic compounds, like the other jozimines.

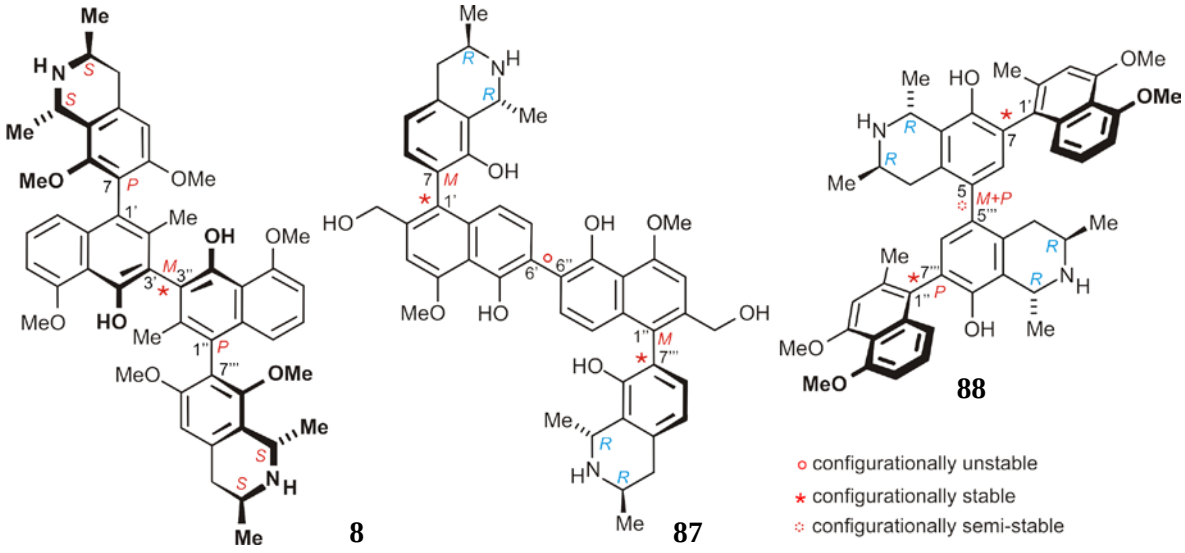


Figure 28. Structures of the structurally closely related known natural shuangancistrotectorine A (**8**), the synthetic dioncopeltine A dimer, jozipeltine A (**87**), and the likewise unnatural dioncophylline A dimer, jozimine A (**88**).

Besides the new alkaloids **84** and **85**, four well-known[22,130,131,135,139-141] monomeric alkaloids were isolated from the *Ancistrocladus* species and identified as ancistrocladine (**5a**), hamatine (**5b**), dioncophylline A (**6**), and ancistrobrevine C (**86**), by means of HPLC-MS, HPLC co-elution, and by comparison of NMR, m.p., and optical rotation data with those of authentic samples, previously obtained by isolation[22,130,131,135,139] or synthesis[140,141] in our group.

4.3 Conclusion

The phytochemical investigation of the investigated African *Ancistrocladus* species seems to occupy an exceptional chemotaxonomical position, since it produces Ancistrocladaceae-type (*i.e.*, with an oxygen function at C-6 and *S*-configuration at C-3) *e.g.*, ancistrocladine (**5a**), and hamatine (**5b**), Dioncophyllaceae-type (*i.e.*, devoid of an oxygen function at C-6 and *R*-configuration at C-3) *e.g.*, dioncophylline A (**6**), and jozimine A_2 (**85**), and mixed Ancistrocladaceae/Dioncophyllaceae-type (*i.e.*, with an oxygen function at C-6 and

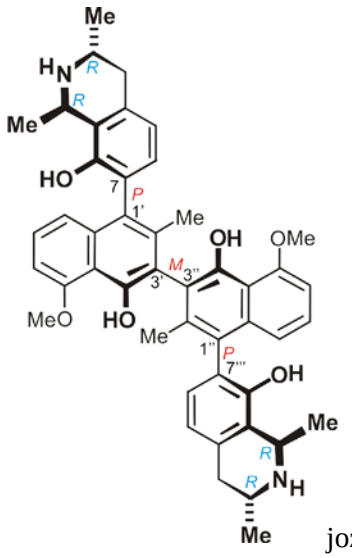
R-configuration at C-3) naphthylisoquinoline alkaloids *e.g.*, 6-*O*-demethylancistrobrevine C (**84**) and ancistrobrevine C (**86**). In this respect, this *Ancistrocladus* species is remarkable in that it is one of the very few plants, like *A. abbreviatus*,[142,146,147] and *A. barteri*,[148] that simultaneously contain typical representatives of all three classes of alkaloids. The discovery will definitely contribute to the phytochemical and taxonomic classification of this African *Ancistrocladus* species.

4.4 Bioactivities of the New Naturally Occurring Alkaloids

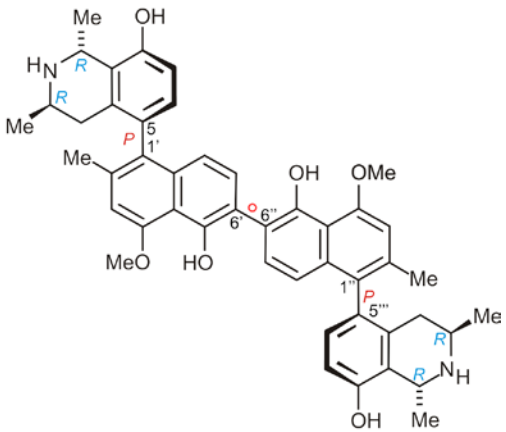
Because of the known pronounced bioactivities of naphthylisoquinoline alkaloids,[27,32,33,37-39] the new compounds **60**–**62**, **64**–**66** (except for **63** and **67**, which were not biotested due to the presence of too small quantities), and **84**–**85** were tested for their *in vitro* activities against protozoan parasites (Table 2). Three of the metabolites, **61**, **62a**, and **62b**, exhibited strong antiplasmodial activities against the strain K1 of *Plasmodium falciparum*. With IC_{50} values of 0.08, 0.07, and 0.03 μM, respectively, they are 3**–**7 times more active than the standard chloroquine (IC_{50} = 0.26 μM), and are, thus, in the range of the most active naturally occurring naphthylisoquinoline alkaloid, dioncophylline C (**68**) (IC_{50} = 0.01 μM against the strain K1).[31] In addition, given their extremely weak cytotoxicities, **61**, **62a**, and **62b** possess high selectivity indexes of up to >3000, and should, thus, according to the TDR/WHO guidelines[149], be considered as lead compounds. Remarkably, the alkaloid **62b**, which is *M*-configured, showed the best antiplasmodial activity in this study, much better even than its *P*-configured atropo-diastereomer **62a**; simultaneously, **62b** had a lower cytoxicity on L6 cells than **62a**. This result shows the impact of axial chirality on the biological properties.

Jozimine A_2 (**85**) showed an excellent antiplasmodial activity (against the strain NF54) in the low-nanomolar ranges (IC_{50} = 1.4 nM) (Table 2), much better than those of the three alkaloids, **61**, **62a** and **62b** above, and dioncophylline C (**68**) (IC_{50} = 8 nM against the strain NF54),[31] thus being far more active than any of the ca. 140 naturally occurring mono- and dimeric naphthylisoquinoline alkaloids tested as yet.[27,30-33,37] Moreover, jozimine A_2 (**85**) had no cytotoxicity (IC_{50} = 15.9 μM) against rat skeletal myoblast (L6) cells, and thus, possessed a very high selectivity index of >15,900. In consequence, jozimine A_2 (**85**) can also be considered as a highly new lead structure.

Moreover, jozimine A_2 (**85**) showed an exceptionally increased antiplasmodial activity compared to its corresponding monomeric half 4′-*O*-demethyldioncophylline A (**89**) (structure shown in Scheme 3 in Chapter 5) (IC_{50} = 0.24 μM, unpublished paper). This significantly enhanced potency may be explained by the increased lipophilicity for jozimine A_2, as estimated by the cLogP (the calculated 1-octanol-water partition coefficient), which is the most important molecular property compared to other physical properties, *e.g.*, molecular mass, the numbers of hydrogen-bond donors, hydrogen-bond acceptors, and aromatic rings.[150,151] More specifically, jozimine A_2 (**85**) has a cLogP value of 9.38[1] in contrast to a value of 4.84 for 4′-*O*-demethyldioncophylline A. Since the lipophilicity value (cLogP) is logarithmic, an increase of ca. 4.5 units in cLogP from 4′-*O*-demethyldioncophylline A (**89**) to jozimine A_2 (**85**) equals a ligand concentration in the highly lipophilic cellular membranes, which is ca. 30,000 times higher. Hence, the improved potency can be explained by the highly elevated number of interactions due to the significantly enhanced concentration of jozimine A_2 (**85**) in the tested cells. However, this interpretation contradicts our previous result that the synthetic dimer jozimine C (Figure 29) showed a distinctively lower antiplasmodial activity than its natural monomeric alkaloid dioncophylline C (**68**),[26] despite jozimine C has the same cLogP, molecular weight, the numbers of OH plus NH count, and O atoms as those for jozimine A_2 (**85**). Since no unambiguous conclusion is possible, the natural product **85** still remains a highly promising compound despite of possessing a high lipophilicity value and a large molecular weight.



jozimine A_2



jozimine C

Figure 29. Structures of the natural product jozimine A_2 (**85**) and the synthetic dimer jozimine C.

[1] All the mentioned cLogP values here were calculated by OSIRIS Property Explorer on the internet http://www.organic-chemistry.org/prog/peo/

Table 2. Anti-infective activities of the compounds **60**–**62**, **64**–**66**, and **84–85**.

	IC_{50} [μM]								
	60	**61**	**62a**	**62b**	**64**	**65**	**66**	**84**	**85**
P. falciparum[a] S: chloroquine 0.26 (on K1)	0.57	0.08	0.07	0.03	0.68	4.20	2.80	2.4	
S: chloroquine 0.003 (on NF54)									0.0014
T. cruzi S: benznidazole 2.0	118.9	95.0	108.5	135.4	62.2	142.1	>213	137.3	13.7
T. brucei rhodesiense S: melarsoprol 0.007	16.7	28.3	7.3	21.1	17.6	17.9	38.8	14.0	0.8
T. brucei brucei S: pentamidin 0.0029	ND	34.0	19.9	12.3	16.4	40.0	ND	ND	ND
L. donovani S: miltefosine 0.351	>228	>220	>220	>220	92.5	>220	>213	78.0	80.2
Cytotoxicity (L6 cells) S: podophyllotoxin 0.017	94.6	51.7	49.4	100.1	32.8	47.3	22.5	59.3	15.9
Selectivity index for the antiplasmodial activity[b]	166	646	705	3,340	48	11	8	25	15,900

ND: not determined. S: Standard.

[a] For compounds **60**–**62**, **64**–**66**, and **84**, the activities against *P. falciparum* were measured on the strain K1, and for compound **85** on the strain NF54.

[b] The index is calculated as the ratio of the IC_{50} values concerning L6 cells to the IC_{50} data relative to *P. falciparum*.

In addition, no activities were found against other protozoan parasites causing tropical diseases, like *Trypanosoma cruzi*, *T. brucei rhodesiense*, *T. brucei brucei* (for **61**, **62**, **64**, **65**, **84**, and **85**, **60** and **66** not measured for lack of substance), and *Leishmania donovani*, showing the remarkably high specificity of the antiplasmodial activity of **61**, **62a**, and **62b**. This specificity was further confirmed by the lack of activities against other, bacterial test systems, like *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Yersinia pseudotuberculosis*, and *Yersinia pestis* (results not shown) exemplarily for the better available alkaloids **61** and **65**.

Although the crude extract of the Chinese plant *A. tectorius* had been reported to show antitumoral activity *in vivo* in the literature,[117] the antitumoral activity of its isolated chemical constituents, the naphthylisoquinoline alkaloids, had not been investigated yet. Therefore, the three main alkaloids, ancistrocladine (**5a**), hamatine (**5b**), and (+)-ancistrocline (**78**), which largely dominate the extract of the Chinese plant, were tested against the human tumor cell line INA-6 (derived from a patient with multiple myeloma). Interestingly, only hamatine (**5b**) and (+)-ancistrocline (**78**) displayed moderate activities against the tested cell line (EC_{50} = 32 μM for each compound). Ancistrocladine (**5a**), the atropo-diastereomer of **5b**, was inactive, probably because it was not sufficiently soluble in these concentrations. The results thus warrant further investigations on the minor alkaloids, which might be the compounds responsible for the reported activity of the extract.

5 Semi-synthesis of Unprecedented Dimeric Naphthylisoquinoline Alkaloids

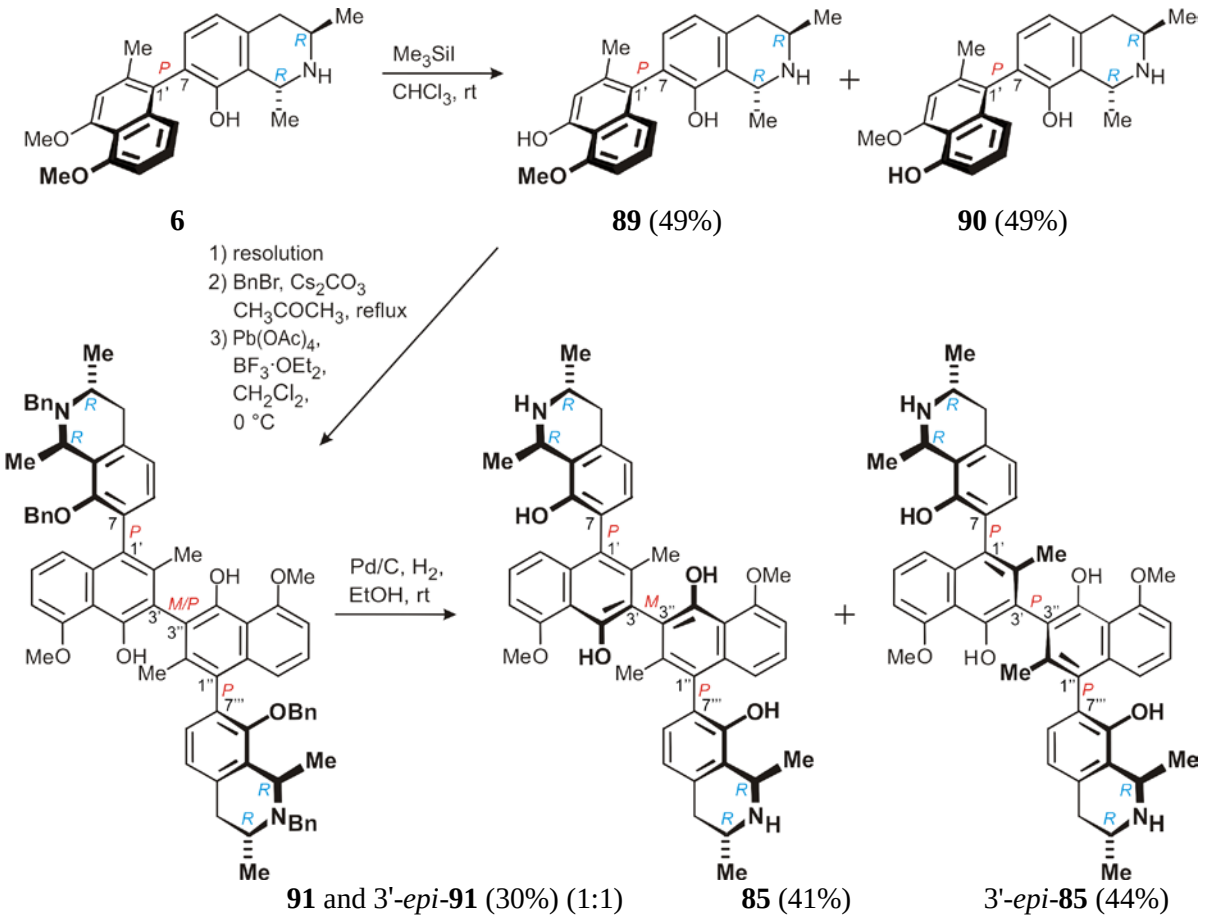
5.1 Synthesis of Jozimine A_2 (**85**) and its 3'-*epi*-Atropo-diastereomer (3'-*epi*-**85**)

The unprecedented dimeric structure of jozimine A_2 (**85**), and its excellent bioactivities (see Chapter 4) made **85** and its as yet unknown atropo-diastereomer 3'-*epi*-**85** attractive synthetic targets: For a further structural confirmation, for the directed search of its as yet unknown 3'-atropo-diastereomer in the plant, and for a comparative analysis of the antiplasmodial activities depending on the configuration of the central axis. On the other hand, the synthesis of **85** imposed a true challenge, since all other synthetically prepared dimers[144,145,152-155] contained a significantly less hindered central axis (only two *ortho*-substituents, see, *e.g*. the structure of jozipeltine A (**87**) in Figure 28 in Chapter 4). In view of the high steric hindrance to be overcome in the coupling step, a biomimetic phenol-oxidative coupling of the assumed natural monomeric precursor **89** or an adequately protected analog, seemed appropriate.

Recently, the directed, atropo-selective total synthesis of the – as yet unknown – 'monomeric' alkaloid **89** has been successfully achieved in small quantities by applying the "lactone concept" as developed in our lab (unpublished paper). Although this, the occurrence of large quantities of its known[22] and also synthetically available[140] *O*-methyl analog, dioncophylline A (**6**), in the same plant, even dominating its spectrum of secondary metabolites, made it easier to take advantage of this easily available, alkaloid for a semi-synthetic access to jozimine A_2 (**85**).

The isolated natural dioncophylline A (**6**) was mono-*O*-demethylated by using trimethylsilyl iodide in $CHCl_3$ in an almost quantitative yield (Scheme 3). Resolution of the obtained 1:1 mixture (determined by HPLC) of the two regioisomeric 4'- and 5'-*O*-demethyl derivatives **89** and **90**[156,157] succeeded by preparative HPLC on a reverse-phase column. Their structures were evidenced by an NOE interaction of 5'-OMe to H-6' in **89** and of 4'-OMe to H-3' in **90**. Oxidative coupling of **89** using $Pb(OAc)_4$[152] or Ag_2O[153] led to complex product mixtures, which necessitated the introduction of specific protection groups for the secondary amino function and the 8-OH group, leaving free only the required OH function at C-4'. In analogy to a related transformation on the known[156] natural product **90**, the *N*,*O*-dibenzyl derivative of **89** was prepared and submitted to an oxidative coupling with $Pb(OAc)_4$ (Scheme 3). After purification on silica gel, HPLC analysis showed only one peak,

while NMR revealed the presence of a 1:1 mixture of the two expected atropo-diastereomers, **91** and 3'-*epi*-**91**, which were inseparable on diverse reverse-phase columns. Different from all previous oxidative couplings to – less hindered – dimeric naphthylisoquinoline alkaloids, the typical deep-violet color of a transient over-oxidated diphenoquinone was not observed (as a consequence of the high steric hindrance at the newly generated axis). The expected coupling was firmly corroborated by HRESIMS in combination with NMR data. The less extreme high-field shift (δ = 2.10 ppm) of 2'-CH_3 in the coupling product in **91** as compared to 1.86 ppm in **85** can be ascribed to the additional deshielding effect of the 8-*O*-benzyl group. The non-separable mixture of **91** and 3'-*epi*-**91** was directly *N*,*O*-deprotected, furnishing the dimeric target molecule, **85**, along with 3'-*epi*-**85** – non-separable atropo-diastereomer, which were eventually resolved and purified by preparative HPLC.



6 **89** (49%) **90** (49%)

91 and 3'-*epi*-**91** (30%) (1:1) **85** (41%) 3'-*epi*-**85** (44%)

Scheme 3. Semi-synthesis of jozimine A_2 (**85**) and its unnatural atropo-diastereomer, 3'-*epi*-jozimine A_2 (3'-*epi*-**85**) from dioncophylline A (**6**).

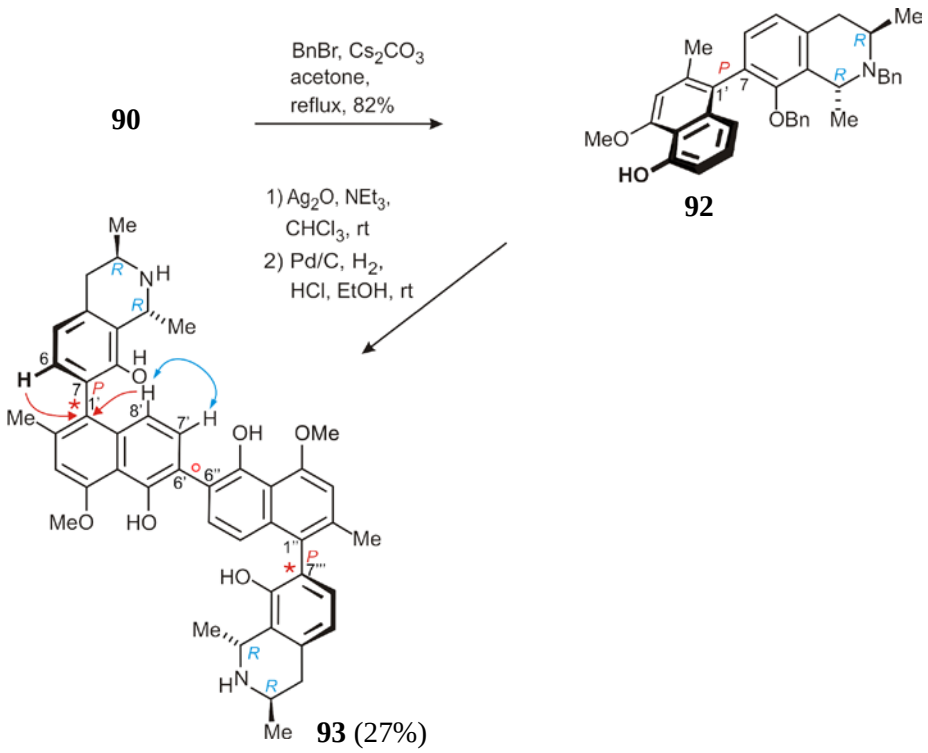
The CD spectrum of the new atropisomer 3'-*epi*-**85** was expectedly opposite to that of its natural isomer, **85**, clearly evidencing the chiroptical dominance of the – hence *P*-configured – central axis over all other stereogenic elements.[27]

This efficient semi-synthesis of jozimine A_2 (**85**), which, given the synthetic availability of **89** (unpublished paper) and **6**,[140] simultaneously constitutes a formal total synthesis of **85**, firmly corroborates its full absolute stereostructure.

Moreover, the first synthesis of its yet unknown atropo-diastereomer, 3'-*epi*-**85** permitted its directed search in the extracts of the *Ancistrocladus* species. A thorough HPLC analysis of the extract from which **85** had been isolated, however clearly revealed the complete absence of 3'-*epi*-**85** and also of **89** in the plant, showing that jozimine A_2 (**85**) is produced from **89** in a highly atroposelective and efficient way in the living cell, with a high degree of enzymatic control.

5.2 Synthesis of Jozimine A_3 (**93**)

The first attempt to obtain jozimine A_3 (**93**) *via* the phenol-oxidative coupling of the *N*,*O*-bis-benzylated derivative of **90** using $Pb(OAc)_2$[158] led to the formation of an unstable compound, which presumably possessed an additional hydroxy or an acetoxy group evidenced by HRESIMS. Then, inspired from the synthesis of jozipeltine A (**87**) (Figure 28 in Chapter 4),[144] Ag_2O was likewise employed on the *N*,*O*-bis-benzylated derivative of **90**, giving rise to a deeply violet-colored reaction mixture. Next, as had been described in some previous cases,[158-160] the intermediate diphenoquinone crude product was reduced by hydrogenation in the presence of Pd/C under acidic conditions. The cleavage of the protective groups completed the synthesis of **93** (Scheme 4).



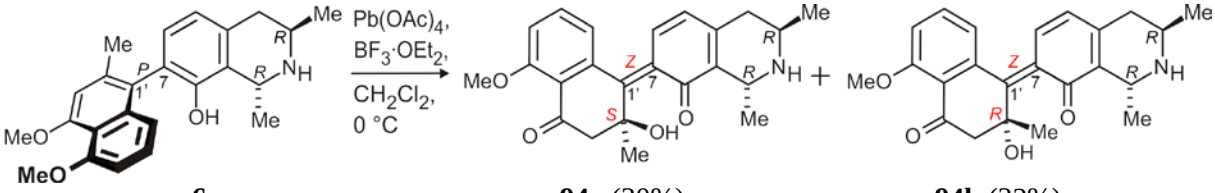
Scheme 4. Synthesis of jozimine A_3 (**93**) from **90** and selected HMBC (red single arrows) and ROESY (blue double arrows) interactions indicative of its constitution.

The successful coupling in the 6′-position of the naphthalene ring was deduced by the symmetric structure evident from 1D-NMR experiments, HMBC correlations from H-6 and H-8′ to C-1′, ROESY interactions between H-7′ and H-8′ (Scheme 4), and the HRESIMS spectrum. The novel quateraryl **93** was named jozimine A_3, since it was a structural isomer of jozimine A_2 (**85**)[161] and jozimine A (**88**).[145] Another similar structure to **93** was jozipeltine A (**87**), which possessed side oxygen functions in the two naphthalene rings instead of the methyl groups in **93**. The newly introduced 6′,6′′-biaryl axis in **93** does not constitute an additional element of chirality as in the case of jozipeltine A (**87**).

The semi-synthesis of jozimine A_3 (**93**) from the secondary metabolite dioncophylline A (**6**) suggests that **93** might also be a natural co-occurring product in the same African *Ancistrocladus* species that produces the predominant alkaloid **6**.[161] With **93** in hands, a co-eluted HPLC analysis, however, revealed that the dimer **93** was not produced by the plant, at least at a not detectable quantity.

5.3 One-step Synthesis of Dioncotetralones A (**94a**) and B (**94b**)

Treatment of dioncophylline A (**6**) without any protective groups with $Pb(OAc)_4$[152,154] was carried out in the presence of BF_3•OEt_2 (Scheme 5). After filtration of the reaction mixture over Celite, the subsequent purification on preparative HPLC afforded two, unexpected, non-dimeric main products. The trivial name dioncotetralone A (**94a**) was proposed for the more rapidly eluting compound and dioncotetralone B (**94b**) for the more slowly eluting one.



6 **94a** (30%) **94b** (32%)

Scheme 5. Synthesis of dioncotetralones A (**94a**) and B (**94b**) from dioncophylline A (**6**).

The molecular formulas of **94a** and **94b**, both were $C_{23}H_{25}NO_4$, as evidenced by HRESIMS. Furthermore, **94a** and **94b** exhibited nearly identical ^{1}H NMR (≤ 0.03 ppm), ^{13}C NMR (≤ 0.5 ppm), and 2D NMR spectra. By contrast, the specific optical rotation values and the CD spectra of both compounds entirely differed, thus, the relationship of **94a** and **94b** were assumed to be diastereomeric.

The ^{1}H and ^{13}C NMR spectra of dioncotetralone A (**94a**) and of dioncotetralone B (**94b**) showed a complete set of signals for the "isoquinoline" unit and the non-methyl-bearing part of the "naphthalene" moiety like that in dioncophylline A (**6**), together with the two doublets of H-3 (3.00 and 3.36 ppm), a singlet of CH_3-2' (1.36 ppm), and C-3' (44.9 ppm), C-2' (59.5 ppm) and a missing methyl group at the 4'-OMe function (Figure 30a). Based on this information, an oxygen function was accordingly linked at C-2'. Two keto functions at C-8 and C-4', and a 7,1'-double bond was deduced by the combination with the chemical shift of C-4' (204.7 ppm), which interacted with H-3' in the HMBC, and the signal of C-1' (160.8 ppm), which correlated with CH_3-2', H-3', and H-8' (Figure 30b).

The most remarkable property of the structures of **94a** and **94b** is the "biaryl axis" since it is a *C,C*-double bond instead of a single bond, so that the "isoquinoline" and the "naphthalene" moiety tend to be planar to each other, which has never been reported among natural or synthetic naphthylisoquinoline alkaloids.

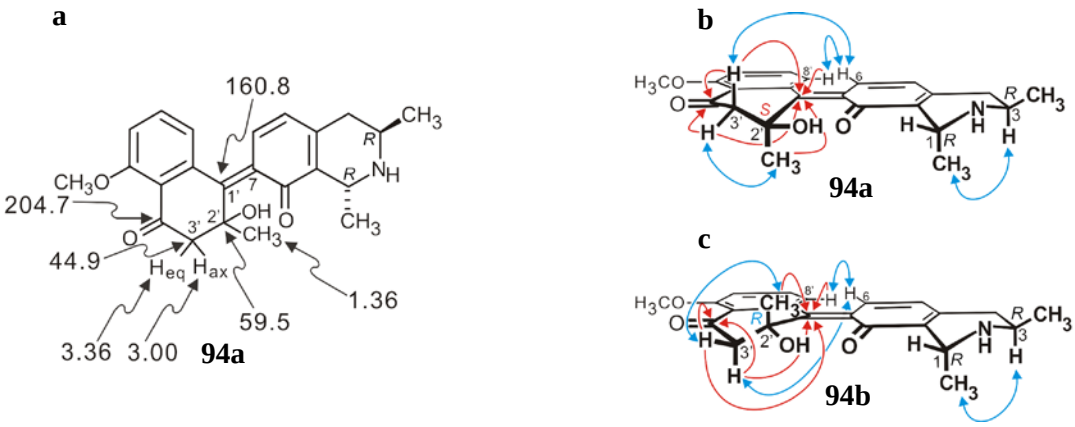


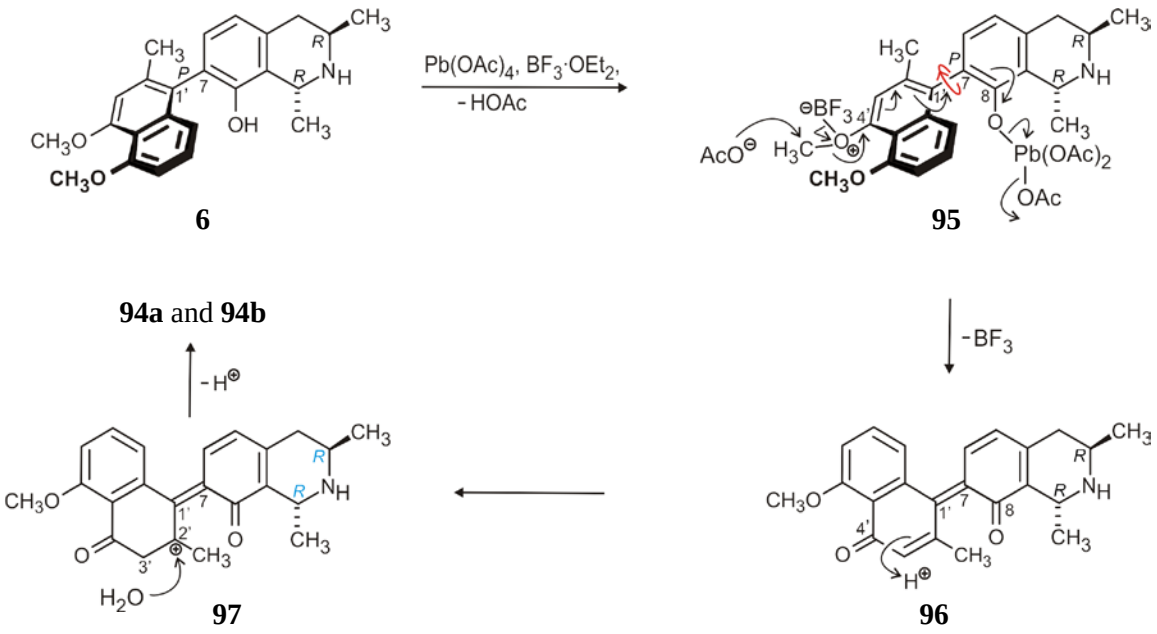
Figure 30. Selected NMR shifts of diocotetralone A (**94a**) (a) and selected HMBC interactions (red single arrows) and NOESY (blue double arrows) in **94a** and **94b** indicative of their constitutions.

The CH_3-2' group of **94a** showed an NOE correlation with one of the H-3' protons, while an interaction with the other 3'-hydrogen was not observed. Thus, the CH_3-2' function should be in the axial position and was, thus, not able to interact with H-3'$_{ax}$. This was probably due to the hydrogen bond between OH-2' and the oxygen atom at C-8, and therefore OH-2' was assigned to be equatorial, as shown in Figure 30b. This was in agreement with the existence of an NOE correlation from H-6 to H-3'$_{ax}$, and no one from H-6 to H-3'$_{eq}$. The 7,1'-double bond was assigned to be *Z*-configured by an NOE interaction between H-8' and H-6. Furthermore, the configurations at C-1 and C-3 both remained the same as those in dioncophylline A (**6**), which was evidenced by the NOE correlations between CH_3-1 and H-3 (Figure 30b). Hence, the constitution of the stereoisomer **94b** was fully elucidated by the same methodology as for **94a** (Figure 30c).

Determination of the absolute configuration of the two diasteromers **94a** and **94b** was rather difficult, due to the new chromophoric system that was introduced by the 7,1'-double bond and the closely attached additional stereogenic center at C-2'. Therefore, a combination of electronic circular dichroism (CD) spectroscopy with quantum chemical CD calculations was applied, a reliable and powerful tool for the elucidation of the absolute stereostructure of novel compounds. This work is currently performed by Y. Hemberger from our group.

A detailed reaction mechanism cannot be described due to the lack of evidence, but the 4'-*O*-demethylation, followed by oxidation, and finally the addition of water, seems very plausible, which is depicted in Scheme 6. The lead atom is linked to the oxygen atom at C-8 with release of acetic acid, and BF_3•Et_2O acts as a Lewis acid weakening the O-CH_3 bond. An acetoxy group will attack the 4'-*O*-methyl group, which sends an electron to the oxygen at

C-4', further migrating to the lead atom, *en route* to the 1',7-biaryl axis and end at the oxygen at another acetoxy function, as described in structure **95**. Simultaneously, the two ketone functions at C-8 and C-4' are formed, and the "naphthalene" ring will rotate anticlockwise around the 7,1'-biaryl axis followed by the formation of the 7,1'-double bond. Therefore, the orthogonal stereo-orientation between the "naphthalene" and the "isoquinoline" moiety is changed into a nearly planar orientation in intermediate **96**, affording a 7,1'-*trans* configuration. Even though there is still a significant steric hindrance between CH_3-2' and the oxygen atom at C-8 in structure **96**, the *trans*-configured intermediate is more energetically favored than the imaginable *cis*-configured one. Such twisting force might be immediately released by addition of H_2O to the 2',3'-double bond, yielding the two products dioncotetralones A (**94a**) and B (**94b**).

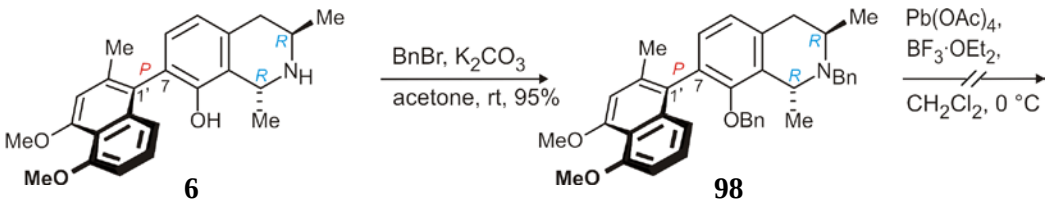


Scheme 6. Proposed mechanism for the formation of dioncotetralones A (**94a**) and B (**94b**).

5.4 Further Semi-Syntheses from Dioncophylline A (**6**)

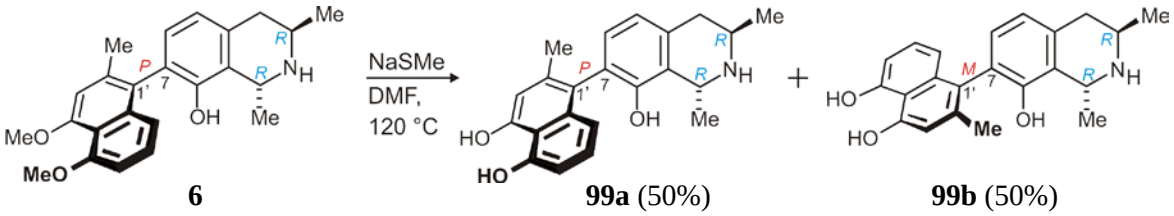
Before we succeeded in the synthesis of jozimine A_2 (**85**) and its 3'-epimer 3'-*epi*-**85**, several other reactions, described in the following part, had been performed.

The 8-*O*- and *N*-dibenzylated derivative **98** of dioncophylline A was subjected to an oxidative coupling reaction with $Pb(OAc)_4$, but no reaction was observed (Scheme 7).



Scheme 7. The attempted dimerization of 8-*O*,*N*-dibenzylated dioncophylline A (**6**).

In an attempt to prepare mono-*O*-demethyldioncophylline A, **6** was heated to 120 °C in DMF in the presence of sodium thiomethoxide,[51] however, the two atropodiastereomers 4',5'-*O*-didemethyldioncophylline A **99a** and **99b** were obtained in an almost 1:1 ratio (Scheme 8).



Scheme 8. *O*-Demethylation on dioncophylline A (**6**).

5.5 Bioactivities of the Synthetic Alkaloids

The two newly synthesized naphthylisoquinoline dimers 3′-*epi*-**85** and **93** exhibited, albeit weaker than that of the natural product jozimine A_3 (**85**), still very good antiplasmodial activities (on strain NF54), with extraordinary IC_{50} values of 0.017 µM for 3′-*epi*-**85** and of 0.015 µM for **93** (Table 3). Furthermore, the two compounds 3′-*epi*-**85** and **93** possessed high or moderate selectivity indexes despite much lower than that of **85**. Dioncotetralone A (**94a**) showed an excellent activity (IC_{50} = 0.09 µM) against the chloroquine-resistant strain K1 of *P. falciparum*, even stronger than that of the standard chloroquine (IC_{50} = 0.16 µM), in contrast to weak antiplasmodial activity (IC_{50} = 3.4 µM) for its atropo-diastereomer dioncotetralone B (**94b**), which shows the significant influence of chirality on the bioactivities (Table 3). The antiplasmodial activities of 3′-*epi*-**85**, **93**, and **94a** are specific, since they exhibit only weak activities against the likewise protozoan parasites *T. brucei rhodesiense*, *T. cruzi*, and *L. donovani*. According to the recommendations of the World Health Organization, WHO,[149] they can be considered as new lead structures.

As for the antitumoral bioactivities of naphthylisoquinoline alkaloids described in Chapter

4, the three alkaloids dioncophylline A (**6**), 4'-*O*-demethyldioncophylline A (**89**), and 5'-*O*-demethyldioncophylline A (**90**) were biotested and found to display excellent activities against the myeloma cell lines, even stronger than dioncoquinones B (**10**), C (**102**) (structure shown in Chapter 6), the epoxide **175** (structure shown in Chapter 9)**,** or the standard melphalan (Table 4). Further *in vivo* biotesting of these three alkaloids and investigations in the mode of action will be part of the future work.

Table 3. Comparison of bioactivities of the synthetic dimers 3′-*epi*-**85** and **93**, and the two atropo-diastereomers **94a** and **94b** with the natural product jozimine A_2 (**85**).

	IC_{50} [μM]				
	85	3′-*epi*-**85**	**93**	**94a**	**94b**
P. falciparum[a] S: chloroquine 0.16 (on K1)				0.09	3.4
S: chloroquine 0.003 (on NF54)	0.0014	0.017	0.015		
T. cruzi S: benznidazole 0.62	13.7	59.1	5.4	34.8	113.2
T. brucei rhodesiense S: melarsoprol 0.003	0.8	9.4	1.1	11.3	41.2
L. donovani S: miltefosine 0.25	80.2	>138	81.8	140.9	116.9
Cytotoxicity (L6 cells) S: podophyllotoxin 0.008	15.9	49.4	1.9	6.6	46.2
Selectivity index for the antiplasmodial activity[b]	15,900	2,906	127	73	14

[a] For compounds **85**, 3′-*epi*-**85**, and **93**, the activities against *P. falciparum* were measured on the strain NF54 and for compounds **94a** and **94b** on the strain K1.

[b] The index is calculated as the ratio of the IC_{50} values concerning L6 cells to the IC_{50} data relative to *P. falciparum*.

Table 4. EC_{50} values (μM) of INA-6 multiple myeloma cells and peripheral mononuclear blood cells (PBMCs) treated with compounds **10**, **102**, **175**, **6**, **89**, or **90** or with melphalan.

	10	**102**	**175**	**6**	**89**	**90**	Melphalan
INA-6[a]	11	14	3.5	0.22	2.5	1.5	2
PBMCs	NR	NR	NR	NR	NR	NR	3

NR: not reached.

[a] Multiple myeloma cells were treated with different concentrations of **10**, **102**, **175**, **6**, **89**, or **90**, or melphalan. The viable fractions of the treated cells were determined by annexin V-FITC/PI staining.

6 Isolation and Characterization of Naphthoquinones from Cell Cultures of *Triphyophyllum peltatum*

6.1 Compounds Isolated from Cell Cultures of *T. peltatum*

Besides the isolation and the synthesis of antiplasmodial naphthylisoquinoline alkaloids, the obtainment of biosynthetically related antitumoral napthoquinones was carried out. Dioncoquinones A (**9**) and B (**10**) were such known compounds showing excellent activities against multiple-myeloma cell lines without any significant cytotoxicities on normal blood cells.[54] In the course of the isolation of compounds **9** and **10** by Dr. S. Rüdenauer and A. Irmer, some traces of further naphthoquinones were detected by HPLC analysis. Thus, larger quantities of cell cultures of *T. peltatum* were phytochemically reinvestigated, giving rise to the isolation of three new natural products, dioncoquinones C (**102**), D (**103**), and E (**104**), and the known,[162,163] but new to the plant, 8-hydroxydroserone (**105**), together with the known[35,136] plumbagin (**100**), droserone (**101**), ancistronaphthoic acid B (**106**), and the new triphoquinol A (**107**) (Figure 31).

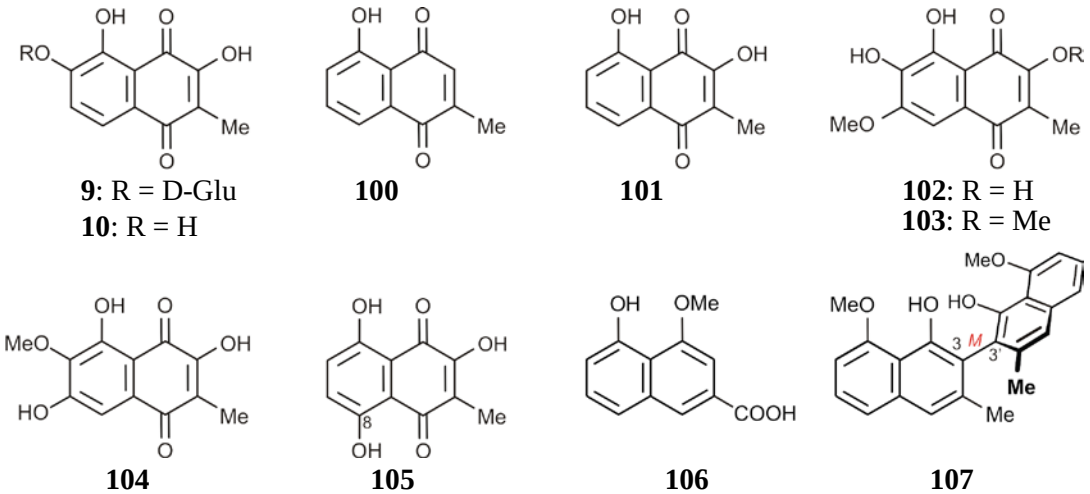


Figure 31. Naphthoquinones isolated from *T. peltatum* cell cultures, dioncoquinones A (**9**), B (**10**), plumbagin (**100**), droserone (**101**), dioncoquinones C (**102**), D (**103**), and E (**104**), 8-hydroxydroserone (**105**), together with ancistronaphthoic acid B (**106**), and triphoquinol A (**107**).

6.2 *T. peltatum*

T. peltatum, *Habropeltatum dawei* and *Dioncophyllum thollonii* are the only three species of the extremely small family Dioncophyllaceae.[47] Of these, *T. peltatum* as a particularly

rewarding plant is the by far most widely investigated species. It thus occupies an outstanding position in our group. The research fields on *T. peltatum* mainly include activity screening of the extracts,[23,30] phytochemical studies,[28,47,52,156,164-172] cultivation of the plant,[173-176] and biosynthetic investigation.[49-51]

6.3 Results and Discussion

The calli of the cell cultures were removed from the medium, lyophilized, ground, and extracted with CH_2Cl_2/MeOH (1:1 *v*/*v*). The crude extract was subjected to an ion-exchange column to remove naphthylisoquinoline alkaloids, followed by normal-phase chromatography permitting isolation of three main naphthoquinones: dioncoquinones A (**9**) and B (**10**) and droserone (**101**).[54] In the course of these investigations, three further naphthoquinones, **102**–**104**, were found in trace quantities, but easily recognized already by their UV absorption spectra. Specifically, the maximum UV absorption, around 419 nm, is characteristic of 3,5-dihydroxy substituted naphthoquinones.[177] In addition, a 3,5,8-trihydroxy substituted naphthoquinone, **105**, was found, possessing a maximum absorption at 485 nm. All these natural products were isolated and purified by preparative HPLC and characterized by ^{1}H-, ^{13}C- and 2D-NMR spectroscopy.

Naphthoquinones **102**–**104** all showed one aromatic proton by ^{1}H NMR, suggesting that their ring systems were higher-substituted as compared to those of dioncoquinones A (**9**) and B (**10**). The highly polar dioncoquinones C (**102**) and E (**104**) were found to have, both, molecular formulas of $C_{12}H_{10}O_6$, as deduced from the number of signals in the ^{13}C NMR spectrum and from HRESIMS, which is more than that of **10** by 30 units (corresponding to CH_2O). The substitution pattern of these naphthoquinones was established using 2D-NMR spectroscopy. The spectra of dioncoquinone C (**102**) showed HMBC correlations from the methyl protons at δ 1.98 (2-CH_3) and the only aromatic proton at δ 7.27 (H-8) to the carboxyl carbon at δ 184.2 (C-1), suggesting that this aromatic proton was located at C-8 (Figure 32). The NOESY correlation between H-8 and the methoxy group at δ 4.01 indicated that the latter was at C-7. In the naphthoquinone **104**, by contrast, no such NOESY correlation was observed between the methoxy group and the aromatic proton, while the methoxy protons at δ 3.91 (6-OCH_3) and H-8 at δ 7.09 displayed HMBC correlations to the carbon signal at δ 139.7 (C-6), indicating that the methoxy group was located at C-6 in **104**. In the structure of naphthoquinone **103**, an additional *O*-methyl group was found to be linked to the oxygen

function at C-3 as compared to that of **102**. The fourth naphthoquinone isolated from the callus cultures was identified as the known 8-hydroxydroserone (**105**), previously found in Droseraceae and Nepenthaceae,[162,163] but not yet in *T. peltatum*. Its structure has one more chelated hydroxy group as compared to those in compounds **102**–**104** (Figure 31). This is in agreement with the larger wavelength (485 nm) of maximum UV absorption observed for **105** compared to the one (416 nm) for dioncoquinone B (**10**) (Figure 33). From a biosynthetic point of view, the new naphthoquinones **102**–**104** and the known one, **105**, are apparently closely related to their less oxygenated analogs, plumbagin (**100**) and droserone (**101**).

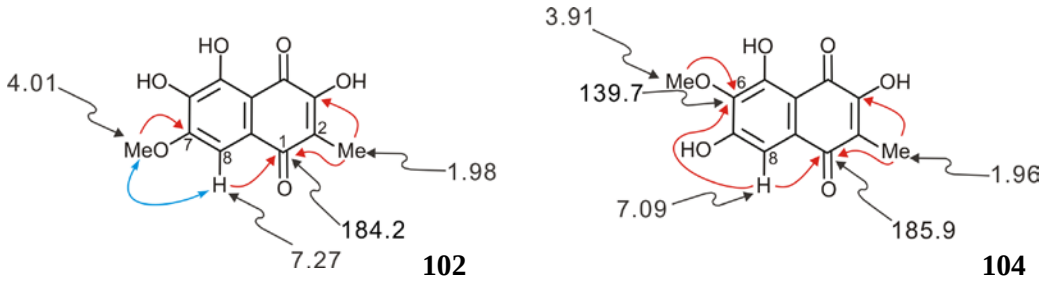


Figure 32. Selected NMR data of **102** (in CD_3COCD_3) and **104** (in CD_3OD): ^1H and ^{13}C NMR shifts (δ in ppm), NOESY correlations (double blue arrows) and HMBC couplings (single red arrow) indicative for their constitutions**.**

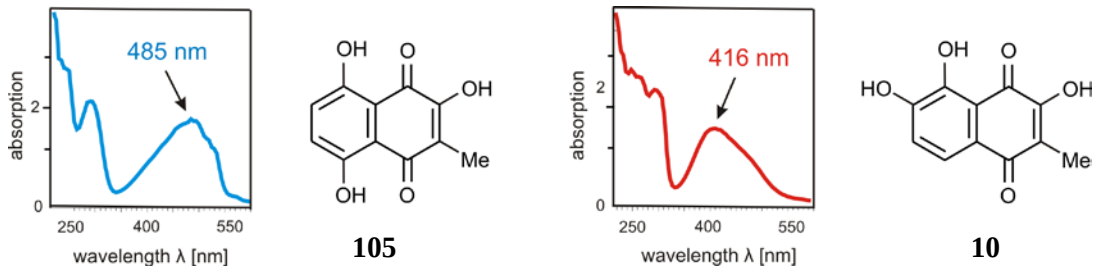


Figure 33. Comparison of the wavelengths of the UV absorption maxima of **105** and **10**.

Ancistronaphthoic acid B (**106**) was isolated for the first time from a Dioncophyllaceae species; it had previously been found in the stem bark and leaves of *Ancistrocladus ealaensis*[35] and in the roots of *Ancistrocladus likoko* (Ancistrocladaceae).[136]

The promising bioactivities of dioncoquinones A (**9**) and B (**10**),[54] in particular the high and selective activity (EC_{50} = 11 µM) of **10** against multiple-myeloma cells, encouraged us to test the isolated four natural analogs **102**–**105** in the same system. Dioncoquinone C (**102**) showed an activity (EC_{50} = 14 µM) comparable to that of dioncoquinone B (**10**), while it was inactive against normal blood cells. Dioncoquinones D (**103**) and E (**104**), and

8-hydroxydroserone (**105**) were less active than **10** and **102**. SAR studies for antitumoral naphthoquinones will be discussed in Chapter 8.

Different from the ^{1}H NMR signals in naphthoquinones, **9**, **10**, and **100**–**106**, compound **107** displayed the signals for one chelated hydrogen at δ 9.53 ppm (s, 1H), three neighboring aromatic protons at δ 7.39 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.8, 7.8 Hz, 1H), and 6.72 ppm (d, J = 7.8 Hz, 1H) and one singlet aromatic hydrogen at δ 7.31 ppm (s, 1H), together with a signal for a methoxy group at δ 3.98 ppm (s, 3H) and a methyl group at δ 2.15 ppm (s, 3H). The crosspeaks in NOESY established the series {2-CH_3 ↔ H-1 ↔ H-8 ↔ H-7 ↔ H-6 ↔ 5-OCH_3 ↔ 4-OH} (Figure 34), from which the fragment of 2-methyl-5-methoxynaphth-4-ol ($C_{11}H_{11}O_2$) was deduced. This, in combination with the molecular formula of $C_{24}H_{22}O_4$, as revealed by HRESIMS, and an optical rotation value of –65° suggested that **107** should be C_2-symmetric. Further, the linkage position at C-3 was demonstrated by an NOE interaction between 4-OH and 2'-CH_3, and the chemical shift of C-3 (120.3 ppm). Therefore, the binaphthalene **107** was established as 2,2'-dimethyl-5,5'-dimethoxy-3,3'-binaphalene-4,4'-diol, and was given a trivial name triphoquinol A.

A chiral HPLC analysis on **107** gave only one peak, hinting probably a highly enantiomerical purity. The CD spectra of **107** displayed a positive Cotton effect at 224 nm (Δε, +39.0) and a negative Cotton effect at 242 nm (Δε, –25.1). Thus, the absolute configuration at the biaryl axis of **107** should be *M*-configured.

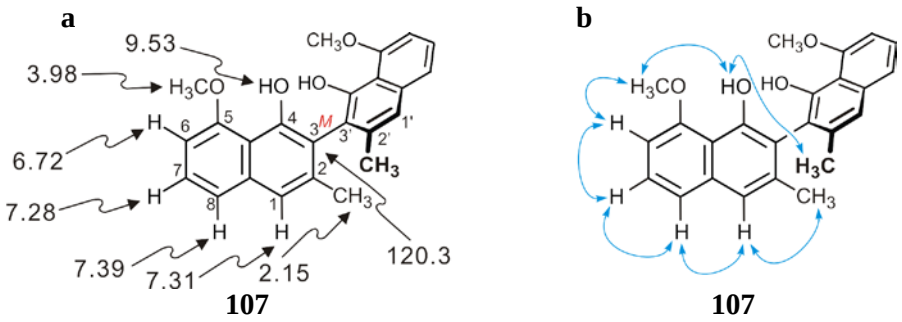


Figure 34. Selected ^{1}H and ^{13}C NMR data (δ in ppm) (a), and NOESY (blue double arrows) correlations for the constitution of **107**.

Similar naturally occurring binaphthols are stypandrol (**108**), which had been previously isolated from *Stypandra imbricate*,[178] diospyrol (**109**), and lemuninols B (**110**) and C (**111**) (Figure 35) from *Diospyros* species.[179,180] The steric hindrance (four *ortho* substituents) next to the biaryl axes in **110** and **111** was comparable to those in some of the naphthylisoquinoline alkaloids like, *e.g.*, in ancistrocladine (**5a**) and hamatine (**5b**). Therefore,

the biaryl axes in **110** and **111** should be rotationally hindered, and should constitute stereogenic elements. However, the issue of the axial chirality was not discussed by the authors,[180] and even the specific optical rotation values were not measured for **110** and **111**.

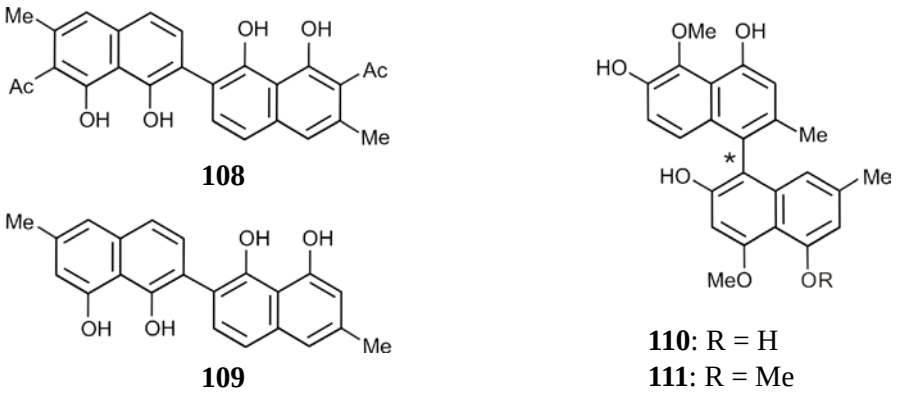


Figure 35. Flat structures of known related naturally occurring binaphthols **108**–**111** (* presumably chiral axis).

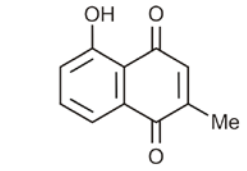
6.4 Conclusion

The discovery of the three new, highly oxygenated naphthoquinones, **102**–**104**, one naphthalene dimer **107**, and two additional known compounds, **105** and **106**, from cell cultures of *T. peltatum* shows the great potential of this plant to produce a broad variety of structurally interesting metabolites. Dioncoquinone C (**102**) possesses an additional methoxy group at C-7 position as comparable to dioncoquinone B (**10**). Moreover, dioncoquinone C (**102**) demonstrates an excellent activity against multiple-myeloma cell lines without any significant toxicity on normal cells, and thus, it can be considered as a new lead compound.

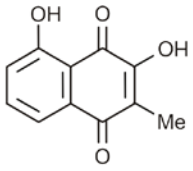
7 Phytochemical Investigations on Nepenthaceae

7.1 Introduction and Results

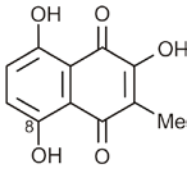
Closely related to the Ancistrocladaceae and Dioncophyllaceae are the Nepenthaceae,[123] which had long attracted the interest of biologists in various fields, including the mechanism to capture and digest insects, the physiological and anatomical features, and the phylogeny and structural evolution.[181-183] In contrast to numerous biological publications on the Nepenthaceae, only three papers were published on their natural products.[162,184,185] Plumbagin (**100**), droserone (**101**), 8-hydroxydroserone (**105**), and nepenthones A (**112** or **113**), C (**114**), D (**115**), and E (**116**) were detected or isolated from the roots of *N. rafflesiana* and *N. thorelii*,[162,184] and plumbagin (**100**), rossoliside (**117**) and plumbaside A (**118**) (Figure 36) were discovered from *N. insignis* in our group.[185] To search for naphthoquinones hopefully possessing anti-MM activities, the three species *Nepenthes alata*, *N. intermedia*, and *N. khashiama* were now chosen for investigation on the secondary metabolites.



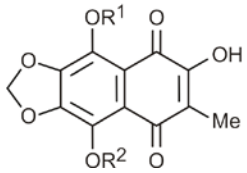
100



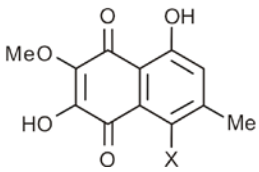
101



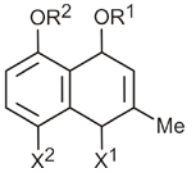
105



	R^1	R^2
112:	H	Me
113:	Me	H



114: X = H
115: X = OH
116: X = OMe



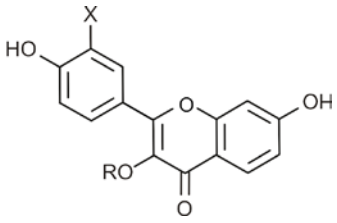
	R^1	R^2	X^1	X^2
117:	H	β-Glu	H	OH
118:	β-Glu	H	OH	H

Figure 36. Structures of the naphthoquinones plumbagin (**100**), droserone (**101**), 8-hydroxydroserone (**105**), nepenthones A (**112** or **113**), C (**114**), D (**115**), E (**116**), rossoliside (**117**), and plumbaside A (**118**), isolated from *N. raflesiana*, *N. thorelii*, and *N. insignis*.

Leaves of plants of the three species of *N. alata*, *N. intermedia*, and *N. khashiama* were collected in the Botanical Garden of Würzburg University and extracted with MeOH : CH_2Cl_2 : 0.01 N aqueous HCl solution (1 : 1 : 0.01 *v*/*v*). A thorough HPLC analysis of the three crude extracts was carried out. None of the peaks showed any absorption at the typical[177] UV wavelength above 400 nm, showing that no detectable quantities of

naphthoquinones were produced by the three plants.

The crude extract of *N. alata* was submitted to liquid-liquid separation with CH_2Cl_2 and aqueous 5% $NaHCO_3$ solution. The water layer was further purified on Sephadex LH-20 eluting with MeOH, leading to the isolation of three known[186-188] flavonoids, **119**–**121** (Figure 37).



	X	R
119:	OH	β-D-glucuronide
120:	OH	α-L-rhamnopyranoside
121:	H	α-L-rhamnopyranoside

Figure 37. Structures of the three flavonoids **119**–**121** isolated from *N. alata*.

7.2 Conclusion

HPLC analysis revealed that the three plants of *N. alata*, *N. intermedia*, and *N. khashiama* do not produce naphthoquinones, while flavonoids dominate the spectra of secondary metabolites. The three well-known[186-188] flavonoids **119**–**121** (Figure 37) were isolated from the plant *N. alata* for the first time.

8 Synthesis of Dioncoquinones B (10) and C (102), and their Analogs

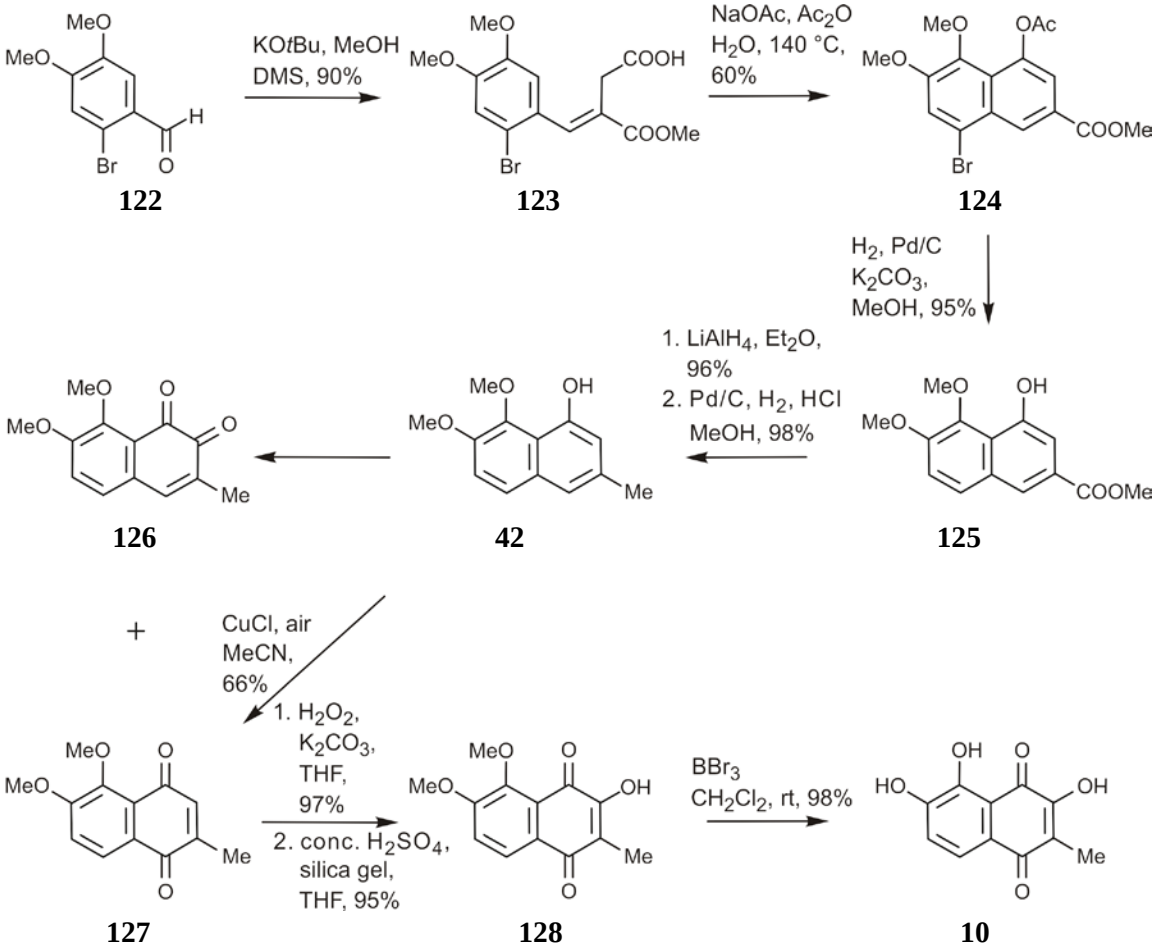
8.1 Synthesis of Dioncoquinones B (**10**) and C (**102**)

Dioncoquinone B (**10**) showed a strong *in vitro* activity against multiple-myeloma cell lines, without any significant toxicity towards normal blood cells.[54] These pharmacological properties made it rewarding to explore the overall effects of dioncoquinone B (**10**) *in vivo*, in model mice, to test its tolerance and efficacy. For this, a prerequisite was to get a large quantity of dioncoquinone B (**10**), which could be in principle accomplished by isolation from plant material. This would have required a large quantity of precious cell cultures of *T. peltatum*, and would also have been time-uneconomical. Thus, an alternative access to dioncoquinone B (**10**) should be achieved by synthetic work. Before the present work, two synthetic pathways to prepare dioncoquinone B (**10**), had been described by A. Hager[114] and M. Moos[189] in their diploma theses (Schemes 9 and 10). In this thesis, a 3rd, improved new route (Scheme 11) for obtaining dioncoquinone B (**10**) and its application on the synthesis of active dioncoquinone C (**102**) are described (Scheme 12).

8.1.1 The First Route to Dioncoquinone B (**10**): by a Stobbe Approach

The synthesis of highly substituted naphthoquinones has been well studied during the past decades.[190] Many strategies have been developed to build up these systems, among them the Dötz reaction,[112] the Hauser-Kraus annulation,[104] and [4+2]-cycloadditions.[93] In analogy to previous work,[191] the initial approach to dioncoquinone B (**10**) was based on the well-developed Stobbe condensation route to a naphthalene, which was then oxidized and modified to provide the required naphthoquinone. This pathway, thus, started with the synthesis of the naphthalene **42** from the known[191] bromo veratrum aldehyde **122** (Scheme 9). A Stobbe condensation[192] with dimethyl succinate resulted in the formation of the *E*-configured (NMR) acid **123**, which was cyclized in acetic anhydride in the presence of sodium acetate[193] to produce the naphthalene **124**. Using palladium on charcoal in methanol in the presence of K_2CO_3,[194] the bromine and the acetate protecting groups were removed to give the free naphthol **125** in an almost quantitative yield. Reduction of the ester group using $LiAlH_4$[194] and palladium on charcoal[194] provided the methylnaphthalene **42**[99] in a 94% yield over two steps. By oxidation of **42** with CuCl in the presence of air,[195] the *para*-naphthoquinone **127**[99] was obtained in a 66% yield, accompanied by the respective

ortho-quinone **126** (ratio 6.5:1). The required α-hydroxy functionality of the target molecule was introduced by epoxidation of the 2,3-double bond[196,197] of **127**, followed by ring opening[198] of the resulting α,β-epoxydiketone. Under optimized conditions using sulfuric acid on silica gel, this reaction sequence provided ancistroquinone C (**128**), a natural product that had been previously isolated from the related plant, *Ancistrocladus abbreviatus*.[54] *O*-Demethylation of **128** with boron tribromide furnished dioncoquinone B (**10**) in a 98% yield, thus completing its first total synthesis (Scheme 9).

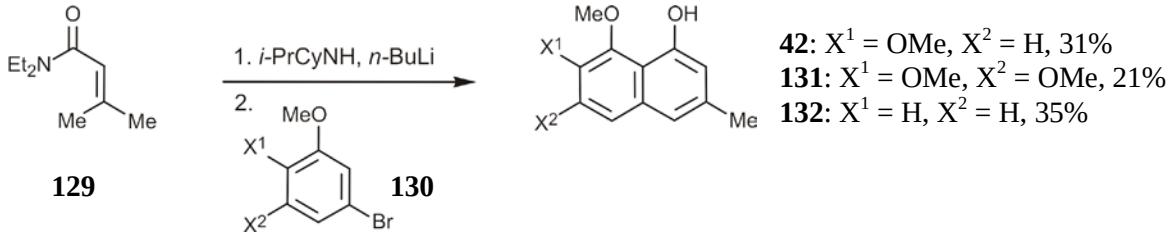


Scheme 9. First total synthesis of dioncoquinone B (**10**), *via* a Stobbe-condensation route.

This first synthetic route, although reliably providing access to dioncoquinone B (**10**) and offering the possibility to synthesize derivatives of this natural product by varying the starting materials, contains some tedious isolation and purification steps, which prompted us to explore less time-consuming alternatives. The improved second-generation synthesis of the same naphthalene intermediate **42** is discussed in the following section.

8.1.2 Diels-Alder Route to Precursors of Dioncoquinone B (**10**) and Dioncoquinone C (**102**), and to the Related Naphthol **132**

For a better access to naphthols **42**, **131**, and **132**, a strategy was envisioned based on the Diels-Alder (DA) reaction between benzynes as dienophiles and lithiated unsaturated amides as dienes established by Watanabe *et al.*[99] This required the amide **129** and 3,4-dimethoxybenzyl bromide (**130**) as starting materials for the DA reaction, through which **42** and its congeners **131** and **132** were prepared, with different substitution patterns in the left ring part. This synthetic route permitted a concise access to several derivatives of dioncoquinone B (**10**). The yield of the naphthalene products depended on the number of electron-donating groups in the benzyne ring. The best results were achieved using mono- and di-substituted bromobenzenes (Scheme 10).



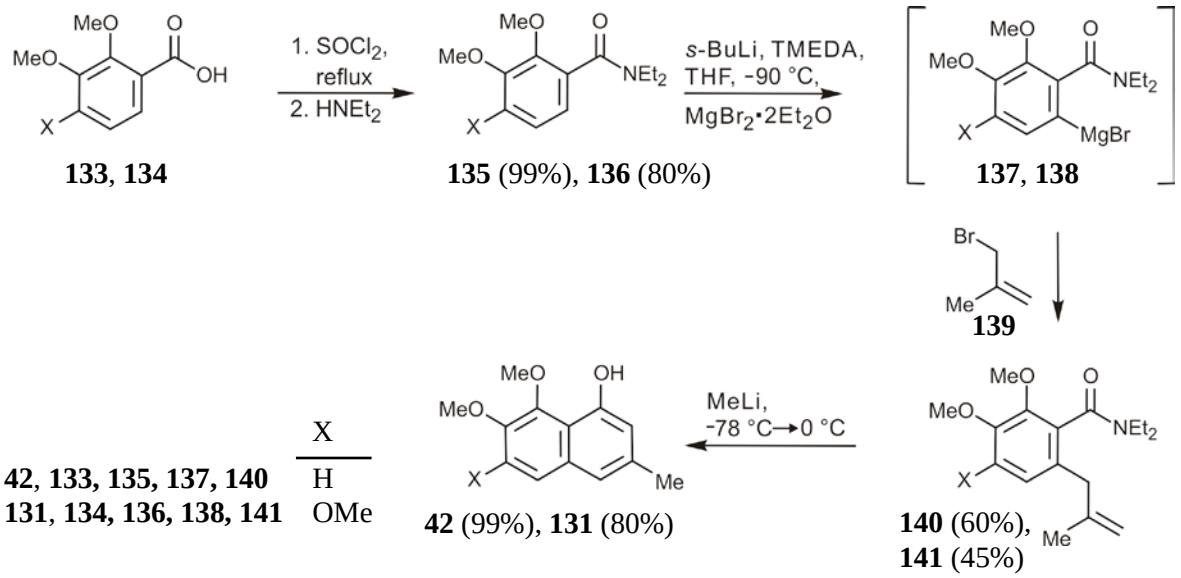
Scheme 10. Synthesis of naphthols *via* a Diels-Alder route.

With this Diels-Alder route to the intermediates **42**, **131**, and **132**, a significantly shorter synthetic route to dioncoquinone derivatives was established, yet in unsatisfactory yields.

8.1.3 The Grignard Approach to Precursors of Dioncoquinone B (**10**) and Dioncoquinone C (**102**), as developed in this thesis

Therefore, another pathway to naphthols **42** and **131** was established, this time based on the addition of a Grignard reagent derived from benzamides **135** and **136** to an allyl bromide.[100-102,199] This route started with the commercially available benzoic acids **133** and **134**, which were converted to the known[200,201] benzamides **135** and **136** using procedures described for other compounds.[202,203] After the directed *ortho*-deprotonation of **135** and **136** using *s*-BuLi, the resulting lithium species was transmetallated with freshly prepared the $MgBr_2 \cdot 2Et_2O$ solution (very important! See 8.2.4),[103] providing Grignard reagents **137** and **138**, respectively. Their reaction with 2-methylallyl bromide (**139**) resulted in the formation of the new *ortho*-allyl benzamides **140** and **141** in satisfactory yields. By treatment with methyl

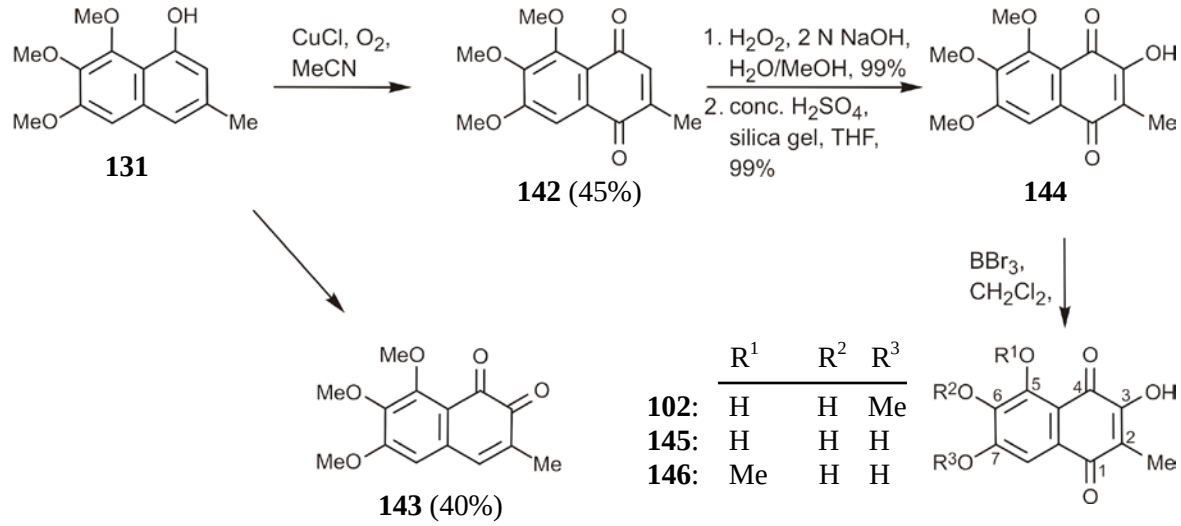
lithium at −78 °C,[100-102,199] **140** and **141** were converted to the desired naphthalenes **42** and **131** in excellent yields (Scheme 11). This route enabled us to synthesize these key intermediates in a very short manner and with high yields.



Scheme 11. Synthesis of the key intermediates **42** and **131** by Grignard reaction of the benzamides **135** and **136**, and 2-methylallyl bromide (**139**), and MeLi-induced cyclization.

8.1.4 Synthesis of Dioncoquinone C (**102**) and Its Analogs

This good synthetic access to several differently substituted naphthalene compounds **42** and **131** now permitted to synthesize a small library of further dioncoquinone B analogs, among them the natural product dioncoquinone C (**102**) (Scheme 12 and Table 5).



Scheme 12. Synthesis of derivatives of dioncoquinone B (**10**) possessing an additional oxygen

function at C-7.

Table 5. Yields of **102**, **145**, and **146** using different reaction conditions in the last step.

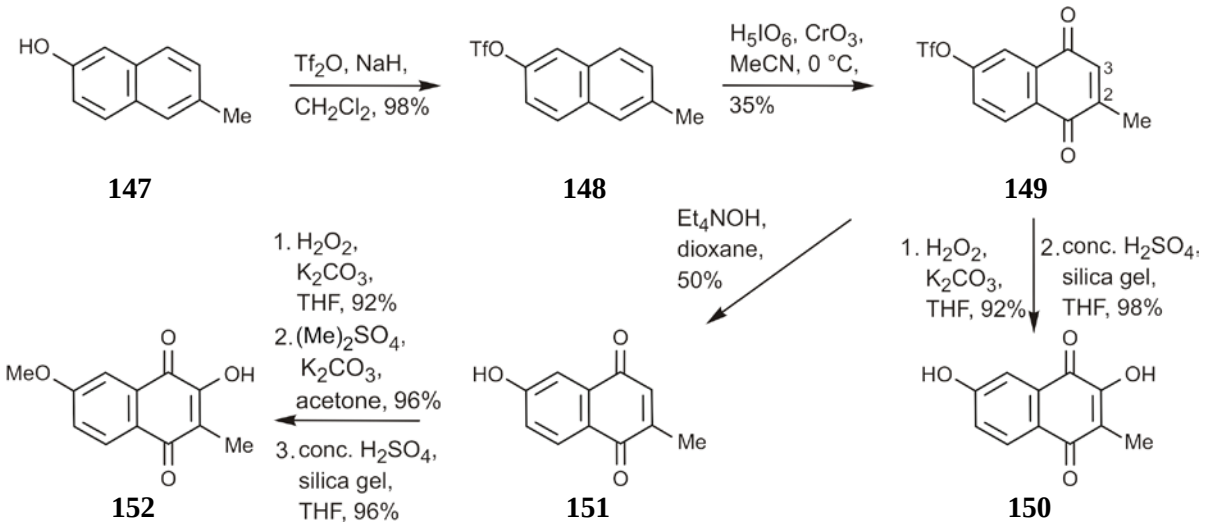
Entry	BBr_3 (eq.)	Time (h)	T (°C)	**102** (%)[a]	**145** (%)[a]	**146** (%)[a]
1	2	2	–78	0	0	0
2	3	2	–78→0	41	10	15
3	10	2	–78→0	67	13	15
4	10	16	–78→rt	0	98	0

[a] Yields after normal-phase column chromatography and preparative HPLC on reversed-phase material.

8.2 Synthesis of Analogs of Dioncoquinone B (**10**)

8.2.1 Synthesis of the Dioncoquinone B Analog **150**

To evaluate the contribution of the 5-OH function to the anti-MM activity of dioncoquinone B (**10**), compound **150**, *i.e.*, the analog without that hydroxy group, was prepared. The synthesis started with the preparation of the new triflate **148** by treatment of the known[194,204,205] naphthol **147** with triflic anhydride (Scheme 13). Selective oxidation of **148** using periodic acid and chromium trioxide[206] at 0 °C afforded the new naphthoquinone **149**. Epoxidation of the 2,3-double bond in **149** with concomitant cleavage of the triflate ester, followed by epoxide opening, produced the dihydroxynaphthoquinone **150**. For the preparation of the monophenolic derivative **152**,[207] the naphthol **151** obtained from the triflate **149**[208] was epoxidized, *O*-methylated, and then converted to the target compound **152** under acidic conditions.

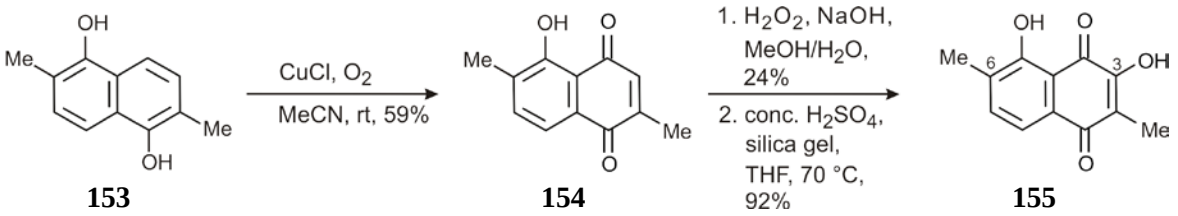


Scheme 13. Synthesis of dioncoquinone B derivatives without a hydroxy function at C-5.

8.2.2 Synthesis of the Dioncoquinone B (**10**) Analog **155**

To explore the effect of the 6-OH group of dioncoquinone B (**10**) on its antitumoral properties, the analog **155** bearing an additional Me substituent at C-6 instead of a hydroxy group was synthesized. To prepare **155**, the known[209] dinaphthol **153** was oxidized to naphthoquinone **154**, followed by an introduction of a hydroxy group at C-3 (Scheme 14).

Besides the strategy of building up **153** by introduction of two methyl groups into 1,8-dinaphthol according to the literature,[209] two other known approaches are based on the introduction of two α-hydroxy groups into 2,6-dimethylnaphthalene by means of biotransformation,[210] or by oxidation with H_2O_2 catalyzed by metalloporphyrins,[211] but both in low yields.

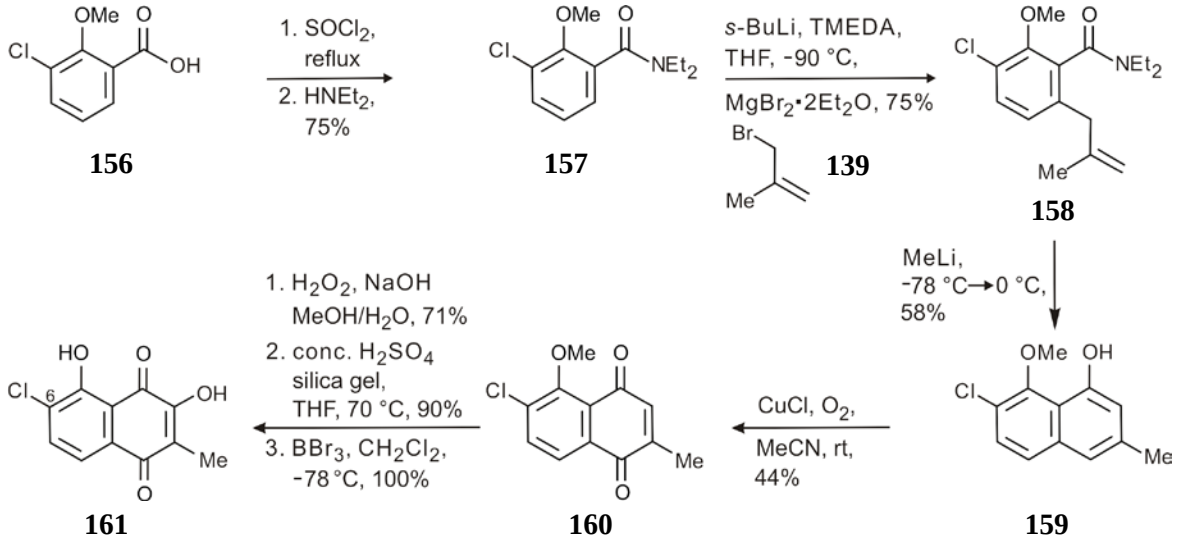


153 **154** **155**

Scheme 14. Synthesis of the 6-methyl analog **155** of dioncoquinone B (**10**).

8.2.3 Synthesis of the Dioncoquinone B (**10**) Analog **161**

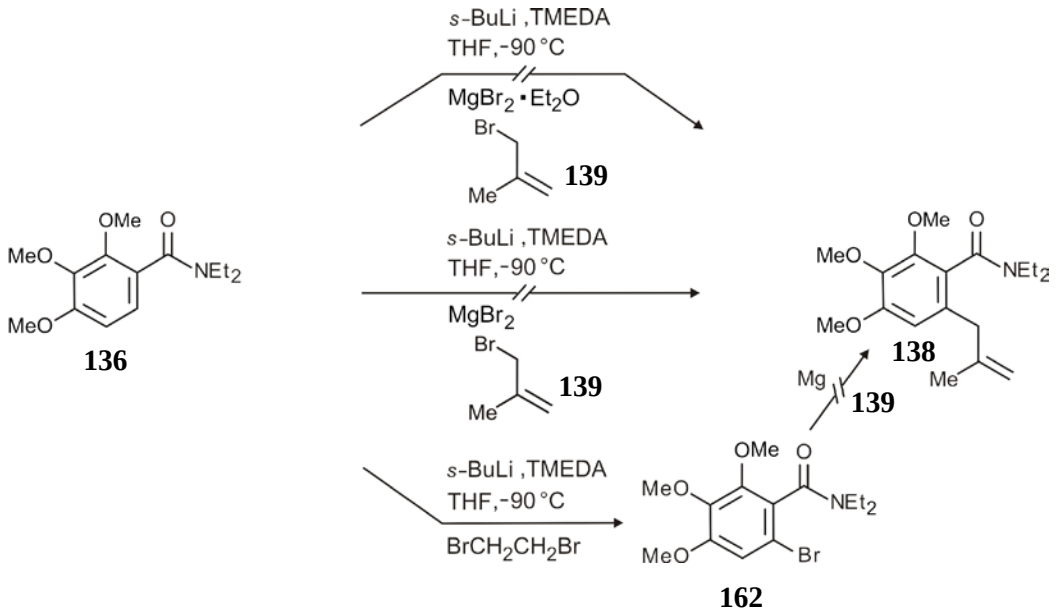
In addition to **155** with its an electron-donating methyl substituent at C-6, another dioncoquinone B analog, **161**, bearing an electron-withdrawing Cl substituent, was prepared. The method to synthesize precursors of dioncoquinones B (**10**) and C (**102**), as described in 8.1.3, was likewise applied in the preparation of their derivative **161** (Scheme 15).



Scheme 15. Synthesis of the 6-chloro analog **161** of dioncoquinone B (**10**).

8.2.4 Attempts to Prepare the Grignard Reagent **138**

Before the successful use of the Grignard approach for the preparation of precursors of dioncoquinones B (**10**) and C (**102**) and their derivatives, the unsuccessful reactions as described in Scheme 16 had been carried out. The key step was to prepare substance **138** from the amide **136**. The starting material **136** was *ortho*-deprotonated using *s*-BuLi, providing the intermediate lithiated species (structure not shown here), to which commercially available $MgBr_2 \cdot Et_2O$ or $MgBr_2$ was added, followed by addition of 2-methylallyl bromide (**139**). As a result, only compound **136** was recovered. In a third attempt, the bromide **162** prepared from **136** was employed to provide a Grignard reagent for access to **138**, which was, however, unsuccessful due to the presence of the strongly electron-withdrawing group amide (Scheme 16). The three attempts revealed that it is essential to use freshly prepared the $MgBr_2 \cdot 2Et_2O$ solution for the success of this reaction.



Scheme 16. Failed reactions to prepare **138** from benzamide **136**.

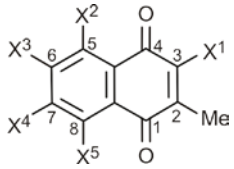
8.3 SAR Studies of Prepared Naphthoquinones

To identify the pharmacophore of these molecules, a number of synthetic intermediates and isolated compounds were examined for their biological activities against multiple-myeloma cells. The results are summarized in Table 6.

The first results of our biological tests enabled us to localize the preliminary structural elements of naphthoquinone derivatives that are responsible for their anti-MM activity and cytotoxicity. To examine the individual roles of the hydroxy functions at the C-3, C-5, and C-6 positions in dioncoquinone B (**10**), we synthesized or isolated derivatives that each contains only two hydroxy groups. The test results (structures **101**, **150** and **165** in Table 6) show that removal of one OH group in any of these positions leads to an almost complete loss of bioactivity. The observation that substance **165** bearing two hydroxy groups at C-5 and C-6 exhibits lower activity and higher toxicity than **10**, combined with the activities of compounds **150** and **151**, jointly evidence that the lack of a hydroxy function at C-3 makes the compound more toxic against normal blood cells. This tendency is supported by the pairwise comparison of the properties of compounds **127** and **128**, of **142** and **144**, of **154** and **155**, of **160** and **174**, of **163** and **168,** of **170** and **171**, and of **172** and **173** with respect to the structural variation at C-3 (Table 6). A possible reason for this is that the hydroxy group and other substituents at C-3 may block Michael addition reactions of possible nucleophiles (e.g., SH groups of proteins) in the cell to the α,β-unsaturated carbonyl fragments in naphthoquinones **127**, **142**, **154**, **160**, **163**, **170**, and **172** thereby inhibiting a variety of cellular functions that direct the

cells into apopotosis.[212] On the other hand, the possibility of a Michael addition reaction seems to be necessary for the anti-MM activities of these compounds, too. It is worth mentioning that shifting the OH groups along the aromatic ring has a significant impact on the biological activities of naphthoquinones. Hydroxy shifts from position 5, 6 to 6, 7 (structure **164**) or 5, 8 (structure **105**) both result in a decrease of the activities of the corresponding compounds. The introduction of an additional OH function in position 7 of **10** as in the naphthoquinone **145** does not have any significant effect on the anti-MM activity of this compound, while its toxicity is increased. No pronounced toxicity was observed, however, in the 7-*O*-methylated derivative of **145**, dioncoquinone C (**102**), while its bioactivity was still high (Table 6). The replacement of an OH group at C-6 of dioncoquinone B (**10**) with a Me group for **155**, or with a Cl substituent for **161** resulted in a decrease of anti-MM activity, which was also observed for substances **171**, **173**, and **174**. Among the numerous derivatives tested, **102** was the most active candidate, with no measurable cytotoxicity against peripheral mononuclear blood cells (PBMCs). This activity is highly specific, and thus rewarding, because in our tests all other mixed OH/OMe/Cl/Me/COOMe- or completely OMe-substituted structures were entirely inactive (structures **128**, **144**, **152**, **155**, **161**, **166**–**169**, **171**, and **173**–**174**).

Table 6. EC_{50} values of INA-6 multiple-myeloma cells and PBMCs treated with naphthoquinones.



Compd.	X^1	X^2	X^3	X^4	X^5	EC_{50} [µM] (INA-6)[a]	EC_{50} [µM] (PBMC)[b]
10	OH	OH	OH	H	H	11	NR
101	OH	OH	H	H	H	>100	NR
102	OH	OH	OH	OMe	H	14	NR
105	OH	OH	H	H	OH	>100	NR
127	H	OMe	OMe	H	H	15	13
128	OH	OMe	OMe	H	H	>100	NR
142	H	OMe	OMe	OMe	H	8	7.5
144	OH	OMe	OMe	OMe	H	>100	NR
145	OH	OH	OH	OH	H	7	70
150	OH	H	OH	H	H	>100	NR
151	H	H	OH	H	H	13	17
152	OH	H	OMe	H	H	>100	50
154	H	OH	Me	H	H	2.3	4
155	OH	OH	Me	H	H	75	NM
160	H	OMe	Cl	H	H	7	5
161	OH	OH	Cl	H	H	>100	NM
163	H	H	OMe	OMe	H	6	6.5
164	OH	H	OH	OH	H	52	NR
165	H	OH	OH	H	H	75	100
166	OH	OH	OMe	H	H	>100	NR
167	OMe	OH	OH	H	H	>100	NR
168	OH	H	OMe	OMe	H	>100	NR
169	H	OMe	H	H	H	4	16
170	H	H	Me	H	H	4.8	3.5
171	OH	H	Me	H	H	55	NM
172	H	H	COOMe	H	H	3.3	1.2
173	OH	H	COOMe	H	H	80	NM
174	OH	OMe	Cl	H	H	45	NM

NR: not reached. NM: not measured.

[a] Activity against the multiple-myeloma cell line INA-6.

[b] Cytotoxicity against normal peripheral mononuclear blood cells (PBMC).

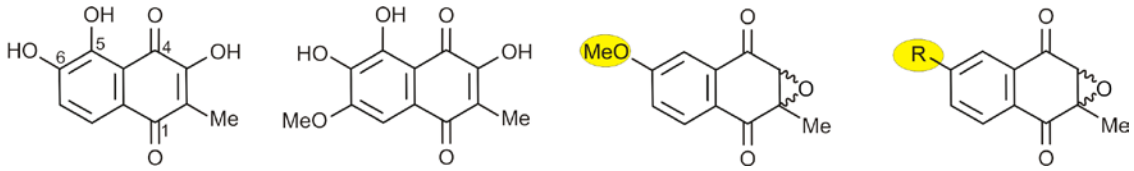
In summary, for a good balance of activity versus toxicity, it seems essential to have OH groups in positions 3, 5, and 6, while position 7 has little influence, which can be seen from the similar activities of dioncoquinone B (**10**), dioncoquinone C (**102**), and 7-hydroxydioncoquinone B (**145**) (Table 6). The role of an OH group in position 8 is not quite clear, but - at least in combination with the lack of oxygen functions at C-6 and C-7 - it seems to lower the activity as seen in structure **105**.

8.4 Conclusion

For the synthetic access to the antitumoral product dioncoquinone B (**10**) in sufficient quantities for *in vivo* tests, two other approaches[114,189] had been described in our group before the present thesis, and here a third one was established based on a directed *ortho* metalation (DOM) reaction. It proved to be the best one as compared to the first two approaches, which required either too many steps or gave too low overall yields. Utilizing the third strategy, the likewise highly antitumoral metabolite dioncoquinone C (**102**) was synthesized, too. For the elaboration of the first preliminary SAR studies, a number of dioncoquinone B analogs were obtained by synthesis and by isolation from cell cultures of *T. peltatum*. Among them, only the new dioncoquinone C (**102**) strongly induced apoptosis in the multiple-myeloma cell lines INA-6 without any significant toxicity. Thus, the two natural products dioncoquinones B (**10**) and C (**102**) constitute two promising basic structures to develop anti-MM candidates. Remarkably both antitumoral compounds have three hydroxy functions at C-3, C-5, and C-6, which are required for their biological properties. Extended SAR studies to further optimize the structures and to explore the *in vivo* anti-MM activity of **10** and **102** and their analogs are currently in progress.

9 Synthesis of Epoxides and SAR Studies

The synthetic intermediate **175** was found to show an excellent activity (EC_{50} = 3.5 µM) against the multiple-myeloma cell lines INA-6 without cytotoxicity towards normal cells, thus, being even more promising than dioncoquinones B (**10**) and C (**102**). To evaluate the contribution of the 6-OMe group on the anti-MM property of **175**, compounds **176** and **177** bearing Me and COOMe functions at C-6 were prepared (Figure 38, Schemes 17 and 19).



dioncoquinone B (**10**)
EC_{50}: 11 µM
CT_{50}: not reached

dioncoquinone C (**102**)
EC_{50}: 29 µM
CT_{50}: not reached

epoxide **175**
EC_{50}: 3.5 µM
CT_{50}: not reached

176: R = Me
177: R = COOMe

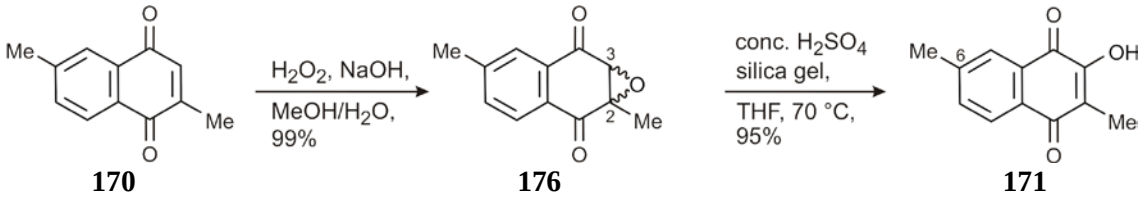
Figure 38. Structures of the bioactive dioncoquinones B (**10**) and C (**102**), the epoxide **175**, and the two synthetic targets **176** and **177**.

9.1 Synthesis of 2,6-Dimethyl-1,4-naphthoquinone-2,3-epoxide (**176**)

The oxidizing agents converting varying 2-methylnaphthalenes to the corresponding naphthoquinones can be divided into two groups: with a metal catalysis and without. The former involves chromium (VI) or cerium (IV) compounds in combination with an oxygen source,[92] and the latter uses aqueous hydrogen peroxide in the presence of glacial acetic acid[213] or hexafluoroacetone hydrate,[214] or *m*-chloroperbenzoic acid.[215]

Of the oxidizing agents, H_5IO_6/CrO_3 was used for 2-methylnaphthalene providing a ratio of 19:1 of 1,4-naphthoquinone to the 5,8-isomer.[206] Additionally, other oxidizing procedures and the regioselective ratios were reported, *e.g.*, H_2O_2/methyltrioxorhenium (89:11),[216] $KHSO_3$/Mn-porphyrins (53:47),[217] CH_3CO_3H/Mn-porphyrins (100:0).[218]

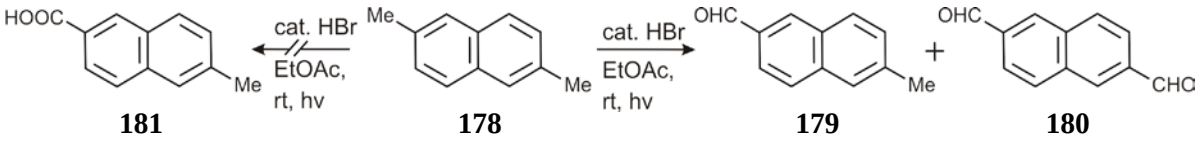
Based on the high oxidative efficiency and the easy availability of H_5IO_6/CrO_3, this reagent combination was applied to 2,6-dimethylnaphthalene providing the quinone **170**.[206] The following two steps for epoxidation and ring-opening to give **171** were similar to those described before (Scheme 17).[196]



Scheme 17. Synthesis of 2,6-dimethyl-1,4-naphthoquinone-2,3-epoxide (**176**) and naphthoquinone **171**.

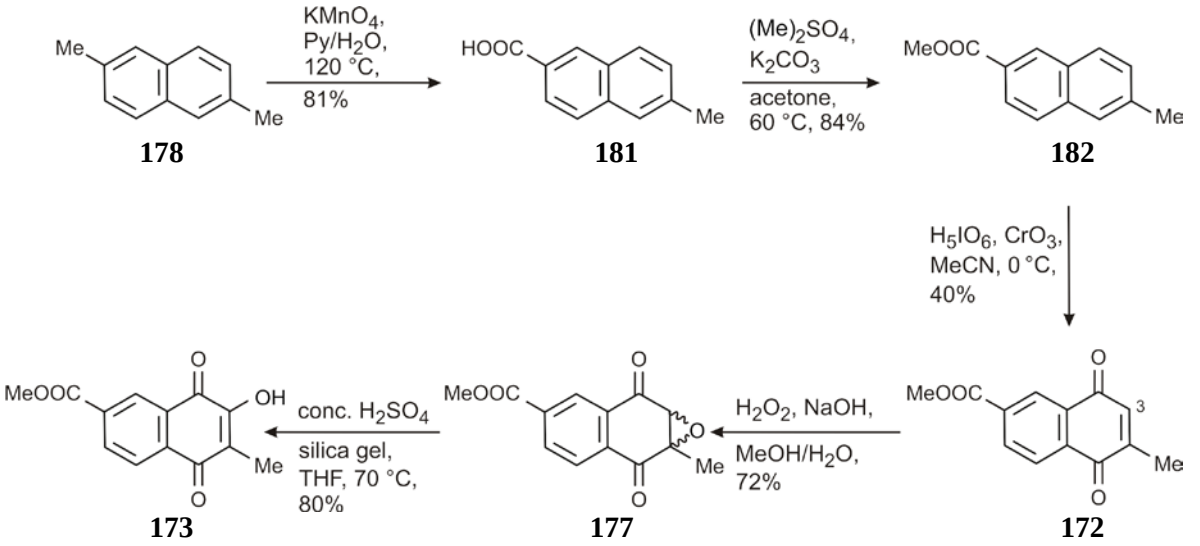
9.2 Synthesis of 6-methoxycarbonyl-2-methyl-1,4-naphthoquinone-2,3-epoxide (**177**)

The attempted conversion of **178** to the carboxylic acid **181** by aerobic photooxidation in the presence of HBr was unsuccessful,[219] affording only the mono- and the dialdehyde **179** and **180** (Scheme 18).



Scheme 18. Aerobic photooxidation on 2,6-dimethylnaphthalene (**178**).

Oxidation of **178** by utilizing potassium permanganate[220,221] afforded the acid **181** in a respectable yield. After conversion of **181** to the methyl ester **182**, it was regioselectively oxidized affording the quinone **172**. Introduction of a hydroxy group at C-3 of **172** *via* the epoxide **177** afforded the desired compound **173** in two steps (Scheme 19). The two synthetic parts (9.1 and 9.2) were performed by the bachelor student B. Wanner under my supervision.

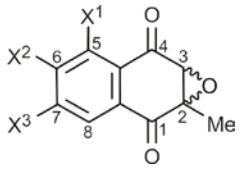


Scheme 19. Synthesis of 6-methoxycarbonyl-2-methyl-1,4-naphthoquinone-2,3-epoxide (**177**) and naphthoquinone **173**.

9.3 SAR Studies on Epoxides

The epoxide **175** showed an extraordinary activity (EC_{50} = 3.5 µM) against MM cell lines as compared to all synthesized naphthoquinones and their synthetic intermediates. Moreover, no significant toxicity was observed for **175** against normal blood cells. All other tested epoxides, **176**, **177**, and **183**–**186** showed high toxicities against normal cells (Table 7). In conclusion, compound **175** exhibited the by far best and highly specific antitumoral activity. Work on further structural optimization, *in vivo* biotestings and investigation of the mode of action is still ongoing.

Table 7. EC_{50} values of INA-6 multiple myeloma cells and PBMCs treated with epoxides.



Compound	X^1	X^2	X^3	EC_{50} [µM] (INA-6)[a]	EC_{50} [µM] (PBMC)[b]
175	H	OMe	H	3.5	NR
176	H	Me	H	2	2
177	H	COOMe	H	0.6	0.4
183	OMe	OMe	H	3	7
184	OMe	OMe	OMe	2	4
185	H	OH	H	13	37
186	OMe	Cl	H	3	5

NR: not reached.

[a] Activity against the multiple-myeloma cell line INA-6.

[b] Cytotoxicity against normal peripheral mononuclear blood cells (PBMC).

10 Total Synthesis of Triphoquinone (187a)

10.1 Introduction

A library of naphthoquinones[54] and naphthalene-related metabolites, *e.g.*, naphthalene dimers, and naphthalene-naphthoquinone dimers (unpublished paper) were recently isolated from cell and root cultures of *T. peltatum* (Dioncophyllaceae) in our group. Of these, one unprecedented axially chiral dimer triphoquinone (**187a**) (Figure 39) was found, consisting of a 1,2-naphthoquinone moiety and a naphthalene unit. To obtain sufficiently large quantities of this substance for bioassays, the total synthesis of **187a** was pursued. The strategy was to synthesize the racemate of triphoquinone *rac*-**187**, whose separation should be achieved by column chromatography on a chiral phase.

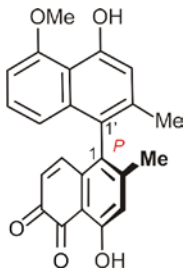
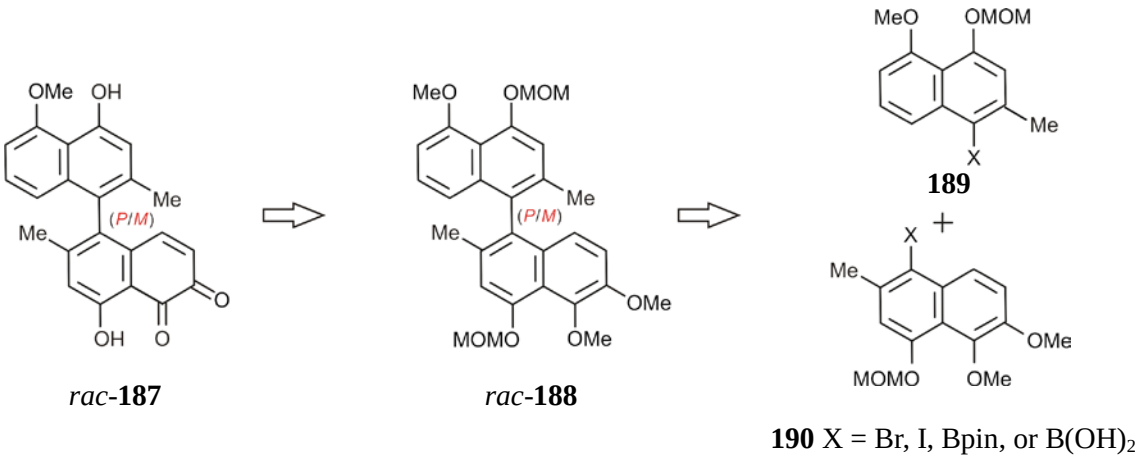


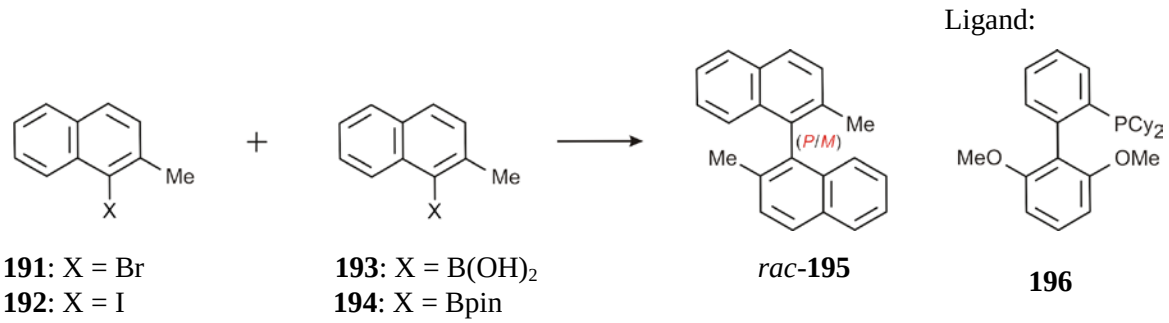
Figure 39. Structure of the target triphoquinone (**187a**).

10.2 Retrosynthetic Analysis

Key step of the synthesis of *rac*-**187** (Scheme 20) was the construction of the binaphthalene *rac*-**188**, with its extremely sterically hindered axis between the two highly oxygenated parts, by an intramolecular or intermolecular *C*-*C* coupling reaction. To save precious precursor material, the plan was to optimize the coupling conditions on racemic 2,2'-dimethyl-1,1'-binaphthalene (*rac*-**195**) as a simplified test system (Scheme 21).



Scheme 20. Retrosynthetic disconnection of *rac*-**187**.



Scheme 21. Synthesis of the simplified binaphthalene *rac*-**195** by Suzuki-Miyaura coupling.

10.3 Synthesis of Biaryls

One of the most successful concepts in the preparation of a biaryl axis is the well-established intramolecular "lactone methodology" in our group.[141] This strategy permits the synthesis of either of the two atropisomers, even with sterically hindered axes, in high chemical and optical yields. A basic requirement within this concept is to construct an ester bridge for the prefixation of the two coupling units,[222,223] which is possible, however, difficult to be constructed in the target **187a**.

A pioneer approach in the stereoselective synthesis of **195** was initially established by Meyers and Cram,[224-226] using an artificial chiral auxiliary moiety in the proximity of the axis as a stereochemically controlling unit. The disadvantage of this strategy is the need of additional steps to attach and remove the chiral auxiliary. An alternative approach to enantiomerically pure **195** described by Hayashi and Ito[227] involved a chiral ligand and a nickel-catalyzed asymmetric coupling between (2-methylnaphthalen-1-yl) magnesium bromide and 2-methylnaphthalen-1-yl bromide. The wide application of this strategy was

hampered by the required functionality patterns necessary for the preparation of Grignard reagents.

Today, Suzuki-Miyaura cross-coupling reactions are certainly the most widely used method for the construction of biaryl and binaphthyl axes for a number of well known reasons, such as its tolerance of a broad range of functional groups and its relatively environment-friendly nature.[228] Despite a growing success, the Suzuki-Miyaura coupling reaction between two sterically hindered partners and the control of a biaryl axial chirality remain great challenges.[229,230] Numerous reports[231-235] demonstrated that achieving satisfactory yields is a practicable, but a difficult task, in particularly when four *ortho*-substituents are present around the biaryl axis in the synthetic target, as exemplarily shown for the synthesis of **195**.

The successful examples[231-235] of the synthesis of **195** involved the coupling 1-iodo-2-methylnaphthalene (**192**) and the boronic acid **193**, or **192** and the boron ester **194** by employing the ligands that were synthesized in several steps by the authors. In this thesis, commercially available ligands were used for the racemic coupling reaction between **191** (bromo- instead of iodo-naphthalene) and **193**, or between **191** and **194**. Subsequently, the optimized reaction condition would be likewise applied on the synthesis of *rac*-**188**.

Significant achievements towards the preparation of highly hindered biaryls have been made particularly in Buchwald's and Fu's groups,[236-240] by applying increasingly efficacious supporting ligands. Of great importance are the commercially available catalyst systems $Pd_2(dba)_3$/P(*t*-Bu)$_3$ and $Pd_2(dba)_3$/S-Phos (**196**), which were first applied in the synthesis of the binaphthalene *rac*-**195** in the present thesis.

The two boron species **193** and **194** were prepared from **191** according to known procedures.[241,242] The conditions for the coupling were modified regarding base-solvent combinations, boron esters *vs*. boronic acid, and temperature. Selected results are summarized in Table 8. A low yield of 33% of **195** (entry 1) was obtained in the presence of $Pd_2(dba)_3$/P(*t*-Bu)$_3$,[240] while a respectable yield of 66% (entry 2) was provided by using $Pd_2(dba)_3$/ S-Phos (**196**).[236,237] The yields did not substantially alter when CsF/toluene (entry 3), CsF/THF (entry 4), or K_3PO_4 /DME (entry 6) was employed. The yield was improved up to 90% when using CsF /DME (entry 5). The yields were reduced when the boronate ester **194** replaced the boronic acid **193** (entries 7–9). In conclusion, the combination of $Pd_2(dba)_3$/S-Phos/DME/CsF proved to be the best coupling reaction, which should, thus, now be applied on the synthesis of *rac*-**188**.

Table 8. Selected results from the symmetric Suzuki-Miyaura couplings.[a]

Entry	Boron species	Solvent	Base	T. [° C]	Yield (%)[b]
1	**193**	THF	KF	80	33%[c]
2	**193**	toluene	K_3PO_4	100	66%
3	**193**	toluene	CsF	100	70%
4	**193**	THF	CsF	60	54%
5	**193**	DME	CsF	80	90%
6	**193**	DME	K_3PO_4	80	74%
7	**194**	DME	CsF	80	40%
8	**194**	DME/H_2O[d]	CsF	80	85%
9	**194**	DME/H_2O[d]	K_3PO_4	80	48%

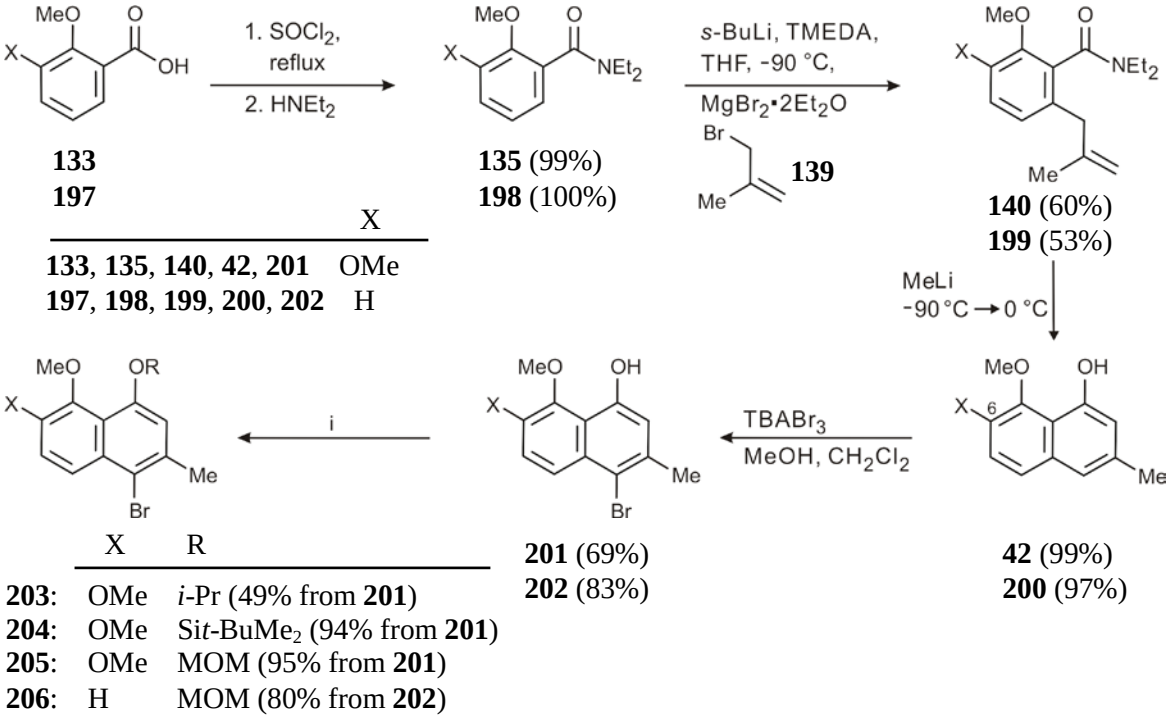
[a] $Pd_2(dba)_3$ and Buchwald's ligand **196** were used in all reactions except for entry 1; Reactant ratio: bromide (**191**) / boron species **193** or **194** = 1.2 : 1; all reactions were run for 20 h; other catalyst systems, e.g., $Pd(dppf)Cl_2$, $Pd_2(dba)_3$/dppf, $Pd(OAc)_2$/dppf, $Pd_2(dba)_3/PCy_3$, were tried, but no coupling was observed.

[b] Determination after isolation by preparative HPLC and/or by analytic HPLC.

[c] $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ were used as catalyst and ligand.

[d] DME/H_2O = 10 : 1.

The strategy to prepare the naphthol **42** described in Scheme 11 in 8.1.3 was likewise applied to synthesize its 6-demethoxy derivative **200** (Scheme 22). Bromination of **42** and **200** yielded the desired monobromonaphthols **201** and **202** according to the literature.[243]



133
197

135 (99%)
198 (100%)

140 (60%)
199 (53%)

	X
133, **135**, **140**, **42**, **201**	OMe
197, **198**, **199**, **200**, **202**	H

201 (69%)
202 (83%)

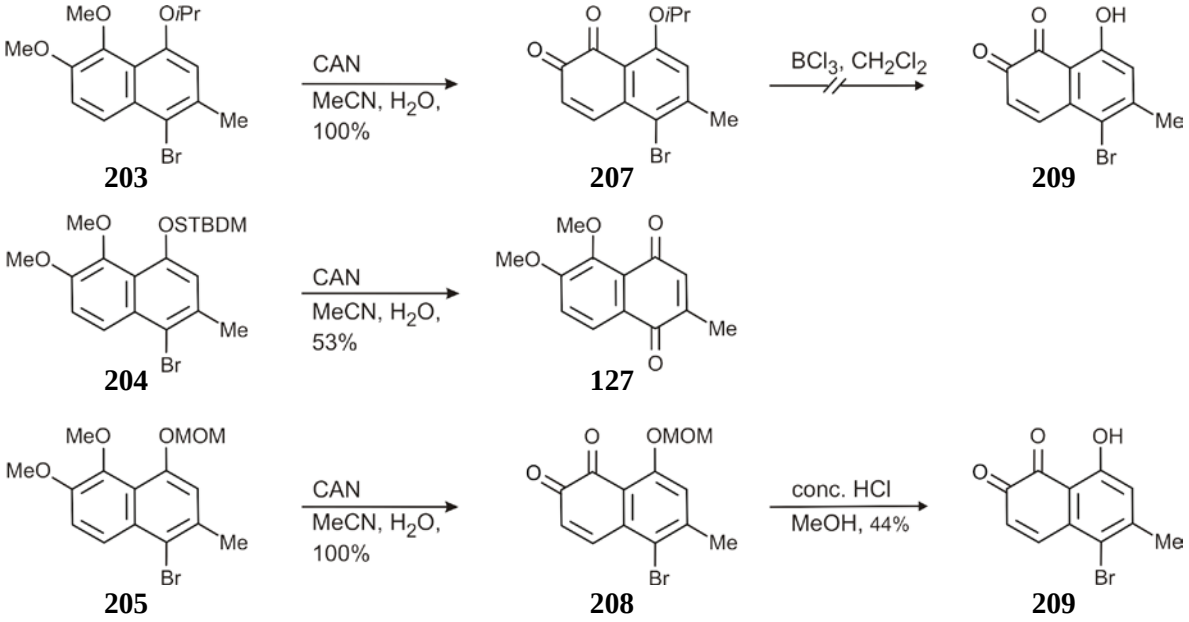
42 (99%)
200 (97%)

	X	R
203:	OMe	*i*-Pr (49% from **201**)
204:	OMe	Si*t*-BuMe$_2$ (94% from **201**)
205:	OMe	MOM (95% from **201**)
206:	H	MOM (80% from **202**)

Scheme 22. Synthesis of the bromonaphthalenes **203**–**206**. Reagents, conditions, and yields; i: **203**, *i*Pr-I, NaH, THF/DMF, rt; **204**, TBDMSCl, imidazole, DMF, 60 °C; **205**, MOMCl, NaH, THF/DMF, rt; **206**, MOMCl, NaH, THF/DMF, rt.

Another problem was the choice of suitable protecting groups for **201** and **202** compatible with the subsequent three reactions: a) the Suzuki-Miyaura coupling reaction, b) transformation of the two methoxy groups at the *ortho*-position of **188** into a 1,2-diketone, and c) removal of the protecting groups. Thus, the naphthol **201** was *O*-derivatized with isopropyl (*i*-Pr), *tert*-butyldimethylsilyl (TBDMS), or methoxylmethyl (MOM) groups to give the corresponding *O*-protected naphthols **203**, **204**, or **205**.

Starting from the isopropyloxy[244] naphthalene **203** by using cerium (IV) ammonium nitrate (CAN)[245-249] in aqueous acetonitrile, the 1,2-naphthoquinone **207** was prepared in a quantitative yield. For cleaving the *O*-isopropyl group, BCl_3[250-252] was used, but unexpectedly no reaction was observed, probably due to the strong electron-withdrawing effect of the two carbonyl groups. The even stronger *O*-dealkylating reagent BBr_3, by contrast, led to decomposition. The oxidation reaction of the silyl ether protected[253-255] naphthol **204** using CAN afforded the known[99] 1,4-naphthoquinone **127**, instead. Treatment of the *O*-methoxymethyl-protected[241,256] intermediate **205** with CAN provided the 1,2-naphthoquinone **208**. Subsequently, the MOM group was successfully cleaved in 3% HCl–MeOH[256] affording the 1,2-quinone **209** (Scheme 23).



Scheme 23. Synthesis of the naphthoquinone **209**. Reagents, condition, and yields.

With a suitable protecting group in hands, compound **202** was converted into the corresponding MOM ether **206**. Compounds **205** and **206** were used to prepare the pinacol boronic esters **210** and **213**, boronic acids **211** and **214**, and iodides **212** and **215** according to known methods (Scheme 24).[234,241,242,257] The already optimized coupling conditions (entry 5, Table 8) were likewise applied on the coupling reactions between **210** and **206**, **210** and **215**, **211** and **206**, **211** and **215**, **213** and **205**, **213** and **212**, **214** and **205**, and **214** and **212**. However, only dehalogenated and deboronated products were formed and the desired dimer *rac*-**188** was not detected in any of these reactions. This may be due to the significantly increased electronic density of the two coupling partners as compared to that in the two simplified substrates in the model reaction. This assumption was also supported by the fact that highly oxygenated binaphthyls or biaryls with highly sterically hindered axes have never been prepared *via* Suzuki coupling reactions according to the literature investigations.

205: X = OMe
206: X = H

	X^1	X^2
210:	OMe	Bpin (80% from **205**)
211:	OMe	$B(OH)_2$ (92% from **205**)
212:	OMe	I (94% from **205**)
213:	H	Bpin (55% from **206**)
214:	H	$B(OH)_2$ (90% from **206**)
215:	H	I (92% from **206**)

Scheme 24. Synthesis of compounds **210**–**215**. Reagents, condition, and yields; i: **210**, K_2CO_3, bispinacolatodiboron, $Pd(PPh_3)_4$, DMF, 120 °C; **211**, $B(OMe)_3$, *n*-BuLi, THF, −78 °C; **212**, I_2, *n*-BuLi, THF, −78 °C; **213**, K_2CO_3, bispinacolatodiboron, $Pd(dppf)Cl_2 \cdot DCM$, toluene/H_2O, 90 °C; **214**, $B(OMe)_3$, *n*-BuLi, THF, −78 °C; **215**, I_2, *n*-BuLi, THF, −78 °C.

10.4 Conclusion

The Buchwald's ligand **196** in combination with $Pd_2(dba)_3$ was proven to be a powerful catalyst system. Specifically, the coupling reaction conditions demonstrated an unprecedented activity and succeeded in the binaphthyls with extremely highly hindered axes (four *ortho* substituents) by a coupling reaction between the naphthyl bromide **191** and the naphthyl boron derivatives **193** or **194**. By contrast, it failed between the two still highly hindered, but electron-rich, coupling partners in the synthesis of *rac*-**188**, which could be due to the highly oxygenated (OMe/OMOM) coupling partners. Therefore, a more powerful catalyst system or an alternative synthetic strategy *e.g.*, a "lactone concept" had to be explored for the total synthesis of *rac*-**187**.

11 Cyclodysidins A–D, Cyclic Lipopeptides from the *Streptomyces* Strain RV15 Derived from a Marine Sponge

11.1 Cyclic Peptides from *Streptomyces* Strain

Bacteria-derived metabolites exhibit a wide variety of bioactivities, including anti-infective, anti-inflammatory, and anticancer activities and include structurally highly diverse natural products, among them polyketides, alkaloids, fatty acids, terpenes, and peptides.[17,258-260] Cyclic lipopeptides were previously isolated from different bacterial genera like e.g., *Streptomyces*, *Mycobacterium*, *Pseudomonas*, and *Bacillus*[261-264] and found to show antimicrobial and anticancer acitivities.[265-267] Prof. U. Hentschel's group further reported the phylogenetic identification of a *Streptomyces* strain RV15 associated with the sponge *Dysidea tupha*.[268] Here, the isolation and full structural elucidation of four new cyclic lipopeptides **216**–**219** (Figure 40) from this marine strain is described. This work was jointly done in cooperation with Dr. U. Abdelmohsen.[269]

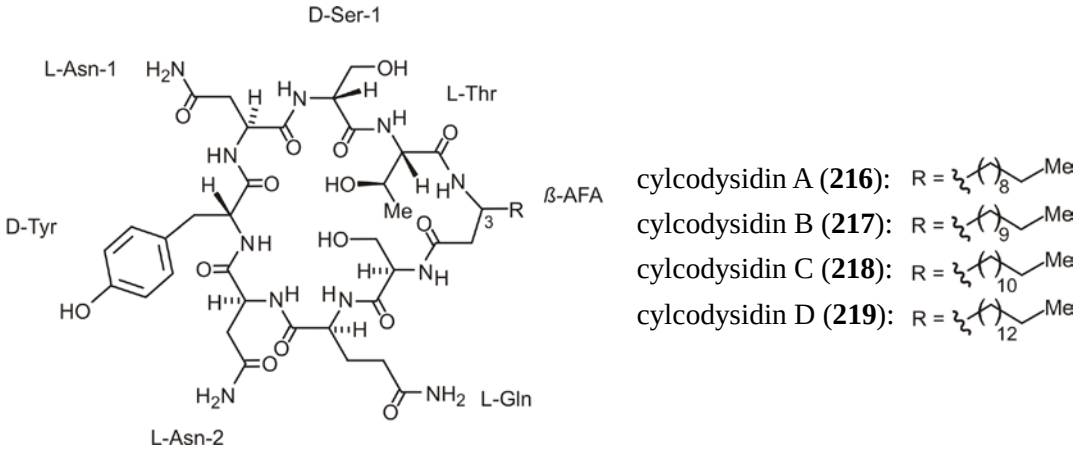


Figure 40. Structures of four new compounds **216**–**219**.

11.2 Results and Discussion

Cyclodysidin A showed a molecular formula of $C_{45}H_{71}N_{11}O_{15}$ by HR-ESIMS analysis (*m/z* 1006.5207 for $[M+1]^+$), with 16 degrees of unsaturation. The presence of several doublets and doublets of doublets at 4–5 ppm, attributed to α-protons of amino acids, and the characteristic chemical shifts for the amide carbonyls at 170–180 ppm suggest the peptidic nature of the molecule. In agreement with the possible occurrence of amide functionalities, the IR spectrum

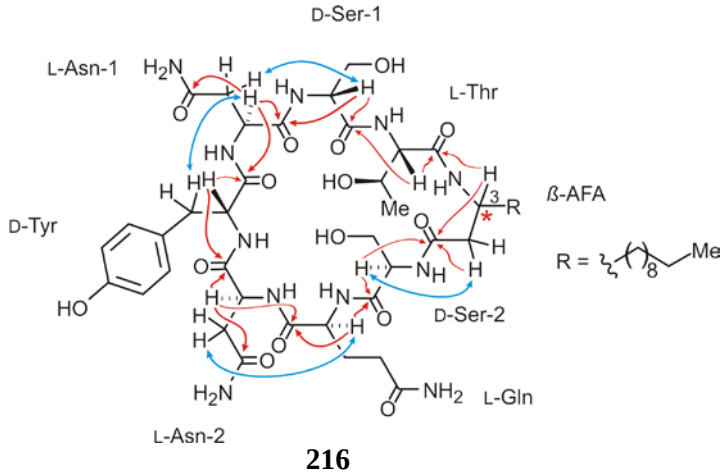
showed bands at 3345 and 1638 cm^{-1}. The compounds turned purple with ninhydrin reagent only upon hydrolysis with 6 M HCl, which gave a first hint at a cyclic structure.

The ^{13}C NMR spectrum displayed 11 ester/amide-type carbonyls (δ 172.4, 172.9, 173.0, 173.7, 174.1, 174.3, 174.4, 174.5, 174.9, 175.1, and 176.6), seven α-methine carbons (δ 52.3, 52.4, 55.6, 56.9, 57.2, 57.4, and 60.0), two primary carbinols (δ 62.3 and 62.4), a secondary carbinol (δ 67.3), aromatic signals for a di-substituted phenyl ring (131.3, 129.0, 157.3, and 116.4), and distinct signals at δ 23.6, 30.1–30.4, 35.7, and 14.4, which is consistent with a terminal hydrocarbon side chain supporting the presence of a lipopeptide metabolite. Analysis of the COSY, HSQC, ROESY, and HMBC data assigned seven partial structures (Table 8): two asparagine (Asn) units, one glutamine (Gln), two serine (Ser), one tyrosine (Tyr), and one threonine (Thr) moiety.

The COSY, HSQC, and HMBC experiments also correlated with a deshielded methylene (H-2, δ 2.43) and a deshielded methane signal (H-3, δ 4.13), contiguous methylene resonances (H4-5 to H11-12, δ 1.25–1.31, brs), and a terminal methyl signal (H-13, δ 0.88), delineating an amino fatty acid residue (β-AFA), which accounted for the presence of a β-aminotridecanoic acid fragment. HMBC correlations from each α-proton (β-proton in the case of β-aminotridecanoic acid) to the carbonyl carbon of the neighboring amino acid and to its own carbonyl carbon were detected. Since only 15 of the calculated 16 degrees of unsaturation accounted for the functionalities in the eight individual fragments, it became obvious that cyclodysidin A had a cyclic structure (Figure 41).

Table 9. NMR-spectroscopic data of cyclodysidin A (**216**) in methanol-d_4 (^{1}H: 600 MHz; ^{13}C: 150 MHz)

AA	δ_C	δ_H, mult	COSY (*J* in Hz)	HMBC	ROESY
Asn1					
CO	173.7				
α	52.4	4.65, dd	*β* (7.5, 6.4)	CO, *β*, *γ*, Tyr-CO	Tyr-*β*
β	37.1	2.76/2.72, m	*α*	CO, *α*, *γ*	
γ	174.9				
Asn2					
CO	174.3				
α	52.3	4.51, dd	*β* (7.9, 5.7)	CO, *β*, *γ*, Gln-CO	
β	37.4	2.52/2.44, m	*α*	CO, *α*, *γ*	Gln-*α*
γ	175.1				
Gln					
CO	174.1				
α	55.6	4.19, dd	*β* (8.3, 5.8)	CO, *β*, *γ*,	Asn2-*β*
β	27.1	2.17/2.10, m	*α*, *γ*	CO, *α*, *γ*, *δ*	
γ	32.9	2.47, m	*β*	*α*, *β*, *δ*	
δ	176.6				
Ser1					
CO	172.9				
α	57.4	4.37, t	*β* (5.6)	CO, β, Asn1-CO	Asn1-*β*
β	62.4	3.84, m	*α*	CO, α	Thr-*β*
Ser2					
CO	173.0				
α	57.2	4.31, t	*B* (5.3)	CO, *β*,	*β*-AFA-2
β	62.3	3.92, m	*α*	CO, *α*	
Thr					
CO	172.4				
α	60.0	4.28, d	*β* (2.6)	CO, *β*, *γ*,	
β	67.3	4.40, m	*α*, *γ*	CO, *α*, *γ*	Ser1-*β*
γ	20.4	1.16, d	*β* (6.5)	*α*, *β*	
Tyr					
CO	174.4				
α	56.9	4.46, dd	*β* (9.2, 4.8)	CO, *β*, Asn2-CO,	
β	36.4	3.14/2.85,	*α* (14.2,4.7)	CO, *α*, 1, 2, 6	Asn1-*α*
Bz-*I*	129.0				
Bz-*o*	131.3	7.06, d	Bz-*m* (8.5)	Bz-*I*, Bz-*m*, Bz-*p*	
Bz-*m*	116.4	6.71, d	Bz-*o* (8.4)	Bz-*I*, Bz-*o*, Bz-*p*	
Bz-*p*	157.3				
β-AFA					
CO	174.5				
2	42.1	2.43, m	3	CO, 3, 4	Ser2-*α*
3	48.8	4.14, m	2, 4	CO, 2, 4, Thr-CO	
4	35.7	1.5, m	3, 5-12	2, 3	
5-12	23.6-33.1	1.25-1.31,	4, 13	4, 13	
13	14.4	0.88, t	5-12 (7.1)	5-12	



216

Figure 41. Selected HMBC (red single arrows) and ROESY (blue double arrows) interactions indicative of the constitution of cyclodysidin A (**216**).

By using CID (collision-induced dissociation) MS/MS, sequence information was derived from the mass differences between the b-series ions[270] and between the *y*-series ions[270] (Table 10).

The sequential arrangement of amino acids was accomplished by interpretation of HMBC and ROESY data as well as fragmentation by CID-MS/MS. The structure of cyclodysidin A (**216**) was thus established as cyclo-(ß-AFA-Ser-Gln-Asn-Tyr-Asn-Ser-Thr).

In addition, three related compounds were isolated by reversed-phase HPLC, showing very similar chromatographic and spectroscopic properties, subsequently named cyclodysidins B (**217**), C (**218**), and D (**219**). By HR-ESIMS (TOF) analysis, compound **217** was found to possess a molecular formula of $C_{46}H_{73}N_{11}O_{15}$, metabolite **218** of $C_{47}H_{75}N_{11}O_{15}$, and peptide **219** of $C_{49}H_{79}N_{11}O_{15}$, i.e., each with 16 degrees of unsaturation. Thus, **217**–**219** were apparently higher homologs of **216**, differing from **216** by the presence of one or more additional CH_2 groups. In the NMR spectra the only differences between these four new metabolites were in the aliphatic part (δ 1.25–1.28 ppm), i.e., in the signals corresponding to hydrocarbon part of the β-amino fatty acid, which, despite a large signal overlap, suggested the same composition in the β-amino acid parts. The UV spectra of all compounds were nearly identical, indicating the same array of chromophores. By CID-MS/MS experiments, the connectivities of the amino acids, as qualitatively determined by NMR (see above), were established to be cyclo-(ß-AFA-Ser-Gln-Asn-Tyr-Asn-Ser-Thr) for all these new cyclic peptides (Figure 40). These compounds had not previously been isolated from other sources.

Table 10. Annotated MS fragments for cyclodysidin A (**216**)

Experimental (Da)	Predicted (Da)	Fragmentation	Sequence after first cleavage	Fragment after second cleavage
478.18	478.18	b/b4-1	NYNSTxSQ	NYNS
505.32	505.32	b/y4	QNYNSTxS	QNYN
583.23	583.24	b/z5+1	xSQNYNST	NYNST
642.39	642.38	b/y5-H2O	YNSTxSQN	TxSQN
787.42	787.43	b/b6-H2O	TxSQNYNS	TxSQNY
833.49	833.48	b6	TxSQNYNS	TxSQNY
849.53	849.46	b/a7-1	NYNSTxSQ	NYNSTxS
878.47	878.46	b/y7-H2O	QNYNSTxS	NYNSTxS
897.52	897.49	b/c7+2	NYNSTxSQ	NYNSTxS
919.52	919.49	b/y7-H2O	STxSQNYN	TxSQNYN
989.54	989.52	M-H2O+1		
1006.46	1006.52	M		

Except for the establishment of the constitution of the new metabolites **216**–**219**, the determination of absolute configurations of the constituting α- and *ß*- amino acids was achieved by the collaboration partners.[269]

11.3 Conclusion

In conclusion, cyclodysidins A–D (**216**–**219**), four new cyclic lipopeptides with α- and *ß*-amino acids, were isolated from the marine sponge-derived *Streptomyces* strain RV15. Their structures were established as cyclo-(*ß*-AFA-Ser-Gln-Asn-Tyr-Asn-Ser-Thr) by spectroscopic analysis using 2D NMR techniques and CID-MS/MS.

12 Summary

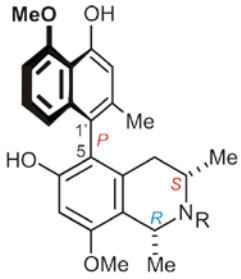
Plant-derived natural products and their analogs continue to play an important role in the discovery of new drugs for the treatment of human diseases. Potentially promising representatives of secondary metabolites are the naphthylisoquinoline alkaloids, which show a broad range of activities against protozoan pathogens, such as plasmodia, leishmania, and trypanosoma. Due to the increasing resistance of those pathogens against current therapies, highly potent novel agents are still urgently needed. Thus, it is worthy to discover new naphthylisoquinoline alkaloids hopefully with pronounced bioactivities by isolation from plants or by synthesis.

The naphthylisoquinoline alkaloids are biosynthetically related to another class of plant-derived products, the naphthoquinones, some of which have been recently found to display excellent anti-multiple myeloma activities without showing any cytotoxicities on normal blood cells. Multiple myeloma still remains incurable, although remissions may be induced with co-opted therapeutic treatments. Therefore, more potent naphthoquinones are urgently required, and can be obtained by isolation from plants or by synthesis.

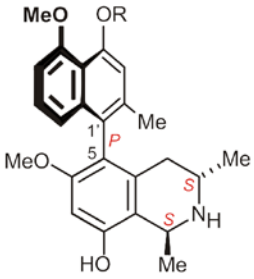
In detail, the results in this thesis are listed as follows:

1) Isolation and characterization of naphthylisoquinoline alkaloids from the stems of a Chinese *Ancistrocladus tectorius* species.

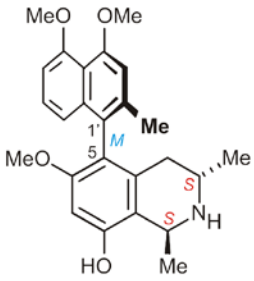
- Nine new naphthylisoquinoline alkaloids, named ancistectorine A_1 (**60**), *N*-methylancistectorine A_1 (**61**), ancistectorine A_2 (**62a**), 5-*epi*-ancistectorine A_2 (**62b**), 4'-*O*-demethylancistectorine A_2 (**63**), ancistectorine A_3 (**64**), ancistectorine B_1 (**65**), ancistectorine C_1 (**66**), and 5-*epi*-ancistrolikokine D (**67**) were isolated from the Chinese *A. tectorius* and fully characterized by chemical, spectroscopic, and chiroptical methods. Furthermore, the *in vitro* anti-infectious activities of **60**–**62** and **63**–**66** have been tested.



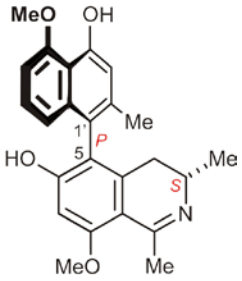
60: R = H
61: R = Me



62a: R = Me
63: R = H



62b



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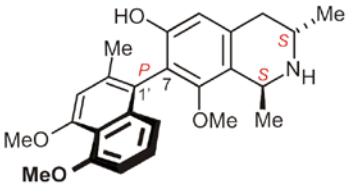
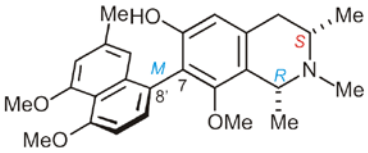
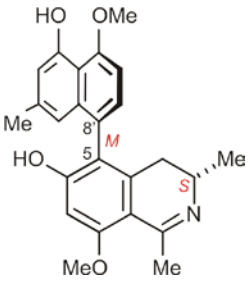


65



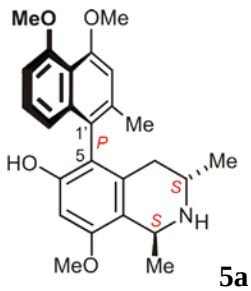
66



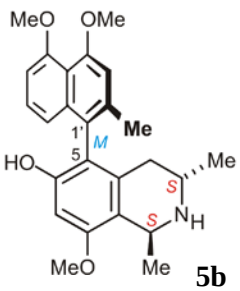
67

- Three of the metabolites, **61**, **62a**, and **62b**, exhibited strong antiplasmodial activities against the strain K1 of *P. falciparum* without showing significant cytotoxicities. With IC_{50} values of 0.08, 0.07, and 0.03 µM, respectively, they were 3–7 times more active than the standard chloroquine (IC_{50} = 0.26 µM). Moreover, these three compounds displayed high antiplasmodial selectivity indexes ranging from 100 to 3300. According to the TDR/WHO guidelines, they could be considered as lead compounds.

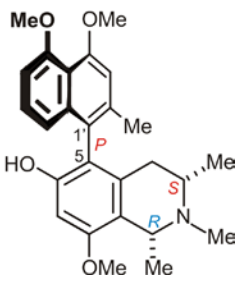
- In addition, seven alkaloids, **69**–**74** (structures not shown here), were isolated from *A. tectorius* that were known, but new to the plant, together with another fourteen known compounds (of these, only the structures of the three main alkaloids, **5a**, **5b**, and **78** are shown here), which had been previously found in the plant. The three metabolites ancistrocladine (**5a**), hamatine (**5b**), and (+)-ancistrocline (**78**) were found to show no or moderate activities against the MM cell lines.



5a



5b



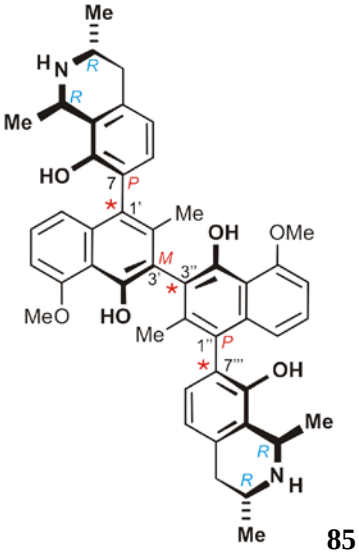
78

2) Isolation and characterization of naphthylisoquinoline alkaloids from the root bark of a new, botanically yet undescribed Congolese *Ancistrocladus* species.

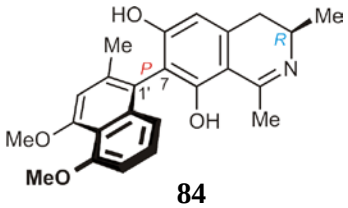
- An unprecedented dimeric Dioncophyllaceae-type naphthylisoquinoline alkaloid,

jozimine A_2 (**84**), as first recognized by G. Bauckmann from an as yet undescribed *Ancistrocladus* species, was purified and characterized as part of this thesis. Its full structural assignment was achieved by spectroscopic and chiroptical methods, and further confirmed by an X-ray diffraction analysis, which had never succeeded for any other dimeric naphthylisoquinoline alkaloids before. Structurally, the dimer is composed of two identical 4'-*O*-demethyldioncophylline A halves, coupled through a sterically hindered central axis at C-3',3" of the two naphthalene moieties. Pharmacologically, jozimine A_2 (**84**) showed an extraordinary antiplasmodial activity (IC_{50} = 1.4 nM) against the strain NF54 of *P. falciparum*.

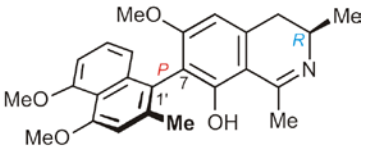
- Beside jozimine A_2 (**85**), another new alkaloid, 6-*O*-demethylancistrobrevine C (**84**), and four known ones, ancistrocladine (**5a**), hamatine (**5b**), ancistrobrevine C (**86**), and dioncophylline A (**6**) were isolated from the *Ancistrocladus* species, the latter in a large quantity (~500 mg), showing that the plant produces Ancistrocladaceae-type, mixed-Ancistrocladaceae/Dioncophyllaceae-type, and Dioncophyllaceae-type naphthyl-isoquinoline alkaloids. Remarkably, it is one of the very few plants, like *A. abbreviatus*, and *A. barteri*, that simultaneously contain typical representatives of all the above three classes of alkaloids.



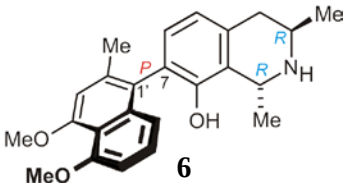
85



84



86

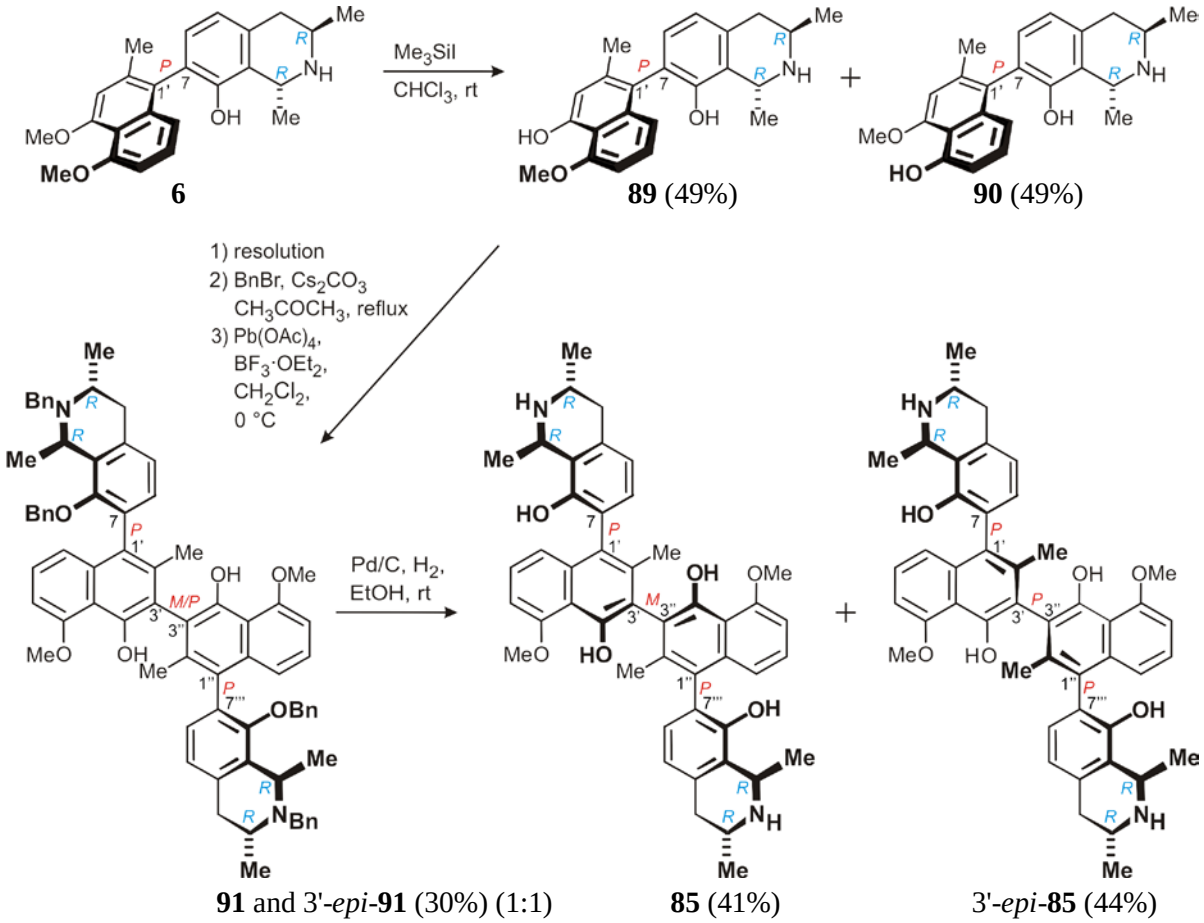


6

3) Semi-synthesis of jozimine A_2 (**85**), 3'-*epi*-**85**, jozimine A_3 (**93**) and other alkaloids from dioncophylline A (**6**).

- The dimeric naphthylisoquinoline alkaloids, jozimine A_2 (**85**) and 3'-*epi*-**85**, constitute rewarding synthetic targets for a comparative analysis of their antiplasmodial activities and for a further confirmation of the assigned absolute configurations of the isolated

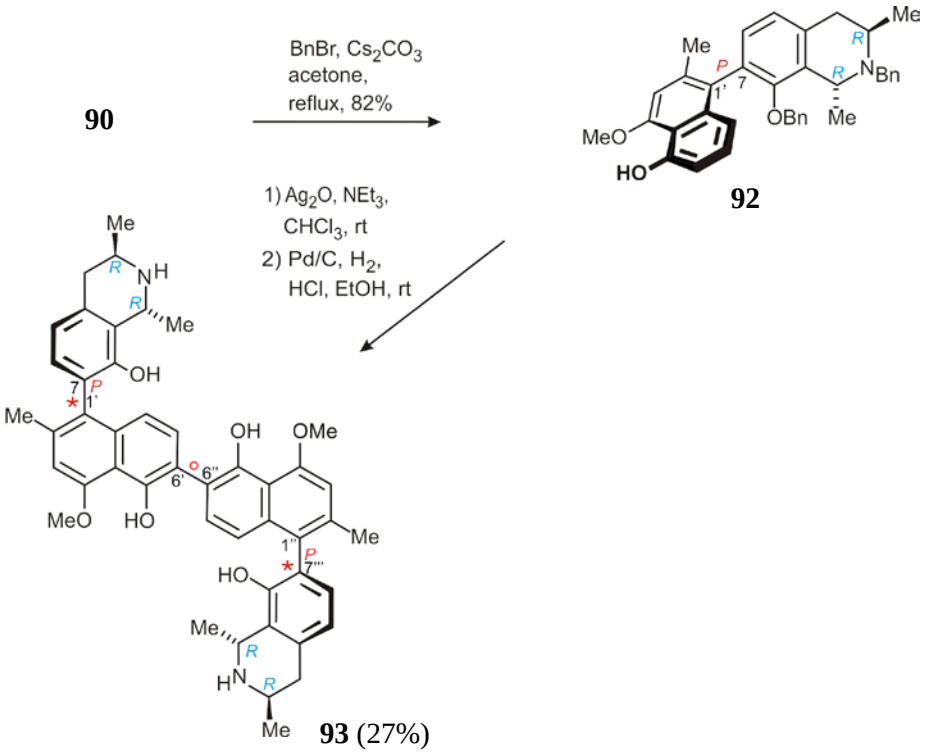
natural product of **85**. They were semi-synthesized in a four-step reaction sequence from dioncophylline A (**6**) in cooperation with T. Büttner. The key step was a biomimetic phenol-oxidative dimerization at C-3' of the *N*,*O*-dibenzylated derivative of **89** by utilizing $Pb(OAc)_4$. This is the first time that the synthesis of such an extremely sterically hindered (four *ortho*-substituents) naphthylisoquinoline alkaloid – with three consecutive biaryl axes! – has been successfully achieved.



6 → **89** (49%) + **90** (49%)

91 and 3'-*epi*-**91** (30%) (1:1) → **85** (41%) + 3'-*epi*-**85** (44%)

- A novel dimeric naphthylisoquinoline, jozimine A_3 (**93**), bearing a 6',6''-central biaryl axis, was semi-synthesized from 5'-*O*-demethyldioncophylline A (**90**) by a similar biomimetic phenol-oxidative coupling reaction as a key step, by employing Ag_2O.

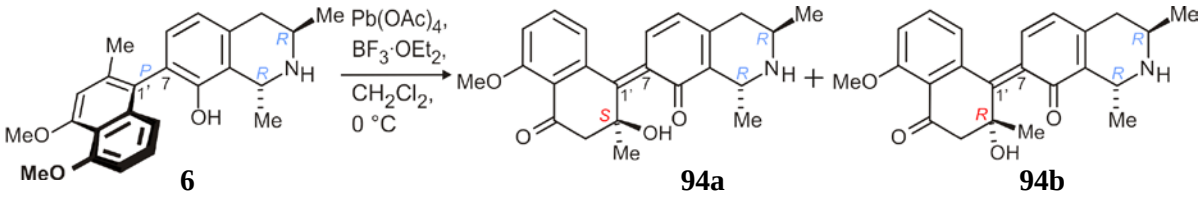


- HPLC analysis with synthetic reference material of 3'-*epi*-**85** and **93** for co-elution revealed that these two alkaloids clearly are not present in the crude extract of the *Ancistrocladus* species from which jozimine A_2 (**85**) was isolated. This evidences that jozimine A_2 (**85**) is very specifically biosynthesized by the plant with a high regio- and stereoslectivity.

- Remarkably, the two synthetic novel dimeric naphthylisoquinoline alkaloids 3'-*epi*-**85** and **93** were found to display very good antiplasmodial activities, albeit weaker than that of the natural and semi-synthetic product **85**. Additionally, the two compounds 3′-*epi*-**85** and **93** possessed high or moderate selectivity indexes, which were much lower than that of **85**. However, they can still be considered as new lead structures.

- Two unprecedented oxidative products of dioncophylline A, the diastereomeric dioncotetralones A (**94a**) and B (**94b**), were synthesized from dioncophylline A (**6**) in a one-step reaction. Remarkably, the aromatic properties in the “naphthalene” and the “isoquinoline” rings of **94a** and **94b** are partially lost and the “biaryl” axis has become a *C*,*C*-double bond, so that the two halves are nearly co-planar to each other, which has never been found among any natural or synthetic naphthylisoquinoline alkaloid. Their

full structural characterization was accomplished by spectroscopic methods and quantum-chemical CD calculations (done by Y. Hemberger). The presumed reaction mechanism was proposed in this thesis. In addition, one of the two compounds, **94a**, exhibited a highly antiplasmodial activity (IC_{50} = 0.09 µM) with low cytotoxicity, and thus, can be considered as a new promising lead structure. Its 2'-*epi*-isomer, **94b**, was inactive, evidencing a significant effect of chirality on the bioactivity.

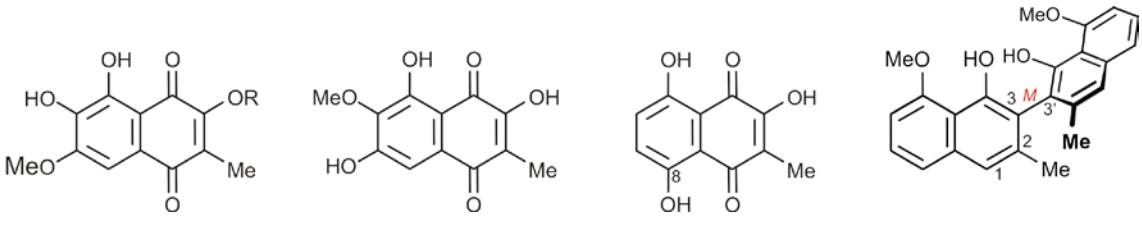


6 **94a** **94b**

- Of a number of naphthylisoquinoline alkaloids tested against the multiple-myeloma cell lines, the three compounds, dioncophylline A (**6**), 4'-*O*-demethyldioncophylline A (**89**), and 5'-*O*-demethyldioncophylline A (**90**) showed excellent activities, even much stronger than dioncoquinones B (**10**), C (**102**), the epoxide **175**, or the standard drug melphalan.

4) Isolation and characterization of bioactive naphthoquinones from cell cultures of *Triphyophyllum peltatum*.

- Three new naphthoquinones, dioncoquinones C (**102**), D (**103**), and E (**104**), the known 8-hydroxydroserone (**105**), which is new to this plant, and one new naphthol dimer, triphoquinol A (**107**), were isolated from cell cultures of *T. peltatum* in cooperation with A. Irmer. Dioncoquinone C (**102**) showed an excellent activity against the MM cells, very similar to that of the previously found dioncoquinone B (**10**), without showing any inhibitory effect on normal cells. The other three naphthoquinones, **103–105**, were inactive or only weakly active.

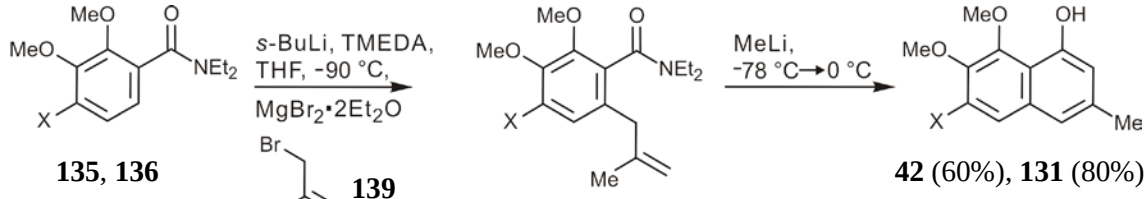


102: R = H
103: R = Me

104 **105** **107**

5) Establishment of a new strategy for a synthetic access to dioncoquinones B (**10**) and C (**102**) on a large scale for *in vivo* experiments and for the synthesis of their analogs for first SAR studies.

- Before the synthesis of dioncoquinone B (**10**) described in this thesis, two synthetic pathways had previously been established in our group. The third approach described here involved the preparation of the joint synthetic intermediate **42** with the previous two routes. The tertiary benzamide **135** was *ortho*-deprotonated by using *s*-BuLi/TMEDA, followed by transmetallation with $MgBr_2 \cdot 2Et_2O$, and reaction with 2-methylallyl bromide (**139**). It resulted in the formation of *ortho*-allyl benzamide **140**, which was cyclized by using methyl lithium to afford the naphthol **42**. This strategy proved to be the best among the established three approaches with regard to its very low number of steps and high yields. By starting with **136**, this third strategy yielded the related bioactive natural product, dioncoquinone C (**102**), which was accessed by total synthesis for the first time.



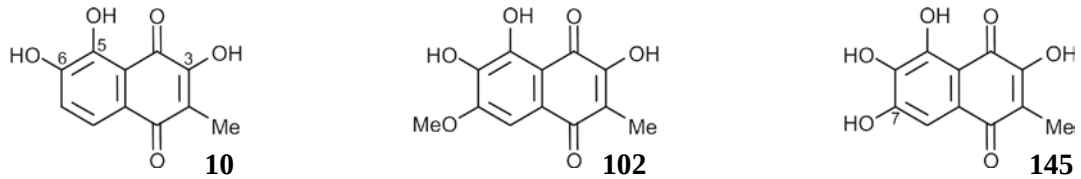
135, **136** **139**

140 (60%), **141** (45%)

42 (60%), **131** (80%)

	X
42, **135**, **140**	H
131, **136**, **141**	OMe

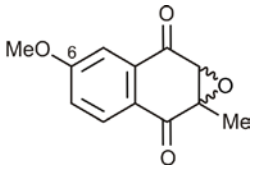
- To identify the pharmacophore of the antitumoral naphthoquinones, a library of dioncoquinone B (**10**) and C (**102**) analogs were synthesized for *in vitro* testing. Among the numerous naphthoquinones tested, the synthetic 7-*O*-demethyldioncoquinone C (or 7-*O*-hydroxyldioncoquinone B) (**145**), constitutes another promising basic structure to develop a new anti-MM agent. Furthermore, preliminary SAR results evidence that the three hydroxy functions at C-3, C-5, and C-6 are essential for the biological properties as exemplarily shown through the compounds **10**, **102**, and **145**. All other mixed OH/OMe- or completely OMe-substituted structures were entirely inactive.



10 **102** **145**

- By a serendipity the expoxide **175** was found to display the best anti-MM activity of all the tested isolated metabolites from *T. peltatum*, the synthesized naphthoquinones, and their synthetic intermediates. Toxic effects of **175** on normal cells were not observed, in contrast to the high toxicities of all other epoxides. Thus, the anti-MM activity of **175** is

of high selectivity. The preliminary SAR studies revealed that the 6-OMe group in **175** is required, thus differed with the above described naphthoquinones (where 6-OH is a requisite in **10**, **102**, and **145**), which evidenced potentially different modes of action for these two classes of compounds.



175

6) The first attempted total synthesis of the new naturally occurring triphoquinone (**187a**), which was recently isolated from the root cultures of *T. peltatum* in our group.

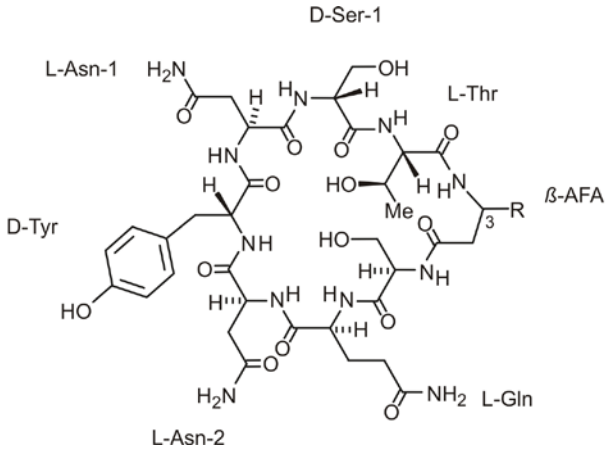
- A novel naphthoquinone-naphthalene dimer, **187a** (structure shown in Chapter 10), was isolated in small quantities from the root cultures of *T. peltatum*. Thus, its total synthesis was attempted for obtaining sufficient amounts for selected biotestings. The key step was planned to prepare the extremely sterically hindered (four *ortho*-substituents) binaphthalene **188** by a coupling reaction between the two 2-methylnaphthalene derivatives. Test reactions involving a system of two simplified 2-methylnaphthylboron species and 2-methylnaphthyl bromide proved the Buchwald ligand as most promising. The optimized conditions were then applied to the two true - highly oxygenated - coupling substrates, between the 2-methylnaphthylboron derivatives **210**, **211**, **213**, or **214** and the 2-methylnaphthyl iodides (or bromides) **215** (**206**), **215** (**206**), **212** (**205**), or **212** (**205**), respectively. Unfortunately, this crucial step failed although various bases and solvent systems were tested. This could be due to the high electron density of the two coupling substrates, both bearing strongly OMOM/OMe-donating function groups. Therefore, a more powerful catalyst system or an alternative synthetic strategy must be explored for the total synthesis of **187a**.

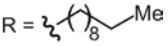
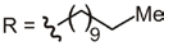
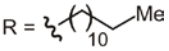
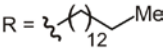
205: X = OMe
205: X = H

	X^1	X^2
210:	OMe	Bpin (80% from **205**)
211:	OMe	$B(OH)_2$ (92% from **205**)
212:	OMe	I (94% from **205**)
213:	H	Bpin (55% from **206**)
214:	H	$B(OH)_2$ (90% from **206**)
215:	H	I (92% from **206**)

7) Phytochemical investigation of the *Streptomyces* strain RV-15 derived from a marine sponge.

- Cyclodysidins A–D (**216**–**219**), four new cyclic lipopeptides with α- and ß-amino acids, were isolated from the *Streptomyces* strain RV15 derived from a marine sponge by Dr. U. Abdelmohsen. Their structures were established as cyclo-(ß-AFA-Ser-Gln-Asn-Tyr-Asn-Ser-Thr) by spectroscopic analysis using 2D NMR techniques and CID-MS/MS in the course of this thesis.



cylcodysidin A (**216**): R = 
cylcodysidin B (**217**): R = 
cylcodysidin C (**218**): R = 
cylcodysidin D (**219**): R = 

In conclusion, the present work contributes to the discovery of novel antiplasmodial naphthylisoquinoline alkaloids and antitumoral naphthoquinones, which will pave the way for future studies on these two classes of compounds.

13 Zusammenfassung

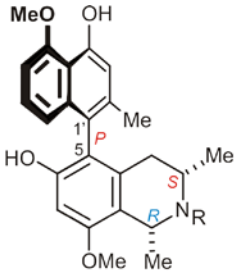
Naturstoffe pflanzlichen Ursprungs und deren Derivate waren seit jeher eine wichtige Quelle für die Entdeckung neuer Arzneistoffe. Darunter stellen die Naphthylisochinolin-Alkaloide eine besonders bedeutsame Klasse an Sekundärmetaboliten dar, die gegen eine breite Vielfalt an pathogenen Protozoen, wie z.B. Plasmodien, Leishmanien und Trypanosomen, aktiv sind. Die zunehmende Resistenz dieser Krankheitserreger gegen vorhandene Therapeutika macht die Erschließung neuer hochwirksamer Substanzen – durch direkte Isolierung aus Pflanzenmaterial oder chemische Synthese – zu einer lohnenswerten Aufgabe.

Kürzlich wurde entdeckt, dass Naphthochinone, eine biosynthetisch eng mit den Naphthylisochinolin-Alkaloiden verwandte Naturstoffklasse, exzellente Aktivitäten gegen das Multiple Myelom aufweist. Diese Krebserkrankung ist mit gegenwärtigen Arzneimitteln nicht heilbar, wenngleich unterstützende Therapeutika zu einer Remission führen können. Die Suche nach pharmakologisch wirksamen Naphthochinonen, mittels Isolierung aus Pflanzen oder durch chemische Synthese, ist daher dringend geboten.

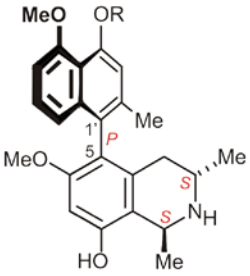
Die Ergebnisse dieser Arbeit umfassen im Detail die folgenden Teilbereiche:

1) Isolierung diverser Naphthylisochinolin-Alkaloide aus dem Stamm der chinesischen *Ancistrocladus tectorius* Spezies.

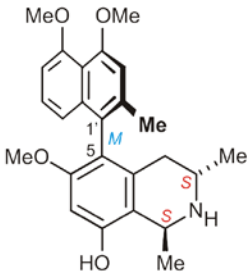
- Es Wurch neun neue Naphthylisochinlin-Alkaloide aus der in China beheimateten Pflanze *A. tectorius*. Diese umfassten die sechs 5,1'-gekuppelten Verbindungen Ancistectorin A_1 (**60**), *N*-Methylancistectorin A_1 (**61**), Ancistectorin A_2 (**62a**), 5-*epi*-Ancistectorin A_2 (**62b**), 4'-*O*-Demethylancistectorin A_2 (**63**), Ancistectorin A_3 (**64**), das 7,1'-gekuppelte Ancistectorin B_1 (**65**), das 7,8'-verknüpfte Ancistectorin C_1 (**66**), sowie das 5,8'-verknüpfte 5-*epi*-Ancistrolikokin D (**65**) die allesamt vollständig charakterisiert und auf ihre antiplasmodiale Aktivität untersucht wurden.



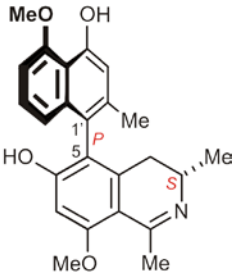
60: R = H
61: R = Me



62a: R = Me
63: R = H



62b



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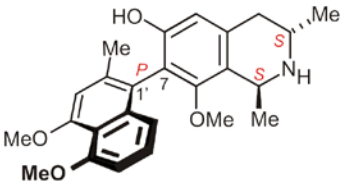
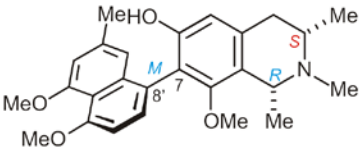
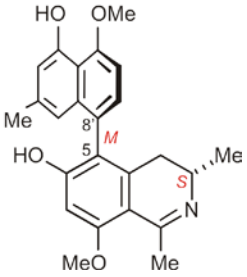


65



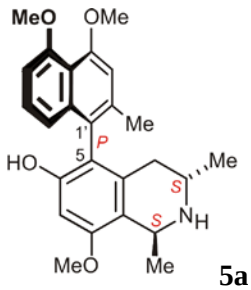
66



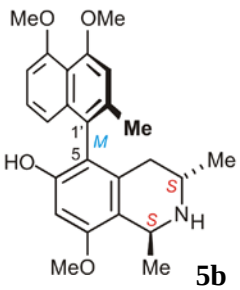
67

- Drei dieser Metabolite, **61**, **62a**, und **62b**, zeigten eine starke antiplasmodiale Aktivität gegen den Stamm K1 von *P. falciparum* und dennoch keine signifikante Cytotoxizität. Mit IC_{50}-Werten von 0.08, 0.07 und 0.03 µM waren sie 3–7 mal aktiver als der Standard Chloroquin (IC_{50} = 0.26 µM). Darüber hinaus verfügten diese drei Verbindungen über einen hohen antiplasmodialen Index von 100 bis 300. Laut WHO-Richtlinien können diese erfolgversprechenden Antimalaria-Wirkstoffe als neue Leitstrukturen angesehen werden.

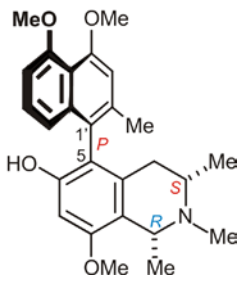
- Des Weiteren wurden sieben bekannte Alkaloide, **69**–**74** (nicht abgebildet), erstmals aus *A. tectorius* isoliert. 14 weitere, aus dieser Pflanze bereits bekannte, Verbindungen (z.B. **5a**, **5b**, und **78**) wurden ebenfalls gefunden. Die drei Hauptalkaloide Ancistrocladin (**5a**), Hamatin (**5b**) und (+)-Ancistroclin (**78**) hatten jedoch keine bzw. nur mäßige Aktivitäten gegen MM-Zelllinien.



5a



5b



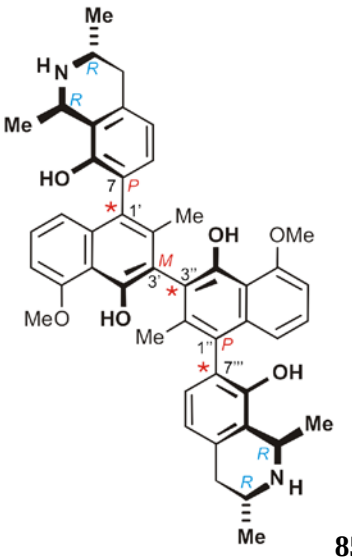
78

2) Isolierung der Naphthylisochinolin-Alkaloide aus der Stammrinde einer neuen und botanisch noch unbeschriebenen, kongolesichen *Ancistrocladus* Spezies.

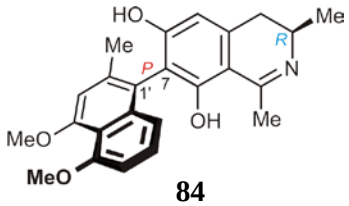
- Ein beispielloses dimeres Naphthylisochinolin-Alkaloid aus der Klasse der

Dioncophyllaceae, Jozimin A_2 (**85**), wurde aus einer bis dahin noch nicht beschriebenen *Ancistrocladus* Spezies in Zusammenarbeit mit G. Bauckmann isoliert. Mithilfe von spektroskopischen und chiroptischen Methoden erfolgte die vollständige Strukturaufklärung. Zum ersten Mal bei einem dimeren Naphthylisochinolin-Alkaloid wurde darüber hinaus dessen Struktur mittels Röntgenstrukturanalyse verifiziert. Die Struktur weist zwei identische miteinander verknüpfte 4'-*O*-Demethyldioncophyllin A Hälften auf, die in den Naphthalin-Einheiten an C-3' und C-3'' sterisch so stark gehindert sind, dass eine dritte rotationsstabile – und daher chirale – Achse vorliegt. Jozimin A_2 (**85**) ragt pharmakologisch betrachtet durch die beste bis dahin gemessene antiplasmodiale Aktivität (IC_{50} = 1.4 nM, *P. falciparum* NF54) aller natürlichen monomeren und dimeren Naphthylisochinoline heraus.

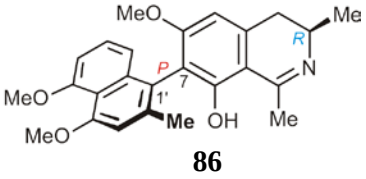
- Neben Jozimin A_2 (**85**) wurde ein weiteres neues Alkaloid, 6-*O*-Demethylancistrobrevin C (**84**), und die vier bekannten Monomere Ancistrocladin (**5a**), Hamatin (**5b**), Dioncophyllin A (**6**), und Ancistrobrevin C (**86**) aus dieser *Ancistrocladus* Spezies isoliert. Man konnte zeigen, dass die Pflanze Naphthylisochinolin-Alkaloide vom Ancistrocladaceae Typ, vom gemischten Ancistrocladaceae/Dioncophyllaceae Typ und vom Dioncophyllaceae Typ produziert. Dies ist umso bemerkenswerter, als dass nur wenige Pflanzen wie *A. abbreviatus* und *A. barteri* bekannt sind, die typische Vertreter aller drei Alkaloid-Klassen beinhalten.



85



84



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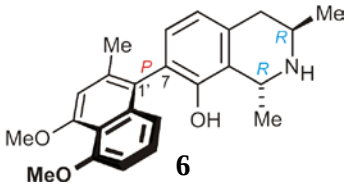
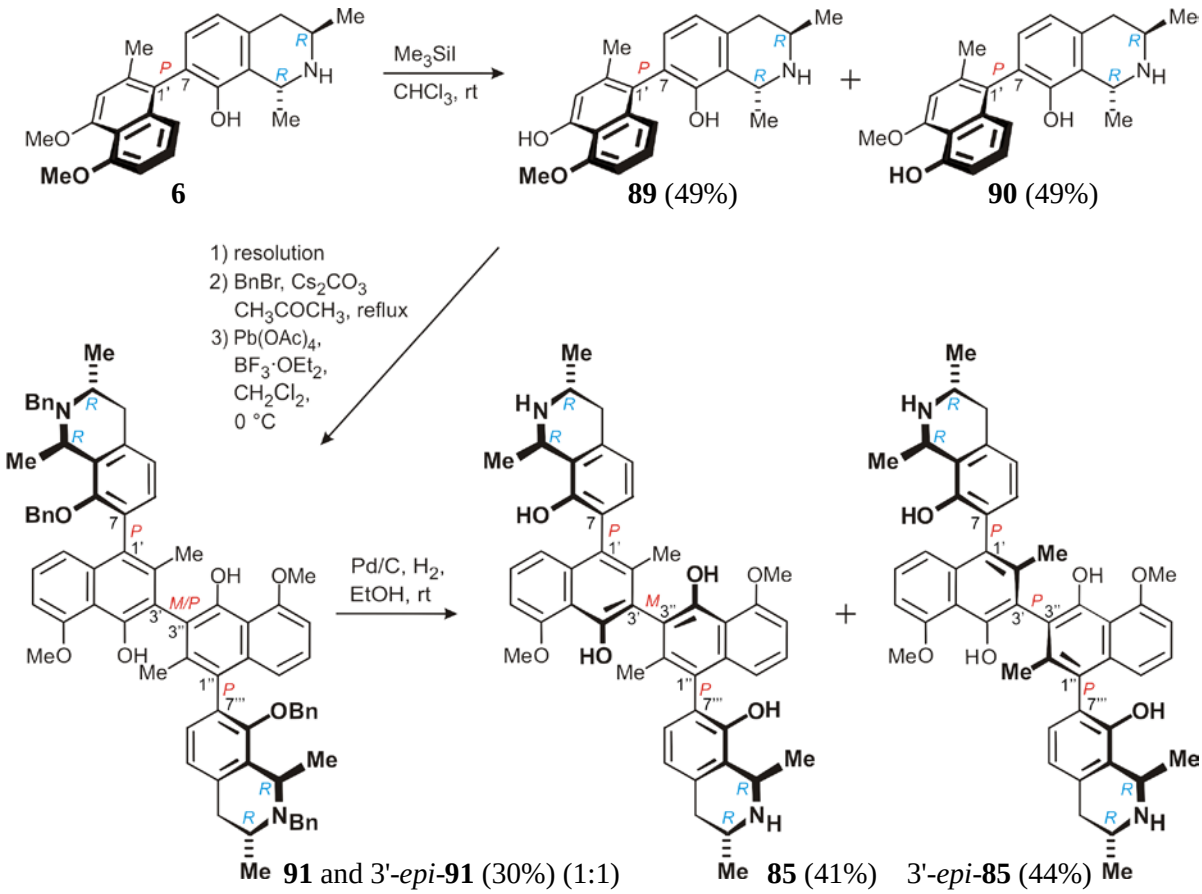


6

3) Semi-Synthese des dimeren Naphthylisochinolin-Alkaloids Jozimine A_2 (**85**) und seiner Derivate.

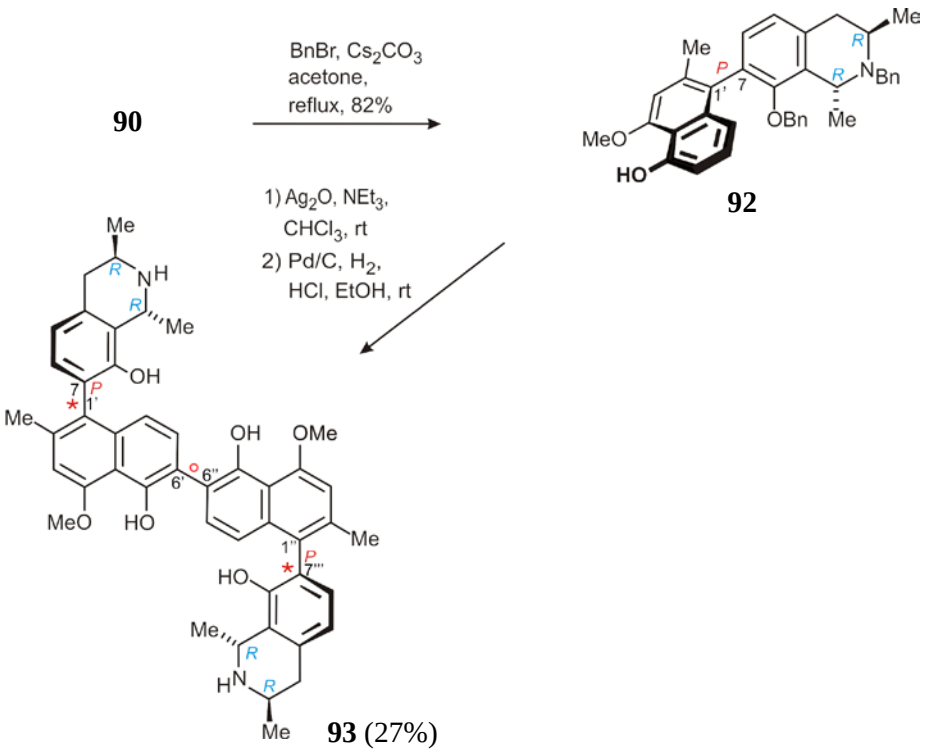
- Aufgrund seiner exzellenten antiplasmodialen Aktivität stellte das Naphthylisochinolin-Alkaloid Jozimin A_2 (**85**), eine lohneswerte Zielstruktur für eine Synthese dar. Die Verbindung wurde durch Semisynthese in vier Stufen aus Dioncophyllin A (**6**) in Zusammenarbeit mit T. Büttner erschlossen. Als Schlüsselschritt erwies sich die biomimetische, oxidative Kupplung von **89** an C-3' unter Verwendung von $Pb(OAc)_4$. Der Aufbau einer solch sterisch gehinderten, zentralen Achse mit vier *ortho*-Substituenten wurde zum ersten Mal an Naphthylisochinolin-Alkaloiden erfolgreich durchgeführt. Zusammen mit Jozimin A_2 (**85**) erhielt man sein 3',3''-Atropisomer 3′-*epi*-**85**.



6 **89** (49%) **90** (49%) **91** and 3'-*epi*-**91** (30%) (1:1) **85** (41%) 3'-*epi*-**85** (44%)

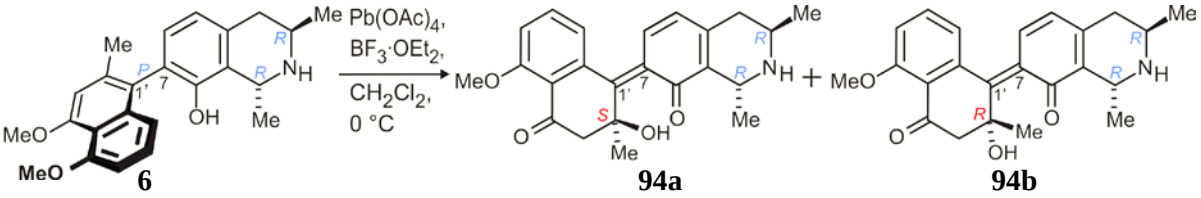
- Parallel dazu wurde Jozimine A_3 (**93**) dargestellt, dessen 6',6''-Zentral-Achse ebenfalls ausgehend von Dioncophyllin A (**6**) in einer Schlüsselsequenz mittels Ag_2O aufgebaut wurde.

- HPLC-Coelutionsexperimente der synthetisch erhaltenen Verbindungen 3'-*epi*-**85** und **93** zeigten zweifelsfrei, dass die beiden Alkaloide nicht im Rohextrakt der bisher unbestimmten *Ancistrocladus*-Art, aus welcher Jozimin A_2 (**85**) isoliert wurde, vorhanden waren. Die Biosynthese von **85** erfolgt in der Pflanze offensichtlich mit hoher Spezifität.



- Die neuen synthetisch hergestellten, dimeren Naphthylisochinolin-Alkaloide 3'-*epi*-**85** und **93** zeigten sehr gute, wenn auch im Vergleich zum natürlichen und semi-synthetisch erhaltenen **85** schwächere, antiplasmodiale Aktivitäten. Desweiteren besitzen die beiden Verbindungen 3′-*epi*-**85** und **93** hohe bzw. moderate Selektivitäts-Indices, welche allerdings weit unter dem Wert von **85** liegen. Nichtsdestotrotz können sie als neue Leitstrukturen betrachtet werden.

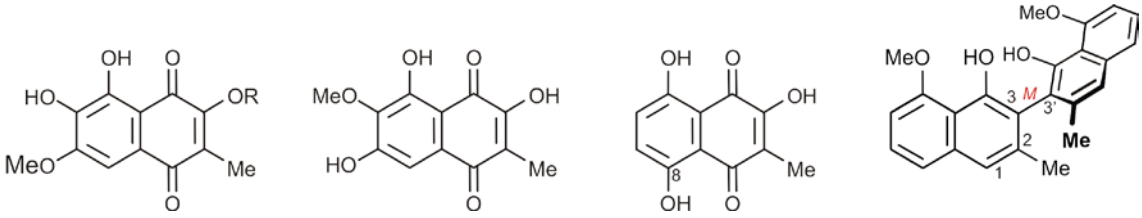
- Im Verlauf der Synthese von Jozimin A_2-Derivaten wurden des weiteren die zwei unbekannten Diastereoisomere, Dioncophynon A (**94a**) and B (**94b**), synthetisiert. Man erhielt diese in einer Stufe aus Dioncophyllin A (**6**). Die Strukturen von **94a** und **94b** zeichneten sich durch einen partiellen Verlust der Aromatizität am Naphthalin-Ring und eine *C,C*-Doppelbindung an der früheren Biarylachse aus. Die gefundenen Strukturmotive waren bis dahin weder von natürlichen noch von synthetischen Naphthylisochinolinen bekannt. Die vollständige Charakterisierung gelang durch spektroskopische Methoden und quantenchemische CD-Berechnungen (Y. Hemberger). Ein möglicher Mechanismus zur Bildung dieser Moleküle wurde ebenfalls in dieser Arbeit vorgestellt. Darüber hinaus zeigte eine dieser Verbindungen, **94a**, eine hohe antiplasmodiale Aktivität (IC_{50} = 0.09 µM) bei gleichzeitig nur geringer Toxizität und konnte daher als vielversprechende Leitstruktur betrachtet werden. Dagegen war **94b** inaktiv, was den signifikanten Effekt stereogener Elemente auf die Bioaktivität unterstrich.



- Aus einer ganzen Reihe von Naphthylisochinolin-Alkaloiden, die bzgl. ihrer Aktivität gegen das Multiple Myelom getestet wurden, zeigten v.a. drei Verbindungen, nämlich Dioncophyllin A (**6**), 4'-*O*-Demethyldioncophyllin A (**89**) und 5'-*O*-Demethyldioncophyllin A (**90**), exzellente Wirksamkeiten und übertrafen dabei sogar die Dioncochinone B (**10**) und C (**102**), das Epoxid **175** und die Referenzsubstanz Melphalan.

4) Isolierung der bioaktiven Naphthochinone aus Zellkulturen von *Triphyophyllum peltatum*.

- Drei neue Dioncochinone C (**102**), D (**103**) und E (**104**), das für diese Pflanze noch unbekannte 8-Hydroxydroseron (**105**) und ein neues Naphthalin-Dimer **107** wurden aus Zellkulturen von *T. peltatum* in Kooperation mit A. Irmer isoliert. Dioncochinon C (**102**) wies eine ausgezeichnete Aktivität gegen MM-Zellen, ähnlich zu der von Dioncochinon B, auf, wobei jedoch kein inhibierender Effekt auf normale Zellen beobachtet wurde. Die anderen drei Naphthochinone **103–105** waren inaktiv oder nur sehr schwach aktiv gegenüber MM-Zellen.



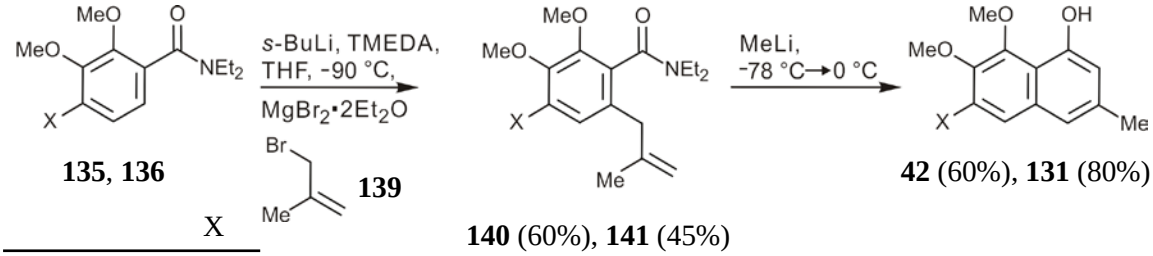
102: R = H
103: R = Me

104 **105** **107**

5) Etablierung neuer Strategien für einen Zugang zu den Dioncochinonen B und C im großen Maßstab für In-vivo-Biotests sowie Synthese von Dioncochinon B-Analoga für SAR-Untersuchungen.

- Vor Beginn dieser Arbeiten zur Synthese von Dioncochinon B (**10**) existierten bereits zwei, in unserem Arbeitskreis erschlossene, Synthesewege. Die hier beschriebene dritte Möglichkeit zur Darstellung von Dioncochinon B (**10**) etablierte einen neuen Zugang zu dem gemeinsamen Intermediat **42**. Man *ortho*-deprotonierte zunächst das tertiäre Amid **135** mit *sec*-BuLi/TMEDA, führte anschließend eine Transmetallierung mit

$MgBr_2 \cdot 2Et_2O$ durch und setzte das Intermediat mit 2-Methylallylbromid (**139**) zum *ortho*-Allylbenzamid **140** um, welches schließlich mit Methyllithium zum Naphthol **42** zyklisiert wurde. Diese Strategie war den beiden früheren Ansätzen hinsichtlich der hohen Ausbeute und der geringen Anzahl an Synthesestufen überlegen. Darauf aufbauend gelang die erste Totalsynthese des bioaktiven Naturstoffes Dioncochinon C (**102**).



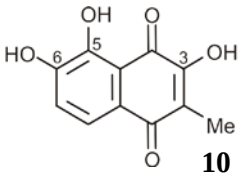
135, **136** **139**

140 (60%), **141** (45%)

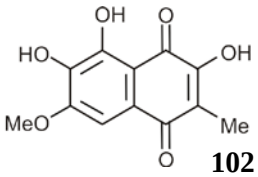
42 (60%), **131** (80%)

	X
42, **135**, **140**	H
131, **136**, **141**	OMe

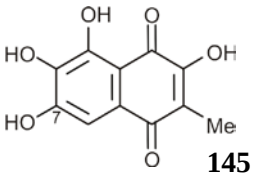
- Zur Untersuchung der Struktur-Wirkungs-Beziehung und zur Identifizierung des Pharmakophors der antitumoralen Naphthochinone wurden ca. 30 Analoga von Dioncochinon B (**10**) und C (**102**) synthetisiert und auf ihre Anti-MM-Wirkung getestet. Unter den zahlreichen dabei untersuchten Derivaten stellte die synthetische Verbindung 7-*O*-Demethyldioncochinon C (oder 7-*O*-Hydroxyldioncochinon B) (**145**) eine weitere vielversprechende Leitstruktur für die Entwicklung neuer Anti-MM-Kandidaten dar. Als besonders bemerkenswert erwiesen sich die antitumoralen Eigenschaften der Verbindungen **10**, **102**, und **145**. Diese besitzen drei Hydroxygruppen an C-3, C-5 und C-6, die für Ihre biologischen Eigenschaften essentiell zu sein scheinen, da alle anderen Strukturen mit einem gemischten OH/OMe-Muster und jene vollständig OMe-substituierten Verbindungen inaktiv waren..



10



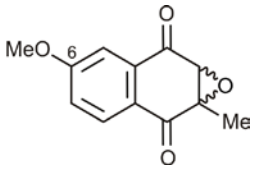
102



145

- Das Expoxid **175**, zeigte unter allen natürlich vorkommenden als auch synthetischen Naphthochinonen und deren Derivaten die beste Aktivität gegen das Multiple Myelom. Gleichzeitig wurde keine Toxizität gegenüber normalen Zellen festgestellt. Dies stand im Gegensatz zu anderen Epoxiden, die über recht hohe Toxizitäten verfügten, wenngleich bei sehr guten Anti-MM-Aktivitäten. Umso bemerkenswerter ist die hohe Selektivität von **175** gegenüber Multiple-Myelom-Zellen. Einleitende SAR Studien zu **175** zeigten, dass die O-Me-Gruppe unbedingt erforderlich ist. Dies lässt auf einen von den

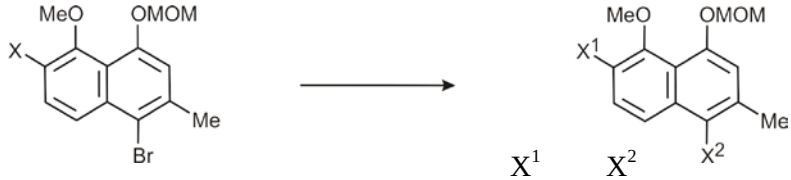
Naphthochinonen **10**, **102** und **145** verschiedenen Wirkmechanismus schließen, da die drei genannten Verbindungen an C-6 eine OH-Funktionalität tragen.



175

6) Die erste Totalsynthese eines neuen natürlichen Dimers aus *T. peltatum*, bestehend aus einer Naphthalin- und einer 1,2-Naphthochinon-Einheit.

- Man isolierte nur in Spuren ein neuartiges Naphthochinon-Naphthalin-Dimer **187a** aus Wurzelkulturen von *T. peltatum*. Die Totalsynthese von **187a** sollte deshalb ausreichende Mengen für ausgewählte Biotests verfügbar machen. Den Schlüsselschritt stellte die Kupplung von zwei sterisch sehr stark gehinderten 2-Methylnaphthalin-Ringen mit jeweils zwei *ortho*-Substituenten dar. Die Kupplung der 2-Methylnaphthylboronsäure -Derivate mit 2-Methylnaphthylbromid führte unter Verwendung des von Buchwald entwickelten Liganden **196**, $Pd_2(dba)_3$ und geeigneten Lösungsmitteln und Basen zum racemischen Produkt. Die für das oben beschriebene System optimierten Bedingungen wurden auf die beiden genuinen – hoch-oxygenierten – Substrate die 2-Methylnaphthyl boronsäure-Derivate **210**, **211**, **213**, oder **214** und 2-Methylnaphthyliodide (oder -bromide) **215** (**206**), **215** (**206**), **212** (**205**) oder **212** (**205**) angewandt. Leider führten zahlreiche Versuche unter Erprobung diverser Basen- und Lösungsmittelsysteme nicht zum Erfolg. Eine mögliche Erklärung liegt in der hohen Elektronendichte der beiden Kupplungspartner, die von den zwei bzw. drei Sauerstoffsubstituenten herrührt. Eine alternative Synthesestrategie oder der Einsatz eines leistungsfähigeren Katalysatorsystems muss deshalb zur Totalsynthese von **187a** in Erwägung gezogen werden.

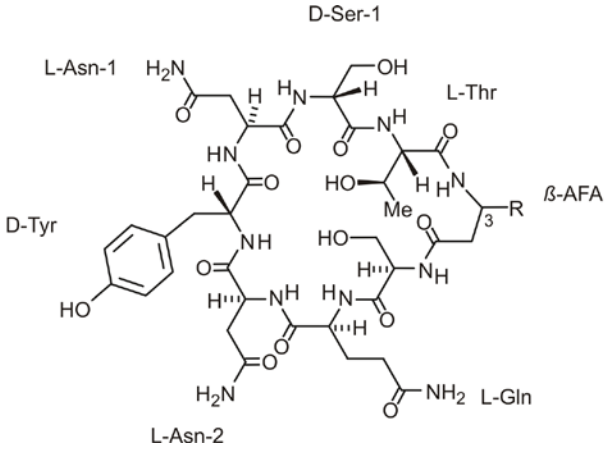


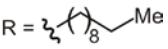
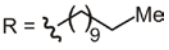
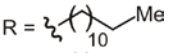
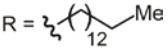
205: X = OMe
206: X = H

	X^1	X^2
210:	OMe	Bpin (80% from **205**)
211:	OMe	$B(OH)_2$ (92% from **205**)
212:	OMe	I (94% from **205**)
213:	H	Bpin (55% from **206**)
214:	H	$B(OH)_2$ (90% from **206**)
215:	H	I (92% from **206**)

7) Phytochemische Untersuchung des marinen *Streptomyces*-Stammes RV-15 aus Schwämmen.

- Die vier neuen cyclischen Lipopeptide Cyclodysidin A-D (**216**–**219**), welche sowohl aus - als auch - Aminosäuren aufgebaut sind, wurden aus RV-15, einem *Streptomyces*-Stamm, der mit Schwämmen vergesellschaft ist, isoliert. In Zusammenarbeit mit Dr. U. Abdelmohsen identifizierte man deren Struktur als Cyclo-(*ß*-AFA-Ser-Gln-Asn-Tyr-Asn-Ser-Thr) mithilfe von 2D-NMR-Spektroskopie und CID-MS/MS.



cylcodysidin A (**216**): R = 
cylcodysidin B (**217**): R = 
cylcodysidin C (**218**): R = 
cylcodysidin D (**219**): R = 

Experimental Section

1 General Aspects

1.1 Analytical Apparatuses

Melting point (*m.p.*): Melting points were recorded on a *Reichert-Jung* Thermovar-Kofler-Heiztisch microscope and are uncorrected.

Ultraviolet spectroscopy (*UV*): The UV-spectra were recorded at room temperature with a *Varian* Cary 50 Conc UV-Visible Spectrophotometer. The UV-spectra of solution media was measured as background. *Varian*-Cary-WinUV-Simple-scan-Application software was employed for processing of the measurements.

Infrared spectroscopy (*IR*): The IR spectra were determined on a *Jasco* FT/IR-410 spectrometer. The spectra were measured at room temperature. $\tilde{\nu}$ refers to the wavelength number. The intensity of the absorption bands is described by: s = strong, m = middle, w = weak, and br = broad.

Nuclear magnetic resonance spectroscopy (*^{1}H NMR, ^{13}C NMR*): The ^{1}H NMR (400 MHz, 600 MHz) and ^{13}C NMR (100 MHz, 150 MHz,) spectra were measured at room temperature on either an AMX 400 or on a DMX 600 spectrometer (both from Bruker). The chemical shifts of the signals are given in units on the δ-scale, with reference to $\delta_{TMS} = 0$. Calibration of the spectra was performed by means of an internal standard using the trace protons from the deuterated solvent, for ^{1}H NMR: $\delta(CDCl_3) = 7.26$; $\delta(CD_3OD) = 3.31$; δ(acetone-d_6) = 2.05; and for ^{13}C NMR: δ ($CDCl_3$) = 77.01; δ (CD_3OD) = 49.15; δ (acetone-d_6) = 29.82. Processing of the spectra was performed using XWIN-NMR-software from *Bruker*. Signal multiplicity is given using the following abbreviations: singlet = s, doublet = d, doublet of doublets = dd, triplet = t, doublet of triplets = dt, quartet = q, and multiplet = m. The coupling constants are described in Hertz (Hz), where ^nJ gives the number of bonds.

Mass spectrometry (*MS*): Electronic ionization (EI) and high-resolution electronic ionization (HREIMS) mass spectra were measured on a *Finnigan* MAT 8200 apparatus with an ionization potential of 70 eV. The bracketed numbers display the intensity of the signals relative to the base peak (I = 100%). Electrospray ionization (ESI) and high-resolution electrospray ionization HRMS (ESI) mass spectra were measured on a *Bruker Daltonics*

microTOF focus, for calculation of the respective mass values of the isotopic distribution, the software modul IsotopePattern of the software Compass 1.1 from *Bruker Daltonics* was used. HPLC-ESI-MS analyses were carried out on an *Agilent* 1100 Series System consisting of an HPLC pump, an MSD Ion Trap mass spectrometer (capillary temperature: 350 °C; ESI-voltage: 3500 V; N_2 as the heating gas), and a diode-array detector (DAD) (*all Agilent Technologies*).

X-ray diffraction analysis: The X-ray crystallography was carried out by Dr. Thomas Kupfer (Prof. Braunschweig's group) in the Institute of Inorganic Chemistry of the University of Würzburg. The crystal data was collected on a Bruker X8APEX diffractometer with a CCD area detector and multi-layer mirror monochromated Mo_K radiation. The structure was solved using direct methods, refined with the Shelx software package[271] and expanded using Fourier techniques. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the structure factors calculations. All hydrogen atoms were assigned to idealized geometric positions.

GC-MSD: For the GC-MSD analyses a *Hewlett Packard* 5890 II gas chromatography was utilized with a *Hewlett Packard* Ultra 2 (cross linked 5% Ph Me silicone 25 m × 0.32 mm × 0.52 µm Film) capillary column connected to a *Hewlett Packard* 59822B ionization gauge controller and a mass-selective detector called *Hewlett Packard* 5917A.

Optical rotation: The optical rotation values were recorded on a *Jasco* P-1020-polarimeter at the sodium-D-line (λ = 589 nm).

Circular dichroism (*CD*): The CD spectra were recorded at room temperature on a *Jasco* J-715 spectropolarimeter with quartz crystal cells. The CD spectra were measured 3 times in the interval from 200 nm to 600 nm using the software *Jasco*-Borwin Version 1.50 and processed with the *Jasco* spectra manager software. The differential absorptions coefficient $\varepsilon\Delta$[cm^2/mol] at different wavelengths λ [nm] was measured in the given solvent. For baseline correction a blank sample of eluent was measured.

1.2 Other Apparatuses

Plant material handling: Air-dried plant material was ground using a *Retsch*-SM1 impact mill with a wire netting of 1 mm hole size.

Freeze-drying: For freeze-drying a *Christ*-Alpha 1-4 equipped with a *vacUUbrand* RZ 8

high-vacuum pump was used.

Kryomat: For low-temperature reactions the desired temperature was achieved using a *Kryomat*-400.

Autoclave: Cultural medium and devices for aseptic works were sterilized with a Vari*clave* 500 E (Fa H+P Labortechnique GmbH) at 121 °C, 20 min and at 210 kPa.

1.3 Chromatographical Methods

Thin layer chromatography (*TLC*): All reactions were monitored by TLC controls using *Merck* aluminum foil silica gel 60 F_{254} plates. TLC control of substances containing basic nitrogen atoms was undertaken in an NH_3 atmosphere. To detect substances on the TLC plates, fluorescent light at either 254 nm or 365 nm, development in iodine chamber, and staining with 5% sulphuric acid in methanol and dried with hot air, Ekkards reagent, or Draggendorff reagent was used.

Column chromatography: The silica gel used was purchased from *Merck* (0.063–0.2 mm), for use with compounds containing nitrogen the silica gel was deactivated by addition of 7.5% (by mass) ammonia. For gel chromatography Sephadex LH-20 was used.

High-pressure liquid chromatography (*HPLC*): Analytical HPLC was performed using equipment from *Jasco*; pump PU-1580, degassing unit DG-1580, auto sampler AS-2055 Plus, mixer LG-1580, column oven CO-1560, diode-array detector MD-2010 Plus. Processing of the measurements was done using the Borwin software from *Jasco*. Unless otherwise noted the HPLC-UV, HPLC-MS experiments were carried out using a Symmetry-C_{18} column (*Waters*; 4.6 × 250 mm, 5 μm) with mobile phases consisting of H_2O + 0.05% TFA (A), MeCN + 0.05% TFA (B); flow rate: 1 mL min^{-1} or 0.8 mL min^{-1}. Preparative HPLC was performed using in an online connected a *Waters*-600E pump, a *Rheodyne*-7125i injector, and a *Waters*-996 diode-array detector. For processing of the measurements and controlling the Millenium Software Version 2.15 from *Waters* was employed. The chromatographical separations were performed on a SymmetryPrep-C_{18} column (*Waters*; 19 × 300 mm, 7 μm).

1.4 Chemicals

Solvents: All used solvents (methanol, acetone, dichloromethane, chloroform, ethyl acetate, *n*-hexane and petroleum ether 40–60 °C) were distilled. Water for the HPLC was purified

with *Millipore-Q*. Acetonitrile and methanol for the HPLC, UV, CD and specific rotation value measurement as well as trifluoroacetic acid were purchased from *Merck* without other purification procedures performed.

Other chemicals: For the preparation of the cultural medium, the used inorganic salts were purchased (if nothing else given) from *Sigma-Aldrich*, the organic materials (phytohormones, vitamins, Gelrite, etc.) from *Carl Roth* (Karlsruhe). All the other chemicals for synthesis were purchased from *Sigma-Aldrich*.

1.5 Cell Cultures of *T. peltatum*

General devices and processes: The pH value of the culture medium was adjusted to 5.8 using aqueous NaOH and HCl solutions, respectively. Each 100-mL Erlenmeyer flask containing a modified MS medium was covered with a cellulose stopper (Neolab Migge Laborbedarf-Vertriebs GmbH, Heidelberg), in addition with an aluminum cap, and then sterilization was carried out by 20-min autoclavation at 121 °C and 210 kPa. All used devices (tweezers, scalpel, scissors, pipettes) were sterilized likewise by autoclavation before use and by fire for several times during every application. For maintains and propagation, the calli were transferred to fresh solid medium every 2 months. The work under aseptic conditions was performed in a Laminar Flow Hood (Biohazard Laminar Flow Class II, Fa UniEquip lab equipment making).

Temperature and light: The cultures were kept constantly at 24 ± 2 °C. In winter this was guaranteed by a thermostat-regulated additional heating. The cultures were kept under fluorescent light with a 14-h photoperiod at 51 μM m^{-2} s^{-1} photosynthetically active radiation (Osram L58W/77 FLUORA in combination with Osram L58W/954 Lumilux de Luxe Daylight).

Medium: The content of the main nutrition elements in the modified MS medium[272] was reduced to 1/5 (20%), with the exception of the calcium and magnesium concentration, whose ratio was reduced to 1/4 (25%) of the original concentration. The modified medium had the following composition, which is shown in Table 11.

Table 11. Composition of the modified Murashige & Skoog medium (MS medium), which was used for the cell cultures of *T. peltatum*.

		modified MS-Medium [mg L^{-1}]
Inorganic mainnutrients	KNO_3	380
	NH_4NO_3	330
	KH_2PO_4	34
	$CaCl_2 \times 2\ H_2O$	88
	$MgSO_4 \times 7\ H_2O$	74
	$FeSO_4 \times 7\ H_2O$	27.8
	Na_2EDTA	37.3
Inorganic micronutrients	KI	0.83
	$MnSO_4 \times H_2O$	16.9
	H_3BO_3	6.2
	$ZnSO_4 \times 7\ H_2O$	10.59
	$Na_2MoO_4 \times 2\ H_2O$	0.25
	$CuSO_4 \times 5\ H_2O$	0.025
	$CoCl_2 \times 6\ H_2O$	0.025
Organic components	nicotinic acid	0.5
	thiamine × HCl	250
	pyridoxal × HCl	0.5
	myo-inositol	100
	glycine	2
	saccharose	30 000
	gelrite	3 500
Phytohormones	6-benzylaminopurine (BAP)	2
	1-naphthylacetic acid (NAA)	0.1

2 Phytochemical Investigation on *A. tectorius*

2.1 Extraction and Isolation

Air-dried twigs from the Chinese plant *A. tectorius* (1500 g) were ground and extracted with 95% EtOH at room temperature. The extract was concentrated in vacuum to give around 30 g of residue, which was dissolved in MeOH and filtered, subsequently submitted to fast centrifugal partition chromatography (FCPC) using a two-phase solvent system consisting of *n*-heptane/EtOAc/MeOH/H_2O (1:9:1:9). The lower phase served as the stationary phase (flow rate 10 mL min^{-1}, rotational speed 800 min^{-1}, ascending mode) to get rid of the high-polarity impurities. The total alkaloid part came out first with the mobile phase, then concentrated under reduced pressure to give a fraction of 10 g. After about 60 min, the stationary phase was flushed out in reversed mode by using MeOH. This 10 g raw extract were subjected to an open silica gel column chromatography with a gradient CH_2Cl_2/MeOH. The above work had been performed by Dr. M. Xu in our group. Four unresolved fractions were completed for further phytochemical research in the present thesis.

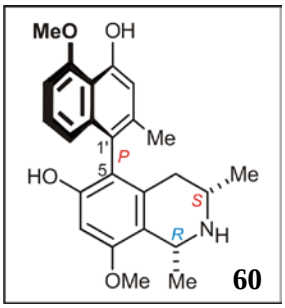
From the four fractions 29 alkaloids (see Table 12) were isolated using normal-phase column chromatography in combination with preparative HPLC on a Symmetry Prep C_{18} column (19 × 300 mm, 5 μm, *Waters*) and Chromolith Prep C_{18} column (4.6 × 50 mm, 5 μm, *Merck*) with a solvent system consisting of (A) H_2O (0.05% trifluoroacetic acid) and (B) MeOH (0.05% trifluoroacetic acid) or (A) H_2O (0.05% trifluoroacetic acid) and (B) CH_3CN (0.05% trifluoroacetic acid).

Table 12. The methods of isolation of 29 alkaloids from the Chinese plant A. *tectorius*.

L[a]	N[b]	N[c]	Gradient	T_R [min]	Mobile phase	Column
5,1′-	**5a**	1-2-1	25%-30%	20.0	CH_3CN/H_2O	Symmetry
	5b	1-1-1	5%-45%	6.2	CH_3CN/H_2O	Chromolith
	60	1-2-2	25%-30%	24.0	CH_3CN/H_2O	Symmetry
	61	4-2-2-1	15%-55%	25.0	CH_3CN/H_2O	Symmetry
	62a	2-4-1	25%-30%	23.4	CH_3CN/H_2O	Symmetry
	62b	2-3-1-1	30%-60%	32.7	CH_3OH/H_2O	Symmetry
	63	2-4-3-1	40%-67%	30.6	CH_3CN/H_2O	Symmetry
	64	2-4-4-2	25%-30%	29.4	CH_3CN/H_2O	Symmetry
	69	1-1-3	5%-45%	6.5	CH_3CN/H_2O	Chromolith
	70	2-4-4-1	25%-35%	29.0	CH_3CN/H_2O	Symmetry
	71	2-3-3	24%-29%	30.0	CH_3CN/H_2O	Symmetry
	75	4-4-5	15%-55%	26.0	CH_3CN/H_2O	Symmetry
	76	1-2-4	25%-30%	25.2	CH_3CN/H_2O	Symmetry
	77	4-4-7	15%-55%	28.0	CH_3CN/H_2O	Symmetry
	78	4-2-1	15%-50%	21.4	CH_3CN/H_2O	Symmetry
	79	4-6-10	15%-50%	17.3	CH_3CN/H_2O	Symmetry
	80	4-6-8-1	35%-60%	27.6	CH_3CN/H_2O	Symmetry
5,8′-	**67**	2-5-1	30%-45%	19.0	CH_3CN/H_2O	Symmetry
7,1′-	**72**	4-6-6b-2	15%-50%	28.5	CH_3CN/H_2O	Symmetry
	73	2-2-2	24%-29%	28.0	CH_3CN/H_2O	Symmetry
	74	4-2-2-2	15%-55%	26.2	CH_3CN/H_2O	Symmetry
	78	2-2-1	24%-29%	23.7	CH_3CN/H_2O	Symmetry
	81	4-6-8-2	15%-50%	29.3	CH_3CN/H_2O	Symmetry
7,3′-	**82**	2-5-2	30%-45%	20.7	CH_3CN/H_2O	Symmetry
7,8′-	**66**	3-2-2a	15%-55%	23.7	CH_3CN/H_2O	Symmetry
N,C-	**7**	3-6	30%-70%	26.9	CH_3CN/H_2O	Symmetry
	83	3-7	30%-70%	28.8	CH_3CN/H_2O	Symmetry

L[a]: linkage pattern. N[b]: the numbering of structures described in this thesis. N[c]: the code of structures described during the course of isolation.

2.2 Ancistectorine A_1 (**60**)



Colorless amorphous powder (3.0 mg).

M.p. 190 °C (MeOH).

$[\alpha]_D^{20}$ = +19.1 (*c* = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 308 (0.44), 321 (0.37), 337 (0.33) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+2.6), 210 (–7.3), 238 (+7.5), 287 (–0.8) nm.

IR (ATR): $\tilde{\nu}$ = 2524 (m), 1669 (m), 1612 (m), 1583 (m), 1428 (w), 1393 (w), 1356 (w), 1333 (w), 1259 (w), 1181 (m), 1129 (m), 1076 (m), 1014 (w), 964 (w), 941 (w), 836 (w), 799 (w) cm^{-1}.

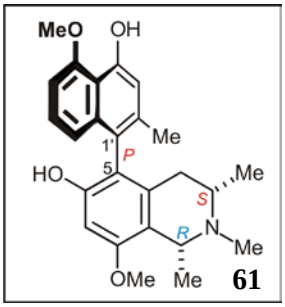
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.19 (3H, d, ^3J = 6.8 Hz, CH_3-3), 1.72 (3H, d, ^3J = 6.8 Hz, CH_3-1), 2.09 (1H, dd, ^2J = 15.8, ^3J = 3.4 Hz, H-4eq), 2.10 (3H, s, CH_3-2'), 2.28 (1H, dd, ^2J = 17.0, ^3J = 11.6 Hz, H-4ax), 3.20 (1H, m, H-3), 3.92 (3H, s, OCH_3-8), 4.08 (3H, s, OCH_3-5'), 4.68 (1H, q, ^3J = 7.2 Hz, H-1), 6.61 (1H, s, H-7), 6.75 (1H, dd, ^3J = 7.5, ^4J = 1.2 Hz, H-8'), 6.82 (1H, s, H-3'), 6.88 (1H, dd, ^3J = 7.5, ^4J = 1.2 Hz, H-6'), 7.19 (1H, dd, ^3J = 7.8, ^3J = 7.8 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.8 (CH_3-1), 20.3 (CH_3-3), 20.4 (CH_3-2'), 33.2 (C-4), 50.9 (C-3), 52.1 (C-1), 56.1 (OCH_3-8), 57.0 (OCH_3-5'), 99.4 (C-7), 104.9 (C-6'), 113.8 (C-3'), 114.6 (C-9), 115.2 (C-10'), 118.6 (C-5), 119.5 (C-8'), 123.5 (C-1'), 127.7 (C-7'), 135.0 (C-10), 137.1 (C-9'), 139.2 (C-2'), 155.4 (C-4'), 157.0 (C-6), 158.2 (C-5'), 158.7 (C-8) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 393 $[M]^+$ (3), 392 $[M–1]^+$ (7), 378 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd for $C_{24}H_{28}NO_4$, 394.2013 $[M+1]^+$; found 394.2012.

2.3 *N*-Methylancistectorine A_1 (**61**)



Colorless amorphous powder (3.0 mg).

M.p. 131 °C (MeOH).

$[\alpha]_D^{20}$ = +81.3 (*c* = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 210 (3.28), 285 (1.19), 334 (0.92) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+3.2), 210 (–6.8), 226 (–3.5), 238 (+4.4), 286 (–3.2) nm.

IR (ATR): $\tilde{\nu}$ = 2524 (m), 1669 (m), 1612 (m), 1583 (m), 1428 (w), 1393 (w), 1356 (w), 1333 (w), 1259 (w), 1181 (m), 1129 (m), 1076 (m), 1014 (w), 964 (w), 941 (w), 836 (w), 799 (w) cm^{-1}.

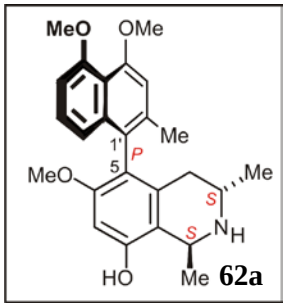
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.25 (3H, d, ^3J = 6.8 Hz, CH_3-3), 1.72 (3H, d, ^3J = 6.8 Hz, CH_3-1), 2.09 (3H, s, CH_3-2'), 2.17 (1H, dd, ^2J = 17.2, ^3J = 3.4 Hz, H-4eq), 2.40 (1H, dd, ^2J = 17.2, ^3J = 11.0 Hz, H-4ax), 3.01 (3H, s, CH_3-*N*), 3.20 (1H, m, H-3), 3.92 (3H, s, OCH_3-8), 4.08 (3H, s, OCH_3-5'), 4.68 (1H, q, ^3J = 7.2 Hz, H-1), 6.63 (1H, s, H-7), 6.75 (1H, dd, ^3J = 7.5, ^4J = 1.2 Hz, H-8'), 6.82 (1H, s, H-3'), 6.87 (1H, dd, ^3J = 7.5, ^4J = 1.2 Hz, H-6'), 7.19 (1H, dd, ^3J = 7.8, ^3J = 7.8 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.2 (CH_3-1), 20.1 (CH_3-3), 20.4 (CH_3-2'), 33.0 (C-4), 41.8 (CH_3-*N*), 56.2 (OCH_3-8), 56.9 (OCH_3-5'), 60.4 (C-3), 62.1 (C-1), 99.4 (C-7), 104.9 (C-6'), 113.8 (C-3'), 114.5 (C-9), 115.2 (C-10'), 118.3 (C-5), 119.6 (C-8'), 123.1 (C-1'), 127.7 (C-7'), 134.7 (C-10), 137.4 (C-9'), 139.4 (C-2'), 155.6 (C-4'), 157.4 (C-6), 157.9 (C-8), 158.3 (C-5') ppm.

MS (EI, 70 eV): *m*/*z* (%) = 407 $[M]^+$ (3), 406 $[M–1]^+$ (10), 392 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd for $C_{25}H_{30}NO_4$, 408.2169 $[M+1]^+$; found 408.2169.

2.4 Ancistectorine A_2 (**62a**)



62a

Colorless amorphous powder (3.1 mg).

M.p. 235 °C (MeOH).

$[\alpha]_D^{20}$ = –17.0 (*c* = 0.09, MeOH).

UV (MeOH): λ_{max} (logε) = 290 (0.61), 305 (0.61), 320 (0.49), 335 (0.42) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+13.2), 227 (–15.0), 240 (+6.9), 284 (–1.6) nm.

IR (ATR): $\tilde{\nu}$ = 3199 (w), 2989 (w), 2541 (w), 1666 (m), 1598 (m), 1583 (m), 1454 (w), 1390 (w), 1333 (w), 1259 (w), 1197 (m), 1126 (m), 1074 (m), 1044 (m), 1005 (w), 970 (w), 837 (w), 798 (w) cm^{-1}.

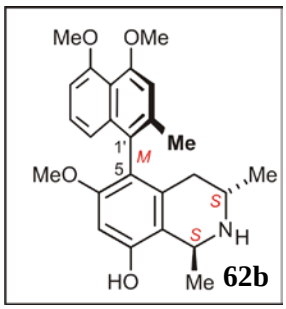
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.21 (3H, d, ^3J = 6.6 Hz, CH_3-3), 1.69 (3H, d, ^3J = 6.6 Hz, CH_3-1), 2.05 (3H, s, CH_3-2'), 2.15 (1H, dd, ^2J = 17.8, ^3J = 11.8 Hz, H-4ax), 2.26 (1H, dd, ^2J = 17.8, ^3J = 4.8 Hz, H-4eq), 3.58 (3H, s, OCH_3-6), 3.64 (1H, m, H-3), 3.92 (3H, s, OCH_3-5'), 3.96 (3H, s, OCH_3-4'), 4.79 (1H, q, ^3J = 6.8 Hz, H-1), 6.59 (1H, s, H-7), 6.79 (1H, dd, ^3J = 8.4, ^4J = 0.9 Hz, H-8'), 6.85 (1H, dd, ^3J = 8.4, ^4J = 0.9 Hz, H-6'), 6.89 (1H, s, H-3'), 7.19 (1H, dd, ^3J = 8.4, ^3J = 8.4 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.5 (CH_3-1), 19.3 (CH_3-3), 20.4 (CH_3-2'), 33.2 (C-4), 45.3 (C-3), 49.6 (C-1), 56.1 (OCH_3-6), 57.0 (OCH_3-5'), 57.2 (OCH_3-4'), 98.9 (C-7), 107.3 (C-6'), 110.6 (C-3'), 113.9 (C-9), 117.9 (C-10'), 118.8 (C-8'), 119.9 (C-5), 126.0 (C-1'), 127.9 (C-7'), 132.8 (C-10), 137.0 (C-2'), 137.8 (C-9'), 156.0 (C-8), 157.8 (C-4'), 158.9 (C-5'), 159.4 (C-6) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 407 $[M]^+$ (12), 406 $[M–1]^+$ (11), 392 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd for $C_{25}H_{30}NO_4$, 408.2169 $[M+1]^+$; found 408.2169.

2.5 5-*epi*-Ancistectorine A_2 (**62b**)



Colorless amorphous powder (1.9 mg).

M.p. 230 °C (MeOH).

$[\alpha]_D^{20}$ = +24.4 (*c* = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 290 (0.61), 305 (0.61), 320 (0.49), 335 (0.42) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (–16.6), 227 (+29.2), 240 (–13.6), 284 (+1.0) nm.

IR (ATR): $\tilde{\nu}$ = 2917 (w), 2535 (w), 1671 (m), 1598 (w), 1582 (w), 1498 (m), 1462 (w), 1390 (w), 1332 (w), 1259 (w), 1200 (m), 1126 (m), 1093 (m), 1073 (w), 1045 (w), 974 (w), 835 (w), 799 (w) cm^{-1}.

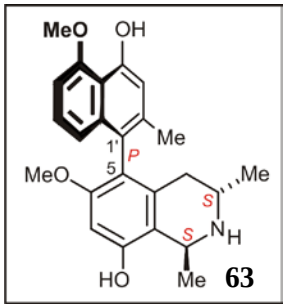
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.19 (3H, d, ^3J = 6.6 Hz, CH_3-3), 1.69 (3H, d, ^3J = 6.6 Hz, CH_3-1), 2.06 (1H, dd, ^2J = 16.8, ^3J = 10.4 Hz, H-4ax), 2.08 (3H, d, ^3J = 6.6 Hz, CH_3-2'), 2.37 (1H, dd, ^2J = 16.8, ^3J = 5.6 Hz, H-4eq), 3.68 (1H, m, H-3), 3.58 (3H, s, OCH_3-6), 3.92 (3H, s, OCH_3-5'), 3.95 (3H, s, OCH_3-4'), 4.80 (1H, q, ^3J = 7.2 Hz, H-1), 6.59 (1H, s, H-7), 6.71 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-8'), 6.85 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-6'), 6.90 (1H, s, H-3'), 7.16 (1H, dd, ^3J = 8.1, ^3J = 8.1 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.5 (CH_3-1), 19.3 (CH_3-3), 20.7 (CH_3-2'), 33.0 (C-4), 45.3 (C-3), 49.6 (C-1), 56.1 (OCH_3-6), 57.0 (OCH_3-4'), 57.1 (OCH_3-5'), 98.8 (C-7), 107.2 (C-6'), 110.6 (C-3'), 113.8 (C-9), 118.0 (C-10'), 119.0 (C-8'), 119.9 (C-5), 126.2 (C-1'), 127.7 (C-7'), 132.8 (C-10), 136.6 (C-2'), 137.9 (C-9'), 155.9 (C-8), 157.8 (C-4'), 158.9 (C-5'), 159.4 (C-6) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 407 $[M]^+$ (12), 406 $[M–1]^+$ (9), 392 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd for $C_{25}H_{30}NO_4$, 408.2169 $[M+1]^+$; found 408.2169.

2.6 4'-*O*-Demethylancistectorine A_2 (**63**)



Colorless amorphous powder (0.6 mg).

M.p. 181 °C (MeOH).

$[\alpha]_D^{20}$ = –15.1 (*c* = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 230 (2.20), 310 (0.40), 335 (0.29) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+12.5), 225 (–15.0), 239 (+7.7), 286 (–2.9) nm.

IR (ATR): $\tilde{\nu}$ = 2940 (w), 2532 (w), 1669 (m), 1629 (w), 1600 (w), 1577 (m), 1499 (w), 1428 (w), 1393 (w), 1367 (w), 1332 (w), 1256 (w),1180 (m), 1134 (m), 1081 (m), 1045 (w), 967 (w), 837 (w), 799 (w) cm^{-1}.

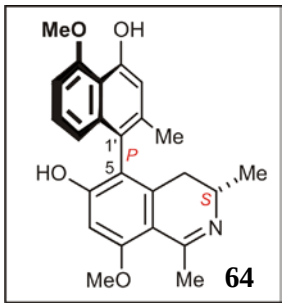
^{1}H NMR (CD_3OD, 600 MHz): δ = 1.21 (3H, d, ^3J = 6.6 Hz, CH_3-3), 1.68 (3H, d, ^3J = 6.6 Hz, CH_3-1), 2.00 (3H, s, CH_3-2'), 2.14 (1H, dd, ^2J = 17.8, ^3J = 11.6 Hz, H-4ax), 2.26 (1H, dd, ^2J = 16.8, ^3J = 5.0 Hz, H-4eq), 3.58 (3H, s, OCH_3-6), 3.63 (1H, m, H-3), 4.08 (3H, s, OCH_3-5'), 4.78 (1H, m, H-1), 6.58 (1H, s, H-7), 6.77 (1H, s, H-3'), 6.80 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-8'), 6.86 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-6'), 7.17 (1H, dd, ^3J = 8.1, ^3J = 8.1 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 18.5 (CH_3-1), 19.4 (CH_3-3), 20.3 (CH_3-2'), 33.2 (C-4), 45.2 (C-3), 49.7 (C-1), 56.1 (OCH_3-6), 56.9 (OCH_3-5'), 98.7 (C-7), 104.7 (C-6'), 113.7 (C-3'), 113.8 (C-9), 115.1 (C-10'), 119.6 (C-8'), 119.6 (C-5), 124.3 (C-1'), 127.4 (C-7'), 133.0 (C-10), 137.1 (C-9'), 138.2 (C-2'), 155.2 (C-4'), 156.0 (C-8), 158.1 (C-5'), 159.5 (C-6) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 393 $[M]^+$ (11), 392 $[M–1]^+$ (16), 378 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd. for $C_{24}H_{28}NO_4$ $[M+1]^+$: 394.2013; found 394.2012.

2.7 Ancistectorine A_3 (**64**)



Colorless amorphous powder (1.5 mg).

M.p. 140 °C (MeOH).

$[\alpha]_D^{20}$ = –146 (*c* = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 320 (0.48), 335 (0.49) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 208 (+20.6), 228 (–17.9), 244 (+8.6), 300 (–7.4), 338 (–9.4) nm.

IR (ATR): $\tilde{\nu}$ = 3388 (w), 3209 (w), 2981 (w), 1667 (m), 1628 (m), 1573 (m), 1508 (w), 1429 (w), 1395 (w), 1354 (w), 1321 (w), 1286 (w), 1260 (w), 1178 (s), 1127 (s), 1080 (s), 964 (w), 939 (w), 836 (m), 799 (m) cm^{-1}.

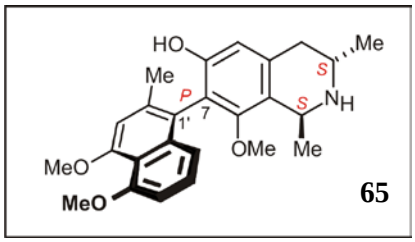
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.21 (3H, d, ^3J = 6.6 Hz, CH_3-3), 2.06 (3H, s, CH_3-2'), 2.30 (1H, dd, ^3J = 16.8, 10.4 Hz, H-4ax), 2.39 (1H, dd, ^2J = 16.8, ^3J = 5.6 Hz, H-4eq), 2.80 (3H, s, CH_3-1), 3.63 (1H, m, H-3), 4.04 (3H, s, OCH_3-8), 4.07 (3H, s, OCH_3-5'), 6.70 (1H, s, H-7), 6.80 (1H, s, H-3'), 6.82 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-8'), 6.88 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-6'), 7.22 (1H, dd, ^3J = 8.1, ^3J = 8.1 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.1 (CH_3-3), 20.4 (CH_3-2'), 24.9 (CH_3-1), 32.9 (C-4), 49.1 (C-3), 56.8 (OCH_3-8), 57.0 (OCH_3-5'), 99.5 (C-7), 105.0 (C-6'), 108.8 (C-9), 113.7 (C-3'), 115.2 (C-10'), 119.2 (C-8'), 121.1 (C-5), 122.0 (C-1'), 128.0 (C-7'), 137.0 (C-9'), 139.0 (C-2'), 142.8 (C-10), 156.0 (C-4'), 158.3 (C-5'), 166.0 (C-8), 167.7 (C-6), 175.6 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 392 $[M+1]^+$ (29), 391 $[M]^+$ (100), 376 $[M–15]^+$ (22).

HRESIMS *m*/*z* calcd for $C_{24}H_{26}NO_4$, 392.1856 $[M+1]^+$; found 392.1856.

2.8 Ancistectorine B_1 (**65**)



65

Colorless amorphous powder (10.1 mg).

M.p. 211 °C (MeOH).

$[\alpha]_D^{20}$ = +32.9 (*c* = 0.09, MeOH).

UV (MeOH): λ_{max} (logε) = 305 (0.55), 320 (0.45), 335 (0.37) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 205 (–9.2), 228 (+12.1), 247 (+0.5), 254 (+1.8), 284 (–2.8), 307 (+0.3) nm.

IR (ATR): $\tilde{\nu}$ = 3323 (w), 2938 (w), 2541 (m), 1666 (m), 1613 (w), 1584 (m), 1455 (w), 1392 (w), 1357 (w), 1336 (w), 1261 (w), 1188 (m), 1127 (m), 1093 (m), 1068 (w), 1014 (w), 975 (w), 934 (w), 898 (w), 836 (w), 798 (w) cm^{-1}.

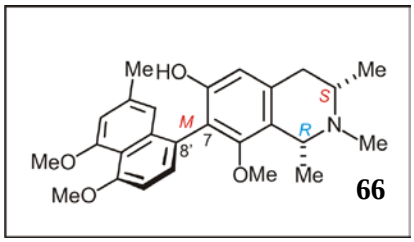
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.50 (3H, d, ^3J = 6.6 Hz, CH_3-3), 1.62 (3H, d, ^3J = 6.6 Hz, CH_3-1), 2.18 (3H, s, CH_3-2'), 2.86 (1H, dd, ^2J = 17.5, ^3J = 11.4 Hz, H-4ax), 3.12 (3H, s, CH_3O-8), 3.15 (1H, dd, ^2J = 17.5, ^3J = 4.8 Hz, H-4eq), 3.87 (1H, m, H-3), 3.91 (3H, s, OCH_3-5'), 3.95 (3H, s, OCH_3-4'), 4.72 (1H, q, ^3J = 6.8 Hz, H-1), 6.58 (1H, s, H-5), 6.85 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-6'), 6.89 (1H, dd, ^3J = 8.1, ^4J = 0.9 Hz, H-8'), 6.90 (1H, s, H-3'), 7.20 (1H, dd, ^3J = 8.1, ^3J = 8.1 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 19.4 (CH_3-3), 19.6 (CH_3-1), 21.0 (CH_3-2'), 34.6 (C-4), 45.3 (C-3), 49.9 (C-1), 57.0 (OCH_3-4'), 57.1 (OCH_3-5'), 60.4 (OCH_3-8), 107.2 (C-6'), 110.3 (C-3'), 111.5 (C-5), 117.9 (C-10'), 118.6 (C-9), 119.9 (C-7), 119.9 (C-8'), 123.7 (C-1'), 127.6 (C-7'), 133.2 (C-10), 137.6 (C-2'), 138.1 (C-9'), 157.3 (C-8), 157.6 (C-6), 158.3 (C-4'), 158.7 (C-5') ppm.

MS (EI, 70 eV): *m*/*z* (%) = 407 $[M]^+$ (9), 406 $[M–1]^+$ (11), 392 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd for $C_{25}H_{30}NO_4$, 408.2169 $[M+1]^+$; found 408.2169.

2.9 Ancistectorine C_1 (**66**)



Colorless amorphous powder (2.0 mg).

M.p. 161 °C (MeOH).

$[\alpha]_D^{20}$ = +5.9 (*c* = 0.09, MeOH).

UV (MeOH): λ_{max} (logε) = 210 (3.08), 305 (0.70) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 209 (+5.6), 216 (+2.0), 236 (–6.3), 284 (+1.57) nm.

IR (ATR): $\tilde{\nu}$ = 2957 (m), 2850 (w), 1682 (s), 1611 (s), 1585 (s), 1455 (w), 1413 (w), 1384 (w), 1322 (w), 1262 (w), 1171 (s), 1142 (w), 1093 (m), 1072 (m), 827 (m) cm^{-1}.

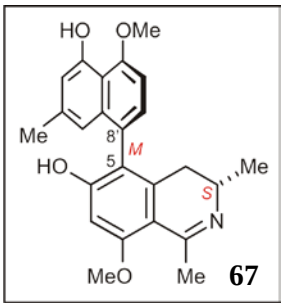
^{1}H NMR (CD_3OD, 400 MHz): δ = 1.60 (3H, d, ^3J = 6.6 Hz, CH_3-3), 1.74 (3H, d, ^3J = 6.6 Hz, CH_3-1), 2.32 (3H, s, CH_3-2'), 3.02 (2H, m, H-4), 3.07 (3H, s, CH_3-*N*), 3.15 (3H, s, CH_3O-8), 3.42 (1H, m, H-3), 3.93 (3H, s, OCH_3-4'), 3.96 (3H, s, OCH_3-5'), 4.62 (1H, q, ^3J =6.8 Hz, H-1), 6.62 (1H, s, H-5), 6.79 (1H, d, ^4J = 1.2 Hz, H-3'), 6.83 (1H, s, ^4J = 1.2 Hz, H-1'), 6.94 (1H, d, ^3J = 8.0 Hz, H-6'), 7.22 (1H, d, ^3J = 8.0 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.4 (CH_3-3), 20.9 (CH_3-1), 22.2 (CH_3-2'), 35.4 (C-4), 42.3 (CH_3-*N*), 56.9 (OCH_3-5'), 57.1 (OCH_3-4'), 61.1 (C-3), 61.2 (OCH_3-8), 62.6 (C-1), 106.5 (C-6'), 110.0 (C-3'), 111.4 (C-5), 117.6 (C-10'), 118.3 (C-9), 119.3 (C-1'), 122.0 (C-7), 124.6 (C-8'), 130.9 (C-7'), 134.7 (C-10), 137.7 (C-2'), 137.7 (C-9'), 157.8 (C-8), 157.8 (C-6), 158.7 (C-4'), 158.7 (C-5') ppm.

MS (EI, 70 eV): *m*/*z* (%) = 421 $[M]^+$ (2), 406 $[M–15]^+$ (100), 390 $[M–31]^+$ (6).

HRESIMS *m*/*z* calcd for $C_{26}H_{32}NO_4$, 422.2326 $[M+1]^+$; found 422.2326.

2.10 5-*epi*-Ancistrolikokine D (**67**)



67

Colorless amorphous powder (0.6 mg).

M.p. 168 °C (MeOH).

$[\alpha]_D^{20}$ = +33.2 (*c* = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 310 (0.47), 320 (0.47), 335 (0.46) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 214 (–6.0), 231 (+5.6), 250 (–2.9), 311 (+1.0), 321 (+1.4), 355 (+0.6) nm.

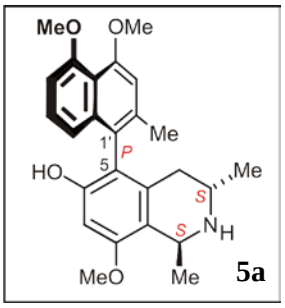
^{1}H NMR (CD_3OD, 600 MHz): δ = 1.20 (3H, d, ^3J = 6.6 Hz, CH_3-3), 2.26 (3H, s, CH_3-2'), 2.27 (1H, dd, ^2J = 17.8, ^3J = 10.2 Hz, H-4ax), 2.70 (1H, dd, ^2J = 17.8, ^3J = 5.2 Hz, H-4eq), 2.79 (3H, s, CH_3-1), 3.78 (1H, m, H-3), 4.04 (3H, s, OCH_3-8), 4.12 (3H, s, OCH_3-5'), 6.53 (1H, d, ^4J = 1.2 Hz, H-1'), 6.68 (1H, s, H-7), 6.68 (1H, d, ^4J = 1.2 Hz, H-3'), 6.95 (1H, d, ^3J = 8.4, H-6'), 7.14 (1H, d, ^3J = 8.4 Hz, H-7') ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 17.9 (CH_3-3), 22.0 (CH_3-2'), 25.0 (CH_3-1), 32.9 (C-4), 49.0 (C-3), 56.8 (OCH_3-8), 56.9 (OCH_3-5'), 99.3 (C-7), 104.5 (C-6'), 108.5 (C-9), 113.5 (C-3'), 114.9 (C-10'), 116.5 (C-1'), 122.5 (C-5), 126.1 (C-8'), 129.8 (C-7'), 137.2 (C-9'), 139.6 (C-2'), 142.7 (C-10), 156.3 (C-4'), 158.1 (C-5'), 165.9 (C-8), 167.8 (C-6), 175.5 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 392 $[M+1]^+$ (29), 391 $[M]^+$ (70), 376 $[M–15]^+$ (12), 188 $[M–15]^{2+}$ (12), 69 $[M–322]^+$ (100), 43 $[M–348]^+$ (37), 44 $[M–347]^+$ (74), 45 $[M–346]^+$ (99).

HRESIMS *m*/*z* calcd. for $C_{24}H_{26}NO_4$ $[M+1]^+$: 392.1856; found 392.1856.

2.11 Known Alkaloids



*Ancistrocladine (**5a**)*

Colorless amorphous solid (30.2 mg).

M.p. 260–263 °C (MeOH).
Lit.: 263–265 °C (MeOH).[146]

$[\alpha]_D^{20}$ = –15.4 (*c* = 0.08, MeOH).
Lit.: –19 (*c* = 0.10, MeOH).[273]
Lit.: –20 (*c* = 0.15, $CHCl_3$).[146]

UV (MeOH): λ_{max} (logε) = 307 (0.57), 322 (0.48), 337 (0.43) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+22.9), 226 (–23.3), 240 (+9.9), 284 (–1.5) nm.

IR (ATR): $\tilde{\nu}$ = 2979 (w), 1670 (w), 1585 (w), 1449 (w), 1392 (w), 1362 (w), 1337 (w), 1260 (w), 1200(w), 1127 (w), 1110 (w), 1077 (w), 833 (w), 798 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.21 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.65 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.10 (s, 3H, CH_3-2'), 2.15 (dd, ^2J = 17.2, ^3J = 11.2 Hz, 1H, H-4ax), 2.27 (dd, ^2J = 17.0, ^3J = 4.8 Hz, 1H, H-4eq), 3.60 (m, 1H, H-3), 3.90 (s, 3H, OCH_3-4'), 3.90 (s, 3H, OCH_3-8), 3.94 (s, 3H, OCH_3-5'), 4.78 (q, ^3J = 7.2 Hz, 1H, H-1), 6.61 (1H, s, H-7), 6.85 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-8'), 6.87 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 6.92 (s, 1H, H-3'), 7.22 (dd, ^3J = 7.9, ^3J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.8 (1-CH_3), 19.3 (3-CH_3), 20.4 (2'-CH_3), 33.2 (C-4), 45.1 (C-3), 49.2 (C-1), 56.2 (4'-OCH_3), 57.0 (8-OCH_3), 57.1 (5'-OCH_3), 98.9 (C-7), 107.4 (C-6'), 110.6 (C-3'), 114.7 (C-9), 117.9 (C-10'), 118.7 (C-5), 118.8 (C-8'), 125.2 (C-1'), 128.1 (C-7'), 133.0 (C-10), 137.7 (C-2'), 137.9 (C-9'), 157.0 (C-6), 157.8 (C-8), 158.0 (C-4'), 158.8 (C-5') ppm.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.65 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.10 (s, 3H, CH_3-2'), 2.15 (dd, ^2J = 17.2, ^3J = 11.2 Hz, 1H, Hax-4), 2.34 (dd, ^2J = 17.0, ^3J = 4.8 Hz, 1H, Heq-4), 3.47 (m, 1H, H-3), 3.90 (s, 3H, OCH_3-4'), 3.96 (s, 3H, OCH_3-8), 3.99 (s, 3H, OCH_3-5'), 4.81 (q, ^3J = 7.2 Hz, 1H, H-1), 6.56 (1H, s, H-7), 6.77 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 6.80 (s, 1H, H-3'), 6.86 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H,

H-8'), 7.24 (dd, ^{3}J = 7.9, ^{3}J = 8.1 Hz, 1H, H-7') ppm.

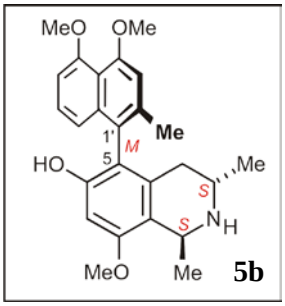
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.6 (1-CH_3), 18.7 (3-CH_3), 20.1 (2'-CH_3), 32.0 (C-4), 44.3 (C-3), 48.0 (C-1), 55.6 (4'-OCH_3), 56.4 (8-OCH_3), 56.6 (5'-OCH_3), 97.3 (C-7), 106.1 (C-6'), 109.2 (C-3'), 115.0 (C-9), 116.4 (C-5), 116.7 (C-10'), 116.9 (C-8'), 120.2 (C-1'), 127.8 (C-7'), 131.9 (C-10), 136.7 (C-9'), 138.9 (C-2'), 154.0 (C-6), 156.7 (C-8), 157.7 (C-4'), 157.8 (C-5') ppm.

MS (EI, 70 eV): *m/z* (%) = 407 $[M]^+$ (4), 406 $[M-1]^+$ (5), 392 $[M-15]^+$ (100).

HRMS (ESI): calcd. for $C_{25}H_{30}NO_4$ $[M+1]^+$: 408.2169; found 408.2169.

The spectroscopic data are in good agreement with those previously published.[130,146,273]

*Hamatine (**5b**)*



Colorless amorphous powder (20.5 mg).

M.p. 235–237 °C (MeOH).
Lit.: 240–242 °C (MeOH).[131]

$[\alpha]_D^{20}$ = +47.0 (*c* = 0.09, CH_3OH).
Lit.: +64.0 (*c* = 0.32, $CHCl_3$).[146]
Lit.: +77.0 (*c* = 0.86, $CHCl_3$).[132]

UV (MeOH): λ_{max} (logε) = 210 (3.43), 304 (0.59), 335 (0.37) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (–16.8), 228 (+25.6), 242 (–8.0), 284 (+0.7) nm.

IR (ATR): $\tilde{\nu}$ = 2517 (m), 1668 (w), 1584 (w), 1452 (w), 1392 (w), 1362 (w), 1338 (w), 1292 (w), 1260 (w), 1198(m), 1127 (m), 1110 (m), 1076 (w), 1013 (w), 971 (w), 833 (w), 810 (w), 798 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 600 MHz): δ = 1.19 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 1.62 (d, ^{3}J = 6.8 Hz, 3H, CH_3-1), 2.06 (dd, ^{2}J = 17.0, ^{3}J = 11.2 Hz, 1H, H-4ax), 2.15 (s, 3H, CH_3-2'), 2.27 (dd, ^{2}J = 17.0, ^{3}J = 5.1 Hz, 1H, H-4eq), 3.68 (m, 1H, H-3), 3.92 (s, 3H, OCH_3-8), 3.92 (s, 3H, OCH_3-5'), 3.96 (s, 3H, OCH_3-4'), 4.78 (q, ^{3}J = 7.2 Hz, 1H, H-1), 6.60 (1H, s, H-7), 6.78 (dd, ^{3}J = 8.4, ^{4}J = 1.2 Hz, 1H, H-8'), 6.86 (dd, ^{3}J = 8.4, ^{4}J = 1.2 Hz, 1H, H-6'), 6.93 (s, 1H,

H-3'), 7.19 (dd, ^{3}J = 7.9, ^{3}J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.8 (1-CH_3), 19.3 (3-CH_3), 20.7 (2'-CH_3), 33.0 (C-4), 45.1 (C-3), 49.2 (C-1), 56.2 (8-OCH_3), 57.0 (5'-OCH_3), 57.0 (4'-OCH_3), 98.9 (C-7), 107.2 (C-6'), 110.6 (C-3'), 114.5 (C-9), 118.0 (C-10'), 118.8 (C-5), 118.9 (C-8'), 125.2 (C-1'), 127.9 (C-7'), 133.0 (C-10), 137.2 (C-2'), 137.9 (C-9'), 157.1 (C-6), 157.8 (C-8), 158.1 (C-4'), 159.0 (C-5') ppm.

MS (EI, 70 eV): *m/z* (%) = 407 $[M]^+$ (4), 406 $[M-1]^+$ (4), 392 $[M-15]^+$ (100).

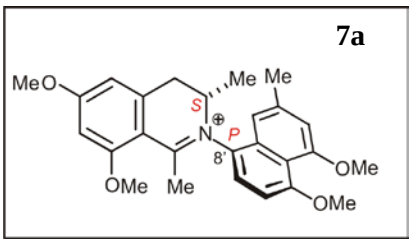
HRESIMS *m/z* calcd. for $C_{25}H_{30}NO_4$ $[M+1]^+$: 408.2169; found 408.2169.

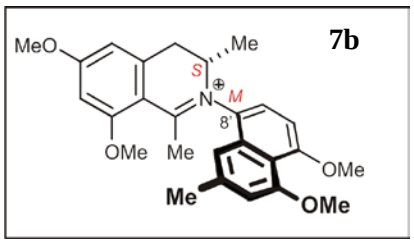
The spectroscopic data are in good agreement with those previously published.[131,132,146]

Ancistrocladinium A (7)

Pale-yellow amorphous powder (10.0 mg).

UV (MeOH): λ_{max} (logε) = 214 (2.73), 325(2.69), 335 (1.65) nm.





*P-Ancistrocladinium A (**7a**)*

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.21 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 2.47 (s, 3H, CH_3-1), 2.47 (s, 3H, CH_3-2'), 3.15 (dd, ^{2}J = 17.0, ^{3}J = 2.6 Hz, 1H, H-4eq), 3.65 (dd, ^{2}J = 17.0, ^{3}J = 6.4 Hz, 1H, H-4ax), 3.96 (s, 3H, OCH_3-4'), 4.00 (s, 3H, OCH_3-5'), 4.03 (s, 3H, OCH_3-6), 4.04 (s, 3H, OCH_3-8), 4.52 (m, 1H, H-3), 6.74 (d, ^{4}J = 2.2 Hz, 1H, H-7), 6.77 (d, ^{4}J = 2.2 Hz, 1H, H-5), 6.84 (d, ^{4}J = 1.0 Hz, 1H, H-1'), 6.94 (d, ^{3}J = 8.3 Hz, 1H, H-3'), 7.04 (d, ^{4}J = 1.0 Hz, H-6'), 7.60 (d, ^{3}J = 8.3 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 16.1 (3-CH_3), 22.3 (2'-CH_3), 24.4 (1-CH_3), 35.9 (C-4), 56.9 (4'-OCH_3), 57.0 (5'-OCH_3), 57.1 (6-OCH_3), 57.2 (8-OCH_3), 62.3 (C-3), 99.1 (C-7), 105.9 (C-6'), 108.9 (C-5), 110.9 (C-3'), 111.3 (C-9), 113.6 (C-1'), 117.4 (C-8'), 127.2 (C-7'), 130.9 (C-10'), 132.7 (C-9'), 141.7 (C-2'), 142.9 (C-10), 159.9 (C-4'), 160.9 (C-5'), 166.4 (C-8),

170.7 (C-6), 178.0 (C-1) ppm.

*M-Ancistrocladinium A (**7b**)*

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.31 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 2.51 (s, 3H, CH_3-2'), 2.52 (s, 3H, CH_3-1), 3.13 (dd, ^{2}J = 17.0, ^{3}J = 2.6 Hz, 1H, H-4eq), 3.82 (dd, ^{2}J = 17.0, ^{3}J = 6.4 Hz, 1H, H-4ax), 3.96 (s, 3H, OCH_3-4'), 4.00 (s, 3H, OCH_3-5'), 4.03 (s, 3H, OCH_3-6), 4.04 (s, 3H, OCH_3-8), 4.25 (m, 1H, H-3), 6.74 (d, ^{4}J = 2.2 Hz, 1H, H-7), 6.77 (d, ^{4}J = 2.2 Hz, 1H, H-5), 6.97 (d, ^{4}J = 1.0 Hz, 1H, H-3'), 6.98 (d, ^{3}J = 8.3 Hz, 1H, H-6'), 7.09 (d, ^{4}J = 1.0 Hz, 1H, H-1'), 7.46 (d, ^{3}J = 8.3 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 15.6 (3-CH_3), 22.3 (2'-CH_3), 24.8 (1-CH_3), 35.0 (C-4), 56.9 (4'-OCH_3), 57.0 (5'-OCH_3), 57.1 (6-OCH_3), 57.2 (8-OCH_3), 59.6 (C-3), 99.1 (C-7), 104.9 (C-6'), 109.4 (C-5), 111.2 (C-3'), 111.3 (C-9), 113.2 (C-1'), 118.1 (C-8'), 127.2 (C-7'), 129.9 (C-10'), 132.1 (C-9'), 142.0 (C-2'), 142.2 (C-10), 159.9 (C-4'), 161.0 (C-5'), 166.4 (C-8), 170.7 (C-6), 178.1 (C-1) ppm.

MS (EI, 70 eV): *m/z* (%) = 420 $[M]^+$ (9), 419 $[M-1]^+$ (15), 405 $[M-15]^+$ (26), 201 $[M-16]^{2+}$ (100).

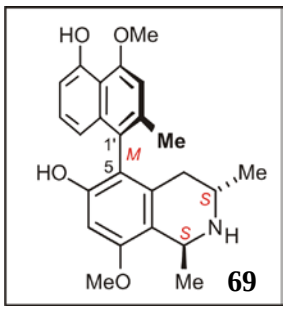
HRMS (ESI): calcd. for $C_{26}H_{30}NO_4$ $[M]^+$: 420.2175; found 420.2174.

The ratio of **7a** and **7b** is determined as *ca*. 1 : 4 by ^{1}H NMR spectroscopy.

The spectroscopic data are in good agreement with those previously published.[40]

*5'-O-Demethylhamatine (**69**)*

Colorless amorphous powder (20.0 mg).



M.p. 170–174 °C (MeOH).
Lit.: 174–180 °C (MeOH).[124]

$[\alpha]_D^{20}$ = +45.3 (c = 0.09, MeOH).
Lit.: +26 (c = 0.10, MeOH).[124]

UV (MeOH): λ_{max} (logε) = 307 (0.57), 322 (0.48), 337 (0.43) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (–13.3), 228 (+22.5), 239 (–8.6), 284 (+0.1) nm.

IR (ATR): $\tilde{\nu}$ = 2514 (w), 1669 (m), 1608 (w), 1427 (w), 1392 (w), 1362 (w), 1334 (w), 1198 (m), 1110 (m), 1077 (m), 1018 (w), 957 (w), 834 (w), 814 (w), 799 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.19 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.62 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.08 (dd, ^2J = 18.0, ^3J = 11.6 Hz, 1H, Hax-4), 2.13 (s, 3H, CH_3-2'), 2.38 (dd, ^2J = 18.0, ^3J = 4.9 Hz, 1H, Heq-4), 3.68 (m, 1H, H-3), 3.92 (s, 3H, OCH_3-8), 4.12 (s, 3H, OCH_3-4'), 4.78 (q, ^3J = 6.8 Hz, 1H, H-1), 6.60 (1H, s, H-7), 6.62 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-8'), 6.72 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 6.93 (1H, s, H-3'), 7.15 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.8 (1-CH_3), 19.3 (3-CH_3), 20.7 (2'-CH_3), 32.9 (C-4), 45.1 (C-3), 49.3 (C-1), 56.2 (8-OCH_3), 57.1 (4'-OCH_3), 98.9 (C-7), 108.2 (C-3'), 110.6 (C-6'), 114.5 (C-9), 115.3 (C-10'), 117.0 (C-5), 118.6 (C-8'), 126.1 (C-1'), 128.9 (C-7'), 132.9 (C-10), 136.8 (C-9'), 137.5 (C-2'), 156.3 (C-5'), 157.1 (C-6), 157.4 (C-4'), 157.8 (C-8) ppm.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.23 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.62 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.13 (dd, ^2J = 18.0, ^3J = 12.0 Hz, 1H, Hax-4), 2.13 (s, 3H, CH_3-2'), 2.27 (dd, ^2J = 17.0, ^3J = 4.0 Hz, 1H, Heq-4), 3.54 (m, 1H, H-3), 3.85 (s, 3H, OCH_3-8), 4.09 (s, 3H, OCH_3-4'), 4.80 (q, ^3J = 7.2 Hz, 1H, H-1), 6.55 (1H, s, H-7), 6.69 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-8'), 6.76 (s, 1H, H-3'), 6.84 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 7.23 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-7') ppm.

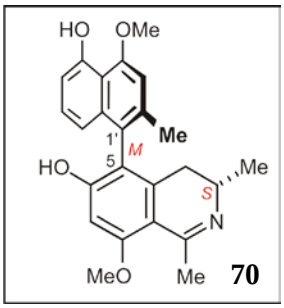
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 18.6 (1-CH_3), 18.7 (3-CH_3), 20.7 (2'-CH_3), 31.8 (C-4), 44.4 (C-3), 47.9 (C-1), 55.6 (8-OCH_3), 56.4 (4'-OCH_3), 97.5 (C-7), 106.7 (C-3'), 111.0 (C-6'), 114.2 (C-10'), 114.8 (C-9), 115.9 (C-5), 116.1 (C-8'), 122.0 (C-1'), 129.5 (C-7'), 131.4 (C-10), 136.2 (C-9'), 136.6 (C-2'), 153.9 (C-6), 155.0 (C-5'), 156.8 (C-4'), 156.8 (C-8) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 393 $[M]^+$ (3), 392 $[M–1]^+$ (5), 378 $[M–15]^+$ (100).

HRESIMS *m*/*z*. calcd. for $C_{24}H_{28}NO_4$ $[M+1]^+$: 394.2019; found 394.2021.

The spectroscopic data are in good agreement with those previously published.[124]

*5'-O-Demethylhamatinine (**70**)*



Yellow amorphous powder (2.4 mg).

M.p. >230 °C (MeOH).
Lit.: not reported (MeOH).[124]

$[\alpha]_D^{20}$ = +19.3 (*c* = 0.10, MeOH).
Lit.: +25.0 (*c* = 0.10, MeOH).[124]

UV (MeOH): λ_{max} (logε) = 230 (2.23), 310 (0.40), 335 (0.38) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 213 (–12.0), 229 (+8.3), 243 (–6.9), 296 (+2.0), 318 (–2.0), 338 (+1.3) nm.

IR (ATR): $\tilde{\nu}$ = 3436 (w), 3223 (w), 2934 (w), 1671 (m), 1575 (m), 1502 (w), 1435 (w), 1353 (w), 1321 (w), 1286 (w), 1267 (w), 1200 (m), 1131 (m), 1079 (m), 840 (w), 801 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 600 MHz): δ = 1.19 (d, ^3J = 6.6 Hz, 3H, CH_3-3), 2.15 (s, 3H, CH_3-2'), 2.23 (dd, ^2J = 16.8, ^3J = 11.2 Hz, 1H, H-4ax), 2.49 (dd, ^2J =16.8, ^3J = 5.6 Hz, 1H, H-4eq), 2.79 (d, ^3J = 1.2 Hz, 3H, CH_3-1), 3.76 (m, 1H, H-3), 4.05 (s, 3H, OCH_3-8), 4.13 (s, 3H, OCH_3-4'), 6.63 (dd, ^3J = 8.1, ^4J = 0.9 Hz, 1H, H-8'), 6.70 (s, 1H, H-7), 6.73 (dd, ^3J = 8.1, ^4J = 0.9 Hz, 1H, H-6'), 6.94 (s, 1H, H-3'), 7.17 (dd, ^3J = 8.1, ^3J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 18.1 (3-CH_3), 20.6 (2'-CH_3), 24.9 (1-CH_3), 32.7 (C-4), 49.1 (C-3), 56.8 (8-OCH_3), 56.9 (4'-OCH_3), 99.5 (C-7), 108.0 (C-3'), 108.8 (C-9), 110.9 (C-6'), 115.2 (C-10'), 116.7 (C-8'), 121.0 (C-5), 124.6 (C-1'), 129.2 (C-7'), 137.1 (C-2'), 137.4 (C-9'), 142.7 (C-10), 156.4 (C-5'), 157.7 (C-4'), 166.0 (C-8), 167.5 (C-6), 175.6 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 392 $[M+1]^+$ (100), 391 $[M]^+$ (73), 376 $[M–15]^+$ (33).

HRESIMS *m*/*z* calcd. for $C_{24}H_{26}NO_4$ $[M+1]^+$: 392.1856; found 392.1856.

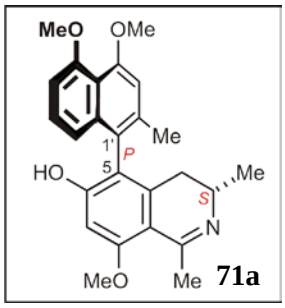
The spectroscopic data are in good agreement with those previously published.[124]

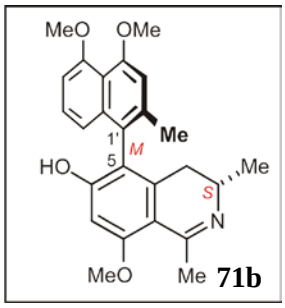
*Ancistrocladinine (**71a**) and Hamatinine (**71b**)*

Colorless amorphous powder (15.0 mg).

UV (MeOH): λ_{max} (logε) = 215 (3.31), 285 (0.88), 320 (0.76), 350 (0.71) nm.

IR (ATR): $\tilde{\nu}$ = 3180 (w), 2979 (w), 1667 (m), 1632 (w), 1574 (m), 1503 (w), 1440 (w), 1391 (w), 1357 (w), 1319 (w), 1288 (w), 1260 (w), 1181 (s), 1125 (s), 1096 (m), 1073 (m), 973 (w), 937 (w), 835 (w), 810 (m) cm^{-1}.





*Ancistrocladinine (**71a**)*

^{1}H NMR (CD_3OD, 600 MHz): δ = 1.21 (d, ^{3}J = 6.6 Hz, 3H, CH_3-3), 2.12 (d, ^{3}J = 6.6 Hz, 3H, CH_3-2'), 2.31 (dd, ^{2}J = 16.8, ^{3}J = 10.4 Hz, 1H, H-4ax), 2.39 (dd, ^{2}J =16.8, ^{3}J = 5.6 Hz, 1H, H-4eq), 2.80 (s, 3H, CH_3-1), 3.75 (m, 1H, H-3), 3.92 (s, 3H, OCH_3-5'), 3.97 (s, 3H, OCH_3-4'), 4.04 (s, 3H, OCH_3-8), 6.71 (s, 1H, H-7), 6.80 (dd, ^{3}J = 8.1, ^{4}J = 0.9 Hz, 1H, H-8'), 6.88 (dd, ^{3}J = 8.1, ^{4}J =0.9 Hz, 1H, H-6'), 6.92 (s, 1H, H-3'), 7.23 (dd, ^{3}J = 8.1, ^{3}J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 18.1 (3-CH_3), 20.6 (2'-CH_3), 24.9 (1-CH_3), 32.9 (C-4), 49.1 (C-3), 56.9 (8-OCH_3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 99.5 (C-7), 107.4 (C-6'), 108.8 (C-9), 110.3 (C-3'), 118.0 (C-10'), 118.3 (C-8'), 121.4 (C-5), 123.6 (C-1'), 128.4 (C-7'), 137.4 (C-2'), 137.9 (C-9'), 142.7 (C-10), 158.6 (C-4'), 159.2 (C-5'), 166.0 (C-8), 167.6 (C-6), 175.6 (C-1) ppm.

*Hamatinine (**71b**)*

^{1}H NMR (CD_3OD, 600 MHz): δ = 1.18 (d, ^{3}J = 6.6 Hz, 3H, CH_3-3), 2.15 (d, ^{3}J = 6.6 Hz, 3H, CH_3-2'), 2.20 (dd, ^{2}J = 16.8, ^{3}J = 10.4 Hz, 1H, H-4ax), 2.49 (dd, ^{2}J = 16.8, ^{3}J = 5.6 Hz, 1H, H-4eq), 2.80 (s, 3H, CH_3-1), 3.75 (m, 1H, H-3), 3.92 (s, 3H, OCH_3-5'), 3.97 (s, 3H, OCH_3-4'), 4.04 (s, 3H, OCH_3-8), 6.71 (s, 1H, H-7), 6.75 (dd, ^{3}J = 8.1, ^{4}J = 0.9 Hz, 1H, H-8'),

6.88 (dd, ^{2}J = 8.1, ^{4}J = 0.9 Hz, 1H, H-6'), 6.92 (s, 1H, H-3'), 7.23 (dd, ^{3}J = 8.1, ^{3}J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 18.1 (3-CH_3), 20.6 (2'-CH_3), 24.9 (1-CH_3), 32.8 (C-4), 49.1 (C-3), 56.9 (8-OCH_3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 99.5 (C-7), 107.4 (C-6'), 108.8 (C-9), 110.3 (C-3'), 118.0 (C-10'), 118.6 (C-8'), 121.4 (C-5), 123.7 (C-1'), 128.3 (C-7'), 137.4 (C-2'), 137.9 (C-9'), 142.7 (C-10), 158.6 (C-4'), 159.2 (C-5'), 166.0 (C-8), 167.6 (C-6), 175.6 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 406 $[M+1]^+$ (38), 405 $[M]^+$ (100), 404 $[M-1]^+$ (25), 392 $[M-13]^+$ (17), 391 $[M-14]^+$ (5), 390 $[M-15]^+$ (12).

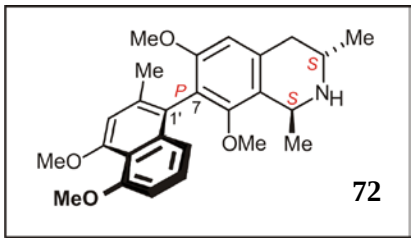
HRESIMS *m*/*z* calcd. for $C_{25}H_{28}NO_4$ $[M+1]^+$ 406.2013; found 406.2012.

The ratio of **71a** and **71b** is determined as *ca*. 1 : 2 by ^{1}H NMR spectroscopy.

The spectroscopic data are in good agreement with those previously published.[274]

*1,2-Dihydroancistrocladisine (**72**)*

Colorless amorphous powder (27.2 mg).



72

M.p. 260–262 °C (MeOH).
Lit.: 260–262 °C (MeOH).[24]

$[\alpha]_D^{20}$ = +34.2 (*c* = 0.1, $CHCl_3$).
Lit.: +49.7 (*c* = 1.44, $CHCl_3$).[126]

UV (MeOH): λ_{max} (logε) = 210 (2.84), 305 (0.67) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 206 (–9.3), 230 (+14.6), 246 (–0.6), 284 (–2.5) nm.

IR (ATR): $\tilde{\nu}$ = 2524 (m), 1669 (m), 1612 (m), 1583 (m), 1428 (w), 1393 (w), 1356 (w), 1333 (w), 1259 (w), 1181 (m), 1129 (m), 1076 (m), 1014 (w), 964 (w), 941 (w), 836 (w), 799 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.52 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 1.64 (d, ^{3}J = 6.8 Hz, 3H, CH_3-1), 2.14 (s, 3H, CH_3-2'), 2.94 (dd, ^{2}J = 17.6, ^{3}J = 11.3 Hz, 1H, Hax-4), 3.13 (s, 3H, OCH_3-8), 3.23 (dd, ^{2}J = 17.6, ^{3}J = 4.8 Hz, 1H, Heq-4), 3.62 (s, 3H, OCH_3-6), 3.91 (s, 3H,

OCH_3-5'), 3.91 (m, 1H, H-3), 3.98 (s, 3H, OCH_3-4'), 4.76 (q, ^3J = 7.2 Hz, 1H, H-1), 6.73 (1H, s, H-5), 6.81 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-8'), 6.84 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-6'), 6.88 (s, 1H, H-3'), 7.18 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 19.4 (3-CH_3), 19.5 (1-CH_3), 20.9 (2'-CH_3), 34.9 (C-4), 45.3 (C-3), 50.0 (C-1) 56.4 (6-OCH_3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 60.5 (8-OCH_3), 107.2 (C-6'), 107.4 (C-5), 110.3 (C-3'), 117.8 (C-10'), 119.8 (C-8'), 120.0 (C-9), 121.2 (C-7), 124.0 (C-1'), 127.6 (C-7'), 133.6 (C-10), 137.2 (C-2'), 138.0 (C-9'), 157.1 (C-8), 158.2 (C-4'), 158.7 (C-5'), 159.9 (C-6) ppm.

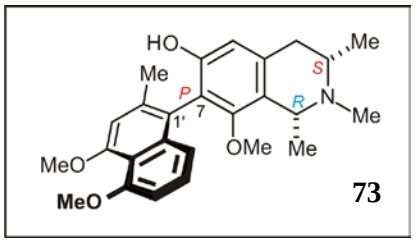
MS (EI, 70 eV): *m/z* (%) = 421 $[M]^+$ (10), 420 $[M–1]^+$ (2), 406 $[M–15]^+$ (100).

HRESIMS *m/z* calcd. for $C_{26}H_{32}NO_4$ $[M+1]^+$: 422.2326; found 422.2326.

The spectroscopic data are in good agreement with those previously published.[24,126,275]

*6-O-Demethyl-8-O-methyl-7-epi-ancistrobrevine D (**73**)*

Colorless amorphous powder (9.0 mg).



73

M.p. 170–172 °C (MeOH).
Lit.: not reported.[127]

$[\alpha]_D^{20}$ = +30.8 (*c* = 0.09, MeOH).
Lit.: +51.8 (*c* = 0.71, $CHCl_3$).[127]

UV (MeOH): λ_{max} (logε) = 305 (0.48), 320 (0.39), 335 (0.32) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 208 (–3.5), 224 (+4.8), 249 (+0.5), 255 (+1.0), 284 (–2.0), 309 (+0.9), 342 (–0.2), 352 (+0.2) nm.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.59 (d, ^3J = 6.6 Hz, 3H, CH_3-3), 1.72 (d, ^3J = 6.6 Hz, 3H, CH_3-1), 2.17 (s, 3H, CH_3-2'), 3.02 (overlapped in *N*-CH_3, 2H, H-4), 3.06 (s, 6H, OCH_3-8, *N*-CH_3), 3.45 (m, 1H, H-3), 3.91 (s, 3H, OCH_3-5'), 3.96 (s, 3H, OCH_3-4'), 4.58 (m, 1H, H-1), 6.63 (s, 1H, H-5), 6.85 (dd, ^3J = 8.1, ^4J = 0.9 Hz, 1H, H-6'), 6.91 (s, 1H, H-3'), 6.96 (dd, ^3J = 8.1, ^4J = 0.9 Hz, 1H, H-8'), 7.21 (dd, ^3J = 8.1, ^3J = 8.1 Hz, 1H, H-7') ppm.

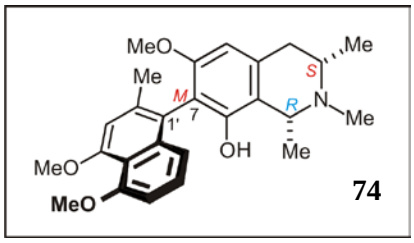
^{13}C NMR (CD_3OD, 100 MHz): δ = 18.3 (3-CH_3), 20.7 (1-CH_3), 21.0 (2'-CH_3), 35.5 (C-4), 42.0 (*N*-CH_3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 60.7 (8-OCH_3), 60.9 (C-3), 62.8 (C-1), 107.1 (C-6'), 110.5 (C-3'), 111.4 (C-5), 117.8 (C-10'), 118.6 (C-9), 119.9 (C-8'), 120.6 (C-7), 123.6 (C-1'), 127.7 (C-7'), 134.8 (C-10), 137.8 (C-2'), 138.1 (C-9'), 157.5 (C-6), 157.5 (C-8), 158.3 (C-4'), 158.8 (C-5') ppm.

MS (EI, 70 eV): *m*/*z* (%) = 421 $[M]^+$ (10), 406 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd. for $C_{26}H_{32}NO_4$ $[M+1]^+$: 422.2326; found 422.2326.

The spectroscopic data are in good agreement with those previously published.[127]

*7-epi-Ancistrobrevine D (**74**)*



74

Colorless amorphous powder (3.9 mg).

M.p. 170–173 °C (MeOH).
Lit.: 177–178 °C.[127]

$[\alpha]_D^{20}$ = +38.9 (*c* = 0.1, MeOH).
Lit.: +46.1 (*c* = 0.1, $CHCl_3$).[127]

UV (MeOH): λ_{max} (logε) = 210 (3.43), 304 (0.59), 335 (0.37) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 210 (–7.0), 230 (+6.0), 273 (+0.45) nm.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.60 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.77 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.10 (s, 3H, CH_3-2'), 3.09 (overlapped in *N*-CH_3, 2H, H-4), 3.10 (s, 3H, CH_3-*N*), 3.50 (m, 1H, H-3), 3.60 (s, 3H, OCH_3-6), 3.92 (s, 3H, OCH_3-5'), 3.97 (s, 3H, OCH_3-4'), 4.63 (q, ^3J = 7.2 Hz, 1H, H-1), 6.56 (1H, s, H-5), 6.78 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-8'), 6.84 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-6'), 6.92 (s, 1H, H-3'), 7.15 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.2 (3-CH_3), 19.5 (1-CH_3), 20.7 (2'-CH_3), 35.9 (C-4), 41.5 (*N*-CH_3), 56.3 (6-OCH_3), 57.0 (4'-OCH_3), 57.2 (5'-OCH_3), 60.7 (C-3), 62.9 (C-1), 103.5 (C-5), 107.3 (C-6'), 110.7 (C-3'), 114.8 (C-9), 115.7 (C-7), 118.1 (C-10'), 119.3 (C-8'), 122.0 (C-1'), 127.6 (C-7'), 134.6 (C-10), 138.5 (C-9'), 138.5 (C-2'), 153.1 (C-8), 158.5 (C-4'), 158.9 (C-5'), 159.4 (C-6) ppm.

MS (EI, 70 eV): *m/z* (%) = 421 $[M]^+$ (4), 406 $[M–15]^+$ (100).

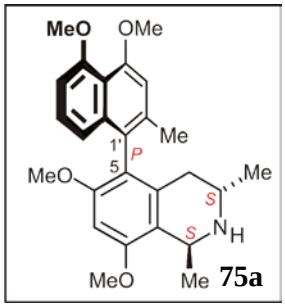
HRESIMS *m/z* calcd. for $C_{26}H_{32}NO_4$ $[M+1]^+$: 422.2326; found 422.2326.

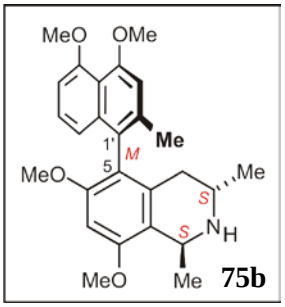
The spectroscopic data are in good agreement with those previously published.[127]

*6-O-Methylhamatine (**75a**) and 6-O-Methylancistrocladine (**75b**)*

Colorless amorphous powder (30.0 mg).

UV (MeOH): λ_{max} (logε) = 307 (057), 322 (0.48), 337 (0.43) nm.





*6-O-Methylancistrocladine (**75a**)*

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.20 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.66 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.04 (s, 3H, CH_3-2'), 2.16 (dd, ^2J =17.2, ^3J = 11.2 Hz, 1H, Hax-4), 2.29 (dd, ^2J = 17.0, ^3J = 4.8 Hz, 1H, Heq-4), 3.60 (m, 1H, H-3), 3.67 (s, 3H, OCH_3-6), 3.93 (s, 3H, OCH_3-5'), 3.96 (s, 3H, OCH_3-4'), 4.01 (s, 3H, OCH_3-8), 4.81 (q, ^3J = 7.2 Hz, 1H, H-1), 6.75 (1H, s, H-7), 6.78 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-8'), 6.86 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 6.89 (s, 1H, H-3'), 7.19 (dd, ^3J = 7.9, ^3J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.7 (1-CH_3), 19.2 (3-CH_3), 20.4 (2'-CH_3), 33.1 (C-4), 45.1 (C-3), 49.3 (C-1), 56.4 (6-OCH_3), 57.0 (8-OCH_3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 95.6 (C-7), 107.2 (C-6'), 110.6 (C-3'), 115.5 (C-9), 117.9 (C-10'), 118.7 (C-8'), 120.8 (C-5), 125.8 (C-1'), 127.9 (C-7'), 133.0 (C-10), 137.0 (C-2'), 137.7 (C-9'), 157.8 (C-6), 157.8 (C-8), 158.9 (C-4'), 159.6 (C-5') ppm.

*6-O-Methylhamatine (**75b**)*

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.19 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.65 (d, ^3J = 6.8 Hz, 3H,

CH_3-1), 2.07 (s, 3H, CH_3-2'), 2.08 (dd, ^2J = 17.2, ^3J = 11.2 Hz, 1H, Hax-4), 2.40 (dd, ^2J = 17.0, ^3J = 4.8 Hz, 1H, Heq-4), 3.65 (m, 1H, H-3), 3.64 (s, 3H, OCH_3-6), 3.92 (s, 3H, OCH_3-5'), 3.96 (s, 3H, OCH_3-4'), 4.01 (s, 3H, OCH_3-8), 4.81 (q, ^3J = 7.2 Hz, 1H, H-1), 6.67 (dd, ^3J = 8.4, 1.2 Hz, 1H, H-8'), 6.78 (1H, s, H-7), 6.85 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 6.91 (s, 1H, H-3'), 7.15 (dd, ^3J = 7.9, ^3J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.7 (1-CH_3), 19.2 (3-CH_3), 20.7 (2'-CH_3), 32.9 (C-4), 45.1 (C-3), 49.3 (C-1), 56.4 (6-OCH_3), 57.0 (8-OCH_3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 95.6 (C-7), 107.2 (C-6'), 110.6 (C-3'), 115.3 (C-9), 117.9 (C-10'), 118.9 (C-8'), 120.8 (C-5), 125.9 (C-1'), 127.9 (C-7'), 133.0 (C-10), 136.6 (C-2'), 137.7 (C-9'), 157.8 (C-6), 157.8 (C-8), 158.9 (C-4'), 159.6 (C-5') ppm.

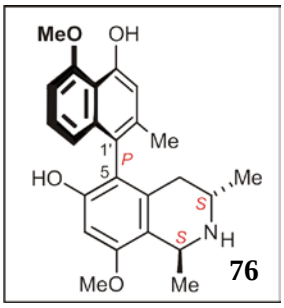
MS (EI, 70 eV): *m*/*z* (%) = 406 $[M–1]^+$ (5), 407 $[M–15]^+$ (100), 421 $[M]^+$ (4).

HRESIMS *m*/*z* calcd. for $C_{26}H_{32}NO_4$ $[M+1]^+$: 422.2326; found 422.2326.

The ratio of **75a** and **75b** is determined as *ca*. 1 : 2 by ^{1}H NMR spectroscopy.

The spectroscopic data are in good agreement with those previously published.[124,132]

*4'-O-Demethylancistrocladine (**76**)*



76

Colorless amorphous powder (9.0 mg).

M.p. 183–185 °C (MeOH).
Lit.: not reported.[120]

$[\alpha]_D^{20}$ = –4.6 (*c* = 0.09, MeOH).
Lit.: +2.5 (*c* = 1.0, MeOH).[120]

UV (MeOH): λ_{max} (logε) = 308 (0.58), 322 (0.51), 337 (0.47) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+18.6), 224 (–19.0), 239 (+9.1), 284 (–3.0) nm.

IR (ATR): $\tilde{\nu}$ = 2936 (w), 2508 (w), 1666 (w), 1612 (w), 1430 (w), 1396 (w), 1362 (w), 1333 (w), 1293 (w), 1258 (w), 1181(m), 1134 (m), 1110 (m), 1079 (m), 1019 (w), 963 (w), 836 (w), 798 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.22 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.64 (d, ^3J = 6.8 Hz, 3H,

CH_3-1), 2.05 (s, 3H, CH_3-2'), 2.15 (dd, ^2J = 17.2, ^3J = 11.2 Hz, 1H, Hax-4), 2.27 (dd, ^2J = 17.0, ^3J = 4.8 Hz, 1H, Heq-4), 3.62 (m, 1H, H-3), 3.92 (s, 3H, OCH_3-8), 4.08 (s, 3H, OCH_3-5'), 4.78 (q, ^3J = 7.2 Hz, 1H, H-1), 6.61 (1H, s, H-7), 6.81 (s, 1H, H-3'), 6.86 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-8'), 6.88 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 7.22 (dd, ^3J = 7.9, ^3J = 8.1 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.8 (1-CH_3), 19.3 (3-CH_3), 20.2 (2'-CH_3), 33.2 (C-4), 45.1 (C-3), 49.3 (C-1), 56.2 (8-OCH_3), 57.0 (5'-OCH_3), 98.9 (C-7), 104.9 (C-6'), 113.8 (C-3'), 114.6 (C-9), 115.3 (C-10'), 118.6 (C-5), 119.5 (C-8'), 123.5 (C-1'), 127.7 (C-7'), 133.2 (C-10), 137.2 (C-9'), 138.9 (C-2'), 155.4 (C-4'), 157.2 (C-6), 158.2 (C-8), 158.8 (C-5') ppm.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.64 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.07 (s, 3H, CH_3-2'), 2.15 (dd, ^2J = 17.2, ^3J = 11.2 Hz, 1H, Hax-4), 2.34 (dd, ^2J = 17.0, ^3J = 4.8 Hz, 1H, Heq-4), 3.48 (m, 1H, H-3), 3.87 (s, 3H, OCH_3-8), 4.10 (s, 3H, OCH_3-5'), 4.81 (q, ^3J = 7.2 Hz, 1H, H-1), 6.54 (1H, s, H-7), 6.78 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-6'), 6.87 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, H-8'), 6.90 (s, 1H, H-3'), 7.23 (dd, ^3J = 7.9, ^3J = 8.1 Hz, 1H, H-7') ppm.

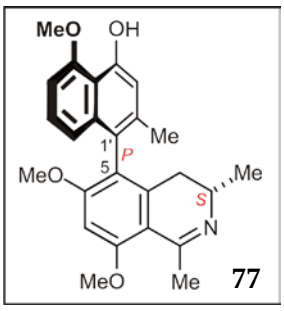
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.6 (1-CH_3), 18.7 (3-CH_3), 19.8 (2'-CH_3), 32.1 (C-4), 44.2 (C-3), 47.9 (C-1), 55.7 (8-OCH_3), 56.5 (5'-OCH_3), 97.2 (C-7), 104.1 (C-6'), 113.7 (C-3'), 114.4 (C-10'), 115.1 (C-9), 116.0 (C-5), 118.3 (C-8'), 118.6 (C-1'), 127.3 (C-7'), 132.0 (C-10), 136.1 (C-9'), 140.7 (C-2'), 154.0 (C-6), 155.3 (C-4'), 156.8 (C-8), 156.9 (C-5') ppm.

MS (EI, 70 eV): *m*/*z* (%) = 393 $[M]^+$ (6), 392 $[M–1]^+$ (16), 378 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd. for $C_{24}H_{28}NO_4$ $[M+1]^+$: 394.2013; found 394.2012.

The spectroscopic data are in good agreement with those previously published.[120]

6-O-Methyl-4'-O-demethylancistrocladine (77)



77

Colorless amorphous powder (6.5 mg).

$[\alpha]_D^{20}$ = –27.5 (*c* = 0.1, MeOH).

Lit.: –3.5 (*c* = 0.38, MeOH).[121]

UV (MeOH): λ_{max} (logε) = 290 (0.61), 305 (0.61), 320 (0.49), 335 (0.42) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 210 (–11), 226 (–30), 240 (+19), 284 (–3.2) nm.

IR (ATR): $\tilde{\nu}$ = 3199 (w), 2989 (w), 2541 (w), 1666 (m), 1598 (m), 1583 (m), 1454 (w), 1390 (w), 1333 (w), 1259 (w), 1197 (m), 1126 (m), 1074 (m), 1044 (m), 1005 (w), 970 (w), 837 (w), 798 (w) cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 1.22 (d, ^3J = 6.6 Hz, 3H, CH_3-3), 1.66 (d, ^3J = 6.6 Hz, 3H, CH_3-1), 2.00 (s, 3H, CH_3-2'), 2.16 (dd, ^2J = 17.8, ^3J = 11.8 Hz, 1H, H-4ax), 2.28 (dd, ^2J = 17.8, ^3J = 4.8 Hz, 1H, H-4eq), 3.66 (m, 1H, H-3), 3.67 (s, 3H, OCH_3-6), 4.00 (s, 3H, OCH_3-8), 4.08 (s, 3H, OCH_3-5'), 4.80 (q, ^3J = 6.8 Hz, 1H, H-1), 6.76 (dd, ^3J = 8.4, ^4J = 0.9 Hz, 1H, H-8'), 6.77 (s, 2H, H-7, 3'), 6.86 (dd, ^3J = 8.4, ^4J = 0.9 Hz, 1H, H-6'), 7.17 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.7 (1-CH_3), 19.3 (3-CH_3), 20.2 (2'-CH_3), 33.1 (C-4), 45.2 (C-3), 49.4 (C-1), 56.4 (6-OCH_3), 56.4 (8-OCH_3), 56.9 (5'-OCH_3), 95.7 (C-7), 104.8 (C-3'), 113.7 (C-6'), 115.2 (C-10'), 115.3 (C-9), 119.5 (C-8'), 120.7 (C-5), 124.1 (C-1'), 127.5 (C-7'), 133.1 (C-10), 137.0 (C-9'), 138.2 (C-2'), 155.3 (C-4'), 158.1 (C-8), 158.2 (C-5'), 159.9 (C-6) ppm.

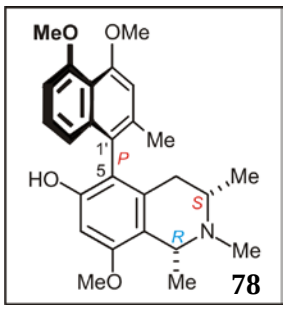
MS (EI, 70 eV): *m/z* (%) = 407 $[M]^+$ (12), 406 $[M–1]^+$ (11), 392 $[M–15]^+$ (100).

HRESIMS *m/z* calcd. for $C_{25}H_{30}NO_4$ $[M+1]^+$: 408.2169; found 408.2169.

The spectroscopic data are in good agreement with those previously published.[121]

*(+)-Ancistrocline (**78**)*

Colorless amorphous powder (30.0 mg).



78

M.p. 220–222 °C (MeOH).
Lit.: 223–224 °C (MeOH).[118]

$[\alpha]_D^{20}$ = +58.6 (*c* = 1.3, $CHCl_3$).
Lit.: +59.1 (*c* = 0.1, $CHCl_3$).[118]

UV (MeOH): λ_{max} (logε) = 307 (0.57), 322 (0.48), 337 (0.43) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 200 (+15.8), 222 (–16.3), 237 (+18.5) nm.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 1.43 (d, ^{3}J = 6.8 Hz, 3H, CH_3-1), 1.87 (dd, ^{2}J = 16.0, ^{3}J = 2.8 Hz, 1H, Heq-4), 2.10 (dd, ^{2}J = 16.0, ^{3}J = 10.8 Hz, 1H, Hax-4), 2.16 (s, 3H, CH_3-2'), 2.30 (m, 1H, H-3), 2.42 (s, 3H, *N*-CH_3), 3.74 (m, 1H, H-1), 3.86 (s, 3H, OCH_3-8), 3.93 (s, 3H, OCH_3-5'), 3.97 (s, 3H, OCH_3-4'), 6.51 (1H, s, H-7), 6.73 (dd, ^{3}J = 8.4, ^{4}J = 1.2 Hz, 1H, H-8'), 6.78 (s, 1H, H-3'), 6.85 (dd, ^{3}J = 8.4, ^{4}J = 1.2 Hz, 1H, H-6'), 7.19 (dd, ^{3}J = 7.9, ^{3}J = 8.1 Hz, 1H, H-7') ppm.

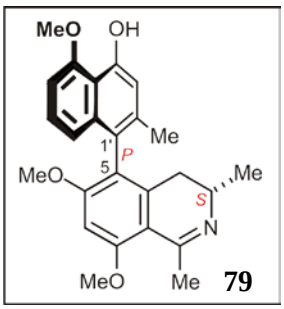
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6 (2'-CH_3), 21.2 (3-CH_3), 22.9 (1-CH_3), 36.1 (C-4), 41.2 (*N*-CH_3), 55.0 (C-3), 55.3 (8-OCH_3), 56.4 (4'-OCH_3), 56.5 (5'-OCH_3), 57.2 (C-1), 96.4 (C-7), 106.0 (C-6'), 109.0 (C-3'), 115.6 (C-9), 116.5 (C-10'), 117.8 (C-8'), 121.2 (C-5), 121.7 (C-1'), 127.3 (C-7'), 136.7 (C-10), 136.9 (C-9'), 138.3 (C-2'), 152.2 (C-6), 156.8 (C-8), 157.2 (C-4'), 157.6 (C-5') ppm.

MS (EI, 70 eV): *m/z* (%) = 421 $[M]^+$ (12), 420 $[M-1]^+$ (11), 406 $[M-15]^+$ (100).

HRESIMS *m/z* calcd. for $C_{26}H_{32}NO_4$ $[M+1]^+$: 422.2326; found 422.2326.

The spectroscopic data are in good agreement with those previously published.[118]

*6-O-Methyl-4'-O-demethylancistrocladinine (**79**)*



79

Colorless amorphous powder (4.0 mg).

$[\alpha]_D^{20}$ = –40.5 (*c* = 0.10, CH_3OH).

Lit.: +41.7 (*c* = 0.29, CH_3OH) (for its 5,1'-*epi*-isomer).[119]

UV (MeOH): λ_{max} (logε) = 227 (3.84), 280 (3.32), 321 (3.10), 336 (3.15) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 208 (+3.4), 228 (–1.5), 244 (–0.4), 300 (–1.2) nm.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.20 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 2.02 (s, 3H, CH_3-2'), 2.34 (dd, ^{2}J = 17.6, ^{3}J = 11.3 Hz, 1H, Hax-4), 2.41 (dd, ^{2}J = 17.6, ^{3}J = 4.8 Hz, 1H, Heq-4), 2.82 (d, ^{4}J = 1.3 Hz, 3H, CH_3-1), 3.73 (m, 1H, H-3), 3.84 (s, 3H, OCH_3-6), 4.09 (s, 3H, OCH_3-5'), 4.15 (s, 3H, OCH_3-8), 6.74 (dd, ^{3}J = 7.5, ^{4}J = 1.2 Hz, 1H, H-8'), 6.79 (1H, s, H-3'), 6.86 (s, 1H, H-7), 6.87 (dd, ^{3}J = 7.5, ^{4}J = 1.2 Hz, 1H, H-6'), 7.20 (dd, ^{3}J = 7.8, ^{3}J = 7.8 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.0 (3-CH_3), 20.4 (2'-CH_3), 25.0 (1-CH_3), 32.6 (C-4),

49.3 (C-3), 57.0 (5'-OCH_3), 57.1 (6-OCH_3), 57.2 (8-OCH_3), 96.1 (C-7), 105.0 (C-6'), 109.3 (C-9), 113.6 (C-3'), 115.1 (C-10'), 119.3 (C-8'), 122.3 (C-1'), 122.3 (C-5), 127.9 (C-7'), 136.8 (C-9'), 138.6 (C-2'), 141.6 (C-10), 155.8 (C-4'), 158.3 (C-5'), 166.5 (C-8), 168.6 (C-6), 176.1 (C-1) ppm.

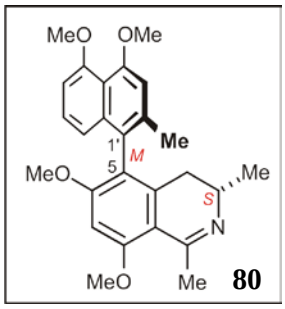
MS (EI, 70 eV): *m/z* (%) = 405 $[M]^+$ (100), 390 $[M–15]^+$ (48).

HRESIMS *m/z* calcd. for $C_{25}H_{28}NO_4$ $[M+1]^+$: 406.2012; found 406.2013.

The spectroscopic data are in good agreement with the data, provided by Dr. M. Xu (unpublished paper in our group).

*6-O-Methylhamatinine (**80**)*

Colorless amorphous powder (2.2 mg).



$[\alpha]_D^{20}$ = +15.6 (*c* = 0.10, CH_3OH).

Lit.: +34.1 (*c* = 0.10, $CHCl_3$).[127]

UV (MeOH): λ_{max} (logε) = 235 (0.98), 320 (0.48), 335 (0.49) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 210 (–16.8), 229 (+12.3), 242 (–8.0) nm.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.20 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 2.09 (s, 3H, CH_3-2'), 2.22 (dd, ^2J =17.6, ^3J = 11.3 Hz, 1H, Hax-4), 2.52 (dd, ^2J = 17.6, ^3J = 4.8 Hz, 1H, Heq-4), 2.82 (d, ^4J = 1.3 Hz, 3H, CH_3-1), 3.78 (m, 1H, H-3), 3.84 (s, 3H, OCH_3-6), 3.93 (s, 3H, OCH_3-5'), 3.97 (s, 3H, OCH_3-4'), 4.16 (s, 3H, OCH_3-8), 6.68 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-8'), 6.86 (1H, s, H-7), 6.86 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-6'), 6.91 (s, 1H, H-3'), 7.20 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7') ppm.

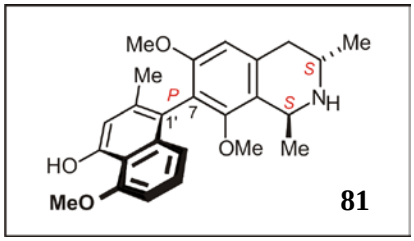
^{13}C NMR (CD_3OD, 100 MHz): δ = 18.0 (3-CH_3), 20.5 (2'-CH_3), 25.0 (1-CH_3), 32.6 (C-4), 49.1 (C-3), 57.0 (4'-OCH_3), 57.1 (5'-OCH_3), 57.1 (6-OCH_3), 57.2 (8-OCH_3), 96.1 (C-7), 107.4 (C-6'), 109.3 (C-9), 110.2 (C-3'), 117.9 (C-10'), 118.5 (C-8'), 122.6 (C-5), 123.9 (C-1'), 128.2 (C-7'), 137.0 (C-2'), 137.7 (C-9'), 141.6 (C-10), 158.4 (C-4'), 159.1 (C-5'), 166.5 (C-8), 168.5 (C-6), 176.0 (C-1) ppm.

MS (EI, 70 eV): *m/z* (%) = 419 $[M]^+$ (10), 418 $[M–1]^+$ (2), 404 $[M–15]^+$ (100).

HRESIMS *m/z* calcd. for $C_{26}H_{30}NO_4$ $[M+1]^+$: 420.2101; found 420.2101.

The spectroscopic data are in good agreement with those previously published.[124,127]

*Ancistrotectoriline B (**81**)*



Colorless amorphous powder (5.0 mg).

$[\alpha]_D^{20}$ = +65.1 (*c* = 0.1, CH_3OH).

Lit.: +79.1 (*c* = 0.1, $CHCl_3$).[121]

UV (MeOH): λ_{max} (logε) = 210 (3.43), 304 (0.59), 335 (0.37) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 205 (–12.7), 231 (+17.6) nm.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.52 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.64 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.09 (s, 3H, CH_3-2'), 2.93 (dd, ^2J = 17.6, ^3J = 11.6 Hz, 1H, H-4ax), 3.12 (s, 3H, OCH_3-8), 3.27 (dd, ^2J = 17.6, ^3J = 4.9 Hz, 1H, H-4eq), 3.62 (s, 3H, OCH_3-6), 3.92 (m, 1H, H-3), 4.08 (s, 3H, OCH_3-5'), 4.75 (m, 1H, H-1), 6.73 (1H, s, H-5), 6.77 (s, 1H, H-3'), 6.81 (dd, ^3J = 7.8, ^4J = 1.2 Hz, 1H, H-8'), 6.85 (dd, ^3J = 7.8, ^4J = 1.2 Hz, 1H, H-6'), 7.16 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 19.3 (3-CH_3), 19.4 (1-CH_3), 20.6 (2'-CH_3), 34.7 (C-4), 45.2 (C-3), 49.6 (C-1), 56.3 (6-OCH_3), 56.8 (5'-OCH_3), 60.3 (8-OCH_3), 104.5 (C-6'), 107.2 (C-5), 113.4 (C-3'), 114.9 (C-10'), 119.8 (C-9), 120.5 (C-8'), 120.8 (C-7), 122.1 (C-1'), 127.0 (C-7'), 133.3 (C-10), 137.1 (C-9'), 138.3 (C-2'), 155.5 (C-4'), 157.0 (C-8), 157.8 (C-5'), 159.9 (C-6) ppm.

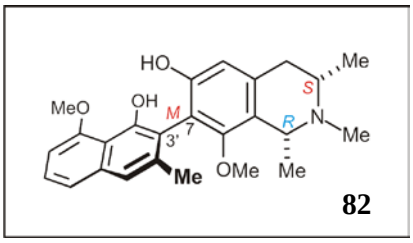
MS (EI, 70 eV): *m/z* (%) = 407 $[M]^+$ (8), 406 $[M–1]^+$ (13), 392 $[M–15]^+$ (100).

HRESIMS *m/z* calcd. for $C_{25}H_{30}NO_4$ $[M+1]^+$: 408.2169; found 408.2169.

The spectroscopic data are in good agreement with those previously published.[121]

Ancistrotanzanine C ***(82)***

Colorless amorphous powder (5.0 mg).



M.p. 147–149 °C (MeOH).

Lit.: not reported.[276]

$[\alpha]_D^{20}$ = –30.4 (*c* = 0.01, CH_3OH).

$[\alpha]_D^{20}$ = –20.0 (*c* = 0.01, $CHCl_3$).

Lit.: –75.5 (*c* = 0.1, $CHCl_3$).[276]

UV (MeOH): λ_{max} (logε) = 285 (0.39), 305 (0.32), 320 (0.33), 335 (0.36) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 204 (–7.2), 216 (+24.6), 237 (–15.2), 265 (–0.2), 319 (–2.0), 338 (–1.6) nm.

IR (ATR): $\tilde{\nu}$ = 2947 (w), 2508 (w), 1667 (w), 1610 (w), 1578 (w), 1435 (w), 1360 (w), 1271 (w), 1183(m), 1130 (m), 1089 (m), 1065 (m), 967 (w), 941(w), 839 (w), 798 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.58 (d, ^3J = 6.6 Hz, 3H, CH_3-3), 1.73 (d, ^3J = 6.6 Hz, 3H, CH_3-1), 2.15 (s, 3H, CH_3-2'), 3.00 (m, 2H, H-4), 3.04 (s, 3H, *N*-CH_3), 3.35 (s, 3H, OCH_3-8), 3.40 (m, 1H, H-3), 4.06 (s, 3H, OCH_3-5'), 4.62 (q, ^3J = 6.6 Hz, 1H, H-1), 6.59 (1H, s, H-5), 6.89 (dd, ^3J = 8.4, ^4J = 0.9 Hz, 1H, H-6'), 7.25 (s, 1H, H-1'), 7.32 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-7'), 7.35 (dd, ^3J = 8.4, ^4J = 0.9 Hz, 1H, H-8') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.5 (3-CH_3), 20.7 (2'-CH_3), 20.9 (1-CH_3), 35.3 (C-4), 42.4 (*N*-CH_3), 56.9 (5'-OCH_3), 60.7 (8-OCH_3), 61.1 (C-3), 62.5 (C-1), 104.9 (C-6'), 111.3 (C-5), 114.8 (C-10'), 117.6 (C-3'), 118.1 (C-9), 118.7 (C-7), 120.1 (C-1'), 122.2 (C-8'), 127.4 (C-7'), 134.4 (C-10), 138.1 (C-9'), 139.1 (C-2'), 153.1 (C-4'), 157.5 (C-6), 157.7 (C-8), 157.8 (C-5') ppm.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.67 (d, ^3J = 6.6 Hz, 3H, CH_3-3), 1.77 (d, ^3J = 6.6 Hz, 3H, CH_3-1), 2.14 (s, 3H, CH_3-2'), 2.92 (m, 1H, H-4), 2.92 (s, 3H, *N*-CH_3), 3.21 (m, 1H, H-4), 3.27 (m, 1H, H-3), 3.33 (s, 3H, OCH_3-8), 4.05 (s, 3H, OCH_3-5'), 4.58 (q, ^3J = 6.6 Hz, 1H, H-1), 6.67 (1H, s, H-5), 6.80 (dd, ^3J = 8.4, ^4J = 0.9 Hz, 1H, H-6'), 7.31 (s, 1H, H-1'), 7.38 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-7'), 7.39 (dd, ^3J = 8.4, ^4J = 0.9 Hz, 1H, H-8'), 9.81 (s, 1H, OH-4'). ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.1 (3-CH_3), 20.2 (1-CH_3), 20.4 (2'-CH_3), 33.4 (C-4),

43.8 (*N*-CH_3), 56.4 (5'-OCH_3), 59.6 (C-3), 59.6 (C-1), 60.7 (8-OCH_3), 104.3 (C-6'), 110.5 (C-5), 113.5 (C-10'), 113.8 (C-3'), 116.0 (C-7), 117.8 (C-9), 120.4 (C-1'), 121.5 (C-8'), 127.2 (C-7'), 133.5 (C-10), 137.0 (C-9'), 138.2 (C-2'), 152.3 (C-4'), 154.5 (C-6), 156.3 (C-8), 156.3 (C-5') ppm.

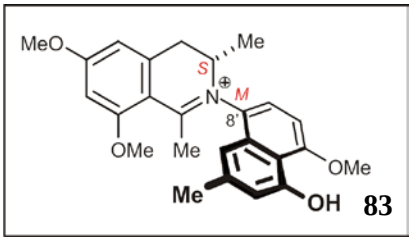
MS (EI, 70 eV): *m*/*z* (%) = 408 $[M+1]^+$ (1), 406 $[M-1]^+$ (2), 393 $[M-14]^+$ (29), 392 $[M-15]^+$ (100), 196 $[M-15]^{2+}$ (11).

HRESIMS *m*/*z* calcd. for $C_{25}H_{30}NO_4$ $[M+1]^+$: 408.2169; found 408.2169.

The spectroscopic data are in good agreement with those previously published.[276,277]

4'-O-Demethylancistrocladinium A ***(83)***

Pale-yellow amorphous powder (3.8 mg).



83

M.p. >230 °C (MeOH).
Lit.: >230 °C (MeOH).[39]

$[\alpha]_D^{20}$ = –8.9 (*c* = 0.10, CH_3OH).
Lit.: –5.5 (*c* = 0.05, CH_3OH).[39]

UV (MeOH): λ_{max} (logε) = 210 (3.32), 305 (0.91), 320 (0.89) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 215 (–0.7), 230 (+0.8), 242 (–0.9), 332 (+0.5) nm.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.31 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 2.46 (s, 3H, CH_3-2'), 2.53 (s, 3H, CH_3-1), 3.13 (dd, ^2J = 17.0, ^3J = 2.6 Hz, 1H, H-4eq), 3.82 (dd, ^2J = 17.0, ^3J = 6.4 Hz, 1H, H-4ax), 4.03 (s, 3H, OCH_3-6), 4.05 (s, 3H, OCH_3-8), 4.17 (s, 3H, OCH_3-5'), 4.26 (m, 1H, H-3), 6.74 (d, ^4J = 2.2 Hz, 1H, H-7), 6.77 (d, ^4J = 2.2 Hz, 1H, H-5), 6.88 (d, ^4J = 1.0 Hz, 1H, H-3'), 7.00 (d, ^3J = 8.3 Hz, 1H, H-6'), 7.02 (d, ^4J = 1.0 Hz, H-1'), 7.46 (d, ^3J = 8.3 Hz, 1H, H-7') ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 15.5 (3-CH_3), 22.1 (2'-CH_3), 24.8 (1-CH_3), 35.0 (C-4), 57.1 (8-OCH_3), 57.2 (6-OCH_3), 57.5 (5'-OCH_3), 59.5 (C-3), 99.0 (C-7), 103.6 (C-6'), 109.5 (C-5), 111.3 (C-9), 112.2 (C-1'), 115.5 (C-3'), 115.6 (C-8'), 126.8 (C-7'), 131.1 (C-10'), 131.6 (C-9'), 142.1 (C-10), 143.2 (C-2'), 157.2 (C-4'), 159.9 (C-5'), 166.5 (C-8), 170.8 (C-6), 178.0 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 406 $[M]^+$ (9), 405 $[M–1]^+$ (15), 391 $[M–15]^+$ (100).

HRESIMS *m*/*z* calcd. for $C_{25}H_{28}NO_4$ $[M]^+$: 406.2012; found 406.2013.

The spectroscopic data are in good agreement with those previously published.[39]

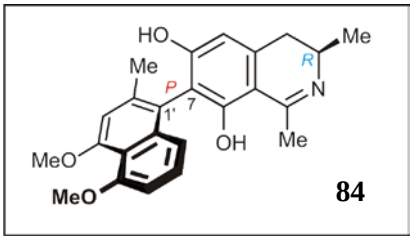
3 Phytochemical Investigation on a Congolese *Ancistrocladus* species

3.1 Extraction and Isolation

Air-dried root bark from a Congolese *Ancistrocladus* species (150 g) was ground and sequentially extracted with CH_2Cl_2 / MeOH (1:1 *v*/*v*). The extract was concentrated *in vacuo* to give 20 g of a crude residue. This residue was subjected to cation exchange chromatography (Amberlyst-15 from Fluka, Ø 3 cm, filling height 20 cm) in portions of 5 g. After eluting unbound material from the column with H_2O and MeOH, the alkaloidal fraction was eluted with saturated aqueous NaCl solution. This fraction was extracted with CH_2Cl_2 and the organic layer was concentrated *in vacuo* to give total 1.5 g of a dry residue.

The residue was dissolved in CH_2Cl_2 and filtered to give pure 500 mg of diocophylline A (**6**), and further resolved by preparative HPLC, with the following gradient: H_2O (0.05% trifluoroacetic acid) (A) / MeOH (0.05% trifluoroacetic acid) (B), 0 min 45% B, 30 min 75% B to afford two new naphthylisoquinoline alkaloids, 6-*O*-demethylancistrobrevine C (**84**) and jozimine A_2 (**85**), together with three known metabolites, ancistrocladine (**5a**), hamatine (**5b**), and ancistrobrevine C (**86**).

3.2 6-*O*-Demethylancistrobrevine C (**84**)



84

Colorless amorphous powder (3.7 mg).

M.p. 145 °C (MeOH).

$[\alpha]_D^{20}$ = +33.6 (*c* = 0.18, CH_3OH).

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 207 (–3.4), 229 (+2.9), 242 (–0.9), 268 (+0.4) nm.

IR (ATR): $\tilde{\nu}$ = 3393 (w), 2508 (w), 1674 (m), 1598 (m), 1391 (w), 1197 (m), 1120 (m), 1074 (m), 827 (w), 797 (w), 752 (w), 718 (w) cm^{-1}.

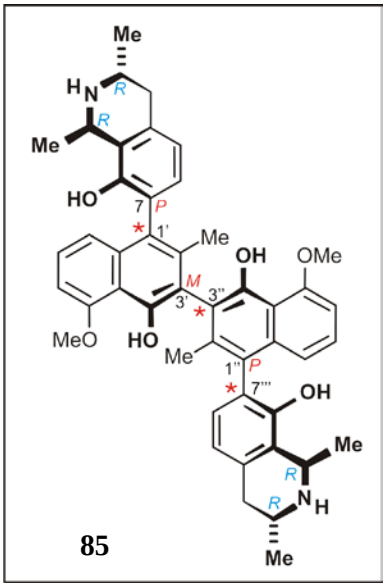
^1H NMR (600 MHz, CD_3OD): δ = 1.49/1.50 (d, ^3J = 6.8 Hz, 3H, CH_3-3)*, 2.17/2.19 (s, 3H, CH_3-2')*, 2.76 (s, 3H, CH_3-1), 2.88/2.91 (dd, ^2J = 18.0, ^3J = 11.2 Hz, 1H, Hax-4)*, 3.12 (dd, ^2J = 17.0, ^3J = 5.1Hz, 1H, Heq-4), 3.93 (s, 3H, OCH_3-5'), 3.99 (s, 3H, OCH_3-4'), 3.99 (m, 1H, H-3), 6.55 (1H, s, H-5), 6.87–6.91 (m, 2H, H-6', 8'), 6.94 (s, 1H, H-3'), 7.23/7.24(dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7')* ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 18.28 (3-CH_3), 20.46/20.49 (2'-CH_3)*, 24.61/24.62 (1-CH_3)*, 35.35/35.37 (C-4)*, 49.67 (C-3), 56.71 (4'-OCH_3), 56.94 (5'-OCH_3), 107.29 (C-6'), 107.65/107.67 (C-10)*, 109.79/109.81 (C-5)*, 110.33 (C-3'), 114.94 (C-7), 118.14 (C-10'), 118.42 (C-8'), 119.46 (C-1'), 128.02, 128.06 (C-7'), 138.23/138.28 (C-9')*, 139.38/139.42 (C-2')*, 141.92/141.96 (C-9)*, 158.96, 159.07 (C-4', 5'), 162.63/162.65 (C-8)*, 166.38/166.40 (C-6)*, 175.95/175.98 (C-1)* ppm.

*: These signals separated for the two isomers.

HRESIMS *m/z* calcd. for $C_{24}H_{26}NO_4$ $[M+1]^+$: 392.1856; found 392.1854.

3.3 Jozimine A_2 (**85**)



85

White crystals (3.0 mg).

M.p. 238–240°C (MeOH).

$[\alpha]_D^{20}$ = –29.8 (*c* = 0.20, MeOH).

UV (MeOH): λ_{max} (logε) = 284 (1.15), 300 (1.23), 325 (1.11), 335 (1.06) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 206 (–3.2), 229 (+6.2), 243 (–4.2), 305 (+0.9) nm.

IR (ATR): $\tilde{\nu}$ = 2850 (w), 1673 (s), 1434 (m), 1392 (m), 1200 (s), 1132 (s), 799 (m), 758 (m) cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.53 (d, ^3J = 6.0 Hz, 6H, CH_3-3 and CH_3-3'''), 1.69 (d, ^3J = 6.0 Hz, 6H, CH_3-1 and CH_3-1'''), 1.83 (s, 6H, CH_3-2' and CH_3-2''), 2.96 (dd, ^2J = 17.6, ^3J = 11.8 Hz, 2H, H-4ax and Hax-4'''), 3.23 (dd, ^2J = 17.6, ^3J = 4.7 Hz, 2H, H-4eq and Heq-4'''), 3.90 (m, 2H, H-3 and H-3'''), 4.11 (s, 6H, OCH_3-5' and OCH_3-5''), 4.88 (m, 2H, H-1 and H-1'''), 6.88 (d, ^3J = 7.8 Hz, 2H, H-5 and H-5'''), 6.92 (dd, ^3J = 7.8, ^4J = 1.2 Hz, 2H, H-8' and H-8''), 7.00 (d, ^3J = 7.8 Hz, 4H, H-6, 6' and H-6''', 6''), 7.25 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 2H, H-7' and H-7'') ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 18.07 (CH_3-2' and CH_3-2"), 18.11 (CH_3-1 and CH_3-1'"), 19.45 (CH_3-3 and CH_3-3'"), 34.62 (C-4 and C-4'"), 45.36 (C-3 and C-3'"), 50.00 (C-1 and C-1'"), 57.28 (5'-OCH_3 and 5"-OCH_3), 105.68 (C-6' and C-6"), 115.23 (C-10' and C-10"), 120.65 (C-8' and C-8"), 121.14 (C-5 and C-5'"), 121.36 (C-3' and C-3"), 122.15 (C-9 and C-9'"), 125.93 (C-7 and C-7'"), 126.28 (C-1' and C-1"), 127.52 (C-7' and C-7"), 132.69 (C-10 and C-10'"), 132.71 (C-6 and C-6'"), 137.41 (C-9' and C-9"), 138.34 (C-2' and C-2"), 152.13 (C-4' and C-4"), 152.82 (C-8 and C-8'"), 157.81 (C-5' and C-5") ppm.

^{1}H NMR (600 MHz, CD_3COCD_3): δ = 1.62 (d, ^3J = 6.0 Hz, 6H, CH_3-3 and CH_3-3'"), 1.75 (d, ^3J = 6.0 Hz, 6H, CH_3-1 and CH_3-1'"), 1.86 (s, 6H, CH_3-2' and CH_3-2"), 3.09 (dd, ^2J = 17.6, ^3J = 11.8 Hz, 2H, H-4ax and Hax-4'"), 3.21 (dd, ^2J = 17.6, ^3J = 4.7 Hz, 2H, H-4eq and Heq-4'"), 4.00 (m, 2H, H-3 and H-3'"), 4.14 (s, 6H, OCH_3-5' and OCH_3-5"), 5.02 (q, ^3J = 6.6 Hz, 2H, H-1 and H-1'"), 6.87 (d, ^3J = 7.8 Hz, 2H, H-5 and H-5'"), 6.95 (d, ^3J = 7.8 Hz, 2H, H-8' and H-8"), 6.98 (d, ^3J = 7.8 Hz, 2H, H-6' and H-6"), 6.99 (d, ^3J = 7.8 Hz, 2H, H-6 and H-6'"), 7.24 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 2H, H-7' and H-7"), 9.73 (s, 2H, OH) ppm.

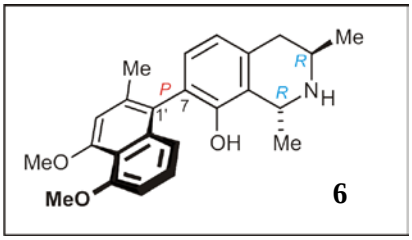
^{13}C NMR (150 MHz, CD_3COCD_3): δ = 17.96 (CH_3-1 and CH_3-1'"), 18.21 (CH_3-2' and CH_3-2"), 19.05 (CH_3-3 and CH_3-3'"), 34.33 (C-4 and C-4'"), 44.68 (C-3 and C-3'"), 48.84 (C-1 and C-1'"), 56.92 (5'-OCH_3 and 5"-OCH_3), 104.84 (C-6' and C-6"), 114.72 (C-10' and C-10"), 120.24 (C-8' and C-8"), 121.08 (C-5 and C-5'"), 121.33 (C-3' and C-3"), 122.15 (C-9 and C-9'"), 124.19 (C-1' and C-1"), 125.60 (C-7 and C-7'"), 126.82 (C-7' and C-7"), 131.82 (C-6 and C-6'"), 132.79 (C-10 and C-10'"), 136.67 (C-9' and C-9"), 138.28 (C-2' and C-2"), 151.80 (C-8 and C-8'"), 152.30 (C-4' and C-4"), 157.46 (C-5' and C-5") ppm.

HRESIMS *m*/*z* calcd. for $C_{46}H_{49}N_2O_6$ $[M+1]^+$: 725.3585; found 725.3581.

Crystal data for **85**: $C_{46}H_{48}N_2O_6$, M_r = 724.86, colorless needle, 0.58 × 0.08 × 0.06 mm^3, Orthorhombic space group $P2_12_12_1$, a = 12.6900(8) Å, b = 17.1715(13) Å, c = 25.5037(18) Å, V = 5557.4(7) Å^3, Z = 4, ρ_{calcd} = 0.866 g·cm^{-3}, μ = 0.057 mm^{-1}, F(000) = 1544, T = 100 (2) K, R_1 = 0.1427, wR^2 = 0.3813, 6042 independent reflections [$2\theta \leq 52.08°$] and 500 parameters. Crystallographic data will be deposited with the Cambridge Crystallographic Data Center. These data will be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

3.4 Known Alkaloids

*Dioncophylline A (**6**)*



6

Yellowish amorphous powder (500 mg).

M.p. 214 °C (MeOH).
Lit.: 214 °C.[22]
Lit.: 228–229 °C.[146]
Lit.: 215 °C.[140]

$[\alpha]_D^{20} = -18.0$ (c = 0.10, $CHCl_3$).

Lit.: $[\alpha]_D^{20} = -14.9$ (c = 1.0, $CHCl_3$).[22]

Lit.: $[\alpha]_D^{20} = -14$ (c = 0.64, $CHCl_3$).[146]

Lit.: $[\alpha]_D^{20} = -14.9$ (c = 0.45, CH_2Cl_2).[140]

UV (MeOH): λ_{max} (logε) = 231 (1.05), 306 (0.52) nm.

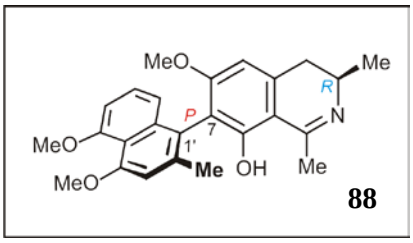
CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 198 (+3.1), 224 (–27.8), 244 (+20.3) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, ^3J = 6.2 Hz, 3H, CH_3-3), 1.52 (d, ^3J = 6.3 Hz, 3H, CH_3-1), 2.18 (s, 3H, CH_3-2'), 2.63 (dd, ^2J = 16.5, ^3J = 11.0 Hz, 1H, Hax-4), 2.86 (dd, ^2J = 16.5, ^3J = 3.8 Hz, 1H, Heq-4), 3.43 (m, 1H, H-3), 3.95 (s, 3H, 4'-OCH_3), 3.99 (s, 3H, 5'-OCH_3), 4.50 (q, 1H, H-1), 6.76 (s, 1H, H-3'), 6.76 (d, ^3J = 7.6 Hz, 1H, H-6'), 6.76 (d, ^3J = 7.9 Hz, 1H, H-5), 6.87 (d, ^3J = 7.9 Hz, 1H, H-6), 6.97 (d, ^3J = 8.2 Hz, 1H, H-8'), 7.23 (dd, ^3J = 8.0, ^3J = 7.9 Hz, 1H, H-7') ppm.

MS (EI, 70 eV): m/z (%) = 377 $[M]^+$ (78), 362 $[M–15]^+$ (100).

HRESIMS m/z calcd. for $C_{24}H_{27}NO_3$ $[M+1]^+$: 377.1991; found 377.1989.

The spectroscopic data are in good agreement with those previously published.[22,140,146,273]



*Ancistrobrevine C (**88**)*

Colorless amorphous powder (8.0 mg).

M.p. 128–130 °C (MeOH).

Lit.: 180–183 °C (MeOH).[142]

Lit.: 160–166 °C (MeOH).[147]

$[\alpha]_D^{20}$ = +26 (*c* = 0.26, $CHCl_3$).

Lit.: $[\alpha]_D^{20}$ = +13 (*c* = 0.69, $CHCl_3$).[142]

Lit.: $[\alpha]_D^{20}$ = –13 (*c* = 0.69, $CHCl_3$).[147]

Even small impurities (3-*epi*-ancistrobrevine C) change the M.p. and $[\alpha]_D^{20}$ values to an unusually large extent, which explains the different values with that in the literature.

UV (MeOH): λ_{max} (logε) = 215 (2.84), 295 (0.50), 335 (0.44), 350 (0.38) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 213 (+10.0), 229 (–8.5), 243 (+5.7), 266 (–0.8), 328 (+3.0) nm.

IR (ATR): $\tilde{\nu}$ = 1671 (w), 1587 (w), 1432 (w), 1200 (w), 1121 (w), 1045 (w), 798 (w), 753 (w), 720 (w), 669 (w) cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 1.53 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 2.15 (s, 3H, CH_3-2'), 2.80 (s, 3H, CH_3-1), 3.00 (dd, ^2J = 18.0, ^3J = 11.2 Hz, 1H, Hax-4), 3.23 (dd, ^2J = 17.0, ^3J = 5.1 Hz, 1H, Heq-4), 3.75 (s, 3H, OCH_3-6), 3.93 (s, 3H, OCH_3-5'), 3.98 (s, 3H, OCH_3-4'), 4.06 (m, 1H, H-3), 6.79 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-8'), 6.82 (1H, s, H-5), 6.87 (dd, ^3J = 7.5, ^4J = 1.2 Hz, 1H, H-6'), 6.93 (s, 1H, H-3'), 7.21(dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 18.2 (CH_3-3), 20.4 (CH_3-2'), 24.5 (CH_3-1), 35.6 (C-4), 49.8 (C-3), 56.7 (4'-OCH_3), 57.0 (5'-OCH_3, 6-OCH_3), 105.4 (C-5), 107.3 (C-6'), 109.1 (C-10), 110.3 (C-3'), 116.3 (C-7), 118.1 (C-10'), 118.4 (C-8'), 120.0 (C-1'), 128.0 (C-7'), 138.1 (C-9'), 138.9 (C-2'), 142.9 (C-9), 158.9 (C-4', 5'), 161.3 (C-8), 167.2 (C-6), 176.6 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 405 $[M]^+$ (100), 404 $[M–1]^+$ (10), 390 $[M–15]^+$ (32).

HRESIMS *m*/*z* calcd. for $C_{25}H_{28}NO_4$ $[M+1]^+$: 406.2010; found 406.2008.

The spectroscopic data are in good agreement with those previously published.[142,147]

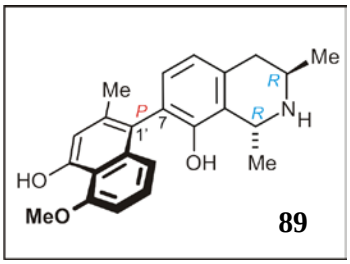
4 Semi-Synthesis of Dimeric Naphthylisoquinoline Alkaloids

4.1 Synthesis of Jozimine A_2 (**85**) and its 3'-epimer 3'-*epi*-**85**

*4'-O-Demethyldioncophylline A (**89**) and 5'-O-demethyldioncophylline A (**90**)*

To a solution of dioncophylline A (**6**) (265.0 mg, 0.70 mmol) in dry chloroform (35 mL), iodotrimethylsilane (448 µL, 3.2 mmol) was added portionwise under argon and stirred over 48 h. The mixture was diluted with water (35 mL) and extracted with chloroform (30 mL × 3). The combined organic layers were concentrated under reduced pressure and the two main products, **89** and **90**, were resolved by preparative HPLC on SymmetryPrep C_{18}, 19 × 300 mm column (*Waters*), using the following solvent gradient: H_2O + 0.05% TFA (A), MeCN + 0.05% TFA (B); flow rate: 10 mL min^{-1}; 0 min 30% B, 35 min 60% B, 36 min 95% B, 41 min 95% B, 42 min 30% B, 46 min 30% B, affording compounds **89** (retention time = 20.9 min) as a pale-yellow solid (124.5 mg, 0.34 mmol, 49%) and **90** (retention time = 20.0 min) as a pale-yellow solid (124.0 mg, 0.34 mmol, 49%).

*4'-O-Demethyldioncophylline A (**89**)*



89

Pale-yellow solid.

M.p. 232–234 °C (MeOH).

Yield: 124.5 mg, (0.34 mmol, 49%).

$[\alpha]_D^{20} = -4.0$ (c = 0.087, $CHCl_3$).

UV (MeOH): λ_{max} (logε) = 231 (1.05), 306 (0.52) nm.

^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (d, ^3J = 6.2 Hz, 3H, 3-CH_3), 1.65 (d, ^3J = 6.3 Hz, 3H, 1-CH_3), 2.07 (s, 3H, 2'-CH_3), 3.00 (dd, ^2J = 17.2, ^3J = 4.8 Hz, 1H, Heq-4), 3.14 (dd, ^2J = 17.2, ^3J = 11.3 Hz, 1H, Hax-4), 3.75 (m, 1H, H-3), 4.08 (s, 3H, 5'-OCH_3), 4.88 (q, 1H, H-1), 6.73 (d, ^3J = 7.4 Hz, 1H, H-6'), 6.78 (s, 1H, H-3'), 6.79 (d, ^3J = 7.6 Hz, 1H, H-5), 6.89 (d, ^3J = 7.9 Hz, 1H, H-8'), 6.94 (d, ^3J = 7.9 Hz, 1H, H-6), 7.19 (dd, ^3J = 7.8, ^3J = 7.9 Hz, 1H, H-7') ppm.

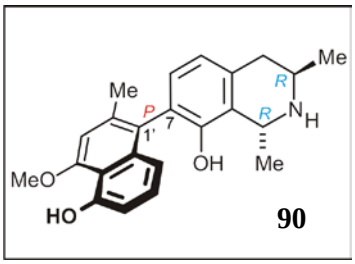
^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (1-CH_3), 18.9 (3-CH_3), 20.5 (2'-CH_3), 34.0 (C-4), 44.3 (C-3), 48.2 (C-1), 56.4 (5'-OCH_3), 104.0 (C-6'), 113.0 (C-6'), 114.1 (C-10'), 119.5 (C-8'), 120.7 (C-9 or 1'), 120.8 (C-1' or 9), 121.0 (C-5), 123.9 (C-7), 126.9 (C-7'), 130.8 (C-6), 131.8 (C-10), 136.3 (C-9'), 138.5 (C-2'), 149.8 (C-8), 155.2 (C-4'), 156.5 (C-5') ppm.

EIMS m/z (rel. int.): 363 $[M]^+$ (12), 349 $[M-14]^+$ (23), 348 $[M-15]^+$ (100).

HRMS (ESI): calcd. for $C_{23}H_{26}NO_3$ $[M+1]^+$: 364.1907; found 364.1906.

*5'-O-Demethyldioncophylline A (**90**)*

Pale-yellow solid.



90

Yield: 124.5 mg, (0.34 mmol, 49%).

M.p. 232–234 °C (MeOH).
Lit.: 232–234 °C (MeOH).[156]

$[\alpha]_D^{20}$ = –10.3 (c = 0.16, $CHCl_3$).
Lit.: –11.1 (c = 0.015, $CHCl_3$).[156]

UV (MeOH): λ_{max} (logε) = 231 (1.05), 306 (0.52) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, ^3J = 6.2 Hz, 3H, 3-CH_3), 1.64 (d, ^3J = 6.3 Hz, 3H, 1-CH_3), 2.09 (s, 3H, 2'-CH_3), 3.04 (dd, ^2J = 17.2, ^3J = 4.8 Hz, 1H, Heq-4), 3.15 (dd, ^2J = 17.2, ^3J = 11.3 Hz, 1H, Hax-4), 3.73 (m, 1H, H-3), 4.07 (s, 3H, 4'-OCH_3), 4.88 (q, 1H, H-1), 6.67 (s, 1H, H-3'), 6.74 (d, ^3J = 7.4 Hz, 1H, H-6'), 6.78 (d, ^3J = 7.6 Hz, 1H, H-5), 6.79 (dd, ^4J = 1.2, ^3J = 7.9 Hz, 1H, H-8'), 6.91 (dd, ^4J = 1.2, ^3J = 7.9 Hz, 1H, H-6), 7.20 (dd, ^3J = 7.8, ^3J = 7.9 Hz, 1 H, H-7') ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (1-CH_3), 18.8 (3-CH_3), 20.7 (2'-CH_3), 34.0 (C-4), 44.3 (C-3), 48.2 (C-1), 56.4 (4'-OCH_3), 106.8 (C-3'), 110.6 (C-6'), 113.9 (C-10'), 116.8 (C-8'), 121.0 (C-5 or 7), 121.1 (C-7 or C-5), 123.7 (C-9 or C-1'), 123.7 (C-1' or C-9), 128.8 (C-7'), 130.5 (C-6), 132.0 (C-10), 136.3 (C-9'), 136.4 (C-2'), 149.6 (C-8), 154.8 (C-5'), 156.6 (C-4') ppm.

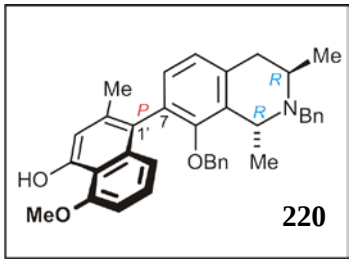
EIMS m/z (rel. int.): 363 $[M]^+$ (23), 349 $[M-14]^+$ (33), 348 $[M-15]^+$ (100).

HRMS (ESI): calcd. for $C_{23}H_{26}NO_3$ $[M+1]^+$: 364.1907; found 364.1906.

The spectroscopic data are in agreement with those in the literature.[156]

*N,8-O-Dibenzyl-4'-O-demethyldioncophylline A (**220**)*

A suspension of compound **89** (22.0 mg, 60.4 µmol), Cs_2CO_3 (43.3 mg, 133 µmol) and benzyl bromide (10.3 mg, 60.4 µmol) in acetone (6 mL) was refluxed for 2 h. Another equivalent of benzyl bromide (10.3 mg, 60.4 µmol) was then added in portions over a period of 6 h. The reaction mixture was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography on deactivated silica gel (7.5% NH_3) with a mobile phase of PE/EtOAc (10:1) yielded **220** (30.2 mg, 55.6 µmol, 92%) as a pale-yellow solid.



Pale-yellow solid.

Yield: 30.2 mg, (55.6 µmol, 92%).

M.p. 162 °C (CH_2Cl_2).

$[\alpha]_D^{20}$ = +32.4 (c = 0.10, CH_2Cl_2).

IR (ATM): $\tilde{\nu}$ = 3374 (w), 2922 (w), 2863 (w), 1651 (m), 1558 (m), 1457 (w), 1396 (w), 1258 (m), 1070 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31–1.37 (m, 6H, 1-CH_3 and 3-CH_3), 2.26 (s, 3H, 2'-CH_3), 2.74-2.79 (m, 2H, 4-CH_2), 3.45 (d, ^2J = 14.0 Hz, 1H, *N*-CH_2Ar), 3.57–3.65 (m, 1H, H-3), 3.95–4.01 (m, 2H, *O*-CH_2Ar), 4.06 (s, 3H, 5'-OCH_3), 4.08–4.12 (m, 1H, H-1), 6.41 – 6.43 (m, 2H, H-5 and H-6), 6.71 (d, ^3J = 7.9 Hz, 1H, H-6'), 6.83 (s, 1H, H-3'), 6.96–7.42 (m, 12H, H-7', H-8' and Ar-H), 9.41 (s, 1H, 4'-OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4 (1-CH_3), 20.6 (2'-CH_3), 21.3 (3-CH_3), 32.7 (C-4), 43.2 (C-3), 45.4 (C-1), 46.7 (*N*-CH_2Ar), 52.2 (5'-OCH_3), 72.1 (*O*-CH_2Ar), 103.2 (C-6'), 112.9 (C-3'), 113.5 (C-4'a), 119.4 (C-8'), 121.6 (C-5), 124.5 (C-1'), 126.1 (Ar-C), 126.2 (C-7'), 126.6 (Ar-C), 127.3 (C-8a), 127.4 (Ar-C), 127.5 (C-7), 127.6 (C-6), 130.1 (Ar-C), 131.0 (Ar-C), 133.4 (Ar-C), 134.2 (C-4a), 137.9 (C-8'a), 138.2 (C-2'), 138.3 (Ar-C), 140.6 (Ar-C), 150.5 (C-8), 154.3 (C-4'), 156.8 (C-5').

EIMS (70 eV) *m/z* (rel int.): 528 (100) $[M\text{-}CH_3]^+$, 437 (6) $[M\text{-}Bn\text{-}CH_3]^+$, 91 (89) $[Bn]^+$.

HRESIMS *m/z*: calculated for $C_{37}H_{38}NO_3$ $[M+H]^+$: 544.2846; found: 544.2843.

*Jozimine A_2 (**85**) and its 3'-epimer 3'-epi-**85***

To a solution of **220** (25.0 mg, 46.0 μmol) in CH_2Cl_2 (4 mL), BF_3▪Et_2O (14.4 mg, 101 μmol) was added at 0 °C and the mixture was stirred for 5 min. A solution of $Pb(OAc)_4$ (22.4 mg, 50.6 μmol) in CH_2Cl_2 (1 mL) was added dropwise and stirring was continued for another 5 min. The reaction was quenched with a saturated aqueous Na_2SO_3 solution (5 mL), and the aequeous phase was extracted with CH_2Cl_2 (3 mL × 2). The combined organic phases were dried over $MgSO_4$, and insoluble parts were filtered off. The residue was concentrated under reduced pressure followed by purification on deactivated silica gel with PE/EtOAc (5:1) as the mobile phase, yielding a mixture of ***M*-91** and ***P*-91** (7.51 mg, 6.92 μmol, 30%) as a pale-yellow solid. Given that the two atropisomers were not separable on SiO_2 or on preparative HPLC, the mixture of the isomers was used for debenzylation without characterization. HRESIMS *m/z*: calculated for $C_{74}H_{73}N_2O_6$: 1085.5463; found: 1085.5459 $[M+H]^+$. The above-obtained mixture of the two atropisomers **91** (7.01 mg, 6.46 μmol) and Pd/C (10%, 1.01 mg) were suspended in EtOH (4 mL). The mixture was stirred for 12 h under normal H_2 pressure. After filtration over a short pad of Celite, the solvent was removed *in vacuo*. Jozimine A_2 (**85**) (1.92 mg, 2.65 μmol, 41%, white crystals) and 3',3''-*epi*-jozimine A_2 (3'-*epi*-**85**) (2.04 mg, 2.82 μmol, 44 %, white solid) were separated by preparative HPLC, using the following column and solvent gradient: Chromolith-SemiPrep column RP-C_{18} (*Merck*, 10 × 100 mm); H_2O + 0.05% TFA (A), MeCN + 0.05% TFA (B); flow rate: 10 mL min^{-1}; 0 min 10% B, 7 min 50% B, 9 min 100% B, 11 min 100% B, 12 min 10% B, 15 min 30% B.

*Jozimine A_2 (**85**)*

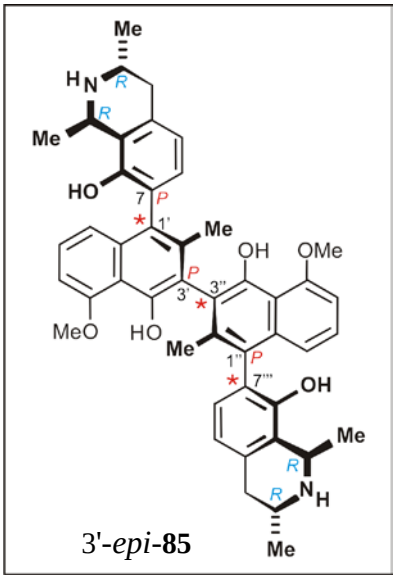
Colorless solid.

M.p. 237–239 °C (MeOH).

$[\alpha]_D^{20}$ = –27.3 (*c* = 0.10, MeOH).

Analytical data of **85** are in complete agreement with the data of the authentic sample, as described in 3.3.

*3'-epi-jozimine A$_2$ (3'-epi-**85**)*



3'-*epi*-**85**

Colorless solid.

M.p. 238–239 °C (MeOH).

$[\alpha]_D^{20}$ = +14.2 (c = 0.10, MeOH).

UV (MeOH): λ_{max} (logε) = 232, 285, 307, 323, 337 nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 340 (+1.2), 304 (–0.7), 243 (+3.5), 230 (–5.8), 215 (+3.4), 207 (–1.4).

IR (ATM): $\tilde{\nu}$ = 2853 (w), 1672 (s), 1456 (m), 1398 (m), 1199 (s), 1132 (s), 798 (m) cm^{-1}.

^{1}H NMR (600 MHz, MeOD): δ = 1.52 (d, ^3J = 6.7 Hz, 3H, 3-CH_3 and 3'''-CH_3), 1.67 (d, ^3J = 6.8 Hz, 3H, 1-CH_3 and 1'''-CH_3), 1.82 (s, 3H, 2'-CH_3 and 2''-CH_3), 2.97 (dd, ^2J = 17.5 Hz, ^3J = 11.6 Hz, 1H, Hax-4 and Hax-4'''), 3.25 (dd, ^2J = 17.3 Hz, ^3J = 5.0 Hz, 1H, Heq-4 and Heq-4'''), 3.88 (m, 1H, H-3 and H-3'''), 4.15 (s, 3H, 5'-OCH_3 and 5''-OCH_3), 4.87 (q, ^3J = 6.6 Hz, 1H, H-1 and H-1'''), 6.90 (d, ^3J = 7.8 Hz, 1H, H-5 and H-5'''), 6.93 (d, ^3J = 7.7 Hz, 1H, H-8' and H-8''), 7.04 (d, ^3J = 7.8 Hz, 1H, H-6 and H-6'''), 7.06 (d, ^3J = 8.5 Hz, 1H, H-6' and H-6''), 7.25 (dd, ^3J = 8.5 Hz, ^3J = 7.8 Hz, 1H, H-7' and H-7'').

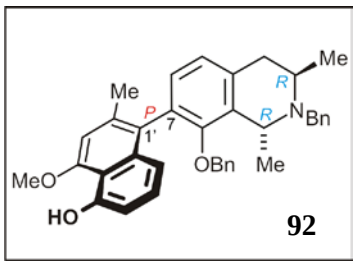
^{13}C NMR (150 MHz, MeOD): δ = 18.2 (1-CH_3 and 1'''-CH_3), 18.3 (2'-CH_3 and 2''-CH_3), 19.4 (3-CH_3 and 3'''-CH_3), 34.8 (C-4 and C-4'''), 45.5 (C-3 and C-3'''), 50.1 (C-1 and C-1'''), 57.3 (5'-OCH_3 and 5''-OCH_3), 105.8 (C-6' and C-6''), 115.4 (C-4a' and C-4a''), 120.6 (C-8' and C-8''), 121.2 (C-5 and C-5'''), 121.8 (C-3' and C-3''), 122.2 (C-8a and C-8'''a), 126.1 (C-7 and C-7'''), 126.4 (C-1' and C-1''), 127.4 (C-7' and C-7''), 132.7 (C-6 and C-6'''), 132.9 (C-4a and C-4'''a), 137.3 (C-8'a and C-8''a), 138.7 (C-2' and C-2''), 152.6 (C-4' and C-4''), 152.6 (C-8 and C-8'''), 157.6 (C-5' and C-5'') ppm.

HRESIMS m/z: calculated for $C_{46}H_{49}N_2O_6$ $[M+H]^+$: 725.3585; found: 725.3592.

4.2 Synthesis of Jozimine A_3 (**93**)

*N,8-O-Dibenzyl-5'-O-demethyldioncophylline A (**92**)*

A suspension of compound **90** (56.8 mg, 156.0 µmol), Cs_2CO_3 (111.7 mg, 343.2 µmol) and benzyl bromide (26.6 mg, 156.0 µmol) in acetone (10 mL) was refluxed for 2 h. Another equivalent of benzyl bromide (26.6 mg, 156.0 µmol) was then added in portions over a period of 12 h. The reaction mixture was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Column chromatography on deactivated silica gel (7.5% NH_3) with a mobile phase of PE/EtOAc (20:1) yielded **92** (72.0 mg, 132.6 µmol, 85%) as a pale-yellow solid.



92

Pale-yellow solid.

Yield: 72.0 mg, (132.6 µmol, 85%).

$[\alpha]_D^{20}$ = +28.0 (*c* = 0.1, $CHCl_3$).

Lit.: +28.8 (*c* = 0.51, $CHCl_3$).[157]

Lit.: +28.8 (*c* = 0.51, $CHCl_3$).[156]

^{1}H NMR (400 MHz, CD_3OD): δ = 1.34 (d, ^3J = 6.8 Hz, 3H, 1-CH_3), 1.40 (d, ^3J = 6.6 Hz, 3H, 3-CH_3), 2.82 (m, 2H, H-4), 3.52 (d, ^3J = 14.0 Hz, 1H, *N*-CH_2Ar), 3.65 (m, 1H, H-3), 3.99 (m, 1H, *N*-CH_2Ar), 4.01-4.18 (m, 3H, *O*-CH_2Ar and 1-H), 4.22 (s, 3H, 4'-OCH_3), 6.47-7.48 (m, 16H, Ar-H) ppm.

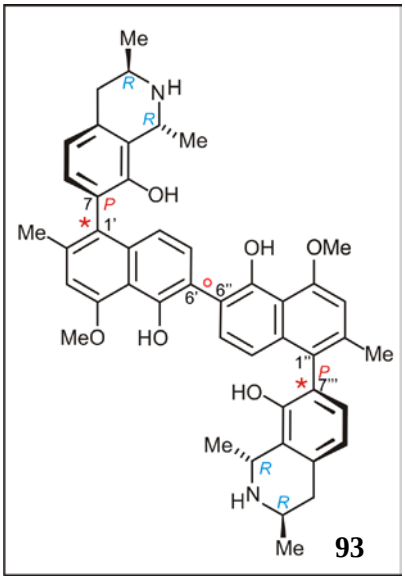
^{13}C NMR (100 MHz, CD_3OD): δ = 20.0 (1-CH_3), 20.5 (3-CH_3), 21.0 (2'-CH_3), 32.9 (C-4), 46.6 (C-3), 50.8 (*N*-CH_2Ar), 52.3 (H-1), 56.8 (4'-OCH_3), 75.5 (*O*-CH_2Ar), 107.8, 110.0, 110.1, 114.7, 117.6, 125.5, 127.5, 128.4, 128.5, 128.7, 128.8, 129.1, 129.4, 130.6, 131.0, 134.0, 136.1, 136.8, 137.3, 138.1, 142.0, 155.8, 155.9, 156.1, 156.6 ppm.

EIMS m/z (rel. int.): 420 $[M-123]^+$ (20), 528 $[M-15]^+$ (100).

The spectroscopic data are in good agreement with those in the literature.[156,157]

*Jozimine A_3 (**93**)*

To a solution of **92** (17.7 mg, 32.5 µmol) in $CHCl_3$ (5 mL) and NEt_3 (10 µL), freshly prepared dry Ag_2O (271.0 mg, 1.17 mmol) was added and stirred for 8 h under air at room temperature. The reaction mixture was filtered on a short pad of Celite using CH_2Cl_2/CH_3OH (100 : 1) as a mobile phase. After evaporation of the solvent *in vacuo*, the deep-violet colored crude product (16.0 mg) was hydrogenated in ethanol (6 mL) in the presence of Pd/C (4.0 mg) under normal H_2 pressure for 4 h. 2 N aqueous HCl solution (20 µL) was added into the mixture and stirred for another 12 h at room temperature. After filtration over a short pad of Celite eluting with CH_2Cl_2/CH_3OH (100 : 1), the solvent was removed under reduced pressure. Jozimine A_3 (**93**) (3.1 mg, 4.4 µmol, 28%) was isolated by preparative HPLC on SymmetryPrep C_{18}, 19 × 300 mm column (Waters) and the following solvent gradient: H_2O + 0.05% TFA (A), MeCN + 0.05% TFA (B); flow rate: 10 mL min^{-1}; 0 min 20% B, 35 min 60% B, 36 min 95% B, 41 min 95% B, 42 min 20% B, 46 min 20% B.



93

Colorless solid.

Yield: 3.1 mg, (4.4 µmol, 28%).

M.p. dec. ≥ 230 °C (MeOH).

$[\alpha]_D^{20}$ = +37.5 (*c* = 0.1, MeOH).

UV (MeOH): λ_{max} (logε) = 235, 263, 286, 312, 329, 339 nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 224 (–6.2), 268 (+2.9), 280 (+7.1), 302 (–3.1), 343 (+1.1).

IR (ATR): $\tilde{\nu}$ = 3733 (s), 1734 (m), 1682 (m), 1601 (m), 1201 (w), 1146 (w), 1051 (m), 799 (m) cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.53 (d, ^3J = 6.8 Hz, 3H, CH_3-3 and CH_3-3'''), 1.72 (d, ^3J = 6.8 Hz, 3H, CH_3-1 and CH_3-1'''), 2.18 (s, 3H, CH_3-2' and CH_3-2''), 2.94 (dd, ^2J = 17.6, ^3J = 11.8 Hz, 1H, H-4ax and Hax-4'''), 3.24 (dd, ^2J = 17.6, ^3J = 5.2 Hz, 1H, H-4eq and Heq-4'''), 3.91 (m, 1H, 3-H and 3''''-H), 4.13 (s, 3H, OCH_3-4' and OCH_3-4''), 4.89 (q, 1H, ^3J = 6.8 Hz, H-1 and H-1'''), 6.75 (d, ^3J = 8.7 Hz, 1H, H-8' and H-8''), 6.89 (d, ^3J = 8.0 Hz, 1H, H-5 and H-5''''), 6.97 (s, 1H, H-3' and H-3''), 6.98 (d, ^3J = 8.0 Hz, 1H, H-6 and H-6''''), 7.22 (d, ^3J = 8.7 Hz, 1H, H-7' and H-7'') ppm.

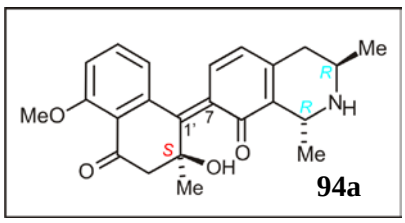
^{13}C NMR (150 MHz, CD_3OD): δ = 18.0 (CH_3-1 and CH_3-1'''), 19.3 (CH_3-3 and CH_3-3'''), 20.7 (CH_3-2' and CH_3-2''), 34.5 (C-4 and C-4'''), 45.2 (C-3 and C-3'''), 49.9 (C-1 and C-1'''), 56.7 (4'-OCH_3 and 4''-OCH_3), 108.4 (C-3' and C-3''), 115.3 (C-10' and C-10''), 116.9 (C-8' and C-8''), 120.8 (C-6' and C-6''), 121.3 (C-5 and C-5'''), 122.2 (C-9 and C-9'''), 125.7 (C-7 and C-7'''), 126.9 (C-1' and C-1''), 132.0 (C-7' and C-7''), 132.5 (C-10 and C-10'''), 132.6 (C-6 and C-6'''), 137.0 (C-2' and C-2''), 137.2 (C-9' and C-9''), 152.3 (C-8 and C-8'''), 152.6 (C-5' and C-5''), 157.7 (C-4' and C-4'') ppm.

HRESIMS m/z: calculated for $C_{30}H_{31}NO_3$: 725.3585 $[M+H]^+$; found: 725.3583.

4.3 Synthesis of Dioncotetralones A (**94a**) and B (**94b**)

To a solution of dioncophylline A (**6**) (11.0 mg, 28.0 µmol) in CH_2Cl_2 (2 mL), BF_3▪Et_2O (73.0 µmol) was added at 0 °C and the mixture was stirred for 5 min. A solution of $Pb(OAc)_4$ (14.7 mg, 33.6 µmol) in CH_2Cl_2 (1 mL) was added dropwise and stirring was continued for another 5 min. The reaction mixture was filtered on a short pad of Celite eluting with a mobile phase of CH_2Cl_2/MeOH (8 : 2). After removal of the organic solvents, the residue was purified on preparative HPLC using the following column and a linear gradient: Chromolith-SemiPrep column RP-C_{18} (*Merck*, 10 × 100 mm); H_2O + 0.05% TFA (A), MeCN + 0.05% TFA (B); flow rate: 10 mL min^{-1}; 0 min 5% B, 7 min 45% B, 9 min 100% B, 11 min 100% B, 12 min 5% B, 15 min 5% B, yielding **94a** (3.2 mg, 8.4 µmol, 30%, retention time = 3.8 min) and **94b** (3.4 mg, 8.9 µmol, 32%, retention time = 4.0 min), both as yellowish solids.

*Dioncotetralone A (**94a**)*



94a

Colorless solid.

Yield: 3.2 mg, (8.4 µmol, 30%).

M.p. >230 °C (CH_3OH).

$[\alpha]_D^{20}$ = +135 (c = 0.21, CH_3OH).

UV (MeOH): λ_{max} (logε) = 255 (0.51), 285 (0.31), 310 (0.34) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 216 (–10.5), 235 (+15.2), 345 (–0.22) nm.

IR (ATR): $\tilde{\nu}$ = 3380 (w), 2934 (w), 2837 (w), 1625 (m), 1588 (m), 1460 (w), 1431 (m), 1292 (w), 1243 (w), 1122 (w), 1086 (m), 1045 (m), 1023 (m), 877 (w), 753 (w) cm^{-1}.

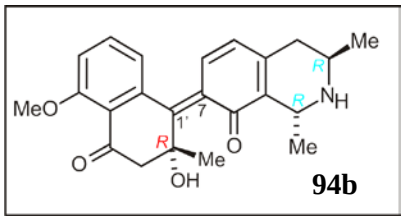
^1H NMR (600 MHz, CD_3OD): δ = 1.36 (s, CH_3-2'), 1.49 (d, ^3J = 6.8 Hz, 3H, CH_3-3), 1.75 (d, ^3J = 6.8 Hz, 3H, CH_3-1), 2.85 (dd, ^3J =11.1, ^2J = 17.4 Hz, 1H, Hax-4), 3.00 (d, ^2J = 19.4 Hz, 1H, Hax-3'), 3.15 (dd, ^3J = 4.4, ^2J = 17.4 Hz, 1H, Heq-4), 3.36 (d, ^2J = 19.4 Hz, 1H, Heq-3'), 3.84 (m, 1H, H-3), 3.92 (s, 3H, OCH_3-5'), 4.78 (q, ^3J = 6.8 Hz, 1H, H-1), 6.53 (d, ^3J = 8.4 Hz, 1H, H-8'), 6.78 (d, ^3J = 8.4 Hz, 1H, H-5), 6.95 (d, ^3J = 8.4 Hz, 1H, H-6), 6.97 (d, ^3J = 8.4 Hz, 1H, H-6'), 7.49 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-7') ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 18.2 (3-CH_3), 19.1 (1-CH_3), 22.8 (2'-CH_3), 34.5 (C-4), 44.9 (C-3'), 46.0 (C-3), 49.4 (C-1), 56.4 (5'-OCH_3), 59.5 (C-2'), 111.7 (C-6'), 114.7 (C-10'), 117.9 (C-10), 118.9 (C-8'), 123.3 (C-5), 124.1 (C-6), 124.3 (C-9'), 132.7 (C-9), 134.4 (C-7), 138.6 (C-7'), 155.3 (C-8), 159.3 (C-5'), 160.8 (C-1'), 204.7 (C-4') ppm.

MS (EI, 70 eV): *m/z* (%) = 362 $[M–17]^+$ (70), 364 $[M–15]^+$ (100), 378 $[M–1]^+$ (16).

HRMS (ESI): calcd. for $C_{23}H_{26}NO_4$ $[M+1]^+$: 380.1848; found 380.1849.

*Dioncotetralone B (**94b**)*



94b

Colorless solid.

Yield: 3.9 mg, (8.9 µmol, 32%).

M.p. 162–165 °C (CH_3OH).

$[\alpha]_D^{20}$ = –206 (*c* = 0.21, CH_3OH).

UV (MeOH): λ_{max} (logε) = 255 (0.45), 285 (0.20), 310 (0.27) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 218 (+10.5), 236 (–18.8), 341 (+0.16) nm.

IR (ATR): $\tilde{\nu}$ = 3380 (w), 3016 (w), 2839(w), 1671 (m), 1591 (m), 1481 (w), 1435 (w), 1273 (m), 1179 (m), 1129 (m), 1033 (w), 831 (w), 799 (m), 782 (w), 721 (m) cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.36 (s, CH_3-2'), 1.49 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 1.78 (d, ^{3}J = 6.8 Hz, 3H, CH_3-1), 2.85 (dd, ^{3}J = 11.1, ^{2}J = 17.4 Hz, 1H, Hax-4), 3.00 (d, ^{2}J = 19.4 Hz, 1H, Hax-3'), 3.15 (dd, ^{3}J = 4.4, ^{2}J = 17.4 Hz, 1H, Heq-4), 3.36 (d, ^{2}J = 19.4 Hz, 1H, Heq-3'), 3.84 (m, 1H, H-3), 3.93 (s, 3H, OCH_3-5'), 4.79 (q, ^{3}J = 6.8 Hz, 1H, H-1), 6.52 (d, ^{3}J = 8.4 Hz, 1H, H-8'), 6.78 (d, ^{3}J = 8.4 Hz, 1H, H-5), 6.96 (d, ^{3}J = 8.4 Hz, 1H, H-6), 6.98 (d, ^{3}J = 8.4 Hz, 1H, H-6'), 7.51 (dd, ^{3}J = 8.4, ^{3}J = 8.4 Hz, 1H, H-7') ppm.

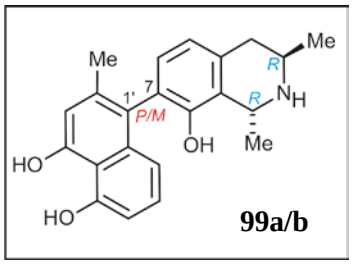
^{13}C NMR (150 MHz, CD_3OD): δ = 18.5 (3-CH_3), 19.0 (1-CH_3), 22.8 (2'-CH_3), 34.5 (C-4), 44.9 (C-3'), 46.1 (C-3), 49.9 (C-1), 56.4 (5'-OCH_3), 59.6 (C-2'), 111.7 (C-6'), 114.5 (C-10'), 118.1 (C-10), 118.9 (C-8'), 123.2 (C-5), 124.1 (C-6), 124.3 (C-9'), 132.7 (C-9), 134.3 (C-7), 138.7 (C-7'), 155.2 (C-8), 159.3 (C-5'), 160.6 (C-1'), 204.6 (C-4') ppm.

MS (EI, 70 eV): *m*/*z* (%) = 362 $[M–17]^+$ (70), 364 $[M–15]^+$ (100), 378 $[M–1]^+$ (16).

HRMS (ESI): calcd. for $C_{23}H_{26}NO_4$ $[M+1]^+$: 380.1848; found 380.1849.

4.4 Synthesis of 4',5'-*O*,*O*-Didemethyldioncophylline A (**99a**/**99b**)

To the solution of dioncophylline A (**6**) (64.0 mg, 169 µmol) in DMF (5 mL), NaSMe (35.6 mg, 508 µmol) was portionwise added under argon and the reaction mixture was stirred at 120 °C overnight. DMF was removed by evaporation under reduced pressure. The residue was filtered on a short pad of Celite and directedly submitted for NMR measurement.



99a/b

Colorless powder.

Yield: 58.9 mg, (169 µmol, 100%).

UV (MeOH): λ_{max} (logε) = 231 (1.45), 306 (0.70) nm.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.52 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 1.53 (d, ^{3}J = 6.8 Hz, 3H, CH_3-3), 1.68 (d, ^{3}J = 6.8 Hz, 3H, CH_3-1), 1.69 (d, ^{3}J = 6.8 Hz, 3H, CH_3-1), 2.07 (s, 3H, CH_3-2'), 2.08 (s, 3H, CH_3-2'), 2.85-2.98 (m, 2H, Hax-4), 3.18-3.30 (m, 2H, Heq-4), 3.90 (m, 2H, H-3),* 4.86 (m, 2H, H-1), 6.64-6.70 (m, 4H, H-6', 8'),* 6.73 (s, 1H, H-3'), 6.74 (s, 1H, H-3'), 6.84 (d, ^{3}J = 8.4 Hz, 2H, H-5),* 6.92 (d, *J* = 8.4 Hz, 2H, H-6),* 7.08 (d, ^{3}J = 8.4, ^{3}J = 8.4 Hz, 2H, H-7') ppm.*

^{13}C NMR (100 MHz, CD_3OD): δ = 18.0 (1-CH_3),* 19.2 (3-CH_3),* 20.6 (2'-CH_3),* 20.7 (2'-CH_3),* 34.6 (C-4), 45.4 (C-3), 50.1 (C-1), 108.9 (C-8'),* 112.2 (C-3'),* 115.0 (C-9'),* 118.1 (C-6'), 121.2 (C-5), 122.0 (C-10), 124.6 (C-1'), 126.0 (C-7), 127.9 (C-7'),* 128.0 (C-7'),* 132.2 (C-9), 132.7 (C-6), 137.9 (C-2'),* 138.0 (C-10'),* 152.3 (C-8), 155.6 (C-4'),* 155.7 (C-5') ppm.*

*: These signals overlapped for the two isomers.

MS (EI, 70 eV): *m*/*z* (%) = 349 $[M-1]^+$ (14), 334 $[M-15]^+$ (100).

HRMS (ESI): calcd. for $C_{22}H_{24}NO_3$ $[M+1]^+$: 350.1746; found 350.1744.

The spectroscopic data are in agreement with those in the literature.[273]

5 Phytochemical Investigation on *T. peltatum*

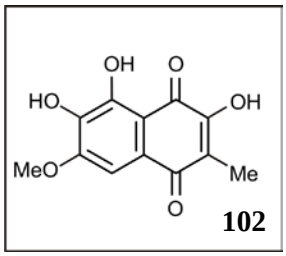
5.1 Extraction and Isolation

Seeds from *T. peltatum* were obtained from the Parc de Tai, Ivory Coast. Voucher specimens of plant species have been deposited in the Herb. Bringmann, University of Würzburg [Nos. 2, 35, and 36 (*T. peltatum*)].

35.2 g lyophilized cell cultures of *T. peltatum* were ground and extracted with CH_2Cl_2 : CH_3OH (1 : 1 *v*/*v*). The extract was condensed under reduced pressure to give 6.6 g of a crude residue, which was subjected to a cation exchange column chromatography eluting successively with methanol, aqueous saturated NaCl solution, methanol, water, acetone and methanol. From the first methanol fraction, the three known main metabolites were detectable by HPLC (T_R = 2.84 min for **9**, 4.81 min for **10**, and 6.33 min for **101**), together with some other minor compounds, **100** and **102**–**107**.

The three main naphthoquinones, dioncoquinones A (**9**) and B (**10**) and droserone (**101**), were isolated on normal-phase silica gel using the gradient of the mixing solvents ($CHCl_3$: CH_3OH : HCOOH = 1 : 0 : 0 → 1 : 0 : 0.005 → 1 : 0 : 0.008 → 1 : 0.05 : 0.008 → 1 : 0.1 : 0.01 → 1 : 0.15 : 0.01 *v*/*v*). The other four naphthoquinones, dioncoquinone C (**102**) (T_R = 10.9 min), dioncoquinone D (**103**) (T_R = 18.9 min), dioncoquinone E (**104**) (T_R = 11.2 min), and 8-hydroxydroserone (**105**) (T_R = 11.0 min) were isolated by preparative HPLC [Symmetry RP-18 (19 × 300 mm, 7 μm); H_2O + 0.05% TFA (A) / CH_3OH + 0.05% TFA (B), 0 min 53% A, 35 min 20% A, 37 min 5% A, 42 min 5% A, 43 min 53% A, 48 min 53% A]. In addition, triphoquinol A (**107**) (T_R = 8.0 min) was obtained by preparative HPLC [Merck Chromolith RP-18 (4.6 × 100mm, 5 μm); H_2O + 0.05% TFA (A) / CH_3CN + 0.05% TFA (B), 0 min 50% A, 10 min 40% A, 12 min 3% A, 14 min 3% A, 15 min 50% A;], and plumbagin (**100**) was detectable.

5.2 Dioncoquinone C (**102**)



102

Yellow solid (1.0 mg).

M.p. > 340 °C (MeOH).

UV (MeOH): λ_{max} (logε) = 255 (2.17), 305 (1.78), 425 (1.11) nm.

^{1}H NMR (MeOD, 600 MHz): δ = 1.97 (s, 3H, CH_3-2), 3.99 (s, 1H, 7-OCH_3), 7.29 (s, 1H, H-8) ppm.

^{13}C NMR (MeOD, 150 MHz): δ = 8.6 (CH_3-2), 56.9 (7-OCH_3), 105.1 (C-8), 110.3 (C-10), 121.5 (C-2), 125.5 (C-9), 140.0 (C-6), 151.2 (C-5), 154.0 (C-7), 156.4 (C-3), 185.7 (C-4 or C-1), 185.8 (C-1 or C-4) ppm.

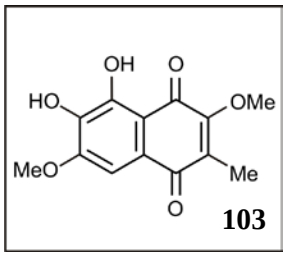
^{1}H NMR (CD_3COCD_3, 600 MHz): δ = 1.98 (s, 3H, CH_3-2), 4.01 (s, 1H, 7-OCH_3), 7.27 (s, 1H, H-8) ppm.

^{13}C NMR (CD_3COCD_3, 150 MHz): δ = 8.6 (CH_3-2), 56.8 (7-OCH_3), 104.8 (C-8), 109.8 (C-10), 121.0 (C-2), 125.3 (C-9), 139.4 (C-6), 150.5 (C-5), 153.6 (C-7), 154.8 (C-3), 184.2 (C-1), 185.1 (C-4) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 250 $[M]^+$ (47), 233 $[M–18]^+$ (23), 220 [M–30] (7), 204 [M–46] (5).

HRESIMS *m*/*z* calcd. for $C_{12}H_9O_6$ $[M–1]^+$: 249.0399; found 249.0404.

5.3 Dioncoquinone D (**103**)



103

Yellow solid (1.0 mg).

M.p. > 340 °C (MeOH).

UV (MeOH): λ_{max} (logε) = 255 (2.17), 305 (1.78), 425 (1.11) nm.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.05 (s, 3H, CH_3-2), 4.01 (s, 3H, 7-OCH_3), 4.05 (s, 3H, 3-OCH_3), 7.26 (s, 1H, H-8), 11.82 (s, 1H, 5-OH) ppm.

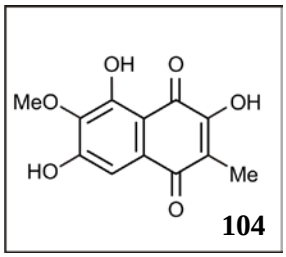
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 9.6 (CH_3-2), 58.0 (7-OCH_3), 61.3 (3-OCH_3), 103.6 (C-8),

110.1 (C-10), 124.4 (C-9), 133.3 (C-2), 138.2 (C-6), 149.2 (C-5), 151.3 (C-7), 157.1 (C-3), 184.4 (C-1), 185.6 (C-4) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 264 $[M]^+$ (43), 247 ($[M–18]^+$ (21), 233 $[M–32]^+$ (11), 217 [M–47] (6).

HRESIMS *m*/*z* calcd. for $C_{13}H_{11}O_6$ $[M–1]^+$: 263.0557; found 263.0561.

5.4 Dioncoquinone E (**104**)



104

Yellow solid (1.6 mg).

M.p. > 340 °C (MeOH).

UV (MeOH): λ_{max} (logε) = 250 (2.26), 300 (1.89), 405 (1.48) nm.

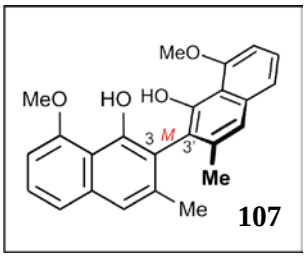
^{1}H NMR (MeOD, 600 MHz): δ = 1.96 (s, 3H, CH_3-2), 3.91 (s, 3H, 6-OCH_3), 7.09 (s, 1H, H-8) ppm.

^{13}C NMR (MeOD, 150 MHz): δ = 8.5 (CH_3-2), 61.1 (6-OCH_3), 109.1 (C-10), 110.2 (C-8), 121.2 (C-2), 130.2 (C-9), 139.7 (C-6), 157.0 (C-3), 157.3 (C-5), 158.6 (C-7), 184.9 (C-4), 185.8 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 259 $[M]^+$ (53), 233 $[M–18]^+$ (27), 220 [M–39] (5), 204 [M–55] (9).

HRESIMS *m*/*z* calcd. for $C_{12}H_9O_6$ $[M–1]^+$: 249.0399; found 249.0404.

5.5 Triphoquinol A (**107**)



107

Colorless powder (3.0 mg).

M.p. 106 °C (MeOH).

$[\alpha]_D^{20}$ = –65.0 (*c* = 0.08, CH_3OH).

UV (MeOH): λ_{max} (logε) = 250 (1.73), 265 (1.64), 310 (1.30) nm.

CD (CH_3OH): λ_{max} ($\Delta\varepsilon$) = 224 (+39.0), 242 (–25.1), 291 (+2.7), 336 (–8.6).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.15 (s, 3H, CH_3-2), 3.98 (s, 3H, CH_3O-5), 6.72 (d, ^3J = 7.8 Hz, 1H, H-6), 7.28 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1H, H-7), 7.31 (s, 1H, H-1), 7.39 (d, ^3J = 7.8 Hz, 1H, H-8), 9.53 (s, 1H, OH-4) ppm.

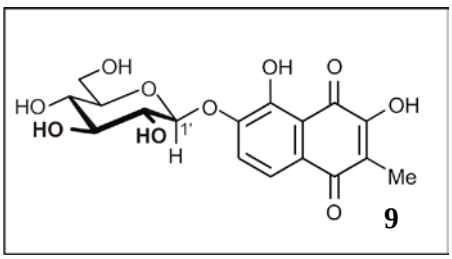
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.5 (CH_3-2), 56.2 (5-OCH_3), 103.4 (C-6), 113.8 (C-10), 119.2 (C-1), 120.3 (C-3), 121.5 (C-8), 125.6 (C-7), 136.4 (C-9), 138.1 (C-2), 150.9 (C-4), 156.4 (C-5) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 374 $[M]^+$ (100), 187 $[M/2]^+$ (14), 172 $[M/2–15]^+$.

HRESIMS *m*/*z* calcd. for $C_{24}H_{23}O_4$ $[M+1]^+$: 375.1518; found 375.1516.

5.6 Known Compounds

*Dioncoquinone A (**9**)*



9

Yellow solid (110.0 mg).

M.p. 191 °C (MeOH).
Lit.: 189 °C (MeOH).[54]

UV (MeOH): λ_{max} (logε) = 250 (2.26), 284 (1.84), 415 (0.94) nm.

IR (ATR): $\tilde{\nu}$ = 3405 (br, m), 2923 (m), 2853 (w), 1638 (s), 1458 (m), 1365 (w), 1262 (m), 1074 (s), 842 (w), 641 (w) cm^{-1}.

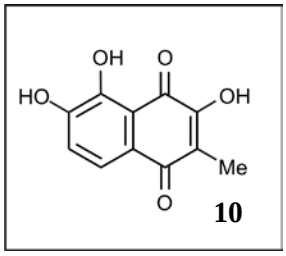
^{1}H-NMR (CD_3OD, 400 MHz): δ = 1.99 (s, 3H, CH_3-2), 3.2–3.5 (m, 4H, 2′, 3′, 4′, 5′-H), 3.70

(dd, ^3J = 11.4, ^3J = 2.3 Hz, 1H, 6′-H), 3.90 (d, ^2J = 11.4 Hz, 1H, 6′-H), 5.06 (d, ^3J = 7.1 Hz, 1H, 1′-H), 7.43 (d, ^3J = 7.2 Hz, 1H, 7-H), 7.54 (m, ^3J = 7.2 Hz, 1H, 8-H) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 220 $[M–162]^+$ (100), 192 $[M–180]^+$ (24), 163 $[M–219]^+$ (19).

The spectroscopic data are in good agreement with that in the literature.[54]

*Dioncoquinone B (**10**)*



10

Orange solid (44.0 mg).

M.p. 220 °C (MeOH).
Lit.: 218 °C (MeOH).[54]

UV (MeOH): λ_{max} (logε) = 250 (2.28), 295 (1.94), 415 (1.28) nm.

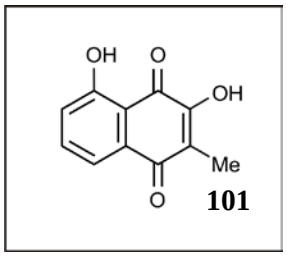
IR (ATR): $\tilde{\nu}$ = 3408 (br, m), 2922 (m), 2853 (w), 1618 (s), 1459 (m), 1297 (s), 1209 (w), 1105 (m), 430 (w) cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.07 (s, 3H, 2-CH_3), 6.03 (s, 1H, 6-OH), 7.02 (s, 1H, 3-OH), 7.15 (d, ^3J = 8.2 Hz, 1H, H-7), 7.61 (d, ^3J = 8.2 Hz, 1H, H-8), 11.19 (s, 1H, 5-OH) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 220 $[M]^+$ (46), 192 $[M–18]^+$ (15), 163 $[M–57]^+$ (13), 146 $[M–74]^+$ (12).

The spectroscopic data are in good agreement with that in the literature.[54]

*Droserone (**101**)*



101

Yellow solid (50.0 mg).

M.p. 178–180 °C (MeOH).
Lit.: 179–181 °C (MeOH).[52]

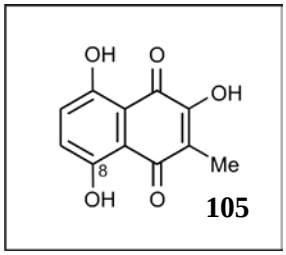
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.10 (s, 3H, CH_3-2), 7.19 (s, 1H, 3-OH), 7.19 (dd, ^3J = 8.1, ^4J = 1.5 Hz , 1H, H-8), 7.60–7.67 (m, 2H, H-6, H-7), 11.09 (s, 1H, 5-OH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.8 (CH_3-2), 117.0 (C-10), 119.7 (C-6), 121.8 (C-2), 123.2 (C-8), 132.7 (C-9), 137.5 (C-7), 152.8 (C-3), 161.2 (C-5), 184.5 (C-4), 190.0 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%): 204 $[M]^+$ (100), 176 $[M–28]^+$ (24), 147 $[M–57]^+$ (36), 121 $[M–83]^+$ (29).

The spectroscopic data are in good agreement with that in the literature.[278]

*8-Hydroxydroserone (**105**)*



105

Red solid (3.0 mg).

M.p. 193 °C ($CDCl_3$).
Lit.: 193 °C ($CDCl_3$).[162]

UV (MeOH): λ_{max} (logε) = 290 (1.70), 485 (1.41) nm.

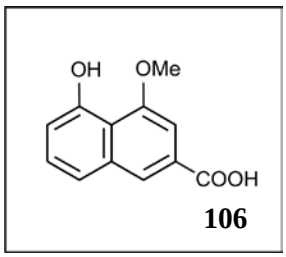
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.09 (s, 3H, CH_3-2), 7.27 (d, ^3J = 8.0 Hz, 1H, H-7), 7.16 (d, ^3J = 8.0 Hz, 1H, H-6), 7.27 (br, s, 1 H, 3-OH), 11.47 (d, 1H, 5-OH), 12.81 (d, 1H, 8-OH) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 8.5 (CH_3-2), 110.4 (C-10), 111.0 (C-9), 121.7 (C-2), 127.7 (C-6), 131.7 (C-7), 154.0 (C-3), 157.3 (C-8), 157.8 (C-5), 182.2 (C-4), 189.1 (C-1) ppm.

HRESIMS *m*/*z* calcd. for $C_{11}H_7O_5$ $[M–1]^+$: 219.0296; found 219.0299.

The spectroscopic data are in good agreement with that in the literature.[162,279]

*Ancistronaphthoic acid B (**106**)*



106

Colorless powder (3.8 mg).

M.p. 225 °C (MeOH).
Lit.: 233 °C.[136]
Lit.: 238 °C ($CHCl_3$).[35]

UV (MeOH): λ_{max} (logε) = 250 (1.84), 300 (1.42), 340 (1.27) nm.

^{1}H NMR (CD_3COCD_3 : C_5D_5N = 1 : 1 *v*/*v*, 600 MHz): δ = 4.10 (s, 3H), 7.08 (dd, ^3J = 8.0, ^4J = 1.2 Hz, 1H, H-6), 7.49 (dd, ^3J = 8.0, ^3J = 8.0 Hz, 1H, H-7), 7.58 (dd, ^3J = 8.0, ^4J = 1.2 Hz, 1H, H-8), 7.65 (d, ^3J = 1.2 Hz, 1H, H-3), 8.48 (d, ^4J = 1.2 Hz, 1H, H-1) ppm.

^{13}C NMR (CD_3COCD_3 : C_5D_5N = 1 : 1 *v*/*v*, 150 MHz): δ = 56.6 (CH_3O-4), 104.1 (C-3), 113.2 (C-6), 117.3 (C-10), 120.9 (C-8), 125.2 (C-1), 129.0 (C-7), 130.2 (C-2), 136.7 (C-9), 155.4 (C-5), 157.1 (C-4), 168.7 (COOH) ppm.

^{1}H NMR (CD_3OD, 600 MHz): δ = 4.13 (s, 3H), 6.93 (dd, ^3J = 6.6, ^4J = 1.2 Hz, 1H), 7.43–7.40 (m, 3H), 8.17 (d, ^4J = 1.2 Hz, 1H) ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 56.8 (CH_3O-4), 103.9 (C-3), 113.8 (C-6), 117.9 (C-10), 121.5 (C-8), 126.0 (C-1), 129.4 (C-7), 129.4 (C-2), 137.3 (C-9), 155.8 (C-5), 157.8 (C-4), 169.6 (COOH) ppm.

^{1}H NMR (CD_3COCD_3, 600 MHz): δ = 4.12 (s, 3H), 6.93 (dd, ^3J = 6.6, ^4J = 1.2 Hz, 1H), 7.52 – 7.41 (m, 3H), 8.20 (d, ^4J = 1.2 Hz, 1H) ppm.

^{1}H NMR (C_5D_5N, 400 MHz): δ = 3.91 (s, 3H), 7.19 (m, overlapped in the NMR solvent signal, 1H), 7.48 (dd, ^3J = 8.0, ^3J = 8.0 Hz, 1H), 7.50 (m, overlapped in the NMR solvent signal, 1H), 7.75 (d, ^4J = 1.2 Hz, 1H), 8.67 (d, ^4J = 1.2 Hz, 1H) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 218 $[M]^+$ (100), 203 $[M–15]^+$ (24), 175 $[203–28]^+$ (34).

HRESIMS *m*/*z* calcd. for $C_{12}H_{10}O_4$ $[M]^+$: 218.0579; found 218.0580.

The spectroscopic data are in good agreement with that in the literature.[35,136]

6 Phytochemical Investigation on *N. alata*

6.1 Extraction and Isolation

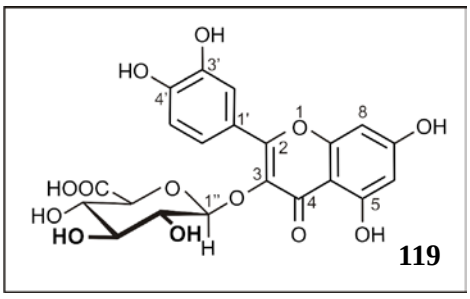
Stem and leaves of *Nepenthes alata*, *N. intermedia*, and *N. khashiama* were collected in the Botanical Garden of the University of Würzburg.

Two pieces of leaves of each plant of *N. alata*, *N. intermedia*, and *N. khashiama* were ground and extracted with CH_2Cl_2 : CH_3OH : 0.01 N HCl (1 : 1 : 0.01 *v*/*v*). The crude extracts were concentrated *in vacuo* and analyzed by HPLC [*Merck* Chromolith RP-18 (4.6 × 100 mm, 5 µm); H_2O + 0.05% TFA (A) / CH_3OH + 0.05% TFA (B), 0 min 90% A, 5 min 50% A, 7 min 3% A, 9 min 3% A, 10 min 90% A]. HPLC analysis revealed that the secondary metabolites in each plant showed rapid rention times ranging from 1.0 to 4.0 min and the maximum UV absorption wavelength below 400 nm. Based on this information, the absence of naphthoquinones in the plants can be concluded.

N. alata was phytochemically investigated for characterization of the main metabolites. 60 gram of the air dried plant were powdered and then extracted with CH_3OH : CH_2Cl_2 : 0.01 N HCl (1 : 1 : 0.01 *v*/*v*) for three times. The crude extract was submitted to liquid-liquid separation in CH_2Cl_2 and aqueous 5% $NaHCO_3$ solution. The organic layer was condensed by evaporation *in vacuo* and then fractionated by Sephadex LH-20 chromatography eluting with CH_3OH, leading to isolation of three known flavonoids **119**–**121**.

6.2 Known Compounds

*Quercetin-3-O-β-D-glucuronide (**119**)*



119

Yellow powder (22.4 mg).

M.p. 158–160 °C (MeOH).
Lit.: 190–192 °C.[280]

$[\alpha]_D^{20}$ = –90.3 (*c* = 0.92, CH_3OH).
Lit.: –24.3 (*c* = 0.66, CH_3OH).[186]

UV (MeOH): λ_{max} (logε) = 203 (4.09), 258 (1.35), 360 (1.08) nm.

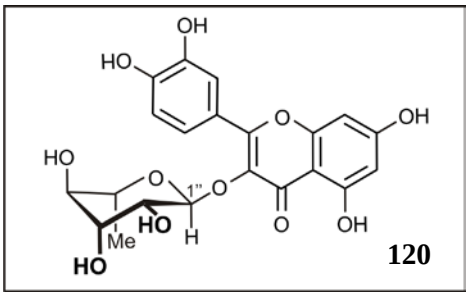
^{1}H NMR (DMSO, 400 MHz): δ = 3.3 (m, 2H, H-3", 5"), 3.4 (m, 1H, H-2"), 3.58 (m, 1H, H-4"), 5.50 (d, ^{3}J = 7.3 Hz, 1H, H-1"), 6.22 (d, ^{4}J = 2.0 Hz, 1H, H-6), 6.43 (d, ^{4}J = 2.0 Hz, 1H, H-8), 6.84 (d, ^{3}J = 8.4 Hz, 1H, H-5'), 7.53 (d, ^{4}J = 2.1 Hz, 1H, H-2'), 7.61 (dd, ^{3}J = 8.4, ^{4}J = 2.1 Hz, 1H, H-6'), 9.26 (s, 1H), 9.81 (s, 1H), 10.97 (s, 1H), 12.56 (s, 1H, 5-OH) ppm.

^{13}C NMR (DMSO, 100 MHz): δ = 71.4 (C-2"), 73.8 (C-3"), 76.0 (C-5"), 76.1 (C-4"), 93.7 (C-8), 98.8 (C-6), 101.1 (C-1"), 103.9 (C-10), 115.3 (C-5'), 116.0 (C-2'), 120.9 (C-1'), 121.8 (C-6'), 133.1 (C-3), 145.0 (C-3'), 148.7 (C-4'), 156.2 (C-2 or 9), 156.3 (C-9 or 2), 161.2 (C-5), 164.3 (C-7), 169.8 (C-6"), 177.2 (C-4) ppm.

HRESIMS *m*/*z* calcd. for $C_{21}H_{17}Na_2O_{13}$ $[M+Na]^+$: 523.0459; found 523.0465.

The spectroscopic data are in good agreement with that in the literature.[186]

*Quercetin-3-O-α-L-rhamnopyranoside (**120**)*



120

Yellow powder (7.0 mg).

M.p. 166–170 °C (MeOH).
Lit.: 175–177 °C.[187]

$[\alpha]_D^{20}$ = –258.1 (*c* = 0.5, CH_3OH).
Lit.: –144.9.[187]

UV (MeOH): λ_{max} (logε) = 203 (1.56), 256 (0.70), 354 (0.52) nm.

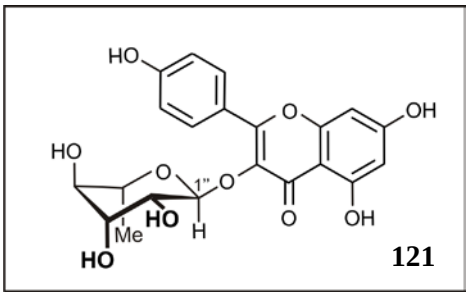
^{1}H NMR (CD_3OD, 400 MHz): δ = 0.94 (d, ^{3}J = 6.0 Hz, 3H, H-6"), 3.34 (m, 1H, H-4"), 3.41 (m, 1H, H-5"), 3.75 (dd, ^{3}J = 9.3, ^{3}J = 3.4 Hz, 1H, H-3"), 4.22 (dd, ^{3}J = 3.5, ^{3}J = 1.8 Hz, 1H, H-2"), 5.35 (d, ^{3}J = 1.6 Hz, 1H, H-1"), 6.20 (d, ^{4}J = 2.1 Hz, 1H, H-6), 6.37 (d, ^{4}J = 2.1 Hz, 1H, H-8), 6.91 (d, ^{3}J = 8.4 Hz, 1H, H-5'), 7.30 (dd, ^{3}J = 8.0, ^{4}J = 2.1 Hz, 1H, H-6'), 7.32 (d, ^{4}J = 2.1 Hz, 1H, H-2') ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 17.8 (C-6"), 72.1 (C-2"), 72.2 (C-5"), 72.3 (C-3"), 73.4 (C-4"), 94.9 (C-8), 100.0 (C-6), 103.7 (C-1"), 106.1 (C-10), 116.5 (C-5'), 117.1 (C-2'), 123.0 (C-6'), 123.1 (C-1'), 136.4 (C-3), 146.6 (C-3'), 150.0 (C-4'), 158.7 (C-9), 159.5 (C-2), 163.4 (C-5), 166.0 (C-7), 179.8 (C-4) ppm.

HRESIMS *m*/*z* calcd. for $C_{21}H_{20}NaO_{11}$ $[M+Na]^+$: 471.0903; found 471.0898.

The spectroscopic data are in good agreement with that in the literature.[187]

*Kaempferol-3-O-α-L-rhamnopyranoside (**121**)*



121

Yellow powder (3.2 mg).

M.p. 164–166 °C (MeOH).

Lit.: 164–166 °C.[188]

UV (MeOH):λ_{max} (logε) = 203 (1.34), 267 (0.31), 347 (0.09) nm.

^{1}H NMR (CD_3OD, 600 MHz): δ = 0.92 (d, ^{3}J = 5.8 Hz, 3H, H-6''), 3.3 (m, 2H, H-4'', 5''), 3.7 (m, 1H, H-3''), 4.22 (dd, ^{3}J = 3.2, ^{3}J = 1.6 Hz, 1H, H-2''), 5.37 (d, ^{3}J = 6.8 Hz, ^{4}J = 1.8 Hz, 2H, H-3', H-5'), 7.77 (dd, ^{3}J = 6.8, ^{4}J = 1.8 Hz, 2H, H-2', 6') ppm.

^{13}C NMR (CD_3OD, 150 MHz): δ = 72.1 (C-2''), 17.8 (C-6''), 72.2 (C-5''), 72.3 (C-3''), 73.3 (C-4''), 94.9 (C-8), 100.0 (C-6), 103.7 (C-1''), 106.1 (C-10), 116.7 (C-2', C-6'), 122.8 (C-1'), 132.1 (C-3', C-5'), 136.4 (C-3), 158.7 (C-9), 161.8 (C-4'), 159.5 (C-2), 163.4 (C-5), 166.1 (C-7), 179.8 (C-4) ppm.

HRESIMS *m*/*z* calcd. for $C_{21}H_{20}NaO_{10}$ $[M+Na]^+$: 455.0903; found 455.0897.

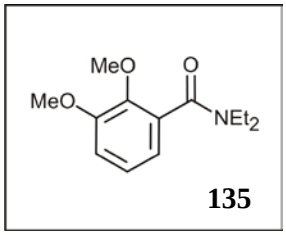
The spectroscopic data are in good agreement with that in the literatures.[186-188]

7 Synthesis of Naphthoquinones

7.1 Synthesis of the Dioncoquinone B Precursor **42**

*N,N-Diethyl-2,3-dimethoxybenzamide (**135**)*

A mixture of thionyl chloride (19.6 g, 164.7 mmol, 11.7 mL) and 2,3-dimethoxy-benzoic acid (10 g, 54.9 mmol) in a 100 mL one-necked flask was refluxed at 80 °C overnight. The excess of thionyl chloride was evaporated under reduced pressure to give the acyl chloride. It was added carefully with stirring at 0 °C to diethylamine (12.0 g, 164.7 mmol, 17.0 mL) in anhydrous THF (80 mL) in a 250-mL one-necked flask. The reaction was continued at room temperature with stirring overnight. The mixture was diluted with water, acidified with 0.5 N aqueous HCl solution, and neutralized with saturated aqueous $NaHCO_3$ solution. THF was removed on a rotatry evaporator and the suspension was extracted with $CHCl_3$ (100 mL × 3), dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and subjected to column chromatography to afford the product.



135

Dark brown liquid.

Yield: 12.7 g, (53.8 mmol, 100%).

IR (ATR): $\tilde{\nu}$ = 2977 (w), 2935 (w), 1629 (s), 1598 (s), 1460 (s), 1423 (s), 1290 (m), 1220 (m), 1086 (s), 1034 (s), 1003 (s), 810 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.21 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.13 (q, ^3J = 7.0 Hz, 2H, CH_2), 3.40 and 3.66 (broad signal, 2H, CH_2), 3.81 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 6.75 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, Ar-H), 6.88 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, Ar-H), 6.87 (dd, ^3J = 8.4, ^3J = 8.4 Hz, 1H, H-5) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (CH_3), 14.0 (CH_3), 38.9 (CH_2), 43.0 (CH_2), 55.9 (CH_3O), 61.6 (CH_3O), 112.7 (CH), 119.0 (C), 124.7 (CH), 132.6 (C), 144.9 (C), 152.8 (C), 168.4 (CO) ppm.

EIMS m/z (rel. int.): 237 $[M]^+$ (17), 236 $[M–1]^+$ (19), 165 $[M–72]^+$ (100).

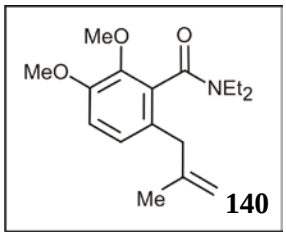
The spectroscopic data are in agreement with those reported in the literature.[200]

*N,N-Diethyl-2,3-dimethoxy-6-(2-methylallyl)benzamide (**140**)*

Preparation of $MgBr_2$▪$2Et_2O$ following a literature known[103] procedure (yet in German):

To 2.43 g magnesium (100 equiv.) in dry diethylether (50 mL) in a three-neck flask under argon, 1,2-dibromoethane (0.5 mL) was added by syringe injection. After the reaction had started, the remaining 1,2-dibromoethane (7.9 mL, total 97.4 mmol) was added under reflux. After 30 min, the flask was cooled to room temperature. The lower, brown phase, containing the $MgBr_2$▪$2Et_2O$ solution (2.62 N) was freshly utilized for the transmetalation step.

To the solution of the benzamide **135** (10.3 g, 43.4 mmol) in THF (100 mL) *s*-BuLi (34.0 mL, 47.7 mmol, 1.1 equiv.) and TMEDA (7.1 mL, 47.7 mmol, 1.1 equiv.) were added at –90 °C under argon by syringe injection and the mixture was stirred for 1.5 h. The solution of the resultant lithiated species was then warmed to –78 °C over 30 min and freshly prepared $MgBr_2$▪$2Et_2O$ (33.0 mL, 86.8 mmol, 2 equiv.) was added. The mixture was stirred for 30 min, allowed to warm to room temperature, again cooled to –78 °C, and stirred for 1 h. The freshly distilled 3-bromo-2-methylpropene (8.7 mL, 86.8 mmol) was added and the solution was allowed to warm to room temperature, and stirred overnight. The reaction mixture was treated with saturated aqueous NH_4Cl solution. Removal of THF by rotary evaporation, extraction with CH_2Cl_2, drying with Na_2SO_4, removal of the solvent, and purification by column chromatography gave **140** as a slightly yellow liquid.



140

Slight yellow liquid.

Yield: 7.60 g, (26.0 mmol, 60%).

IR (ATR): $\tilde{\nu}$ = 2977 (w), 2937 (w), 1627 (s), 1430 (s), 1376 (w), 1272 (s), 1058 (s), 890 (w), 804 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.27 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.18 (m, 2H, CH_2), 3.25 (m, 2H, CH_2), 3.61 (m, 2H, CH_2), 3.85 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.62 (s, 1H, CH_{2a}), 4.85 (s, 1H, CH_{2b}), 6.88 (s, ^3J = 8.0 Hz, 1H, Ar-H), 6.92 (s, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

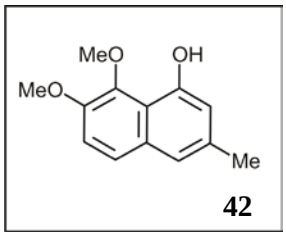
^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5 (CH_3), 13.5 (CH_3), 22.1 (CH_3), 38.2 (CH_2), 40.0 (CH_2), 42.7 (CH_2), 55.5 (CH_3O), 61.1 (CH_3O), 112.0 (CH_2), 112.4 (CH), 125.1 (CH), 128.3 (C), 132.4 (C), 143.8 (C), 144.5 (C), 150.6 (C), 167.2 (CO) ppm.

EIMS m/z (rel. int.): 291 $[M]^+$ (8), 219 $[M–72]^+$ (100), 218 $[M–73]^+$ (58).

HRMS (ESI): calcd. for $C_{18}H_{27}NNaO_4$ $[M+Na]^+$: 314.1732; found 314.1735.

*5,6-Dimethoxy-2-methyl-4-naphthol (**42**)*

To the *ortho*-allyl benzamide **140** (4.82 g, 16.5 mmol) in 50 mL THF, 2.2 equiv. of MeLi were added with stirring at –78 °C. The reaction mixture was slowly warmed up to 0 °C over 5 h, followed by addition of saturated aqueous NH_4Cl solution, evaporation of THF under reduced pressure, and extraction with EtOAc. The organic layer was dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography to afford the naphthol **42** as a colorless solid.



42

Yield: 3.57 g, (16.4 mmol, 98%).

M.p. 36–37 °C (PE/EtOAc).

Lit.: 36–37 °C (EtOAc).[99]

IR (ATR): $\tilde{\nu}$ = 3341 (br w), 2914 (w), 2359 (m), 2341 (m), 1610 (m), 1575 (w), 1356 (m), 1267 (m), 1045 (s), 976 (m), 947 (m), 843 (m), 802 (m), 784 (m), 684 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.73 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.06 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.20 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.47 (d, 1H, ^3J = 8.0 Hz, Ar-H), 9.55 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (CH_3), 57.2 (CH_3O), 62.1 (CH_3O), 112.5 (CH), 115.7 (CH), 116.4 (C), 118.3 (CH), 124.6 (C), 131.9 (C), 135.6 (C), 143.3 (C), 146.7 (C), 153.3 (C) ppm.

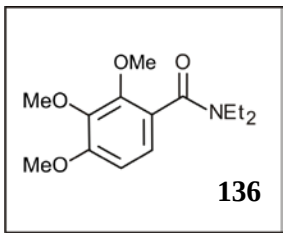
EIMS m/z (rel. int.): 218.0 $[M]^+$ (100), 203 $[M–15]^+$ (62), 175 $[M–43]^+$ (32).

The spectroscopic data are in agreement with those in the literature.[99]

7.2 Synthesis of Dioncoquinone C (**102**)

*N,N-Diethyl-2,3,4-trimethoxybenzamide (**136**)*

A mixture of thionyl chloride (1.4 g, 11.8 mmol, 837 μL) and 2,3,4-trimethoxybenzoic acid (**134**) (500.3 mg, 2.36 mmol) in a 10 mL one-necked flask was refluxed at 80 °C overnight. The excess of thionyl chloride was evaporated under reduced pressure to give the acyl chloride. It was added carefully with stirring at 0 °C to diethylamine (517.8 mg, 7.1 mmol, 732 μL) in anhydrous THF (10 mL) in a 100-mL one-necked flask. The reaction was continued at room temperature with stirring overnight. The mixture was diluted with water, acidified with 0.5 N aqueous HCl solution, and neutralized with saturated aqueous $NaHCO_3$ solution. THF was removed on a rotary evaporator and the residue was extracted with $CHCl_3$ (100 mL × 3), dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and subjected to column chromatography to afford the product.



136

Light yellow liquid.

Yield: 504 mg, (1.89 mmol, 80%).

IR (ATR): $\tilde{\nu}$ = 2972 (w), 2937 (w), 1610 (s), 1458 (s), 1433 (s), 1315 (m), 1265 (s), 1220 (m), 1002 (s), 837 (m), 794 (s), 758 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.21 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.15 (q, ^2J = 7.0 Hz, 2H, CH_2), 3.20 and 3.40 (broad signal, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.64 (d, ^3J = 8.4 Hz, 1H, Ar-H), 6.87 (*d*, ^3J = 8.4 Hz, 1H, Ar-H) ppm.

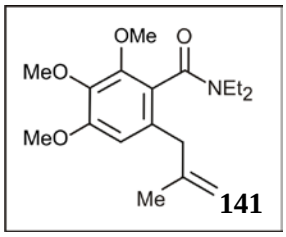
^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7 (CH_3), 13.9 (CH_3), 39.0 (CH_2), 43.1 (CH_2), 56.0 (CH_3O-4), 60.9 (CH_3O-2), 61.6 (CH_3O-3), 107.6 (C-5), 121.6 (C-6), 124.8 (C-1), 142.0 (C-2), 149.8 (C-3), 154.2 (C-4), 168.4 (CO) ppm.

EI-MS (70eV) *m/z* (%): 267 $[M]^+$ (19), 195 $[M–72]^+$ (100).

In the literature,[201] no spectroscopic data were reported.

*N,N-Diethyl-2,3,4-trimethoxy-6-(2-methylallyl)benzamide (**141**)*

To the solution of the benzamide **136** (10.3 g, 9.3 mmol) in THF (100 mL), *s*-BuLi (7.3 mL, 10.3 mmol, 1.1 equiv.) and TMEDA (1.5 mL, 10.3 mmol, 1.1 equiv.) were added at –90 °C under argon by syringe injection and the mixture was stirred for 1.5 h. The solution of the lithiated species was then warmed to –78 °C over 30 min and freshly prepared $MgBr_2 \cdot 2Et_2O$ (7.1 mL, 18.6 mmol, 2 equiv.) was added. The mixture was stirred for 30 min, allowed to warm to room temperature, again cooled to –78 °C, and stirred for 1 h. The freshly distilled 3-bromo-2-methylpropene (1.9 mL, 18.6 mmol) was added and the solution was allowed to warm to room temperature, and stirred overnight. The reaction mixture was treated with saturated aqueous NH_4Cl. Removal of THF by rotary evaporation, extraction with CH_2Cl_2, drying with Na_2SO_4, removal of the solvent, and purification by column chromatography gave **141** as a slightly yellow liquid.



141

Light yellow liquid.

Yield: 1.35 g (4.2 mmol, 45%).

IR (ATR): $\tilde{\nu}$ = 2977 (w), 2937 (w), 1625 (s), 1456 (s), 1425 (s), 1400 (s), 1319 (m), 1284 (m), 1141 (s), 1105 (s), 1033 (s), 890 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.22 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.68 (s, 3H, CH_3), 3.09 (m, 2H, CH_2), 3.15 (s, 2H, CH_2), 3.54 (m, 2H, CH_2), 3.82 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.70 (s, 1H, CH_{2a}), 4.84 (s, 1H, CH_{2b}), 6.52 (s, 1H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (CH_3), 13.9 (CH_3), 22.5 (CH_3), 38.6 (CH_2), 41.0 (CH_2), 43.1 (CH_2), 56.2 (CH_3O), 61.1 (CH_3O), 61.8 (CH_3O), 108.7 (CH_2), 113.1 (CH), 125.1 (C), 131.7 (C), 140.4 (C), 144.0 (C), 149.6 (C), 153.5 (C), 167.7 (CO).

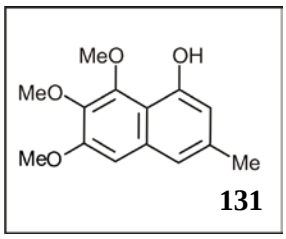
EIMS m/z (rel. int.): 321 $[M]^+$ (10), 249 $[M–72]^+$ (100).

HRMS (ESI): calcd. for $C_{17}H_{25}NNaO_3$ $[M+23]^+$: 344.1833; found 344.1834.

*5,6,7-Trimethoxy-2-methyl-4-naphthol (**131**)*

To the *ortho*-allyl benzamide **141** (1.35 g, 4.2 mmol) in 50 mL THF, 2.2 equiv. of MeLi were added with stirring at –78 °C. The reaction mixture was slowly warmed up to 0 °C over 5 h, followed by addition of saturated aqueous NH_4Cl solution, evaporation of THF on a rotary evaporator, and extraction with EtOAc. The combined organic layers were dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography to afford the naphthol **131** as a colorless solid.

Colorless solid.



131

Yield: 790 mg, (3.2 mmol, 76%).

M.p. 80–81 °C (PE/EOAc).
Lit.: 80–81 °C (Ethanol).[281]

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.39 (s, 3H, OCH_3), 3.94 (s, 6H, OCH_3), 4.13 (s, 3H, OCH_3), 6.63 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 9.34 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (CH_3), 55.8 (CH_3O), 61.2 (CH_3O), 62.2 (CH_3O), 102.9 (CH), 110.5 (CH), 110.9 (C), 117.3 (CH), 132.8 (C), 137.1 (C), 139.0 (C), 148.3 (C), 152.9 (C), 155.6 (C) ppm.

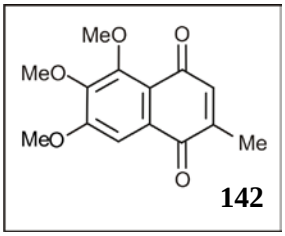
EIMS m/z (rel. int.): 248 $[M]^+$ (100), 233 $[M–15]^+$ (42), 205 $[M–43]^+$ (19).

The spectroscopic data are in agreement with those in the literature.[281]

*5,6,7-Trimethoxy-2-methyl-1,4-naphthoquinone (**142**)*

A suspension of CuCl (238 mg, 2.38 mmol) and methylnaphthol **131** (760 mg, 3.1 mmol) in acetonitrile (50 mL) was stirred for 2 h with a strong current of oxygen bubbling through it. The reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel (PE/EtOAc) to give **142** as an orange-colored solid.

Yellow powder.



142

Yield: 365 mg, (1.4 mmol, 45%).

M.p. 142–143 °C (PE/EOAc).
Lit.: 142–143 °C (Ethanol).[281]

IR (ATR): $\tilde{\nu}$ = 2945 (w), 2837 (w), 1654 (s), 1629 (m), 1572 (s), 1484 (m), 1457 (m), 1433 (w), 1408 (m), 1375 (w), 1355 (s), 1315 (s), 1279 (s), 1224 (m), 1198 (m), 1181 (m), 1159 (m), 1116 (s), 1077 (m), 1019 (m), 1005 (s), 987 (m), 934 (m), 911 (m), 900 (m), 865 (m), 820 (m), 811 (m), 781 (m), 722 (m), 701 (m), 650 (w), 631 (w) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.11 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.99 (s, 1H, OCH_3), 6.66 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H) ppm.

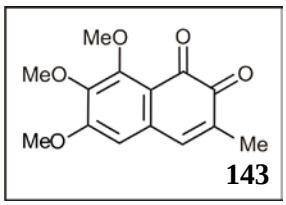
^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (CH_3), 56.4 (CH_3O), 61.3 (CH_3O), 61.6 (CH_3O), 106.3 (C), 119.7 (C), 129.5 (C), 132.5 (C), 137.6 (C), 145.5 (C), 147.9 (C), 154.0 (C), 157.2 (C), 183.6 (C), 185.1 (C) ppm.

EIMS m/z (rel. int.): 262 $[M]^+$ (100), 247 $[M–15]^+$ (69).

The spectroscopic data are in agreement with those in the literature.[281]

*6,7,8-Trimethoxy-3-methyl-1,2-naphthoquinone (**143**)*

Red powder.



143

Yield: 384 mg, (1.46 mmol, 47%).

M.p. 182 °C (PE/EOAc).
Lit.: 184 °C (PE/EOAc).[189]

IR (ATR): $\tilde{\nu}$ = 3092 (w), 2945 (w), 2920 (w), 2847 (w), 2359 (w), 1661 (s), 1648 (s), 1632 (s), 1575 (s), 1491 (s), 1455 (m), 1406 (m), 1368 (m), 1329 (s), 1267 (s), 1200 (s), 1147 (s), 1084 (m), 1030 (m), 1000 (m), 976 (m), 964 (m), 934 (m), 919 (m), 865 (m), 809 (m), 780 (m), 738 (m), 686 (m), 668 (m), 647 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.72 (s, 1 H, H-3), 7.17 (s, 1 H, Ar-H), 7.93 (s, 1 H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (CH_3), 56.4 (CH_3O), 61.4 (CH_3O), 61.5 (CH_3O), 109.0 (C), 118.1 (C), 133.2 (C), 135.6 (C), 141.6 (C), 143.7 (C), 158.4 (C), 159.1 (C), 176.8 (C), 181.8 (C) ppm.

EIMS m/z (rel. int.): 262 $[M]^+$ (4), 234 $[M–28]^+$ (100), 219 $[M–43]^+$ (88).

HRMS (ESI): calcd. for $C_{13}H_{12}O_5Na$ $[M+Na]^+$: 285.0733; found 285.0733.

The spectroscopic data are in agreement with those in the literature.[189]

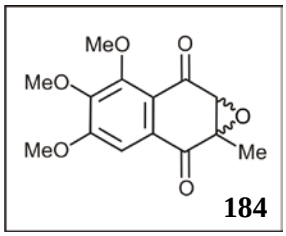
*5,6,7-Trimethoxy-2-methyl-1,4-naphthoquinone-2,3-epoxide (**184**)*

5,6,7-trimethoxy-2-methyl-naphthoquinone (68.0 mg, 260 μmol) and 130 μL (0.5 equiv.) of 1 N NaOH aqueous solution were dissolved in 10.5 mL of mixing solvents ($MeOH/H_2O$ = 4 : 1) at room temperature. After stirring at this temperature for 10 minutes, 40 μL of 35% aqueous hydrogen peroxide (1.5 equiv.) was added and stirred for 1.5 h. The reaction mixture was neutralized with 1 N aqueous HCl solution, and extracted with EtOEt (30 mL × 3). The combined organic phases were dried over Na_2SO_4, and the solvent was concentrated *in vacuo*. The crude product was purified with column chromatography.

Pale-yellow powder.

Yield: 72.0 mg, (257 μmol, 99%).

M.p. 110 °C (PE/EOAc).
Lit.: 110 °C ($MeOH/H_2O$).[189]



184

IR (ATR): $\tilde{\nu}$ = 2979 (w), 2946 (w), 1681 (s), 1654 (m), 1631 (w), 1571 (s), 1485 (m), 1461 (m), 1409 (w), 1346 (s), 1315 (m), 1279 (s), 1193 (m), 1161 (m), 1116 (s), 1099 (s), 1072 (m), 999 (s), 987 (m), 928 (m), 902 (m), 871 (m), 820 (m), 806 (m), 785 (m), 762 (m), 731 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70 (s, 3H, CH_3), 3.79 (s, 1H, H-3), 3.94 (s, 6H, OCH_3), 3.97 (s, 3H, OCH_3), 7.29 (s, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 56.4 (CH_3O), 61.2 (CH_3O), 61.6 (CH_3O), 62.1

(CH), 106.3 (C), 120.1 (C), 129.0 (C), 137.6 (C), 148.2 (C), 153.5 (C), 157.7 (C), 183.6 (C), 185.1 (C) ppm.

EIMS m/z (rel. int.): 278 $[M]^+$ (95), 235 $[M–43]^+$ (100).

HRMS (ESI): calcd. for $C_{14}H_{14}NaO_6$ $[M+Na]^+$: 301.0683; found 301.0682.

The spectroscopic data are in agreement with those in the literature.[189]

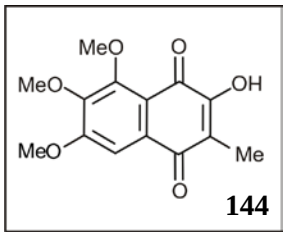
*3-Hydorxy-5,6,7-trimethoxy-2-methyl-1,4-naphthoquinone (**144**)*

To the solution of the epoxide (54.0 mg, 194 μmol) in THF (5 mL), silica gel (288 mg) and concentrated H_2SO_4 (248 μL) were added. The solvent was evaporated in vaccum (200 mbar) at 60 °C for 20 min on a rotary evaporator. To the resultant red solid, H_2O (20 mL) was added, neutralized with 5% aqueous K_2CO_3 solution, and acidified with 1 N aqueous HCl solution. The mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* affording the crude product **144** as a yellow solid, which was purified by column chromatography.

Yellow powder.

Yield: 53 mg, (192 μmol, 99%).

M.p. 175 °C (PE/EtOAc).
Lit.: 177 °C ($CHCl_3$).[189]



144

IR (ATR): $\tilde{\nu}$ = 3329 (s), 2948 (w), 2841(w), 1655 (s), 1641 (m), 1573 (s), 1486 (m), 1460 (m), 1412 (m), 1382 (m), 1346 (s), 1258 (s), 1210 (s), 1181 (m), 1144 (s), 1105 (m), 1080 (s), 1021 (m), 998 (s), 965 (m), 910 (m), 869 (m), 816 (w), 787 (m), 761 (m), 746 (s), 720 (m), 704 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.05 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 7.54 (s, 1H, OH), 7.66 (s, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ = 8.5 (CH_3), 56.5 (CH_3O), 61.3 (CH_3O), 61.6 (CH_3O), 106.8 (C), 116.3 (C), 117.7 (C), 130.7 (C), 146.6 (C), 153.7 (C), 154.7 (C), 158.5 (C), 178.9 (C), 184.3 (C)

ppm.

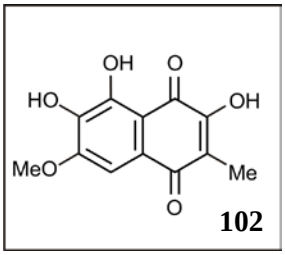
EIMS m/z (rel. int.): 278.0 $[M]^+$ (100), 263 $[M-15]^+$ (28), 235 $[M-43]^+$ (19).

HRMS (ESI): calcd. for $C_{14}H_{14}NaO_6$ $[M+Na]^+$: 301.0683; found 301.0682.

The spectroscopic data are in agreement with those in the literature.[189]

*3,5,6-Trihydroxy-7-methoxy-2-methyl-1,4-naphthoquinone (dioncoquinone C, **102**)*

A solution of BBr_3 in CH_2Cl_2 (1 M, 1.36 mmol, 1.36 mL) was added dropwise to a solution of naphthoquinone **144** (38.0 mg, 136 μmol) in dry CH_2Cl_2 (3 mL) at −78 °C under stirring. The reaction mixture was warmed to 0 °C within 2 h, then diluted with water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic layer was extracted with 5% aqueous K_2CO_3 solution, and the water layer was acidified with half-concentrated aqueous HCl solution, extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated, and subjected to preparative HPLC for purification.



102

Yellow solid.

Yield: 22.8 mg, (91.0 μmol, 67%).

M.p. >340 °C.

IR (ATR): $\tilde{\nu}$ = 3384 (m), 3921 (w), 1600 (s), 1571 (s), 1463 (w), 1319 (m), 1238 (s), 1151 (s), 1072 (s), 997 (w), 804 (w), 740 (w) cm^{-1}.

^1H NMR (600 MHz, CD_3COCD_3): δ = 1.98 (s, 3H, 2-CH_3), 4.01 (s, 1H, 7-OCH_3), 7.27 (s, 1H, 8-H) ppm.

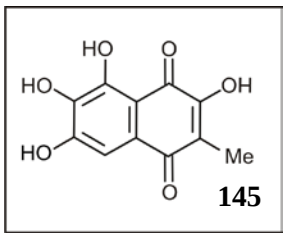
^{13}C NMR (150 MHz, CD_3COCD_3): δ = 8.6 (2-CH_3), 56.8 (7-OCH_3), 104.8 (C-8), 109.8 (C-10), 121.0 (C-2), 125.3 (C-9), 139.4 (C-6), 150.5 (C-5), 153.6 (C-7), 154.8 (C-3), 184.2 (C-1), 185.1 (C-4) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 250 $[M]^+$ (47), 233 $[M-17]^+$ (23), 220 $[M-30]^+$ (7), 204 $[M-46]^+$ (5).

HRESIMS *m/z* calcd. for $C_{12}H_9O_6$ $[M-1]^+$: 249.0399; found 249.0405.

*3,5,6,7-Tetrahydroxy-2-methyl-1,4-naphthoquinone (**145**)*

A solution of BBr_3 in CH_2Cl_2 (1 M, 1.04 mmol, 1.04 mL) was added dropwise to a solution of naphthoquinone **144** (27.0 mg, 104.0 μmol) in dry CH_2Cl_2 (3 mL) at −78 °C under stirring. The reaction mixture was warmed to room temperature within 2 h, and continued to stir overnight, then diluted with water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were extracted with 5% aqueous K_2CO_3 solution, and the water layer was acidified with half-concentrated aqueous HCl solution, extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried over Na_2SO_4, concentrated, and subjected to column chromatography.



145

Dark red solid.

Yield: 24.0 mg, (102 μmol, 98%).

M.p. 245–250 °C (EtOAc).

IR (ATR): $\tilde{\nu}$ = 3178 (m), 1614 (m), 1463 (m), 1311 (s), 1184 (s), 1090 (m), 1041 (m), 742 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H, 2-CH_3), 7.12 (s, 1H, 8-H), 9.24 (s, 1H, OH), 11.4 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.7 (CH_3-2), 108.8 (C), 109.7 (CH), 121.1 (C), 126.1 (C), 137.6 (C), 151.6 (C), 152.5 (C), 155.0 (C), 184.3 (CO), 184.7 (CO) ppm.

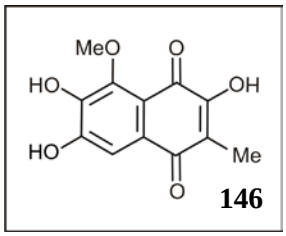
EIMS m/z (rel. int.): 236 $[M]^+$ (100), 208 $[M-28]^+$ (25).

HRESIMS *m/z* calcd. for $C_{11}H_7O_6$: 235.0248 $[M-H]^+$; found: 235.0249 $[M-H]^+$.

*3,6,7-Trihydroxy-5-methoxy-2-methyl-1,4-naphthoquinone (**146**)*

A solution of BBr_3 in CH_2Cl_2 (1 M, 321 μmol, 321 μL) was added dropwise to a solution

of naphthoquinone **144** (30.0 mg, 107 μmol) in dry CH_2Cl_2 (3 mL) at –78 °C under stirring. The reaction mixture was warmed to 0 °C within 2 h, then diluted with water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were extracted with 5% aqueous K_2CO_3 solution, and the water layer was acidified with half-concentrated aqueous HCl solution, extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated, and subjected to preparative HPLC.



146

Yellow solid.

Yield: 4.0 mg, (16.0 μmol, 15%).

M.p. > 340 °C (EtOAc).

IR (ATR): $\tilde{\nu}$ = 3489 (m), 3325 (s), 1647 (s), 1564 (s), 1385 (s), 1331 (s), 1196 (m), 1147 (m), 1095 (m), 1052 (m), 802 (w), 746 (w) cm^{-1}.

^1H NMR (600 MHz, CD_3COCD_3): δ = 7.39 (s, 1H, 8-H), 3.86 (s, 1H, 5-OCH_3), 1.93 (s, 3H, 2-CH_3) ppm.

^{13}C NMR (150 MHz, CD_3COCD_3): δ = 8.5 (CH_3-2), 61.6 (CH_3O-5), 111.3 (C-8), 116.6 (C-9), 117.7 (C-2), 127.8 (C-10), 143.8 (C-6), 149.5 (C-5), 152.0 (C-7), 155.3 (C-3), 179.4 (C-4), 184.8 (C-1) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 250 $[M]^+$ (100).

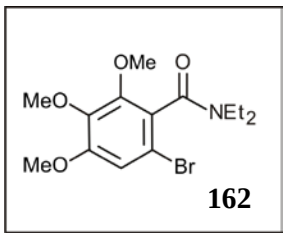
HRESIMS *m*/*z* calcd. for $C_{12}H_9O_6$ $[M–1]^+$: 249.0399; found: 249.0404.

*6-Bromo-N,N-diethyl-2,3,4-trimethoxy-benzamide (**162**)*

s-BuLi (1.22 mL, 1.72 mmol, 1.1 equiv.) and TMEDA (256 μL, 1.72 mmol, 1.1 equiv.) was added into *N*,*N*-diethyl-2,3,4-trimethoxybenzamide (**136**) (417 mg, 1.56 mmol) in THF (10 mL) by syringe injection at –90 °C under nitrogen and the reaction mixture was stirred for 1.5 h. To the solution of the lithiated species, 1,2-dibromoethane (586 mg, 3.12 mmol, 270 μL) in 5 mL THF was carefully added at –90 °C. After 1 h, the mixture was allowed to warm to room temperature and treated with saturated aqueous NH_4Cl solution. The organic solvent THF was removed by rotary evaporation and the water layer was extracted with EtOEt (20

mL × 3). The combined layers were dried with Na_2SO_4 and concentrated to dryness. The crude product was purified with column chromatography.

Colorless liquid.



162

Yield: 260 mg, (0.70 mmol, 45%).

IR (ATR): $\tilde{\nu}$ = 2973 (w), 2936 (w), 1633 (s), 1589 (m), 1455 (m), 1424 (m), 1389 (m), 1302 (m), 1285 (m), 1136 (m), 1104 (s), 1033 (m), 1009 (m), 936 (w), 844 (w), 793 (w), 738 (w), cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.16 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.39 (m, 1H, CH_{2a}), 3.55(m 1H, CH_{2b}), 3.76 (s, 6H, CH_3O-2, CH_3O-4), 3.80 (s, 3H, CH_3O-3), 6.76 (s, 1H, H-5) ppm.

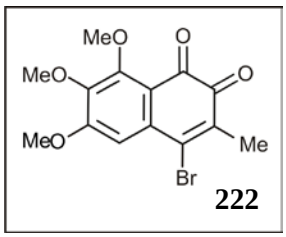
^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (CH_3), 13.7 (CH_3), 38.9 (CH_2), 42.9 (CH_2), 56.3 (CH_3O-4 or CH_3O-2), 60.9 (CH_3O-2 or CH_3O-4), 61.8 (CH_3O-3), 111.9 (C-5), 112.8 (C-1 or 6), 126.4 (C-6 or 1), 141.7 (C-2), 150.6 (C-3), 154.1 (C-4), 165.9 (CO) ppm.

EIMS m/z (rel. int.): 345 $[M]^+$ (20), 347 $[M]^+$ (19), 273 $[M–72]^+$ (100), 275 $[M–72]^+$ (97), 266 $[M–80]^+$ (50).

HRMS (ESI): calcd. for $C_{14}H_{20}BrNNaO_4$ $[M+Na]^+$: 368.0468; found 368.0467; $C_{14}H_{20}BrNNaO_5$ $[M+Na]^+$: 370.0448; found 370.0447.

*5,6,7-Trimethoxy-1-bromo-2-methyl-1,2-naphthoquinone (**222**)*

BBr_3 (22.3 µL, 235 µmol) was added into a solution of 5,6,7-trimethoxy-2-methyl-1,2-naphthoquinone (30.8 mg, 117 µmol) in dry CH_2Cl_2 (3 mL) at –78 °C. The reaction mixture was stirred for 1 h, quenched with cold water, and then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography.



222

Red powder.

Yield: 32.0 mg, (94 μmol, 40%).

M.p. 168–170 °C (CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 2920 (w), 2850 (w), 1661 (m), 1565 (m), 1488 (m), 1462 (m), 1397 (w), 1322 (m), 1287 (s), 1261 (s), 1149 (m), 1091 (m), 966 (m), 920 (m), 847 (m), 784 (m), 752 (m), 669 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.24 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 7.537 (s, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3), 56.6 (CH_3O), 61.6 (CH_3O), 61.9 (CH_3O), 111.3 (CH), 117.6 (C), 132.2 (C), 138.0 (C), 143.1 (C), 144.5 (C), 157.9 (C), 158.5 (C), 176.5 (CO), 178.9 (CO) ppm.

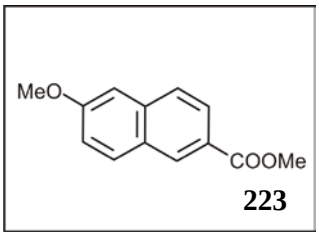
MS (EI, 70 eV): *m*/*z* (%) = 312 $[M–28]^+$ (70), 314 $[M–28]^+$ (70), 297 $[M–56]^+$ (33), 299 $[M–56]^+$ (32), 233 $[M–110]^+$ (100).

HRMS (ESI): calcd. for $C_{14}H_{13}BrNaO_5$ $[M+Na]^+$: 362.9838; found 362.9833; $C_{14}H_{13}BrNaO_5$ $[M+Na]^+$: 364.9820; found 364.9816.

7.3 Synthesis of the Dioncoquinone B Analog **151**

*Methyl-6-Methoxy-naphthalene-2-carboxylate (**223**)*

K_2CO_3 (6.2 g, 45 mmol) was added into the solution of 6-hydroxy-naphthalene-2-carboxylic acid (1.5 g, 8 mmol) in acetone (40 mL) at 0 ºC. The mixture was magnetically stirred for 30 min, then dimethylsulfate (5.04 g, 3.8 mL, 40 mmol) was injected into the flask *via* a syring. The reaction mixture was refluxed for 2 h, quenched by addition of water (40 mL), and then extracted with CH_2Cl_2 (60 mL × 3) after removal of acetone. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography with the mobile phase of (PE/EtOAc = 95 : 5).



223

Colorless powder.

Yield: 1.66 g, (7.7 mmol, 96%).

M.p. 125–127 °C (PE/EOAc).
Lit.: 128–129 °C (EtOH).[282]

IR (ATR): $\tilde{\nu}$ = 2950 (w), 2817 (w), 2847 (w),1705 (m), 1625 (m), 1600 (m), 1484 (m), 1434 (m), 1290 (m), 1201 (s), 1125 (s), 1095 (m), 1023 (m), 974 (m), 949 (m), 864 (m), 818 (m), 769 (m), 754 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3H, CH_3O-6), 3.97 (s, 3H, $COOCH_3$), 7.16 (d, ^4J = 2.5 Hz, 1H, H-5), 7.19 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.75 (d, ^3J = 8.4 Hz, 1H, H-4), 7.84 (d, ^3J = 8.4 Hz, 1H, H-8), 8.02 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-3), 8.53 (d, ^4J = 2.5 Hz, 1H, H-1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.0 ($COOCH_3$), 55.5 (CH_3O-6), 105.8 (C-5), 119.8 (C-7), 125.4 (C-3), 126.1 (C-3), 127.0 (C-4), 128.0 (C-10), 131.0 (C-1 and C-8), 137.3 (C-9), 159.7 (C-6), 167.5 ($COOCH_3$) ppm.

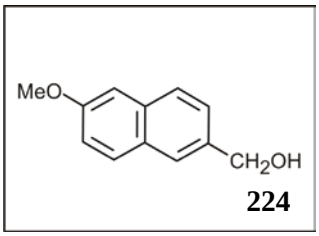
EIMS m/z (rel. int.): 216 $[M]^+$ (100), 185 $[M–31]^+$ (90), 157 $[M–59]^+$ (34).

The spectroscopic data are in good agreement with those in the literature.[282]

*6-Methoxy-2-hydroxymethylnaphthalene (**224**)*

$LiAlH_4$ (874 mg, 23 mmol) was dissolved in dry THF (30 mL) in a 100 mL three-neck flask. The solution of **223** (1.6 g, 7.4 mmol) in dry THF (40 mL) was dropped into the flaks under stirring. The reaction mixture was refluxed for 1.5 h, quenched by addition of water (30 mL), neutralized with half-concentrated aqueous HCl solution and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography with the mobile phase of PE/EtOAc = 8 : 2.

Colorless powder.



224

Yield: 1.21 g, (6.4 mmol, 86%).

M.p. 115–117 °C (PE/EOAc).
Lit.: 120–122 °C (EtOH).[282]

IR (ATR): $\tilde{\nu}$ = 3239 (w), 2979 (w), 1632 (w), 1604 (w), 1484 (m), 1453 (m), 1390 (m), 1263 (m), 1236 (m), 1213 (m), 1160 (m), 1022 (s), 889 (m), 856 (s), 815 (s), 756 (m), 697 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H, CH_3O-6), 4.82 (s, 2H, CH_2OH), 7.15 (m, 2H, Ar-H), 7.45 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, Ar-H), 7.73 (m, 3H, Ar-H) ppm.

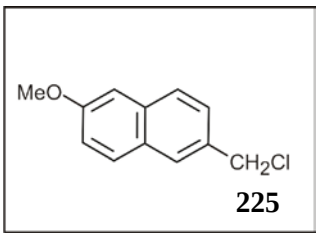
^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5 ($COOCH_3$), 65.8 (CH_2OH), 106.0, 119.2, 125.8, 126.1, 127.4, 129.0, 129.6, 134.3, 136.3, 158.0 ($COOCH_3$) ppm.

EIMS m/z (rel. int.): 188 $[M]^+$ (100), 171 $[M–16]^+$ (31).

HRMS (ESI): calcd. for $C_{12}H_{12}NaO_2$ $[M+Na]^+$: 211.0725; found 211.0725.

The spectroscopic data are in agreement with those in the literature.[282]

*2-Chloromethyl-6-O-methylnaphthalene (**225**)*



225

Yield: 0.18 g, (0.89 mmol, 12%).

M.p. 55–56 °C (PE/EOAc).
Lit.: 57–59 °C (EtOH).[283]

IR (ATR): $\tilde{\nu}$ = 2963 (w), 1629 (m), 1603 (m), 1483 (m), 1454 (m), 1390 (m), 1269 (m), 1231 (s), 1173 (m), 1121 (w), 1027 (s), 899 (m), 854 (m), 816 (m), 757 (m), 705 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 (s, 3H, CH_3O-6), 4.54 (s, 2H, CH_2Cl), 6.94 (d, ^4J = 2.5 Hz, 1H, H-5), 7.00 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.28 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-3), 7.53 (m, 3H, H-1, H-4, H-8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.0 (CH_2Cl), 55.4 (CH_3O-6), 105.9 (C-5), 119.4 (C-7), 127.0 (C-3), 127.6 (C-1 or C-8), 127.7 (C-8 or C-1), 128.7 (C-9), 129.6 (C-4), 132.7 (C-2),

134.5 (C-10), 158.3 (C-6) ppm.

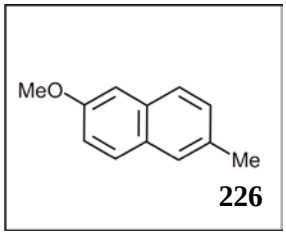
EIMS m/z (rel. int.): 206 $[M]^+$ (21), 171 $[M-35]^+$ (100).

HRMS (ESI): calcd. for $C_{11}H_{12}O$ $[M-35]^+$: 171.0889; found 171.0888.

The spectroscopic data are in agreement with those in the literature.[283]

*6-Methoxy-2-methylnaphthalene (**226**)*

To a solution of **224** (1.2 g, 6.3 mmol) in methanol (30 mL) in a 100 mL flask was added concentrated aqueous HCl solution (1.25 mL) and Pd/C (64 mg, 5%). The reaction mixture was stirred in the H_2-atomosphere at room temperature for 40 min, and filtered through a short pad of Celite and eluted with methanol. The eluent was concentrated by evaporation before addition of water (50 mL), and the mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* affording the product.



226

Colorless powder.

Yield: 1.1 g, (6.2 mmol, 98%).

M.p. 71–72 °C (PE/EOAc).
Lit.: 75–76 °C.[204]

IR (ATR): $\tilde{\nu}$ = 3003 (w), 2963 (w), 1604 (m), 1502 (s), 1482 (m), 1462 (w), 1388 (m), 1263 (s), 1226 (s), 1158 (m), 1117 (m), 1032 (s), 927 (w), 853 (s), 803 (s), 754 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3H, CH_3-2), 3.91 (s, 3H, CH_3O-6), 7.11 (d, ^4J = 2.5 Hz, 1H, Ar-H), 7.12 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, Ar-H), 7.28 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.54 (d, ^4J = 2.5 Hz, 1H, Ar-H), 7.65 (m, 2H, Ar-H) ppm.

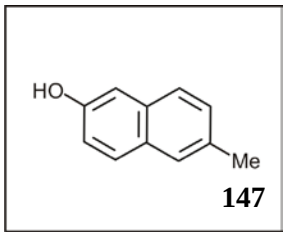
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3-2), 55.4 (CH_3O-6), 105.9, 118.8, 126.8, 126.9, 128.8, 128.9, 129.4, 132.9, 133.2, 157.2 ($COOCH_3$) ppm.

EIMS m/z (rel. int.): 172 $[M]^+$ (100), 129 $[M-43]^+$ (58).

The spectroscopic data are in agreement with those in the literature.[204]

*6-Hydroxy-2-methylnaphthalene (**147**)*

A solution of BBr_3 in CH_2Cl_2 (1 M, 8.7 mmol, 8.7 ml) was added dropwise to a solution of **226** (1.0 g, 5.8 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, then diluted with water (40 mL) and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography.



147

Colorless powder.

Yield: 0.94 g (5.6 mmol, 97%).

M.p. 115–118 °C (PE/EOAc).
Lit.: 118–123 °C.[204]

IR (ATR): $\tilde{\nu}$ = 3245 (w), 1604 (m), 1517 (w), 1481 (w), 1390 (w), 1350 (w), 1206 (m), 1174 (m), 1145 (m), 1035 (w), 861 (s), 798 (m), 648 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3H, CH_3-2), 7.05 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.10 (d, ^4J = 2.5 Hz, 1H, H-5), 7.27 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-3), 7.54 (d, ^4J = 2.5 Hz, 1H, H-1), 7.58 (d, ^3J = 8.4 Hz, 1H, H-4), 7.65 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3-2), 109.6 (C-5), 117.9 (C-7), 126.4 (C-4), 127.0 (C-1), 129.0 (C-3), 129.3 (C-8 or C-10), 129.4 (C-10 or C-8), 132.9 (C-9), 133.3 (C-2), 152.9 (C-6) ppm.

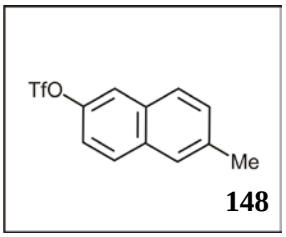
EIMS m/z (rel. int.): 158 $[M]^+$ (100), 128 $[M–30]^+$ (18).

The spectroscopic data in agreement with those in the literature.[204]

*2-Methyl-6-[(trifluoromethanesulfonyl)oxyl]-naphthalene (**148**)*

To a solution of 6-hydroxy-2-methylnaphthalene (0.90 g, 5.4 mmol) in CH_2Cl_2 (20 mL),

NaH (0.65 g of a 60% powder in oil, 16.2 mmol) was added under nitrogen and the solution was stirred for 30 min at 0 ºC. A solution of Tf_2O (0.82 g, 5.8 mmol) in CH_2Cl_2 (15 mL) was added dropwise over a period of 15 min and after stirring for 5 min, the reaction mixture was directly filtered through a short pad of silica gel and then washed with CH_2Cl_2 giving a white solid after removal of the solvent.



148

White solid.

Yield: 1.5 g, (5.3 mmol, 98%).

M.p. 45 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 1600 (m), 1425 (m), 1402 (m), 1210 (s), 1132 (s), 1105 (m), 920 (m), 884 (m), 822 (m), 798 (m), 742 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H, CH_3-2), 7.32 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, Ar-H), 7.41 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, Ar-H), 7.66 (d, ^4J = 2.5 Hz, 1H, Ar-H), 7.70 (d, ^4J = 2.5 Hz, 1H, Ar-H), 7.76 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.82 (d, ^3J = 8.4 Hz, 1H, Ar-H) ppm.

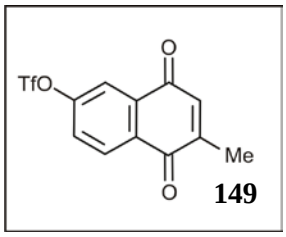
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3-2), 119.0, 119.1 (q, ^2J = 320.9 Hz, CF_3), 119.5, 127.0, 127.8, 130.0, 130.0, 131.6, 132.8, 137.3, 146.7 (C-6) ppm.

EIMS m/z (rel. int.): 290 $[M]^+$ (68), 157 $[M–133]^+$ (100), 129 $[M–161]^+$ (77).

HRMS (ESI): calcd. for $C_{12}H_9F_3NaO_3S$ $[M+Na]^+$: 313.0117; found 313.0117.

*2-Methyl-6-[(trifluoromethanesulfonyl)oxyl]-1,4-naphthoquinone (**149**)*

To a solution of H_5IO_6 (2.44 g, 10.7 mmol) and CrO_3 (17.8 mg, 178 μmol) in acetonitrile (30 mL), the ester (517 mg, 1.78 mmol) in acetonitrile (5 mL) was added dropwise with vigorous stirring at 0 ºC. After stirring at 0 ºC overnight, the reaction mixture was filtered over a short normal-phase silica gel column, and washed quickly with CH_2Cl_2. After evaporation of the solvent *in vacuo*, the desired product was purified by column chromatography (PE/EtOAc = 97 : 3).



149

Yellow solid.

Yield: 192 mg, (0.59 mmol, 35%).

M.p. 82 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 1661 (m), 1595 (m), 1583 (m), 1424 (m), 1352 (w), 1295 (m), 1201 (s), 1132 (s), 918 (m), 866 (m), 826 (m), 744 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.22 (d, ^4J = 1.6 Hz, 3H, CH_3-2), 6.93 (d, ^4J = 1.6 Hz, 1H, H-3), 7.61 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.94 (d, ^4J = 2.5 Hz, 1H, H-5), 8.25 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

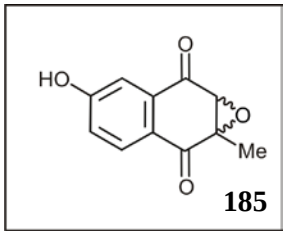
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (2-CH_3), 117.3 (C-5), 118.8 (q, J = 320.9 Hz, CF_3), 126.5 (C-7), 129.7 (C-8), 131.8 (C-10), 134.6 (C-9), 136.0 (C-3), 149.0 (C-3), 153.1 (C-6), 183.0 (C-4), 184.0 (C-1) ppm.

EIMS m/z (rel. int.): 320 $[M]^+$ (100), 188 $[M–132]^+$ (35).

HRMS (ESI): calcd. for $C_{12}H_7F_3O_5SNa$ $[M + 23]^+$: 342.9858; found 342.9858.

*6-Hydroxy-2-methyl-1,4-naphthoquinone-2,3-epoxide (**185**)*

Aqueous H_2O_2 solution (30%, 14.8 mmol, 1.46 mL) was added with stirring to the quinone **149** (53 mg, 165 μmol) in THF (4 mL) at 0 ºC. 874 μL (874 μmol) 1 N aqueous Na_2CO_3 solution was added carefully untile the orange solution had turned colorless. Stirring was continued at 0 ºC for 3.5 h, and 1.5 mL ice-cold saturated aqueous Na_2SO_3 solution was carefully added. The mixture was stirred for 20 min, diluted with water and extracted with $CHCl_3$ (20 mL × 3). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give the epoxide **185** as a pure product after column chromatography.



185

Colorless solid.

Yield: 31.0 mg, (152 μmol, 92%).

M.p. 181 °C ($MeOH/H_2O$).

IR (ATR): $\tilde{\nu}$ = 3417 (w), 1694 (m), 1671 (m), 1592 (m), 1577 (m), 1321 (m), 1257 (m), 1233 (m), 1218 (m), 1089 (m), 1012 (s), 785 (s), 743 (s) cm^{-1}.

^1H NMR (400 MHz, CD_3COCD_3): δ = 1.65 (s, 3H, CH_3-2), 3.92 and 3.54 (s, 1H, H-3), 7.27 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.32 (d, ^4J = 2.5 Hz, 1H, H-5), 7.92 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

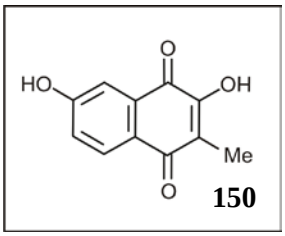
^{13}C NMR (100 MHz, CD_3COCD_3): δ = 15.0 (2-CH_3), 62.1 (C-2), 62.4 (C-3), 112.8 (C-5), 122.4 (C-7), 125.4 (C-10), 130.8 (C-8), 135.4 (C-9), 163.8 (C-6), 191.2 (C-1), 192.3 (C-4) ppm.

EIMS m/z (rel. int.): 204 $[M]^+$ (100), 189 $[M–15]^+$ (99).

HRMS (ESI): calcd. for $C_{11}H_8NaO_4$ $[M + 23]^+$: 227.0315; found: 227. 0315.

*3,6-Dihydroxy-2-methyl-1,4-naphthoquinone (**150**)*

To the solution of the epoxide **185** (7.7 mg, 23.0 μmol) in THF (1 mL), silica gel (35.0 mg) and concentrated H_2SO_4 (28.5 μL) were added. The solvent was evaporated in vaccum (200 mbar) at 70 °C for 20 min on a rotary evaporator. To the resultant red solid, H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was extracted with 5% aqueous K_2CO_3 solution until it had turned colorless. The water layer was acidified with half-concentrated aqueous HCl solution and extracted with CH_2Cl_2 until the color in the water layer was colorless again. Removal of the organic solvent gave the crude product as a red solid, which was purified by column chromatography (PE/EtOAc/FA = 7 : 3 : 0.01).



150

Yellow solid.

Yield: 4.2 mg, (12.5 μmol, 54%).

M.p.> 340 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 3280 (m), 1666 (m), 1651 (m), 1631 (m), 1573 (m), 1375 (m), 1303 (m), 1258 (m), 1062 (m), 1014 (s), 887 (m), 795 (s) cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 1.99 (s, 3H, CH_3-2), 7.07 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H,

H-7), 7.37 (d, ^4J = 2.5 Hz, 1H, H-5), 7.89 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

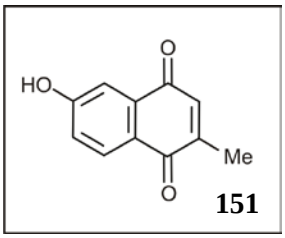
^{13}C NMR (150 MHz, CD_3OD): δ = 8.5 (2-CH_3), 112.9 (C-5), 121.0 (C-2), 121.6 (C-7), 126.1 (C-10), 129.7 (C-8), 133.6 (C-9), 156.4 (C-3), 163.5 (C-6), 182.3 (C-4), 186.6 (C-1) ppm.

EIMS m/z (rel. int.): 204 $[M]^+$ (100), 176 $[M–28]^+$ (27).

HRMS (ESI): calcd. for $C_{11}H_8NaO_4$ $[M+Na]^+$: 227.0314; found 227.0315.

*6-Hydroxy-2-methyl-1,4-naphthoquinone (**151**)*

To a solution of the trifluoromethanesulfonic ester **149** (150 mg, 470 μmol) in dioxane (2 mL), 10% aqueous Et_4NOH solution (689 mg, 940 μmol, 673 μL) was carefully added at ambient temperature. The mixture was stirred for 30 min, diluted with CH_2Cl_2 (10 mL) and water (10 mL), and neutralized with 1 N aqueous HCl solution. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.



151

Yellow solid.

Yield: 44.0 mg, (235 μmol, 50%).

M.p. 175 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 3361 (s), 1662 (s), 1650 (s), 1594 (s), 1573 (s), 1457 (m), 1350 (m), 1329 (m), 1267 (m), 1235 (m), 1203 (m), 1134 (m), 887 (m), 848 (m), 692 (m) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OCD_3): δ = 2.13 (d, ^4J = 1.6 Hz, 3H, CH_3-2), 6.82 (d, ^4J = 1.6 Hz, 1H, H-3), 7.22 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.39 (d, ^4J = 2.5 Hz, 1H, H-5), 7.95 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

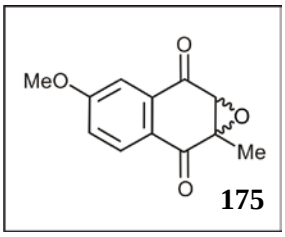
^{13}C NMR (100 MHz, CD_3OCD_3): δ = 16.4 (2-CH_3), 112.4 (C-5), 121.3 (C-7), 125.9 (C-10), 130.0 (C-8), 135.6 (C-9), 135.9 (C-3), 149.4 (C-2), 163.4 (C-6), 184.5 (C-1), 185.5 (C-4) ppm.

EIMS m/z (rel. int.): 188 $[M]^+$ (100), 160 $[M–28]^+$ (23).

HRMS (ESI): calcd. for $C_{11}H_7O_3$ $[M–1]^+$: 187.0400; found187.0401.

*6-Methoxy -2-methyl-1,4-naphthoquinone-2,3-epoxide (**175**)*

K_2CO_3 (98.0 mg, 710 μmol) was added to the solution of the epoxide **185** (29.0 mg, 142 μmol) in acetone (3 mL) at 0 ºC. The mixture was magnetically stirred for 30 min, then dimethylsulfate (89.5 mg, 67.4 μL, 710 μmol) was injected into the flask *via* a syringe and stirred for 3 h. The reaction mixture was quenched by addition of water (20 mL), neutralized with 1 N aqueous HCl solution, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried with Na_2SO_4, concentrated to dryness, purified by column chromatography to afford the desired epoxide as a colorless solid.



175

Colorless solid.

Yield: 30.3 mg, (139.2 μmol, 98%).

M.p. 89 °C ($MeOH/H_2O$).

IR (ATR): $\tilde{\nu}$ = 1684 (s), 1592 (s), 1494 (m), 1433 (m), 1294 (s), 1232 (s), 1192 (m), 1057 (m), 1026 (m), 948 (m), 856 (s), 780 (m), 740 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 3H, CH_3-2), 3.83 (s, 1H, H-3), 3.91 (s, 3H, CH_3O-6), 7.21 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.37 (d, ^4J = 2.5 Hz, 1H, H-5), 7.97 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (2-CH_3), 56.1 (CH_3O-6), 61.4 (C-2), 61.6 (C-3), 110.0 (C-5), 121.7 (C-7), 125.5 (C-10), 130.1 (C-8), 134.3 (C-9), 164.7 (C-6), 190.8 (C-1), 192.0 (C-4) ppm.

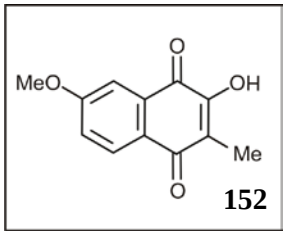
EIMS m/z (rel. int.): 218 $[M]^+$ (100), 203 $[M–15]^+$ (82), 119 $[M–99]^+$ (51).

HRMS (ESI): calcd. for $C_{12}H_{10}NaO_4$: 241.0471 $[M+Na]^+$; found: 241.0470.

*3-Hydroxy-6-methoxy-2-methyl-1,4-naphthoquinone (**152**)*

To the solution of the epoxide **175** (14.0 mg, 64 μmol) in THF (1 mL), silica gel (95.0 mg) and concentrated H_2SO_4 (82 μL) were added. The solvent was evaporated in vaccum (200 mbar) at 60 °C for 20 min on a rotary evaporator. To the resultant red solid, H_2O (10 mL) and

CH_2Cl_2 (20 mL) were added. The mixture was basified with 5% aqueous K_2CO_3 solution, acidified with 1 M aqueous HCl solution, and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.



152

Yellow solid.

Yield: 13.6 mg, (62.7 μmol, 96%).

M.p. 162–163 °C (PE/EtOAc).
Lit.: 174–175 °C (Benzene).[207]

IR (ATR): $\tilde{\nu}$ = 3365 (w), 1720 (w), 1639 (m), 1590 (s), 1495 (s), 1383 (w), 1344 (m), 1316 (s), 1271 (s), 1231 (s), 1070 (s), 1024 (s), 876 (m), 863 (s), 745 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3-2), 3.93 (s, 3H, CH_3O-6), 7.19 (dd, ^3J = 8.4, ^4J = 2.5 Hz, 1H, H-7), 7.51 (d, ^4J = 2.5 Hz, 1H, H-5), 8.05 (d, ^3J = 8.4 Hz, 1H, H-8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8 (2-CH_3), 56.1 (CH_3O-6), 110.1 (C-5), 120.6 (C-2), 120.9 (C-7), 126.5 (C-10), 129.2 (C-8), 131.4 (C-9), 153.1 (C-3), 163.6 (C-6), 181.6 (C-4), 184.7 (C-1) ppm.

EIMS m/z (rel. int.): 218 $[M]^+$ (100), 190 $[M–28]^+$ (26).

HRMS (ESI): calcd. for $C_{12}H_{10}NaO_4$: 241.04713 $[M+Na]^+$; found: 241.04718.

In the literature,[207] no spectroscopic data were reported.

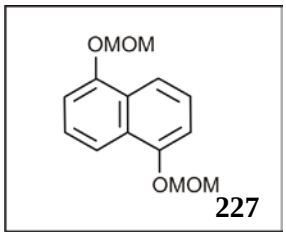
7.4 Synthesis of the Dioncoquinone B Analogs **155** and **161**

*1,5-Dimethoxymethoxy naphthalene (**227**)*

To a solution of 1,5-dihydroxynaphthalene (9.80 g, 61.2 mmol) in dry THF (180 mL) and DMF (20 mL), sodium hydride (3.5 g of a 60% powder in oil, 87.5 mmol) was added at 0 °C. After stirring for 30 min, a solution of MOMCl (5.10 mL, 68.7 mmol) in dry EtOEt (20 mL) was dropwise added. The reaction mixture was heated at 50 °C for 30 min and cooled to room temperature. THF and DMF were removed by evaporation under reduced pressure. H_2O was poured into the flask and the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried with Na_2SO_4, concentrated *in vacuo*, and purified by crystallization

from 20 mL methanol to afford **227**.

Colorless crystal.



227

Yield: 4.78 g (19.2 mmol, 31%).
Lit.: 80%.[209]

M.p.107 °C (MeOH).
Lit.: 109 °C (MeOH).[209]

IR (ATR): $\tilde{\nu}$ = 2995 (w), 2950 (w), 2937 (w), 2830 (w), 1592 (m), 1508 (m), 1419 (m), 1389 (m), 1340 (w), 1308 (w), 1255 (m), 1203 (w), 1147 (s), 1088 (m), 1011 (s), 914 (s), 862 (m), 766 (s), 654 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.56 (s, 6H, OCH_3), 5.42 (s, 4H, CH_2), 7.17 (d, ^3J = 7.6 Hz, 2H, Ar-H), 7.43 (dd, ^3J = 7.9 Hz, 2H, Ar-H), 7.98 (d, ^3J = 8.2 Hz, 2H, Ar-H) ppm.

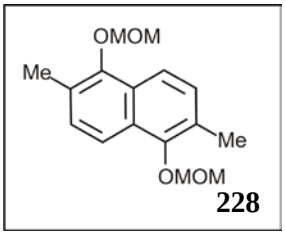
MS (EI = 70 eV): m/z (%) 248 $[M]^+$ (31), 45 $[M–203]^+$ (100).

The physical and spectroscopic data are in agreement with that in the literature.[209]

*1,5-Dimethoxymethoxy-2,6-dimethylnaphthalene (**228**) and 1,5-Dimethoxymethoxy-2-methyl naphthalene (**229**)*

To a solution of naphthalene **227** (1.50 g, 6.04 mmol) in dry EtOEt (60 mL) and distilled TMEDA (3.80 mL), *s*-BuLi (15.1 mL, 1.6 M, 24.2 mmol) was added into the flask slowly at –78 °C under nitrogen atmosphere. After stirring for 2 h, the reaction mixture was allowed to warm up to room temperature and stirred for another 1 h at 0 °C. MeI (3.1 mL, 49.6 mmol) was added into the flask and stirred for 2 h. The reaction mixture was poured into 100 mL H_2O and the organic solvent was removed by evaporation. The crude product was extracted with $CHCl_3$ (50 mL × 3) and the combined organic layers were dried with Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (PE/EtOAc = 19 : 1).

*1,5-Dimethoxymethoxy-2,6-dimethyl naphthalene (**228**)*



228

White solid.

Yield: 475 mg (1.72 mmol, 28%).
Lit.: 80%.[209]

M.p. 107 °C ($CHCl_3$).
Lit.: 105 °C (MeOH).[209]

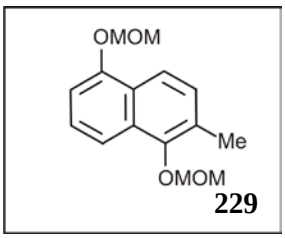
IR (ATR): $\tilde{\nu}$ = 2995 (w), 2925 (w), 2827 (w), 1603 (w), 1502 (w), 1465 (w), 1421 (w), 1369 (m), 1336 (w), 1234 (m), 1151 (m), 1076 (m), 1043 (m), 972 (s), 918 (s), 862 (m), 816 (s), 750 (w), 723 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.49 (s, 6H, CH_3), 3.69 (s, 6H, OCH_3), 5.16 (s, 4H, CH_2), 7.33 (d, ^3J = 8.5 Hz, 2H, Ar-H), 7.83 (d, ^3J = 8.5 Hz, 2H, Ar-H) ppm.

MS (EI = 70 eV): m/z (%) 276 $[M]^+$ (31), 45 $[M–231]^+$ (100).

The physical and spectral data are in agreement with that in the literature.[209]

*1,5-Dimethoxymethoxy-2-methylnaphthalene (**229**)*



229

White solid.

Yield: 398 mg (1.52 mmol, 25%).

M.p. 48 °C ($CHCl_3$).

IR (ATR): $\tilde{\nu}$ = 2993 (w), 2939 (w), 2835 (w), 1601 (w), 1506 (w), 1477 (w), 1421 (w), 1369 (m), 1238 (m), 1151 (s), 1086 (s), 1034 (s), 976 (s), 918 (s), 868 (m), 827 (m), 793 (s), 746 (s), 700 (w), 665 (m), 611 (w) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.56 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2), 5.41 (s, 2H, CH_2), 7.12 (d, ^3J = 7.6 Hz, 1H, Ar-H), 7.37 (d, ^3J = 8.5 Hz, 1H, Ar-H), 7.45 (t, ^3J = 7.9 Hz, 1H, Ar-H), 7.81 (d, ^3J = 8.5 Hz, 1H, Ar-H), 8.07 (d, ^3J = 8.5 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0 (CH_3), 56.5 (OCH_3), 58.0 (OCH_3), 95.0 (CH), 100.1

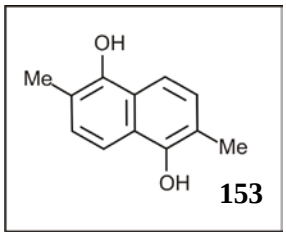
(CH), 107.7 (CH), 115.6 (CH), 118.4 (CH), 126.2 (CH), 127.5 (C), 128.9 (C), 130.0 (C), 151.2 (CO), 153.4 (CO) ppm.

MS (EI = 70 eV): m/z (%) 262 $[M]^+$ (31), 45 $[M–217]^+$ (100).

HRMS (ESI): calcd. for $C_{15}H_{18}NaO_4$ $[M+Na]^+$: 285.1097; found 285.1096.

*1,5-Dihydroxy-2,6-dimethylnaphthalene (**153**)*

Compound **228** (120 mg, 507 μmol) was dissolved in methanol (4 mL) and concentrated aqueous HCl solution (330 μL). The solution was stirred for 2 h at room temperature followed by addition of H_2O (10 mL). The precipitation was filtered, washed with water and dried with the high vaccum to afford the desired product.



153

White solid.

Yield: 91 mg (484 μmol, 95%).

M.p. 210 °C ($CHCl_3$).
Lit.: 205 °C (PE).[209]

IR (ATR): $\tilde{\nu}$ = 3348 (br m), 2921 (w), 2840 (w), 1608 (m), 1504 (m), 1354 (m), 1277 (s), 1236 (s), 1205 (m), 1173 (s), 953 (w), 877 (s), 806 (s), 677 (s) cm^{-1}.

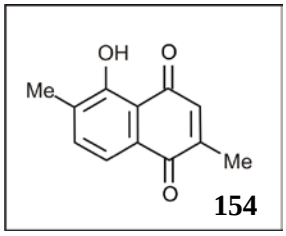
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.39 (s, 6H, CH_3), 7.18 (d, ^3J = 8.5 Hz, 2H, Ar-H), 7.20 (d, ^3J = 8.5 Hz, 2H, Ar-H), 7.88 (s, 2H, OH) ppm.

The physical and spectral data are in agreement with those in the literature.[209]

*5-Hydroxy-2,6-dimethylnaphthalene (**154**)*

A suspension of CuCl (42.0 mg, 424 μmol) and 1,5-dihydroxy-2,6-dimethylnaphthalene (**153**) (91.0 mg, 484 μmol) in acetonitrile (10 mL) was stirred at room temperature for 10 h with a strong current of oxygen bubbling through it. The reaction mixture was diluted with

water (20 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel (PE/EtOAc = 8 : 2) to give **154** as an orange solid.



154

Orange crystal.

Yield: 58 mg (287 μmol, 59%).

M.p. 148 °C ($CHCl_3$).
Lit.: 152 °C (PE).[209]

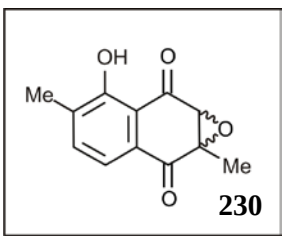
IR (ATR): $\tilde{\nu}$ = 3080 (w), 2921 (w), 2840 (w), 1639 (s), 1601 (m), 1429 (s), 1360 (s), 1252 (s), 1201 (s), 1138 (m), 1059 (m), 980 (m), 914 (m), 849 (m), 820 (m), 779 (s), 735 (m), 650 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.42 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 6.75 (s, 1H, Ar-H), 7.44 (d, ^3J = 7.6 Hz, 1H, Ar-H), 7.53 (d, ^3J = 7.6 Hz, 1H, Ar-H), 12.3 (s, 1H, OH) ppm.

The physical and spectroscropic data are in agreement with those in the literature.[209]

*2,3-Epoxy-2,6-dimethyl-1,4-naphthoquinone (**230**)*

To a solution of naphthoquinone **154** (58.0 mg, 287 μmol) in 1.0 mL H_2O/MeOH (1/4 *v*/*v*), 71.0 μL (142 μmol) 2 N aqueous NaOH solution was added at 0 °C. After 10 min, 44.0 μL 30% aqueous H_2O_2 solution was added to the reaction mixture and stirred for 4 h at 0 °C. The precipitation was filtered and dried in the high vacuum. Aqueous saturated NH_4Cl solution was added into the dark reaction mixture and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and the crude product was purified on the column chromatography (PE/EtOEt = 18 : 1).



230

Colorless powder.

Yield: 15.0 mg (68.7 μmol, 24%).

M.p. 74 °C ($CHCl_3$).

IR (ATR): $\tilde{\nu}$ = 2924 (w), 2844 (w), 1689 (s), 1645 (s), 1423 (s), 1340 (s), 1308 (s), 1250 (s), 1165 (m), 1138 (m), 1092 (m), 1059 (m), 980 (m), 922 (m), 883 (m), 856 (m), 806 (w). 750 (s), 644 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.71 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.80 (s, 1H, CH), 7.51 (s, 2H, Ar-H), 11.52 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (Me), 16.3 (Me), 61.7 (CH), 119.8 (CH), 138.0 (CH) ppm.

HRMS (ESI): calcd. for $C_{12}H_{10}NaO_4$ $[M+Na]^+$: 241.0471; found 241.0469.

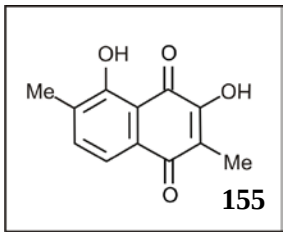
*3,5-Dihydroxy-2,6-dimethyl-1,4-naphthoquinone (**155**)*

To a solution of the epoxide **230** (13.0 mg, 59.6 μmol) in THF (1.0 mL), SiO_2 (75.0 mg) and concentrated H_2SO_4 (61 μL) were added. THF was removed in vaccum (200 mbar) at 60 °C for 20 min on a rotatory evaporator. H_2O (20 mL) was poured into the reaction mixture and the suspension were extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified with column chromatography.

Yellow powder.

Yield: 12.0 mg (55.0 μmol, 92%).

M.p. 179 °C (CH_2Cl_2).



155

IR (ATR): $\tilde{\nu}$ = 3267 (br m), 2922 (m), 2852 (w), 1711 (w), 1620 (m), 1429 (m), 1360 (m), 1306 (s), 1254 (s), 1211 (s), 1097 (s), 1059 (s), 984 (m), 837 (m), 737 (s), 671 (s) cm^{-1}.

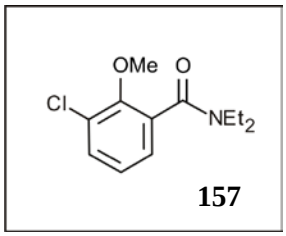
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.26 (br, 1H, OH), 7.46 (d, ^{3}J = 7.8 Hz, 1H, Ar-H), 7.56 (d, ^{3}J = 8.0 Hz, 1H, Ar-H), 11.43 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0 (Me), 16.0 (Me), 112.4 (C), 119.6 (CH), 121.9 (C), 130.8 (C), 133.9 (C), 138.0 (CH), 152.9 (C), 160.1 (C), 184.5 (CO), 185.0 (CO) ppm.

HRMS (ESI): calcd. for $C_{12}H_{10}NaO_4$ $[M+Na]^+$: 241.0471; found 241.0470.

*N,N-Diethyl-3-chloro-2-methoxy-benzamide (**157**)*

A mixture of thionyl chloride (3.8 g, 32.1 mmol, 2.28 mL) and 3-chloro-2-methoxy-benzoic acid (2.0 g, 10.7 mmol) in a 10 mL one-necked flask was refluxed at 80 °C overnight. The excess of thionyl chloride was evaporated under reduced pressure affording the acyl chloride, which was dissolved in THF (30 mL). To the above solution, diethylamine (2.34 g, 32.1 mmol, 3.32 mL) in THF (10 mL) was added carefully with stirring at 0 °C. The reaction was continued at room temperature with stirring overnight. The mixture was diluted with water, acidified with 0.5 N aqueous HCl solution, and neutralized with saturated aqueous $NaHCO_3$ solution. THF was evaporated under reduced pressure and the suspension was extracted with CH_2Cl_2 (60 mL × 3). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and subjected to column chromatography affording the product.



157

Dark brown liquid.

Yield: 2.5 g, (10.5 mmol, 98%).

IR (ATR): $\tilde{\nu}$ = 2974 (w), 2937 (w), 1629 (s), 1461 (m), 1471 (m), 1289 (m), 1244 (m), 1099 (s), 1071 (m), 997 (m), 790 (m), 759 (m), 728 (m), 648 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.22 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.10 (q, ^3J = 7.0 Hz, 2H, CH_2), 3.35 and 3.70 (broad signal, 2H, CH_2), 3.84 (s, 3H, CH_3O), 7.0–7.1 (m, 2H, Ar-H), 7.34 (dd, ^3J = 8.4, ^4J = 2.0 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (CH_3), 14.0 (CH_3), 39.2 (CH_2), 43.1 (CH_2), 62.0 (CH_3O), 125.2 (CH), 126.0 (CH), 128.2 (C), 130.9 (CH), 133.6 (C), 151.9 (C), 167.6 (CO) ppm.

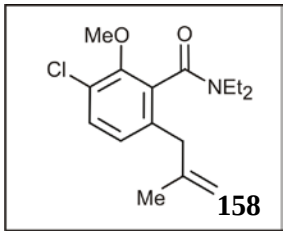
EIMS m/z (rel. int.): 241 $[M]^+$ (13), 243 $[M]^+$ (4), 169 $[M–72]^+$ (100), 171 $[M–72]^+$ (28).

HRMS (ESI): calcd. for $C_{12}H_{16}ClNNaO_2$ $[M+Na]^+$: 264.0762; found 264.0763.

*N,N-Diethyl-3-chloro-2-methoxy-(2-methyl-allyl)-benzamide (**158**)*

To a solution of **157** (1.86 g, 7.69 mmol) in THF (30 mL), *s*-BuLi (6.03 mL, 8.46 mmol,

1.1 equiv.) and TMEDA (1.26 mL, 8.46 mmol, 1.1 equiv.) was added by syringe injection at –90 °C under argon and stirred for 1.5 h. The solution of the resultant lithiated species was then warmed to –78 °C over 30 min. Freshly prepared $MgBr_2$•$2Et_2O$ (5.85 mL, 15.38 mmol, 2 equiv.) was added to the flask. The mixture was stirred for 30 min, allowed to warm to room temperature, again cooled to –78 °C, and stirred for 1 h. Following addition of 3-bromo-2-methyl-propene (1.6 mL, 15.38 mmol, 2 equiv.), the solution was allowed to warm to room temperature overnight. The reaction mixture was treated with saturated aqueous NH_4Cl solutions, and extracted with CH_2Cl_2 (80 mL × 3). The combined organic layers were dried with Na_2SO_4, and concentrated to dryness under reduced pressure. The crude product was purified with column chromatography.



158

Colorless liquid.

Yield: 1.8 g, (6.1 mmol, 79%).

IR (ATR): $\tilde{\nu}$ = 2972 (w), 2938 (w), 1629 (s), 1461 (m), 1432 (m), 1400 (m), 1282 (m), 1222 (m), 1098 (m), 1045 (m), 942 (m), 890 (m), 802 (m), 732 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.24 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.06 (q, ^3J = 7.0 Hz, 2H, CH_2), 3.24 (s, 2H, CH_2), 3.56 (q, ^3J = 7.0 Hz, 1H, CH_2), 3.84 (s, 3H, CH_3O), 4.68 (s, 1H, CH_{2a}), 4.85 (s, 1H, CH_{2b}), 6.94 (s, ^3J = 8.0 Hz, 1H, Ar-H), 7.28 (s, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (CH_3), 13.8 (CH_3), 22.4 (CH_3), 38.7 (CH_2), 40.6 (CH_2), 43.1 (CH_2), 61.9 (CH_3O), 113.4 (CH_2), 125.7 (C), 126.4 (CH), 130.0 (CH), 133.8 (C), 136.5 (C), 143.4 (C), 151.9 (C), 166.8 (CO) ppm.

EIMS m/z (rel. int.): 295 $[M]^+$ (14), 297 $[M]^+$ (4), 223 $[M–72]^+$ (100), 225 $[M–72]^+$ (36).

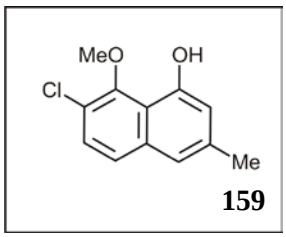
HRMS (ESI): calcd. for $C_{16}H_{22}ClNNaO_2$ $[M+Na]^+$: 318.1231; found 318.1233.

*6-Chloro-5-methoxy-2-methyl-4-naphthol (**159**)*

To a solution of *N*,*N*-diethyl-3-chloro-2-methoxy-(2-methyl-allyl)-benzamide (**158**) (780 mg, 2.64 mmol) in THF (20 mL), MeLi (2.2 equiv.) was added with stirring at –78 °C. The

reaction mixture was slowly warmed upto 0 °C over 5 h, followed by addition of saturated aqueous NH_4Cl solution, removal of THF, and extraction with EtOAc (30 mL × 3). The combined organic layers were dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc = 96 : 4) affording the naphthol **159** as a colorless solid.

Colorless solid.



159

Yield: 342 mg, (1.54 mmol, 58%).

M.p. 62 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 3352 (w), 2950 (w), 2912 (w),1636 (m), 1596 (m), 1577 (m), 1504 (m), 1443 (m), 1366 (m), 1347 (s), 1259 (m), 1159 (m), 1094 (m), 1060 (m), 976 (m), 939 (m), 847 (s), 780 (m), 671 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3), 4.09 (s, 3H, OCH_3), 6.81 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.10 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.31 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.43 (d, 1H, ^3J = 8.0 Hz, Ar-H), 9.27 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (CH_3), 62.4 (CH_3O), 113.5 (CH), 116.4 (C), 118.8 (CH), 120.8 (C), 125.4 (CH), 127.9 (CH), 135.6 (C), 138.4 (C), 151.5 (C), 153.1 (C) ppm.

EIMS m/z (rel. int.): 222.0 $[M]^+$ (100), 224 $[M]^+$ (34), 207 $[M–15]^+$ (78), 209 $[M–15]^+$ (26), 179 $[M–43]^+$ (60), 181 $[M–43]^+$ (20).

HRMS (ESI): calcd. for $C_{12}H_{11}ClNaO_2$ $[M+Na]^+$: 245.0340; found 245.0340.

*6-Chloro-5-methoxy-2-methyl-1,4-naphthoquinone (**160**)*

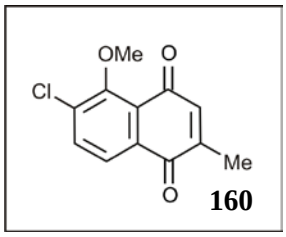
To a suspension of CuCl (46.5 mg, 0.46 mmol) in MeCN (20 mL), the naphthol **159** (131 mg, 0.59 mmol) in MeCN (20 mL) was dropwise added over 15 min under stirring at room temperature with a strong current of oxygen bubbling through it. After the starting material was consumed completely, the reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were dried over Na_2SO_4,

and concentrated *in vacuo*. The crude product was purified with column chromatography.

Yellow powder.

Yield: 62.0 mg, (0.26 mmol, 44%).

M.p. 122–125 °C (PE/EtOAc).



160

IR (ATR): $\tilde{\nu}$ = 2952 (w), 2923 (w), 1728 (w), 1656 (s), 1630 (m), 1568 (m), 1460 (m), 1401 (m), 1356 (m), 1254 (s), 1044 (m), 961 (m), 910 (m), 853 (s), 810 (m), 745 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.75 (s, 1H, Ar-H), 7.72 (s, 1H, ^{3}J = 8.0 Hz, Ar-H), 7.86 (s, 1H, ^{3}J = 8.0 Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (CH_3), 61.8 (CH_3O), 123.9 (CH), 126.0 (C), 132.8 (C), 135.1 (CH), 137.1 (C), 137.5 (CH), 146.6 (C), 155.8 (C), 183.6 (CO), 184.9 (CO).

EIMS m/z (rel. int.): 236 $[M]^+$ (100), 238 $[M]^+$ (38), 207 $[M–30]^+$ (17), 209 $[M–30]^+$ (6).

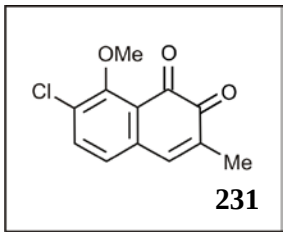
HRMS (ESI): calcd. for $C_{12}H_9ClNaO_3$ $[M+Na]^+$: 259.0132; found 259.0133.

6-Chloro-5-methoxy-2-methyl-1,2-naphthoquinone ***(231)***

Red powder.

Yield: 23.0 mg, (97 μmol, 16%).

M.p. 108–110 °C (PE/EtOAc).



231

IR (ATR): $\tilde{\nu}$ = 2923 (w), 2852 (w), 1726 (w), 1658 (s), 1628 (m), 1569 (m), 1462 (m), 1371 (m), 1278 (m), 1255 (m), 1207 (m), 1090 (m), 1039 (m), 960 (m), 817 (m), 787 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.98 (s, 1H, ^{3}J = 8.0 Hz, Ar-H), 7.16 (s, 1H, Ar-H), 7.61 (s, 1H, ^{3}J = 8.0 Hz, Ar-H).

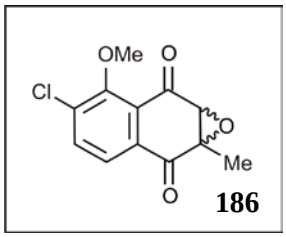
^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7 (CH_3), 61.8 (CH_3O), 124.8 (C), 125.8 (CH), 132.4 (C), 136.0 (C), 136.8 (C), 137.0 (CH), 141.4 (CH), 159.5 (C), 178.0 (CO), 180.9 (CO).

EIMS m/z (rel. int.): 208 $[M–28]^+$ (100), 210 $[M–28]^+$ (34).

HRMS (ESI): calcd. for $C_{12}H_9ClNaO_3$ $[M+Na]^+$: 259.0132; found 259.0133.

*6-Chloro-5-methoxy-1,4-naphthoquinone-2,3-epoxide (**186**)*

The quinone **160** (41.0 mg, 173 μmol) and 86 μL (0.5 equiv.) of 1 N aqueous NaOH solution were dissolved in 16 mL of mixing solvents ($MeOH/H_2O/THF$ = 4 : 1: 1) at room temperature. After stirring for 10 minutes, 54 μL of 35% aqueous H_2O_2 solution (3.0 equiv.) was added and stirred for 2 h. The reaction mixture was neutralized with 1 N aqueous HCl solution, and extracted with EtOEt (30 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated in reduced pressure. The crude product was purified with column chromatography.



186

Colorless powder.

Yield: 29.0 mg, (122 mmol, 71%).

M.p. 85 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2923 (w), 2853 (w), 1699 (s), 1572 (m), 1467 (m), 1404 (m), 1330 (m), 1289 (m), 1240 (s), 1141 (m), 1075 (m), 1029 (m), 965 (s), 851 (m), 750 (m), 717 (s) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.72 (s, 3H, CH_3), 3.86 (s, 1H, H-3), 3.97 (s, 3H, OCH_3), 7.70 (s, 2H, Ar-H) ppm.

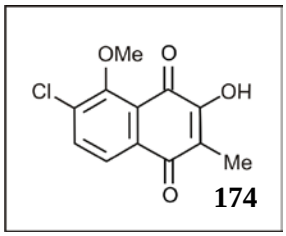
^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.7 (CH_3), 61.8 (CH), 62.0 (C), 62.8 (CH), 124.0 (CH), 127.0 (C), 132.5 (C), 135.6 (CH), 136.7 (C), 155.6 (C), 190.9 (C), 191.9 (C) ppm.

EIMS m/z (rel. int.): 252 $[M]^+$ (91), 254 $[M]^+$ (33), 237 $[M–15]^+$ (52), 239 $[M–15]^+$ (17), 209 $[M–43]^+$ (100), 211 $[M–43]^+$ (36).

HRMS (ESI): calcd. for $C_{12}H_9ClNaO_4$ $[M+Na]^+$: 275.0082; found 275.0081.

*6-Chloro-3-hydorxy-5-methoxy 2-methyl-1,4-naphthoquinone (**174**)*

To a solution of **186** (26.0 mg, 103 μmol) in THF (2.0 mL), SiO_2 (153.0 mg) and concentrated H_2SO_4 (132 μL) were added. The solvent was rotary evaporated in vaccum (200 mbar) at 60 ºC for 25 min. The resultant red solid was diluted with H_2O (10 mL), basified with 5% aqueous K_2CO_3 solution, neutralized with 1 N aqueous HCl solution, and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified on a column chromatography affording the product as a yellow solid.



174

Yellow powder.

Yield: 23.0 mg, (91 mmol, 90%).

M.p. 155–158 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 3347 (m), 2922 (w), 2851 (w), 1702 (m), 1645 (s), 1569 (m), 1462 (m), 1406 (m), 1380 (m), 1341 (s), 1273 (m), 1197 (s), 1132 (m), 1090 (s), 1030 (m), 961 (s), 899 (s), 809 (m), 741 (m), 668 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 7.53 (s, 1H, OH), 7.75 (s, 1H, ^3J = 8.0 Hz, Ar-H), 7.91 (s, 1H, ^3J = 8.0 Hz, Ar-H) ppm.

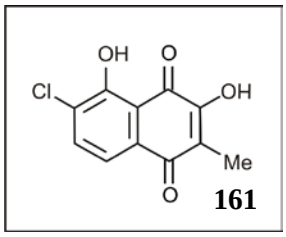
^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8 (CH_3), 61.8 (CH_3O), 119.5 (C), 123.3 (C), 124.0 (CH), 133.5 (C), 136.0 (C), 136.4 (CH), 153.6 (C), 156.2 (C), 179.6 (CO), 184.0 (CO) ppm.

EIMS m/z (rel. int.): 252 $[M]^+$ (91), 254 $[M]^+$ (33), 234 $[M–18]^+$ (23), 236 $[M–18]^+$ (8), 209 $[M–43]^+$ (28), 211 $[M–43]^+$ (10).

HRMS (ESI): calcd. for $C_{12}H_9ClNaO_4$ $[M+Na]^+$: 275.0082; found 275.0080.

*3,5-Dihydroxy-6-chloro-2-methyl-1,4-naphthoquinone (**161**)*

BBr_3 (32 μL, 336 μmol) was added to a solution of **174** (17.0 mg, 67 μmol) in CH_2Cl_2 (2 mL) under stirring and argon at 0 °C. After 2 h, the cold bath was removed. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator affording the desired product.



161

Yellow powder.

Yield: 16.0 mg, (67 mmol, 100%).

M.p. 150–152 °C (CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 3205 (w), 2921 (w), 2852 (w), 1620 (s), 1431 (s), 1389 (m), 1353 (m), 1285 (s), 1196 (s), 1123 (s), 1083 (s), 1022 (m), 744 (s), 720 (s) cm^{-1}.

^1H NMR (400 MHz, CD_3COCD_3): δ = 2.02 (s, 3H, CH_3-2), 7.56 (s, 1H, ^3J = 8.0 Hz, H-8), 7.84 (s, 1H, ^3J = 8.0 Hz, H-7), 9.66 (s, 1H, OH-3), 11.86 (s, 1H, OH-5) ppm.

^{13}C NMR (100 MHz, CD_3COCD_3): δ = 8.8 (CH_3-2), 115.5 (C-9), 119.7 (C-8), 122.8 (C-2), 128.0 (C-6), 132.2 (C-10), 137.6 (C-7), 155.3 (C-3), 157.3 (C-5), 184.2 (C-1), 186.2 (C-4) ppm.

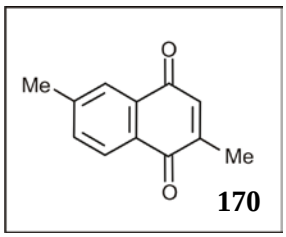
EIMS m/z (rel. int.): 238 $[M]^+$ (100), 240 $[M]^+$ (33), 210 $[M–28]^+$ (27), 212 $[M–18]^+$ (9).

HRMS (ESI): calcd. for $C_{11}H_6ClO_4$ $[M–1]^+$: 236.9960; found 236.9961.

7.5 Synthesis of the Dioncoquinone B Analogs **171** and **173**

*2,6-Dimethyl-1,4-naphthoquinone (**170**)*

To the solution of H_5IO_6 (1.16 g, 5.09 mmol) and CrO_3 (12.8 mg, 0.128 mmol) in acetonitrile (20 mL), 2,6-dimethylnaphthalene (200.0 mg, 1.28 mmol) in acetonitirile (7 mL) was added dropwise with vigorous stirring at 0 ºC. After several minutes, a white precipitation was formed. The reaction mixture was stirred for another 45 min, filtered on a short pad of silica gel, and eluted with CH_2Cl_2. After removal of CH_2Cl_2, the crude product was purified by column chromatography (PE/EtOAc = 90 : 10).



170

Yellow powder.

Yield: 142.0 mg, (0.763 mmol, 60%).

M.p. 130–132 °C (PE/EtOAc).

Lit.: 135–136 °C (MeOH).[93]

IR (ATR): $\tilde{\nu}$ = 3025 (w), 2950 (w), 2923 (w), 2850 (w), 1654 (s), 1596 (s), 1351 (m), 1298 (s), 1259 (s), 1028 (w), 939 (w), 896 (w), 843 (m), 800 (w), 739 (w), 690 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.68 (s, 1H, Ar-H), 7.39 (d, ^3J = 8.0 Hz, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 7.85 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (CH_3), 21.8 (CH_3), 126.3 (CH), 126.6 (CH), 129.9 (C), 132.1 (C), 134.3 (CH), 135.4 (CH), 144.7 (C), 148.1 (C), 185.2 (C), 185.3 (C) ppm.

MS (EI = 70 eV): m/z (%) 186 $[M]^+$ (100), 158 $[M–28]^+$ (49), 118 $[M–68]^+$ (51).

The spectroscopic data are in agreement with those in the literature.[93]

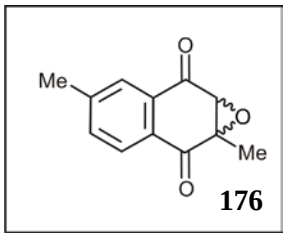
*6-Methyl-1,4-naphthoquinone-2,3-epoxide (**176**)*

67.0 µL (134 µmol) 2 N NaOH was added with stirring to the naphthoquinone **170** (50.0 mg, 269 µmol) in 1.0 mL H_2O/MeOH (1/4 *v*/*v*) at 0 °C. After 10 min, 41.1 µL 30% aqueous H_2O_2 solution was added to the reaction mixture and stirred for 4 h. The precipitation was filtered and purified by column chromatography affording the product as a colorless solid.

Colorless solid.

Yield: 50.4 mg, (249 µmol, 93%).

M.p.95–96 °C (MeOH/H_2O).
Lit.: 97–98 °C.[284]



176

IR (ATR): $\tilde{\nu}$ = 3030 (w), 2929 (w), 2850 (w), 1685 (s), 1599 (s), 1448 (w), 1373 (w), 1338 (m), 1302 (s), 1248 (m), 1207 (w), 1128 (w), 1051 (w), 945 (m), 860 (s), 781 (m), 733 (s), 661 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.81 (s, 1H, CH), 7.52 (d, ^3J = 7.9 Hz, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.89 (d, ^3J = 7.9 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (Me), 21.9 (Me), 61.5 (C), 61.6 (CH), 127.3 (CH),

127.8 (CH), 129.9 (C), 132.1 (C), 135.5 (CH), 145.8 (C), 191.8 (C), 192.2 (C) ppm.

MS (EI = 70 eV): m/z (%) 202 $[M]^+$ (57), 187 $[M–15]^+$ (100), 174 $[M–28]^+$ (32).

In the literature,[284] no spectroscopic data are described.

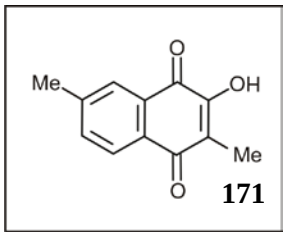
*3-Hydroxy-2,6-methyl-1,4-naphthoquinone (**171**)*

To the solution of the epoxide **176** (38.0 mg, 188 μmol) in THF (1 mL), SiO_2 (285 mg) and concentrated H_2SO_4 (233 μL) was added. THF was removed at 60 °C and in vaccum (200 mbar) for 10 min on a rotary evaporator. H_2O (20 mL) and CH_2Cl_2 (20 mL) were added to the resultant solid. The mixture was basified with 5% aqueous K_2CO_3 solution, acidified with 1 N aqueous HCl solution, and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by crystallization from CH_2Cl_2.

Yellow powder.

Yield: 36.0 mg (178 μmol, 95%).

M.p.194 °C (CH_2Cl_2).
Lit.: 194 °C (PE).[285]



171

IR (ATR): $\tilde{\nu}$ = 3354 (s), 2954 (w), 2929 (w), 2852 (w), 1637 (s), 1595 (s), 1427 (w), 1381 (m), 1340 (s), 1302 (s), 1271 (s), 1184 (s), 1161 (s), 1074 (s), 1009 (m), 947 (w), 874 (w), 845 (m), 738 (s), 673 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.29 (s, 1H, OH), 7.52 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.99 (d, ^3J = 7.8 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8 (Me), 21.8 (Me), 120.5 (C), 126.7 (CH), 127.1 (CH), 129.5 (C), 130.9 (C), 135.6 (CH), 144.1 (C), 153.2 (C), 181.7 (C), 185.2 (C) ppm.

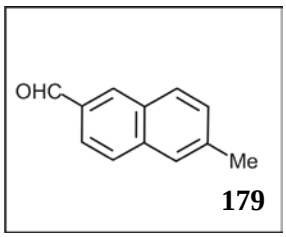
MS (EI = 70 eV): m/z (%) 202 $[M]^+$ (100), 174 $[M–28]^+$ (33), 131 $[M–71]^+$ (40).

The spectroscopic data are in agreement with those in the literature.[285]

*2-Formyl-6-methyl-naphthalene (**179**) and 2,6-Diformyl-naphthalene (**180**)*

The solution of 2,6-dimethylnaphthalene (400 mg, 2.56 mmol) in EtOAc (43.0 mL) and concentrated aqueous HBr solution (58.3 µL, 512 µmol) was exposed to high pressure mercury lamp with 450 watts Hanovia for 17 h under a strong current of oxygen. After removal of the solvent on a rotary evaporation, the crude product was purified on silical gel column chromatography affording two main products **168** and **169** (PE/EtOAc = 90 : 10).

*2-Formyl-6-methylnaphthalene (**179**)*



179

White powder.

Yield: 156.0 mg (838 µmol, 33%).

M.p. 115 °C (PE/EtOAc).
Lit.: 120 °C (Hexane).[250]

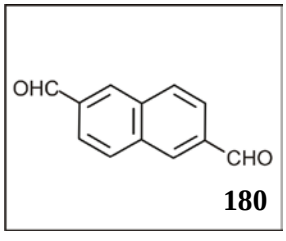
IR (ATR): $\tilde{\nu}$ = 3350 (w), 3100 (w), 2926 (w), 2843 (w), 1687 (s), 1623 (m), 1574 (w), 1473 (m), 1373 (w), 1335 (m), 1263 (m), 1225 (w), 1167 (m), 1115 (m), 974 (w), 895 (m), 833 (s), 775 (m), 717 (m), 636 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H, CH_3), 7.39 (d, ^{3}J = 8.5 Hz, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 7.79 (d, ^{3}J = 8.5 Hz, 1H, Ar-H), 7.86 (d, ^{3}J = 8.5 Hz, 1H, Ar-H), 7.90 (d, ^{3}J = 8.5 Hz, 1H, Ar-H), 10.1 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (Me), 123.0 (CH), 127.3 (CH), 128.5 (CH), 129.4 (CH), 129.5 (CH), 131.0 (C), 133.6 (C), 134.5 (CH), 136.9 (C), 139.6 (C), 192.3 (CHO) ppm.

MS (EI = 70 eV): m/z (%) 170 $[M]^+$ (100), 141 $[M–29]^+$ (81), 115 $[M–55]^+$ (82).

*2,6-Diformylnaphthalene (**180**)*



180

White powder.

Yield: 14.0 mg (65.0 µmol, 3%).

M.p. 172 °C (PE/EtOAc).
Lit.: 173 °C (CH_3COCH_3).[286]

IR (ATR): $\tilde{\nu}$ = 2924 (w), 2841 (w), 2720 (w), 1682 (s), 1601 (m), 1500 (w), 1373 (w), 1331 (m), 1273 (m), 1223 (s), 1155 (m), 1107 (m), 980 (w), 893 (m), 818 (m), 758 (s), 630 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, ^3J = 8.4 Hz, 2H, Ar-H), 8.12 (d, ^3J = 8.2 Hz, 2H, Ar-H), 8.40 (s, 2H, Ar-H), 10.2 (s, 2H, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.3 (CH), 130.8 (CH), 133.9 (CH), 136.0 (C), 136.4 (C), 192.0 (CHO) ppm.

MS (EI = 70 eV): m/z (%) 184 $[M]^+$ (100), 155 $[M–29]^+$ (62), 127 $[M–57]^+$ (55).

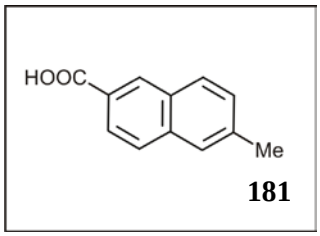
The spectroscopic data are in agreement with those in the literature.[286]

*6-Methyl-2-naphthoic acid (**181**)*

2,6-Dimethylnaphthalene (416 mg, 2.66 mmol) and $KMnO_4$ (2.10 g, 13.3 mmol) in pyridine (35 mL) and water (12 mL) was refluxed for 2 h and the other portion of $KMnO_4$ (0.84 g, 5.32 mmol) was added and kept for 0.5 h. The reaction mixture was cooled to room temperature followed by addition of 1 N aqueous NaOH solution (1.0 mL). The mixture was filtered with Celite and eluted with methanol (100 mL). The eluent was concentrated *in vacuo*, and the crude product was purified with column chromatography (PE/EtOAc/FA = 80 : 20 : 5).

White solid.

Yield: 403 mg (2.16 mmol, 81%).



181

M.p.225–227 °C (FA).
Lit.: 225–227 °C (MeOH).[287]

IR (ATR): $\tilde{\nu}$ = 3400 (br m), 2980 (w), 2916 (w), 2830 (w), 1670 (s), 1574 (m), 1475 (m), 1415 (w), 1383 (m), 1290 (m), 1244 (m), 1194 (m), 1099 (m), 958 (w), 906 (w), 877 (w), 800

(m), 764 (m), 712 (m), 637 (m) cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 2.51 (s, 3H, CH_3), 7.39 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 7.79 (d, ^3J = 8.6 Hz, 1H, Ar-H), 7.86 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.98 (d, ^3J = 8.6 Hz, 1H, Ar-H), 8.52 (s, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ = 23.4 (Me), 126.6 (CH), 127.7 (CH), 128.3 (CH), 129.5 (CH), 129.8 (CH), 130.1 (CH), 131.6 (C), 132.3 (C), 137.1 (C), 139.4 (C), 168.6 (COOH) ppm.

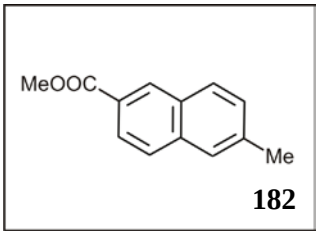
MS (EI = 70 eV): m/z (%) 186 $[M]^+$ (100), 169 $[M–17]^+$ (30), 141 $[M–45]^+$ (57).

The spectroscopic data are in agreement with those in the literature.[287]

*Methyl 6-methyl-2-naphthoate (**182**)*

K_2CO_3 (162 mg, 1.18 mmol) was added to the solution of carboxylic acid **181** (73.0 mg, 392 µmol) in acetone (10 mL) at 0 °C. The mixture was magnetically stirred for 30 min, then dimethylsulfate (63 µL, 1.22 mmol) was added and refluxed for 1 h. The reaction mixture was allowed to cool to room temperature followed by addition of H_2O (5 mL). After removal of acetone, the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4, condensed *in vacuo* and purified with column chromatography.

Colorless solid.



182

Yield: 66.0 mg (330 µmol, 84 %).

M.p. 119–120 °C (CH_2Cl_2).
Lit.: 116–117 °C (MeOH).[287]

IR (ATR): $\tilde{\nu}$ = 2954 (w), 2926 (w), 2851 (w), 1707 (s), 1628 (w), 1473 (w), 1435 (m), 1336 (w), 1286 (s), 1190 (s), 1124 (m), 1093 (s), 972 (m), 897 (m), 843 (w), 810 (s), 777 (m), 750 (m), 723 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 7.37 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 7.77 (d, ^3J = 8.6 Hz, 1H, Ar-H), 7.84 (d, ^3J = 8.4 Hz, 1H, Ar-H),

8.02 (d, ^{3}J = 8.6 Hz, 1H, Ar-H), 8.56 (s, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (Me), 52.3 (Me), 125.5 (CH), 126.8 (C), 127.0 (CH), 127.6 (CH), 129.1 (CH), 129.3 (CH), 130.1 (C), 131.0 (CH), 136.0 (C), 138.6 (C), 167.6 (COO) ppm.

MS (EI = 70 eV): m/z (%) 200 $[M]^+$ (78), 169 $[M–31]^+$ (100), 141 $[M–59]^+$ (51).

The spectroscopic data are in agreement with those in the literature.[287]

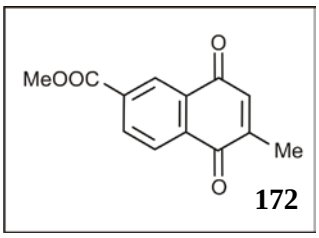
*Methyl 6-carboxylate-2-methyl-1,4-naphthoquinone (**172**)*

To the solution of H_5IO_6 (299 mg, 1.31 mmol) and CrO_3 (3.3 mg, 33.0 μmol) in acetonitrile (7 mL), the naphthalene **182** (66.0 mg, 330 μmol) in acetonitirile (7 mL) was added dropwise. After stirring at 0 ºC for 4 h, the reaction mixture was filtered over a short pad of normal-phase silica gel, and eluted quickly with CH_2Cl_2. After evaporation of the solvent *in vacuo*, the desired product was purified by column chromatography (PE/EtOAc = 97 : 3).

Yellow powder.

Yield: 30.0 mg (130 μmol, 40%).

M.p. 149–152 °C (CH_2Cl_2).
Lit.: 149–152 °C (MeOH).[288]



172

IR (ATR): $\tilde{\nu}$ = 2950 (w), 2929 (w), 2852 (w), 1716 (s), 1660 (s), 1603 (m), 1439 (m), 1356 (w), 1259 (s), 1120 (m), 972 (m), 939 (m), 912 (m), 874 (m), 766 (m), 688 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 6.90 (s, 1H, Ar-H), 8.15 (d, ^{3}J = 8.0 Hz, 1H, Ar-H), 8.35 (d, ^{3}J = 8.0 Hz, 1H, Ar-H), 8.68 (s, 1H, Ar-H) ppm.

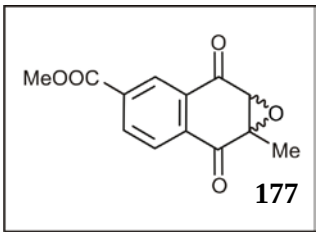
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (Me), 52.9 (Me), 127.0 (CH), 127.7 (CH), 132.5 (C), 134.4 (CH), 134.9 (C), 135.0 (C), 136.2 (CH), 148.7 (C), 165.6 (COO), 184.2 (CO), 185.1 (CO) ppm.

MS (EI = 70 eV): m/z (%) 230 $[M]^+$ (100), 199 $[M–31]^+$ (95), 171 $[M–59]^+$ (47).

The spectroscopic data are in agreement with those in the literature.[288]

*Methyl 6-carboxylate-2-methyl-1,4-naphthoquinone-2,3-epoxide (**177**)*

67.0 µL (134 µmol) 2 N aqueous NaOH solution was added with stirring to the naphthoquinone **172** (62.0 mg, 269 µmol) in 1.0 mL H_2O/MeOH (1/4 *v*/*v*) at 0 °C. After 10 min, 41.1 µL 30% H_2O_2 solution was added to the reaction mixture and stirred for 4 h. The precipitation was filtered and and purified by column chromatography affording the product as a colorless solid.



177

Colorless solid.

Yield: 48.0 mg (193 µmol, 72%).

M.p. 135 °C (MeOH/H_2O).
Lit.: 136 °C.[289]

IR (ATR): $\tilde{\nu}$ = 2954 (w), 2929 (w), 1716 (s), 1691 (s), 1606 (m), 1444 (m), 1400 (w), 1338 (w), 1263 (s), 1184 (m), 1122 (m), 974 (w), 947 (m), 876 (w), 850 (w), 795 (w), 759 (m), 714 (s), 640 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (s, 3H, CH_3), 3.40 (s, 1H, CH), 3.97 (s, 3H, CH_3), 8.07 (d, ^3J = 8.04 Hz, 1H, Ar-H), 8.36 (d, ^3J = 8.04 Hz, 1H, Ar-H), 8.57 (s, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (Me), 53.1 (Me), 61.7 (CH), 62.0 (C), 128.0 (CH), 128.4 (CH), 132.3 (C), 135.2 (CH), 135.7 (C), 135.7 (C), 165.3 (COOH), 191.1 (CO), 191.7 (CO) ppm.

MS (EI = 70 eV): m/z (%) 246 $[M]^+$ (36), 231 $[M–15]^+$ (100), 218 $[M–28]^+$ (87), 215 $[M–31]^+$ (35), 187 $[M–59]^+$ (27).

In the literature,[289] no spectroscopic data are described.

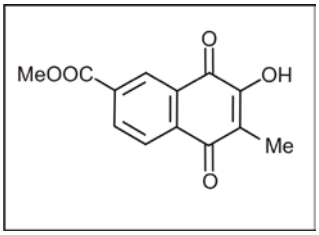
*Methyl 6-carboxylate-3-hydroxy-2-methyl-1,4-naphthoquinone (**173**)*

To a solution of the epoxide **177** (23.0 mg, 93.0 μmol) in THF (1.0 mL), SiO_2 (141 mg) and concentrated H_2SO_4 (115 μL) was added. THF was removed in vacuum (200 mbar) at 60 °C for 20 min on a rotary evaporator. To the resultant red solid, H_2O (20 mL) and CH_2Cl_2 (20 mL) were added. The mixture was basified with 5% aqueous K_2CO_3 solution, acidified with 1 N aqueous HCl solution, and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.

Yellow powder.

Yield: 18.0 mg (73.0 μmol, 80%).

M.p. 218 °C (CH_2Cl_2).
Lit.: 213 °C (Benzene).[289]



173

IR (ATR): $\tilde{\nu}$ = 3367 (s), 2950 (w), 2921 (w), 1726 (s), 1641 (s), 1599 (m), 1427 (w), 1379 (w), 1340 (m), 1288 (s), 1238 (s), 1190 (s), 1101 (s), 1072 (s), 937 (m), 881 (w), 802 (w), 727 (s), 663 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 8.20 (d, ^3J = 8.0 Hz, 1H, Ar-H), 8.38 (d, ^3J = 8.0 Hz, 1H, Ar-H), 8.71 (s, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0 (Me), 53.0 (Me), 121.5 (C), 127.3 (CH), 127.6 (CH), 129.7 (C), 134.5 (C), 135.6 (CH), 135.8 (C), 153.8 (C), 165.5 (C), 180.6 (C), 184.5 (C) ppm.

MS (EI = 70 eV): m/z (%) 246 $[M]^+$ (100), 218 $[M–28]^+$ (30), 215 $[M–31]^+$ (30), 187 $[M–59]^+$ (38).

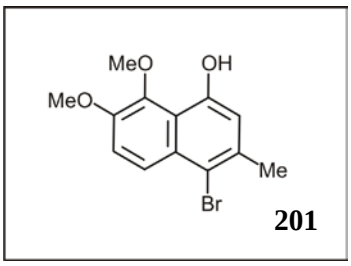
The spectroscopic data are in agreement with those in the literature.[289]

8 Synthesis of Triphoquinone (187a)

*4-Bromo-5,6-dimethoxy-2-methyl-4-naphthol (**201**)*

To a solution of 5,6-dimethoxy-2-methyl-4-naphthol (**42**) (1.17 g, 5.36 mmol) in CH_2Cl_2/MeOH (3/2 *v*/*v*) (50 mL), $TBABr_3$ (2.71 g, 5.63 mmol) in CH_2Cl_2/MeOH(3/2 *v*/*v*) (50 mL) was slowly dropped under stirring at 0 °C over 2 h. The reaction mixture was stirred at room temperature overnight. After addition of H_2O (100 mL), the organic solvents were removed on a rotary evaporator. The suspension was extracted with EtOEt (100 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified with flash column chromatography (PE/EtOAc = 95 : 5).

Colorless solid.



201

Yield: 1.09 g, (3.7 mmol, 69%).
Lit.: 50%.[189]

M.p. 103 °C (PE/EtOAc).
Lit.: 103 °C (PE/EtOEt).[189]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3H, CH_3), 3.99 (s, 3H, CH_3O), 4.07 (s, 3H, CH_3O), 6.77 (s, 1H, Ar-H), 7.31 (d, ^3J = 8.0 Hz, 1H, Ar-H), 8.04 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

EIMS m/z (rel. int.): 298 $[M]^+$ (100), 296 $[M]^+$ (97), 283 $[M–15]^+$ (46), 281 $[M–15]^+$ (41).

The spectroscopic data are in agreement with those in the literature.[189]

*1-Bromo-5,6-dimethoxy-4-methoxymethoxy-2-methylnaphthalene (**205**)*

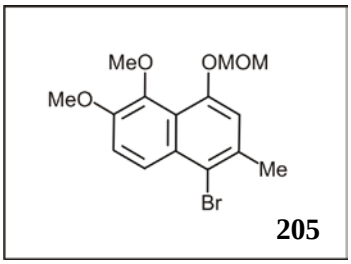
A mixture of the bromide **201** (286.0 mg, 0.96 mmol) and sodium hydride (115.0 mg of a 60% powder in oil, 2.89 mmol) in dry THF (10 mL) and DMF (1 mL) was stirred at 0 °C under an argon atmosphere for 1 h. Methoxymethyl chloride (364 μL, 4.80 mmol) in THF (8 mL) was added dropwise to the above mixture over 15 min and the resulting suspension was stirred at 0 °C for 2 h followed by addition of H_2O (30 mL). After removal of THF, the

suspension was extracted with EtOEt (30 mL × 4). The combined organic layers were extracted with H_2O (50 mL), dried over Na_2SO_4, and concentrated to dryness affording the product after purification by flash column chromatography (PE/EtOAc = 19 : 1).

Colorless solid.

Yield: 310 mg, (0.91 mmol, 95%).

M.p. 74 °C ($CHCl_3$).



205

IR (ATR): $\tilde{\nu}$ = 2990 (w), 2937 (w), 2832(w), 1601 (w), 1498 (w), 1463 (w), 1442 (w), 1336 (m), 1278 (m), 1241 (m), 1149 (m), 1133 (m), 1043 (s), 1005 (w), 945 (s), 918 (m), 783 (m), 703 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.27 (s, 2H, CH_2), 6.97 (s, 1H, Ar-H), 7.33 (d, 1H, ^3J = 8.0 Hz, Ar-H), 8.08 (d, 1H, ^3J = 8.0 Hz, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.5 (CH_3), 56.8 (CH_3), 61.8 (CH_3), 96.7 (CH_2), 115.8 (CH), 116.0 (CH), 117.4 (C), 121.8 (C), 124.1 (CH), 130.1 (C), 134.0 (C), 143.6 (C), 150.0 (C), 151.9 (C) ppm.

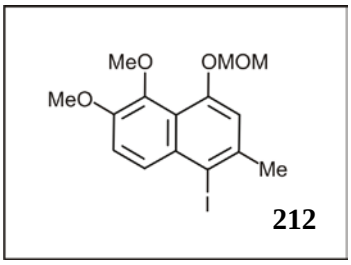
EIMS m/z (rel. int.): 342 $[M]^+$ (100), 340 $[M]^+$ (97), 297 $[M–45]^+$ (24), 295 $[M–45]^+$ (23).

HRMS (ESI): calcd. for $C_{15}H_{17}BrNaO_4$ $[M+Na]^+$: 363.0201 and 365.0177; found 363.0202 and 365.0178.

*1-Iodo-5,6-dimethoxy-4-methoxymethoxy-2-methylnaphthalene (**212**)*

To a solution of **205** (243 mg, 0.72 mmol) in THF (15 mL), *n*-BuLi (534 µL, 1.6 M in hexanes, 1.1 equiv.) was added dropwise at −78 °C and the mixture was stirred for 30 min. Iodine (217 mg, 0.86 mmol, 1.2 equiv.) in THF (10 mL) was added dropwise at −78 °C and the reaction was stirred for another 30 min followed by addition of saturated aqueous $Na_2S_2O_3$ solution (20 mL). The reaction mixture was warmed to room temperature and THF was removed under reduced pressure. The suspension was extracted with CH_2Cl_2 (100 mL ×

3), and dried over anhydrous Na_2SO_4. The combined layers were concentrated *in vacuo*, and the residue was chromatographed on silica gel to afford pure iodide.



212

Pale-yellow solid.

Yield: 260 mg, (0.67 mmol, 94%).

IR (ATR): $\tilde{\nu}$ = 2968 (w), 2933 (w), 2830 (w), 1599 (m), 1553 (w), 1462 (m), 1441 (m), 1330 (m), 1276 (s), 1239 (m), 1148 (s), 1131 (s), 1042 (s), 1001 (s), 941 (s), 918 (s), 804 (w), 779 (m), 703 (m) cm^{-1}.

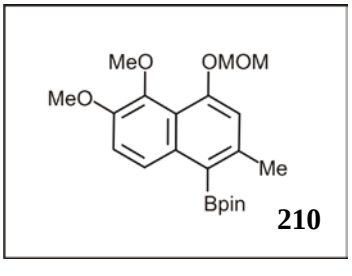
^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2), 7.01 (s, 1H, Ar-H), 7.30 (d, 1H, ^3J = 8.0 Hz, Ar-H), 8.05 (d, 1H, ^3J = 8.0 Hz, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (CH_3), 56.6 (CH_3), 56.9 (CH_3), 61.8 (CH_3), 96.7 (CH_2), 97.7 (C), 115.1 (CH), 115.9 (CH), 121.0 (C), 129.5 (CH), 132.3 (C), 138.9 (C), 143.4 (C), 150.0 (C), 153.0 (C) ppm.

MS (EI = 70 eV): m/z 388 $[M]^+$ (100), 344 $[M–44]^+$ (54).

*2-(5,6-Dimethoxy-4-methoxymethoxy-2-methyl-naphthalen-1-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**210**)*

Compound **205** (143 mg, 419 μmol), potassium acetate (411 mg, 4.19 mmol), and bispinacolatodiboron (319 mg, 1.26 mmol) in DMF (10 mL) was degassed under argon for 10 min. $Pd(PPh_3)_4$ (48.0 mg, 41.9 μmol) was added and the reaction mixture was degassed again and then heated at 120 °C overnight. The mixture was allowed to cool to room temperature, filtered on a short pad of Celite, and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE/EtOAc = 9 : 1) affording the product as a colorless solid.



210

Colorless solid.

Yield: 130.1 mg, (335.0 μmol, 80%).

M.p. 50–53 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2977 (w), 2938 (w), 1591 (m), 1567 (w), 1512 (m), 1468 (m), 1447 (m), 1323 (m), 1294 (s), 1276 (m), 1236 (m), 1152 (m), 1134 (s), 1048 (s), 1022 (m), 968 (s), 861 (m), 790 (m), 703 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 12H, Bpin-CH_3), 2.52 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2), 6.86 (s, 1H, Ar-H), 7.22 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.88 (d, 1H, ^3J = 8.2 Hz, Ar-H) ppm.

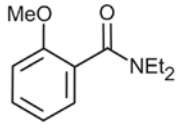
^{13}C NMR (100 MHz, $CDCl_3$) (*C-B* is not observed): δ = 22.6 (CH_3), 25.0 (Bpin-CH_3), 56.4 (CH_3O), 57.0 (CH_3O), 61.6 (CH_3O), 83.8 (Bpin), 96.3 (CH_2), 115.3 (CH), 120.3 (C), 124.5 (CH), 135.6 (CH), 140.5 (CH), 143.9 (C), 149.2 (C), 153.8 (C), 162.6 (C) ppm.

EIMS m/z (rel. int.): 388 $[M]^+$ (100), 343 $[M–45]^+$ (31), 149 $[M–209]^+$ (99).

HRMS (ESI): calcd. for $C_{21}H_{29}NaO_6{}^{10}B$ $[M+23]^+$: 410.1986; found 410.1982.

*N,N-Diethyl-2-methoxy-benzamide (**198**)*

A mixture of thionyl chloride (11.7 g, 98.5 mmol, 7.00 mL) and 2-methoxy-benzoic acid (5.0 g, 32.9 mmol) in a 25 mL one-necked flask was refluxed at 80 °C overnight. The excess of thionyl chloride was removed by evaporation under reduced pressure to give 2-methoxy-benzoyl chloride, to which a solution of diethylamine (7.18 g, 98.5 mmol, 10.2 mL) in anhydrous THF (80 mL) was added carefully with stirring at 0 °C. The reaction was continued at room temperature overnight. The mixture was diluted with water, acidified with 0.5 N aqueous HCl solution, and neutralized with saturated aqueous $NaHCO_3$ solution. After removal of THF, the suspension was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and subjected to column chromatography to afford the product.



198

Dark brown liquid.

Yield: 6.6 g, (32.9 mmol, 100%).

IR (ATR): $\tilde{\nu}$ = 2972 (w), 2935 (w), 1625 (s), 1600 (s), 1492 (m), 1461 (m), 1427 (s), 1292 (m), 1274 (m), 1243 (s), 1122 (m), 1087 (s), 1045 (m), 1022 (m), 943 (s), 877 (m), 753 (s), 627 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.22 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.10 (q, ^3J = 7.0 Hz, 2H, CH_2), 3.54 (m, 2H, CH_2), 3.78 (s, 3H, CH_3O), 6.87 (d, ^3J = 8.4, 1H, Ar-H), 6.93 (dd, ^3J = 8.4, ^4J = 2.0 Hz, 1H, Ar-H), 7.15 (dd, ^3J = 8.4, ^4J = 2.0 Hz, 1H, Ar-H), 7.28 (dd, ^3J = 8.4, ^4J = 2.0 Hz, 1H, Ar-H) ppm.

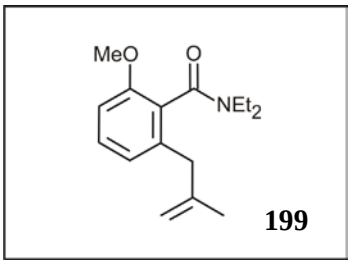
^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0 (CH_3), 14.0 (CH_3), 38.9 (CH_2), 42.9 (CH_2), 55.6 (CH_3O), 111.1 (CH), 120.8 (CH), 127.1 (C), 127.5 (CH), 130.0 (CH), 155.3 (C), 168.9 (CO) ppm.

EIMS m/z (rel. int.): 207 $[M]^+$ (12), 106 $[M–1]^+$ (30), 135 $[M–72]^+$ (100).

The spectroscopic data are in agreement with those in the literature.[290]

*N,N-Diethyl-2-methoxy-(2-methyl-allyl)-benzamide (**199**)*

To a solution of the benzamide **198** (6.2 g, 30.0 mmol) in THF (50 mL), *s*-BuLi (33.0 mmol, 23.5 mL, 1.1 equiv.) and TMEDA (33.0 mmol, 4.9 mL, 1.1 equiv.) were added at –90 °C under argon by syringe injection and the mixture was stirred for 1.5 h. The solution of the resultant lithiated species was then warmed to –78 °C over 0.5 h and freshly prepared $MgBr_2$▪$2Et_2O$ (60.0 mmol, 22.8 mL, 2 equiv.) was added. The above mixture was stirred for 0.5 h, allowed to warm to room temperature, again cooled to –78 °C, and stirred for another 1 h. Following addition of distilled 3-bromo-2-methylpropene (8.0 mL, 60.0 mmol), the reaction mixture was allowed to warm to room temperature, and stirred overnight. The mixture was treated with saturated aqueous NH_4Cl solution (50 mL). After removal of THF on a rotary evaporator, the suspension was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried with Na_2SO_4, concentrated to dryness followed by purification by column chromatography giving **199** as a yellowish liquid.



199

Colorless liquid.

Yield: 4.30 g, (16.1 mmol, 53%).

IR (ATR): $\tilde{\nu}$ = 2969 (w), 2942 (w), 1617 (s), 1596 (m), 1579 (s), 1468 (s), 1429 (s), 1377 (m), 1289 (s), 1253 (s), 1064 (s), 897 (s), 879 (m), 782 (s), 759 (s), 749 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.20 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.65 (s, 3H, CH_3), 3.04 (m, 2H, CH_2) , 3.23 (m, 2H, CH_2), 3.36 (m, 1H, CH_{2a}), 3.71 (m, 1H, CH_{2b}), 3.72 (s, 3H, CH_3O), 4.65 (s, 1H, CH_{2a}), 4.80 (s, 1H, CH_{2b}), 6.71 (s, ^3J = 8.0 Hz, 1H, Ar-H), 6.80 (s, ^3J = 8.0 Hz, 1H, Ar-H), 7.19 (dd, ^3J = 8.0, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

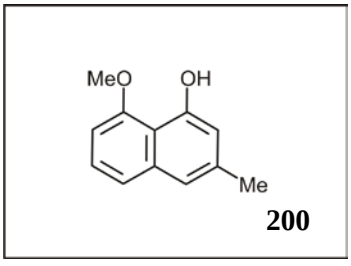
^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (CH_3), 13.4 (CH_3), 22.4 (CH_3), 38.3 (CH_2), 40.8 (CH_2), 42.7 (CH_2), 55.5 (CH_3O), 108.5 (CH), 112.8 (CH_2), 122.0 (CH), 126.9 (C), 129.0 (CH), 137.5 (C), 143.9 (C), 155.5 (C), 168.0 (CO) ppm.

EIMS m/z (rel. int.): 261 $[M]^+$ (18), 189 $[M–72]^+$ (100), 161 $[M–100]^+$ (66).

HRMS (ESI): calcd. for $C_{16}H_{23}NNaO_2$ $[M+23]^+$: 284.1621; found 284.1622.

*5-Methoxy-2-methyl-4-naphthol (**200**)*

To a solution of the *ortho*-allyl benzamide **199** (4.20 g, 16.1 mmol) in 30 mL THF, 2.2 equiv. of MeLi were added with stirring at –78 °C. The reaction mixture was slowly warmed up to 0 °C over 3 h, followed by addition of saturated aqueous NH_4Cl solution (50 mL). After removal of THF by evaporation under reduced pressure, the suspension was extracted with EtOAc (100 mL × 3). The combined organic layers were dried with Na_2SO_4, and concentrated to dryness. The crude product was purified by column chromatography to afford the naphthol **200** as a colorless solid.



200

Colorless solid.

Yield: 2.90 g, (15.4 mmol, 97%).

M.p. 88 °C (PE/EtOAc).
Lit.: 89 °C (PE/EtOEt).[189]

IR (ATR): $\tilde{\nu}$ = 3355 (m), 2972 (w), 2920 (w), 1639 (m), 1611 (m), 1578 (m), 1436 (m), 1385 (m), 1370 (s), 1278 (s), 1234 (m), 1160 (m), 1090 (s), 1057 (m), 962 (m), 837 (s), 748

(s), 716 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 4.01 (s, 3H, OCH_3), 6.69 (dd, 1H, ^3J = 8.2, ^4J = 1.6 Hz, Ar-H), 6.78 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.15 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.27 (dd, 1H, ^3J = 8.0, ^3J = 8.0 Hz, Ar-H), 7.34 (dd, 1H, ^3J = 8.2, ^4J = 1.6 Hz, Ar-H), 9.26 (s, 1H, OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 55.4 (CH_3O), 103.2 (CH), 112.5 (CH), 113.2 (C), 118.4 (CH), 121.4 (CH), 125.8 (CH), 137.0 (C), 138.0 (C), 154.3 (C), 156.3 (C) ppm.

EIMS m/z (rel. int.): 188 $[M]^+$ (100), 173 $[M–15]^+$ (49), 145 $[M–43]^+$ (36).

The spectroscopic data are in agreement with those in the literature.[189]

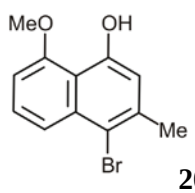
*1-Bromo-5-methoxy-2-methyl-4-naphthol (**202**)*

To a solution of **200** (0.86 g 4.57 mmol) in CH_2Cl_2/MeOH (3/2 *v*/*v*) (30 mL), $TBABr_3$ (2.31 g, 4.80 mmol) in CH_2Cl_2/MeOH (3/2 *v*/*v*) (50 mL) was slowly dropped under stirring at 0 °C over 3 h. The reaction mixture was stirred at room temperature for 2 h followed by addition of H_2O (100 mL). The organic solvents were removed on a rotary evaporator. The suspension was extracted with EtOEt (100 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc = 95 : 5).

Colorless solid.

Yield: 1.02 g, (3.8 mmol, 83%).

M.p. 127 °C (PE/EtOAc).
Lit.: 127 °C (PE/EtOEt).[189]



202

IR (ATR): $\tilde{\nu}$ = 3367 (s), 2938 (w), 2842 (w), 1631 (m), 1606 (m), 1562 (m), 1426 (m), 1353 (m), 1291 (m), 1258 (m), 1238 (m), 1190 (m), 1090 (s), 1065 (m), 996 (m), 956 (m), 877 (m), 795 (s), 751 (s), 740 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CH_3), 4.03 (s, 3H, OCH_3), 6.76 (d, 1H, ^3J = 8.2

Hz, Ar-H), 6.81 (s, 1H, Ar-H), 7.38 (dd, 1H, ^3J = 8.0, ^3J = 8.0 Hz, Ar-H), 7.89 (d, 1H, ^3J = 8.2 Hz, Ar-H), 9.37 (s, 1H, OH) ppm.

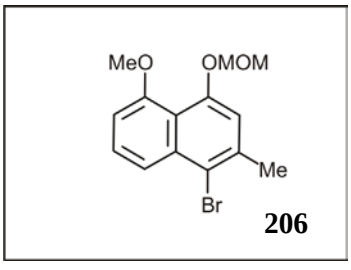
^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7 (CH_3), 55.8 (CH_3O), 104.0 (CH), 112.9 (CH), 113.2 (C), 114.4 (CH), 121.1 (CH), 127.1 (CH), 134.9 (C), 138.4 (C), 153.9 (C), 156.3 (C) ppm.

EIMS m/z (rel. int.): 268 $[M]^+$ (97), 266 $[M]^+$ (100), 253 $[M–15]^+$ (30), 253 $[M–15]^+$ (31), 225 $[M–43]^+$ (33), 223 $[M–43]^+$ (34).

The spectroscopic data are in agreement with those in the literature.[189]

*1-Bromo-5-methoxy-4-methoxymethoxy-2-methylnaphthalene (**206**)*

A mixture of the bromide **202** (315 mg, 1.18 mmol) and sodium hydride (141 mg of a 60% powder in oil, 3.54 mmol) in dry THF (15 mL) and DMF (1 mL) was stirred at 0 °C under an argon atmosphere for 1 h. Methoxymethyl chloride (448 µL, 5.90 mmol) in THF (8 mL) was then added dropwise over 15 min and the resulting suspension was stirred at room temperature overnight followed by addition of H_2O (30 mL). After removal of THF, the mixture was extracted with EtOEt (30 mL × 4). The combined organic layers were washed with H_2O (50 mL × 2) and brine (50 mL × 2), and then dried over Na_2SO_4 and concentrated to dryness giving the crude product, which was purified by flash column chromatography (PE/EtOAc = 15 : 1).



206

Yellowish solid.

Yield: 300 mg, (0.95 mmol, 80%).

M.p. 64 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2958 (w), 2911 (w), 1598 (m), 1571 (m), 1460 (w), 1386 (s), 1349 (m), 1257 (m), 1222 (w), 1145 (m), 1084 (m), 1049 (m), 950 (m), 915 (m), 795 (m), 738 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2), 6.85 (d, 1H, ^3J = 8.2 Hz, Ar-H), 7.00 (s, 1H, Ar-H), 7.44 (dd, 1H, ^3J = 8.0, ^3J = 8.0 Hz, Ar-H), 7.95 (d, 1H, ^3J = 8.2 Hz, Ar-H) ppm.

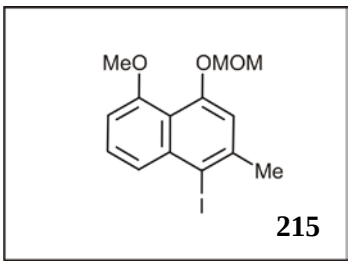
^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (CH_3), 56.5 (CH_3O), 56.6 (CH_3O), 97.0 (CH_2), 106.2 (CH), 116.3 (CH), 117.7 (C), 118.3 (C), 120.1 (CH), 127.7 (CH), 135.6 (C), 136.9 (C), 153.2 (C), 156.9 (C) ppm.

EIMS m/z (rel. int.): 312 $[M]^+$ (32), 310 $[M]^+$ (32), 282 $[M–30]^+$ (25), 280 $[M–30]^+$ (25), 149 $[M–162]^+$ (100).

HRMS (ESI): calcd. for $C_{14}H_{15}BrNaO_3$ $[M+23]^+$: 333.0097 and 335.0076; found 333.0097 and 335.0076.

*1-Iodo-4-methoxymethoxy-2-methylnaphthalene (**215**)*

To a solution of **206** (209 mg, 0.67 mmol) in THF (15 mL), *n*-BuLi (504 μL, 1.6 M in hexanes, 1.2 equiv.) was added dropwise at –78 °C and the mixture was stirred for 30 min followed by careful addition of a solution of iodine (205 mg, 0.81 mmol, 1.2 equiv.) in THF (10 mL). The reaction mixture was stirred for another 30 min followed by addition of saturated aqueous $Na_2S_2O_3$ solution (20 mL). The mixture was warmed to room temperature. After removal of THF by evaporation under reduced pressure, the mixture was extracted with CH_2Cl_2 (100 mL × 3), and dried over anhydrous Na_2SO_4. The combined layers were concentrated *in vacuo*, and the residue was chromatographed on silica gel to afford the iodide.



215

Yellowish solid.

Yield: 222 mg, (0.62 mmol, 92%).

IR (ATR): $\tilde{\nu}$ = 2901 (w), 2831 (w), 1593 (m), 1567 (m), 1460 (m), 1383 (m), 1341 (m), 1253 (m), 1147 (m), 1126 (m), 1084 (m), 1047 (s), 999 (m), 949 (m), 916 (m), 838 (m), 795 (m), 740 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2), 6.75 (d, 1H, ^3J = 8.0 Hz, Ar-H), 6.92 (s, 1H, Ar-H), 7.31 (dd, 1H, ^3J = 8.0, ^3J = 8.0 Hz, Ar-H), 7.80 (d, 1H, ^3J = 8.0 Hz, Ar-H) ppm.

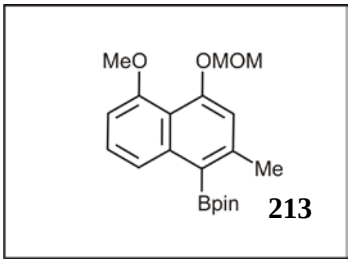
^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7 (CH_3), 56.6 (CH_3), 56.7 (CH_3), 96.9 (CH_2), 98.1 (C), 106.3 (CH), 115.6 (CH), 117.6 (C), 125.7 (CH), 127.9 (CH), 137.9 (C), 141.6 (C), 154.5 (C),

157.0 (C) ppm.

MS (EI = 70 eV): m/z 358 $[M]^+$ (80), 328 $[M–30]^+$ (50).

*2-(5-Methoxy-4-methoxymethoxy-2-methyl-naphthalen-1-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**213**)*

Compound **206** (38.0 mg, 122 μmol), potassium acetate (120 mg, 1.22 mmol), and bispinacolatodiboron (85 mg, 366 μmol) in a suspension of H_2O (150 μL) and toluene (2 mL) was degassed under argon for 10 min. Pd(dppf)Cl_2•DCM (10.0 mg, 12.2 μmol) was added and the reaction mixture was degassed again and then heated at 90 °C for 6 h. The mixture was allowed to cool to room temperature, diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography affording the product as a colorless solid.



213

Colorless solid.

Yield: 24.0 mg, (95 μmol, 55%).

M.p. 62 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2976 (w), 1611 (w), 1588 (m), 1461 (m), 1371 (m), 1307 (s), 1256 (s), 1140 (m), 1119 (m), 1044 (m), 1030 (m), 964 (m), 945 (m), 920 (m), 856 (m), 754 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 12H, Bpin-CH_3), 2.54 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2), 6.77 (d, 1H, ^3J = 8.2 Hz, Ar-H), 6.87 (s, 1H, Ar-H), 7.32 (dd, 1H, ^3J = 8.2, ^3J = 8.2 Hz, Ar-H), 7.68 (d, 1H, ^3J = 8.2 Hz, Ar-H) ppm.

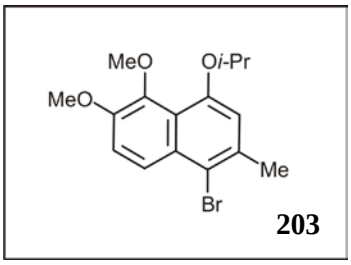
^{13}C NMR (100 MHz, $CDCl_3$) (*C-B* is not observed): δ = 22.7 (CH_3), 25.1 (Bpin-CH_3), 56.4 (CH_3O), 56.5 (CH_3O), 83.5 (Bpin), 83.9 (Bpin), 96.7 (CH_2), 105.5 (CH), 115.7 (CH), 116.8 (C), 120.8 (CH), 126.4 (CH), 141.0 (C), 142.5 (C), 155.0 (C), 157.0 (C) ppm.

EIMS m/z (rel. int.): 358 $[M]^+$ (25), 328 $[M–30]^+$ (10), 167 $[M–191]^+$ (41), 149 $[M–209]^+$ (100).

HRMS (ESI): calcd. for $C_{20}H_{27}NaO_5{}^{10}B$ $[M+23]^+$: 380.1880; found 381.1882.

*1-Bromo-4-isopropoxy-5,6-dimethoxy-2-methylnaphthalene (**203**)*

A mixture of the naphthol **201** (63.0 mg, 0.212 mmol) and Cs_2CO_3 (96.3 mg, 0.296 mmol) in dry acetone (3 mL) was stirred at room temperature under an argon atmosphere for 1 h. To the above solution, 2-iodopropane (92.0 μL, 0.848 mmol) was added and stirred in reflux overnight. After addition of H_2O (3 mL) and removal of acetone, the reaction mixture was extracted with EtOAc (30 mL × 4). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to dryness affording the crude product, which was purified by flash column chromatography.



203

Colorless solid.

Yield: 53.0 mg, (156 μmol, 49%).

M.p. 60–62 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2958 (w), 2928 (w), 2836 (w), 1595 (m), 1559 (m), 1463 (m), 1442 (m), 1384 (m), 1349 (m), 1331 (m), 1277 (s), 1241 (s), 1114 (m), 1084 (m), 1060 (s), 1007 (m), 824 (m), 805 (m), 782 (m), 782 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (d, ^3J = 6.0 Hz, 6H, CH_3), 2.54 (s, 3H, CH_3), 3.86 (s, 3H, CH_3O), 3.97 (s, 3H, CH_3O), 4.61 (septet, 1H, CH), 6.75 (m, 1H, Ar-H), 7.32 (dd, ^3J = 8.0 Hz, 1H, Ar-H), 8.07 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

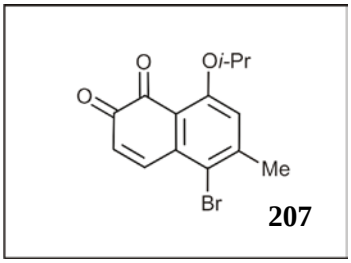
^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (2 × CH_3), 24.4 (CH_3), 57.1 (CH_3O), 62.0 (CH_3O), 72.0 (CHO), 114.3 (CH), 115.7 (C), 115.9 (CH), 122.6 (C), 124.0 (CH), 130.3 (CH), 134.0 (C), 144.2 (C), 150.1 (C), 152.8 (C) ppm.

EIMS m/z (rel. int.): 340 $[M]^+$ (43), 338 $[M]^+$ (43), 298 $[M–42]^+$ (57), 296 $[M–42]^+$ (57), 283 $[M–57]^+$ (54), 281 $[M–57]^+$ (54), 149 $[M–191]^+$ (100).

HRMS (ESI): calcd. for $C_{16}H_{19}BrNaO_3$ $[M+23]^+$: 361.0410 and 363.0391; found 361.0407 and 363.0389.

*1-Bromo-4-isopropoxy-2-methyl-5,6-naphthoquinone (**207**)*

To a solution of **203** (10.0 mg, 31 μmol) in CH_3CN (1 mL), a solution of ammonium cerium (IV) nitrate (CAN) (42.4 mg, 77.0 μmol) in H_2O (1 mL), was added at 0 °C and stirred for 15 min. After addition of cold H_2O (10 mL), the reaction mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* affording the desired product in a quantitative yield.



207

Red solid.

Yield: 9.6 mg, (31 μmol, 100%).

M.p. 88–90 °C (CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 2971 (w), 2927 (w), 1686 (m), 1662 (s), 1570 (w), 1532 (w), 1450 (w), 1372 (m), 1305 (m), 1245 (m), 1224 (m), 1177 (m), 1104 (s), 1021 (w), 946 (m), 911 (m), 827 (w), 794 (m), 695 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, ^3J = 6.0 Hz, 6H, CH_3), 2.49 (s, 3H, CH_3), 4.67 (septet, 1H, CH), 6.45 (d, ^3J = 8.0 Hz, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 8.09 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

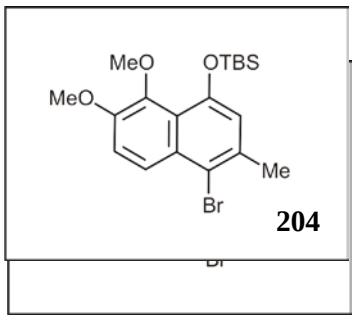
^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (2 × CH_3), 25.7 (CH_3), 72.8 (CH), 119.6 (C), 120.2 (CH), 128.6 (CH), 131.1 (C), 135.3 (C), 144.6 (CH), 148.4 (C), 160.5 (C), 177.0 (C), 180.7 (C) ppm.

EIMS m/z (rel. int.): 282 $[M–28]^+$ (75), 280 $[M–28]^+$ (75), 212 $[M–98]^+$ (50), 210 $[M–98]^+$ (51), 131 $[M–178]^+$ (100).

HRMS (ESI): calcd. for $C_{14}H_{13}BrNaO_3$ $[M+23]^+$: 330.9940 and 332.9920; found 330.9942 and 332.9922.

*1-Bromo-4-t-butyl-dimethyl-silane-5,6-dimethoxy-2-methylnaphthalene (**204**)*

To a solution of the naphthol **201** (104.0 mg, 0.350 mmol) and imidazole (190.0 mg, 2.8 mmol) in DMF (3 mL), TBDMSCl (527.0 mg, 3.5 mmol) was added at room temperature and the mixture was stirred at 60 °C for 16 h. The reaction mixture was quenched by addition of water (30 mL), and then extracted with EtOEt (30 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* affording a residue, which was purified by flash column chromatography on silica gel (PE/EtOAc = 98 : 2).



204

Colorless solid.

Yield: 135.0 mg, (328 μmol, 94%).

M.p. 68–70 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2927 (w), 2856 (w), 1594 (m), 1557 (m), 1469 (m), 1444 (m), 1348 (m), 1277 (m), 1246 (s), 1085 (m), 1061 (m), 1005 (m), 903 (w), 833 (s), 803 (m), 777 (s), 673 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 6H, $SiCH_3$), 1.04 (s, 9H, CH_3), 2.52 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.76 (s, 1H, Ar-H), 7.32 (d, ^3J = 8.0 Hz, 1H, Ar-H), 8.08 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.0 (3 × $SiCH_3$), 19.0 (SiC), 24.1 (CH_3), 26.5 (3 × CH_3), 56.9 (CH_3O), 62.1 (CH_3O), 115.7 (CH), 116.1 (C), 119.4 (CH), 123.2 (C), 124.0 (CH), 130.3 (CH), 134.1 (C), 144.1 (C), 149.5 (C), 150.5 (C) ppm.

EIMS m/z (rel. int.): 410 $[M]^+$ (8), 412 $[M]^+$ (8), 338 $[M–72]^+$ (100), 340 $[M–72]^+$ (100), 323 $[M–87]^+$ (23), 325 $[M–87]^+$ (23).

HRMS (ESI): calcd. for $C_{19}H_{27}BrNaO_3Si$ $[M+23]^+$: 433.0805 and 435.0789; found 433.0808 and 435.0791.

*5,6-Dimethoxy-2-methyl-1,4-naphthoquinone (**127**)*

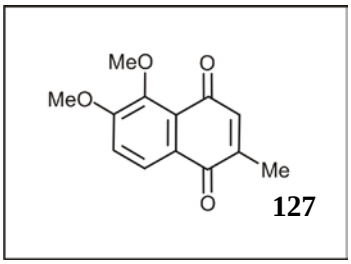
To a solution of **204** (57.0 mg, 138 μmol) in CH_3CN (1.5 mL), a solution of ammonium cerium (IV) nitrate (CAN) (197.6 mg, 360 μmol) in H_2O (1.5 mL) was added at 0 °C and

stirred for 15 min. The reaction mixture was added cold H_2O (10 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 8 : 2).

Yellowish solid.

Yield: 17.0 mg, (73.0 μmol, 53%).

M.p. 182–185 °C (EtOAc).
Lit.: 184–185 °C (MeOH).[99]



127

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.13 (d, ^4J = 1.5 Hz, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.71 (q, ^4J = 1.5 Hz, 1H, Ar-H), 7.26 (d, ^3J = 8.0 Hz, 1H, Ar-H), 7.93 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

EIMS m/z (rel. int.): 232 $[M]^+$ (100), 217 $[M–15]^+$ (26), 203 $[M–28]^+$ (12).

The spectroscopic data are in agreement with those in the literature.[99]

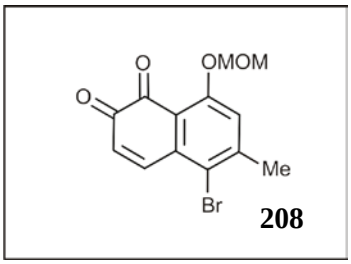
*1-Bromo-4-methoxymethoxy-2-methyl-5,6-naphthoquinone (**208**)*

To a solution of the naphthalene **205** (29.0 mg, 87.0 μmol) in CH_3CN (1.5 mL), a solution of ammonium cerium (IV) nitrate (CAN) (119.0 mg, 217 μmol) in H_2O (1.5 mL) was added at 0 °C and stirred for 13 min. The reaction mixture was added cold H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* affording the desired product in a quantitative yield.

Red solid.

Yield: 27.0 mg, (87 μmol, 100%).

M.p. 152 °C (CH_2Cl_2).



208

IR (ATR): $\tilde{\nu}$ = 2924 (w), 1687 (w), 1657 (s), 1572 (w), 1540 (w), 1455 (w), 1365 (w), 1304

(m), 1249 (m), 1225 (m), 1181 (m), 1142 (m), 1093 (s), 1051 (s), 980 (w), 944 (s), 913 (s), 797 (m), 689 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2), 6.48 (d, ^3J = 8.0 Hz, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 8.08 (d, ^3J = 8.0 Hz, 1H, Ar-H) ppm.

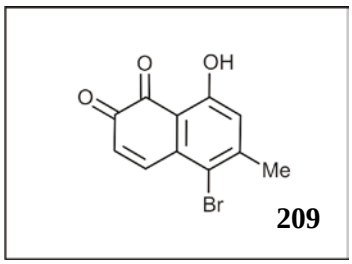
^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6 (CH_3), 57.0 (CH_3O), 95.0 (OCH_2O), 121.1 (CH), 121.2 (C), 128.6 (CH), 135.1 (C), 141.6 (C), 144.7 (CH), 148.8 (C), 159.2 (C), 177.1 (C), 180.3 (C) ppm.

EIMS m/z (rel. int.): 312 $[M+2]^+$ (10), 314 $[M+2]^+$ (100), 282 $[M–28]^+$ (10), 284 $[M–28]^+$ (31), 222 $[M–88]^+$ (22), 224 $[M–88]^+$ (22), 45 $[M–266]^+$ (100).

HRMS (ESI): calcd. for $C_{13}H_{11}BrNaO_4$ $[M+23]^+$: 332.9733 and 334.9723; found 332.9735 and 334.9725.

*1-Bromo-4-hydroxy-2-methyl-5,6-naphthoquinone (**209**)*

130 µL concentrated HCl was added into the solution of **208** (13.0 mg, 42 µmol) in MeOH (1.5 mL) and stirred for 3 h at room temperature. After addition of H_2O (20 mL), the reaction mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* giving the crude product, which was purified by flash column chromatography affording a red solid.



209

Red solid.

Yield: 5.0 mg, (19.0 µmol, 44%).

M.p. 122 °C (PE/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2922 (w), 2852 (w), 1671 (w), 1634 (w), 1457 (w), 1376 (w), 1335 (w), 1289 (w), 1211 (w), 1181 (w), 1141 (w), 1031 (s), 951 (m), 874 (m), 801 (s), 768 (m), 696 (m), 683 (m) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.48 (s, 3H, CH_3), 6.49 (d, ^3J = 8.0 Hz, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 8.01 (d, ^3J = 8.0 Hz, 1H, Ar-H), 12.25 (s, 1H, OH) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.5 (CH_3), 114.8 (C), 120.5 (C), 123.4 (CH), 128.5 (CH), 133.2 (C), 143.6 (CH), 151.8 (C), 165.4 (C), 180.1 (C), 180.8 (C) ppm.

EIMS m/z (rel. int.): 240 $[M-90]^+$ (75), 238 $[M-100]^+$ (75), 212 $[M-48]^+$ (29), 210 $[M-48]^+$ (31).

HRMS (ESI): calcd. for $C_{11}H_7BrNaO_3$ $[M+23]^+$: 288.9471 and 290.9447; found 288.9473 and 290.9449.

9 Cyclodysidins A–D

Streptomyces strain RV15 was fermented in 16 2 L-Erlenmeyer flasks, each containing 1 L of ISP 2 medium at 30 °C for 10 d with shaking at 150 rpm. After 10 d of cultivation, sterilized XAD-16 resin (30 g L^{-1}) was added. Resin was collected 6 h later by filtration and eluted with acetone. The acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (500 mL × 3). The combined extracts were concentrated under reduced pressure and stored at 4 °C for chromatographic fractionation. After fractionation of crude extract (10 g) by silica gel chromatography, the fraction (935 mg) eluted with 40% chloroform in methanol was further chromatographed on Sephadex LH-20. The fraction (56 mg) eluted with 70% methanol in water, was enriched in cyclic peptides. Further purification was carried out by preparative HPLC using an acetonitrile (MeCN) and water solvent mixture complemented by 0.05% trifluoroacetic acid: (10% MeCN : H_2O to 100% MeCN over 20 min at a flow rate of 10 mL min^{-1}), giving four pure compounds. This isolation work was performed by Dr. Usama Ramadan Abdelmohsen from Prof. Ute Hentschel's research group. The structure elucidation of four new cyclopeptides **216**–**219** was done in our group.

The eight partial fragments, two asparagine (Asn) units, one glutamine (Gln), two serine (Ser), one tyrosine (Tyr), one threonine (Thr) moiety, and a *β*-amino acid in each compound was identified by analysis of the COSY, HSQC, ROESY, and HMBC data.

9.1 Cyclodysidin A (**216**)

A white amorphous powder (2.0 mg, rention time = 7.3 min).

M.p. 290–294 °C(CH_3CN/H_2O).

$[\alpha]_D^{20}$ = –19 (*c* 0.55, MeOH).

UV (MeOH) λ_{max} (logε) = 220 (5.75), 235 (12.0) nm.

^1H and ^{13}C NMR data, see Table 9.

HRMS (ESI): calcd. for $C_{45}H_{71}N_{11}O_{15}$ $[M+1]^+$: 1006.5209; found 1006.5207.

9.2 Cyclodysidin B (**217**)

A white amorphous powder (1.5 mg, rention time = 7.7 min).

M.p. 321–325 °C (CH_3CN/H_2O).

$[\alpha]_D^{20}$ = –15.3 (*c* 0.55, MeOH).

UV (MeOH) λ_{max} (logε) = 223 (3.8), 238 (13.1) nm.

^1H and ^{13}C NMR data, see Table 13.

HRMS (ESI): calcd. for $C_{46}H_{73}N_{11}O_{15}$ $[M+1]^+$: 1020.5366; found 1020.5364.

8.3 Cyclodysidin C (**218**)

A white amorphous powder (2.0 mg, rention time = 8.2 min).

M.p. 332–336 °C(CH_3CN/H_2O).

$[\alpha]_D^{20}$ = –22.5 (*c* 0.55, MeOH).

UV (MeOH) λ_{max} (logε) = 222 (4.3), 237 (14.2) nm.

^1H and ^{13}C NMR data, see Table 14.

HRMS (ESI): calcd. for $C_{47}H_{75}N_{11}O_{15}$ $[M+1]^+$: 1034.5522; found 1034.5536.

9.4 Cyclodysidin D (**219**)

A white amorphous powder (1.7 mg, rention time = 8.5 min).

M.p. 345–350 °C(CH_3CN/H_2O).

$[\alpha]_D^{20}$ = –27.7 (*c* 0.55, MeOH).

UV (MeOH) λ_{max} (logε) = 224 (6.6), 238 (13.6) nm.

^1H and ^{13}C NMR data, see Table 15.

HRMS (ESI): calcd. for $C_{49}H_{79}N_{11}O_{15}$ $[M+1]^+$: 1062.5835; found 1062.5832.

Table 13. NMR-spectroscopic data of cyclodysidin B (**217**) in methanol-d_4 (^{1}H: 600 MHz; ^{13}C: 150 MHz)

AA	δ_C	δ_H, mult	COSY (*J* in Hz)	HMBC	ROESY
Asn-1					
CO	173.7				
α	52.4	4.65, dd	*β* (7.5, 6.4)	CO, *β*, *γ*, Tyr-CO	Tyr-*β*
β	37.1	2.76/2.72, m	*α*	CO, *α*, *γ*	
γ	174.9				
Asn-2					
CO	174.3				
α	52.3	4.51, dd	*β* (7.9, 5.7)	CO, *β*, *γ*, Gln-CO	
β	37.4	2.52/2.44, m	*α*	CO, *α*, *γ*	Gln-*α*
γ	175.1				
Gln					
CO	174.1				
α	55.6	4.19, dd	*β* (8.3, 5.8)	CO, *β*, *γ*, Ser2-CO	Asn2-*β*
β	27.1	2.17/2.10, m	*α*, *γ*	CO, *α*, *γ*, *δ*	
γ	32.9	2.47, m	*β*	*α*, *β*, *δ*	
δ	176.6				
Ser-1					
CO	172.9				
α	57.4	4.37, t	*β* (5.6)	CO, β, Asn1-CO	Asn1-*β*
β	62.4	3.84, m	*α*	CO, α	Thr-*β*
Ser-2					
CO	173.0				
α	57.2	4.31, t	*B* (5.3)	CO, *β*, *β*-AFA-CO	*β*-AFA-2
β	62.3	3.92, m	*α*	CO, *α*	
Thr					
CO	172.4				
α	60.0	4.28, d	*β* (2.6)	CO, *β*, *γ*, Ser1-CO	
β	67.3	4.40, m	*α*, *γ*	CO, *α*, *γ*	Ser1-*β*
γ	20.4	1.16, d	*β* (6.5)	*α*, *β*	
Tyr					
CO	174.4				
α	56.9	4.46, dd	*β* (9.2, 4.8)	CO, *β*, Asn2-CO, 1	
β	36.4	3.14/2.85, dd	*α* (14.2,4.7)	CO, *α*, 1, 2, 6	Asn1-*α*
	129.0				
	131.3	7.06, d	Bz-*m* (8.5)	Bz-*I*, Bz-*m*, Bz-*p*	
	116.4	6.71, d	Bz-*o* (8.4)	Bz-*I*, Bz-*o*, Bz-*p*	
	157.3				
β-AFA					
CO	174.5				
2	42.1	2.43, m	3	CO, 3, 4	Ser2-*α*
3	48.8	4.14, m	2, 4	CO, 2, 4, Thr-CO	
4	35.7	1.5, m	3, 5-12	2, 3	
5-12	23.6-33.1	1.25-1.31, m	4, 13	4, 13	
13	14.4	0.88, t	5-12 (7.1)	5-12	

Table 14. NMR-spectroscopic data of cyclodysidin C (**218**) in methanol-d_4 (^{1}H: 600 MHz; ^{13}C: 150 MHz)

AA	δ_C	δ_H, mult	COSY (*J* in Hz)	HMBC	ROESY
Asn-1					
CO	173.9				
α	52.5	4.67, dd	*β* (7.6, 6.5)	CO, *β*, *γ*,	Tyr-*β*
β	37.3	2.77/2.73, m	*α*	CO, *α*, *γ*	
γ	174.8				
Asn-2					
CO	174.3				
α	52.4	4.54, dd	*β* (7.9, 5.8)	CO, *β*, *γ*,	
β	37.6	2.53/2.44, m	*α*	CO, *α*, *γ*	Gln-*α*
γ	174.9				
Gln					
CO	174.2				
α	55.8	4.21, m	*β*	CO, *β*, *γ*,	Asn2-*β*
β	27.0	2.16/2.10, m	*α, γ*	CO, *α*, *γ*, *δ*	
γ	32.9	2.46, m	*β*	*α*, *β*, *δ*	
δ	176.7				
Ser-1					
CO	172.9				
α	57.0	4.38, m	*β*	CO, *β*,	Asn1-*β*
β	62.7	3.85, m	*α*	CO, *α*	Thr-*β*
Ser-2					
CO	173.0				
α	57.6	4.34, t	*β* (5.4)	CO, *β*,	*β*-AFA-2
β	62.6	3.93, m	*α*	CO, *α*	
Thr					
CO	172.3				
α	60.3	4.28, d	*β* (2.5)	CO, *β*, *γ*,	
β	67.7	4.40, m	*α, γ*	CO, *α*, *γ*	Ser1-*β*
γ	20.6	1.17, d	*β* (6.6)	*α*, *β*	
Tyr					
CO	174.5				
α	57.0	4.48, dd	*β* (9.4, 4.9)	CO, *β*,	
β	36.7	3.14/2.85, dd	*α* (14.3,4.8)	CO, *α*, 1, 2, 6	Asn1-*α*
	129.2				
	131.5	7.06, d	Bz-*m* (8.6)	Bz-*I*, Bz-*m*,	
	116.5	6.72, d	Bz-*o* (8.5)	Bz-*I*, Bz-*o*,	
	157.5				
β-AFA					
CO	174.6				
2	42.3	2.43, m	3	CO, 3, 4	Ser2-*α*
3	48.9	4.13, m	2, 4	CO, 2, 4,	
4	35.8	1.5, m	3, 5-11	2, 3	
5-14	23.9-33.2	1.25-1.31, m	4, 15	4, 15	
15	14.6	0.88, t	5-14 (6.5)	5-14	

Table 15. NMR-spectroscopic data of cyclodysidin D (**219**) in methanol-d_4 (^{1}H: 600 MHz; ^{13}C: 150 MHz)

AA	δ_C	δ_H, mult	COSY (*J* in Hz)	HMBC	ROESY
Asn-1					
CO	173.7				
α	52.4	4.65, dd	*β* (7.5, 6.5)	CO, *β*, *γ*, Tyr-CO	Tyr-*β*
β	37.2	2.77/2.71, m	*α*	CO, *α*, *γ*	
γ	175.0				
Asn-2					
CO	174.3				
α	52.3	4.53, m	*β*	CO, *β*, *γ*, Gln-CO	
β	37.3	2.52/2.44, m	*α*	CO, *α*, *γ*	Gln-*α*
γ	175.2				
Gln					
CO	174.1				
α	55.9	4.21, dd	*B* (8.4, 5.9)	CO, *β*, *γ*, Ser2-CO	Asn2-*β*
β	27.4	2.18/2.10, m	*α, γ*	CO, *α*, *γ*, *δ*	
γ	32.8	2.48, m	*β*	*α*, *β*, *δ*	
δ	176.7				
Ser-1					
CO	172.9				
α	57.4	4.37, m	*β*	CO, *β*, Asn1-CO	Asn1-*β*
β	62.5	3.84, m	*α*	CO, *α*	Thr-*β*
Ser-2					
CO	173.1				
α	57.3	4.33, m	*β*	CO, *β*, β-AFA-CO	*β*-AFA-2
β	62.3	3.92, m	*α*	CO, *α*	
Thr					
CO	172.3				
α	60.1	4.28, d	*β* (2.5)	CO, *β*, *γ*, Ser1-CO	
β	67.4	4.40, m	*α, γ*	CO, *α*, *γ*	Ser1-*β*
γ	20.5	1.16, d	*β* (6.4)	*α*, *β*	
Tyr					
CO	174.5				
α	57.0	4.47, dd	*β* (9.3, 4.9)	CO, *β*, Asn2-CO,	
β	36.6	3.14/2.85, dd	*α*	CO, *α*, 1, 2, 6	Asn1-*α*
1	129.2				
2,6	131.1	7.06, d	Bz-*m* (8.5)	Bz-*I*, Bz-*m*, Bz-p	
3,5	116.4	6.72, d	Bz-*o* (8.4)	Bz-*I*, Bz-*o*, Bz-p	
4	157.5				
β-AFA					
CO	174.6				
2	42.2	2.43, m	3	CO, 3, 4	Ser2-*α*
3	48.6	4.14, m	2, 4	CO, 2, 4, Thr-CO	
4	35.6	1.5, m	3, 5-11	2, 3	
5-16	23.6-33.3	1.26-1.32, m	4, 17	4, 17	
17	14.4	0.88, t	5-16 (7.2)	5-16	

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Publications

1. Gerhard Bringmann, Guoliang Zhang, Anastasia Hager, Michael Moos, Andreas Irmer, Ralf Bargou, Manik Chatterjee. Antitumoral activities of dioncoquinones B and C and related naphthoquinones gained from total synthesis or isolation from plants. *Eur. J. Med. Chem*. **2011**, *46*, 5778-5789.

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Posters and Oral Presentations at Congresses and Symposia

1. 43th Natural Products Meeting: Chemistry, Biology and Ecology in Halle, Germany (27. 04. 2012); Participant.

2. 42th Natural Products Meeting: Chemistry, Biology and Ecology in Bayreuth, Germany (14. 10. 2011); Oral Presentation: “Cyclodysidins A–D, New Cyclic Lipopeptides from the Marine Sponge-derived *Streptomyces* Strain RV15”.

3. GSLS Annual Retreat (29. 07. 2011 – 31. 07. 2011) in Nürnberg, Germany; Poster Presentation: “Jozimine A_2, the First Natural Dioncophyllaceae-type Naphthylisoquinoline Alkaloid Dimer with Three Chiral Axes and High Antimalarial Activity”.

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4. Poster Design and Presentation (23. 02. 2010), Graduate School of Life Sciences, Würzburg, Germany.

Affidavit

I hereby declare that my thesis entitled: **“Phytochemical Research on Two *Ancistrocladus* Species, Semi-Synthesis of Dimeric Naphthylisoquinoline Alkaloids, and Structure Optimization of Antitumoral Naphthoquinones”** is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis.

Furthermore, I verify that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Würzburg

Date Signature

Guoliang Zhang