Julius-Maximilians-
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WÜRZBURG

TOTAL SYNTHESIS OF MONO- AND DIMERIC NAPHTHYLISOQUINOLINE ALKALOIDS AND RELATED ANALOGS

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Submitted by
William Shamburger from Bountiful, Utah

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My most sincere gratitude is directed towards
Prof. Dr. Dr. h.c. mult. G. Bringmann for the continuous support during the preparation of this work, the nearly limitless scientific freedom granted, and the excellent working conditions.

Parts of the results achieved during the preparation of this thesis have been subject to publications[86, 107] and poster presentations.

Dedicated to my beloved friends Gonzales and Pablo

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GENERAL SECTION

1 Introduction

In late December 2019 the spread of a type of pneumonia, which was at that time unknown, was first identified in the capital city Wuhan of the province Hubai in Central China.[1, 2] After the numbers of cases had increased dramatically, the central government of China imposed a lockdown for the whole city. Despite this drastic and unprecedented measure, the disease continued to spread and was considered an epidemic in China by January 2020[3] and in early March of the same year the WHO officially announced it to be of pandemic magnitude.[4] Mid 2020 more than 750,000 people fell victim to this disease caused by a corona virus now known as SARS-CoV-2.[5]

With the ongoing globalization, viruses at first located at a distinct area, then circulating all over the world is seemingly becoming more or less normality considering the rapid spread of the bird flu, H5N1,[6] in 2004, and the swine flu, in 2009.[7] In contrast to SARS-CoV-2, the two viruses connected to these diseases did not only cause considerably fewer casualties, but their worldwide impact was not even close to the one caused by COVID-19. Besides human health it immensely affected economic and social life.[8] In Germany, for example, the citizens were ordered to stay at home and avoid any contact to others for months. Only people with occupations considered as systemically relevant were allowed to go to work. This impressively shows the immense influence a disease can have in fields far beyond physical health. And, while we are currently still struggling with COVID-19 and its ‘collateral damages’, chances are good that a vaccine in sufficiently large quantities will be available in the near future.

Still, Africa in particular is threatened by COVID-19 as it is anyhow struggling with diseases such as tuberculosis, cholera, AIDS, and malaria.[9] The latter one alone caused 405,000 fatalities in 2019 and Africa accounts for 90% of these cases.[10] While there are commercially available antimalarial drugs, the emergence of drug-resistant *Plasmodium falciparum* strains is a big problem regarding the fight against malaria underscoring the need for the discovery and development of new drug entities.[11-13]

And while COVID-19 is a new and as yet sparsely investigated disease, malaria has been treated by folk medicine for hundreds of years with tinctures or extracts from plants. Today, the isolation and structural elucidation of metabolites from these plants is a good starting point in finding active entities. A prominent example of a compound that was identified by this procedure is quinine (**1**) (Figure 1).[14] It is a secondary metabolite from the bark of several species of *Cinchona* plants, which was the first and during the height of European colonialism only drug used for treating malaria. The most commonly applied antimalarial drugs chloroquine (**2**) and mefloquine (**3**) followed the precedent of this natural product. But, as mentioned above, strains of *P. falciparum* have developed resistances against these drugs.

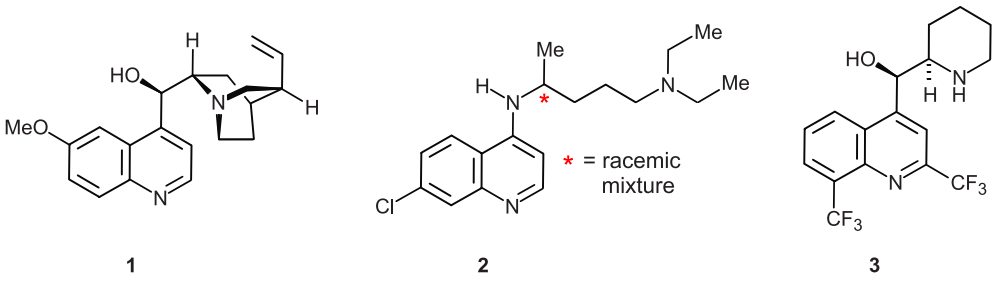


Figure 1. Structures of the antimalarial compounds quinine (**1**), chloroquine (**2**), and mefloquine (**3**).

In the tropical areas of Africa and Asia plants of the two families Dioncophyllaceae and Ancistrocladaceae are widely used in folk medicine, thus, as an example, extracts of *Ancistrocladus tectorius* are used in treating malaria.[15] Our research group is devoted to the isolation, structural elucidation, and synthesis of natural products exclusively produced from these lianas with pharmacological activities, the naphthylisoquinoline alkaloids.

Over the past 30 years an extraordinary number of most different types of these secondary metabolites have been obtained by our group both by isolation and by synthesis.[16-21] Based on their biosynthetic origin of their isoquinoline and naphthalene halves from polyketide precursors, with subsequent formation of the biaryl axis by phenol-oxidative coupling, these alkaloids have a distinct but yet multifaceted molecular architecture in common.[22] The biaryl linkage can be located *ortho* or *para* to phenolic oxygens, i.e. at C-1', C-3', C-

6', or C-8' of the naphthalene part and at C-5 or C-7 of the isoquinoline moiety or even at the nitrogen atom. This structural diversity resulting from the different coupling types is further enhanced by the occurrence of a whole series of homo- or hetero-dimers and by the presence or absence of an oxygen function at C-6, by the *O*- and *N*-methylation pattern, and the hydrogenation degree in the isoquinoline part.

Typical representatives are the dioncophyllines A (**4a**) and C (**5a**), which possess two stereogenic centers and a rotationally hindered axis, and intriguing dimeric analogs such as michellamine B (**6**), jozimine A_2 (**7a**), and mbandakamine A (**8**), which have even three biaryl linkages. In comparison to **6**, the central biaryl axes of **7a** and **8** are rotationally hindered, giving rise to a remarkable series of three consecutive chiral axes (Figure 2).[23-27] Structurally even more fascinating are cyclombandakamine A_1 (**9**) and spirombandakamine A_1 (**10**); these complex polycyclic structures are obviously derived from dimers related to **8**, exhibiting rigid architectures due to the presence of condensed rings.[28, 29] In addition to such mono- and dimeric naphthylisoquinoline alkaloids, which are all based on a *C*,*C*-coupling, some – still quite few – structurally totally unprecedented *N*,*C*-coupled analogs have been discovered, such as ancistrocladinium A (**11**) and B (**12**).[30]

Depending on their individual structures, naphthylisoquinolines exhibit promising antiinfective activities against pathogens that cause tropical diseases such as malaria,[26] leishmaniasis,[30, 31] or trypanosomiasis.[32] More recently, some of them have likewise been found to display strong cytotoxic activities against multiple myeloma,[33, 34] human leukemia,[34-36] or pancreatic cancer cells.[20, 37-40] Their fascinating structures, bioactivities, and syntheses are documented in several reviews.[16, 41-43]

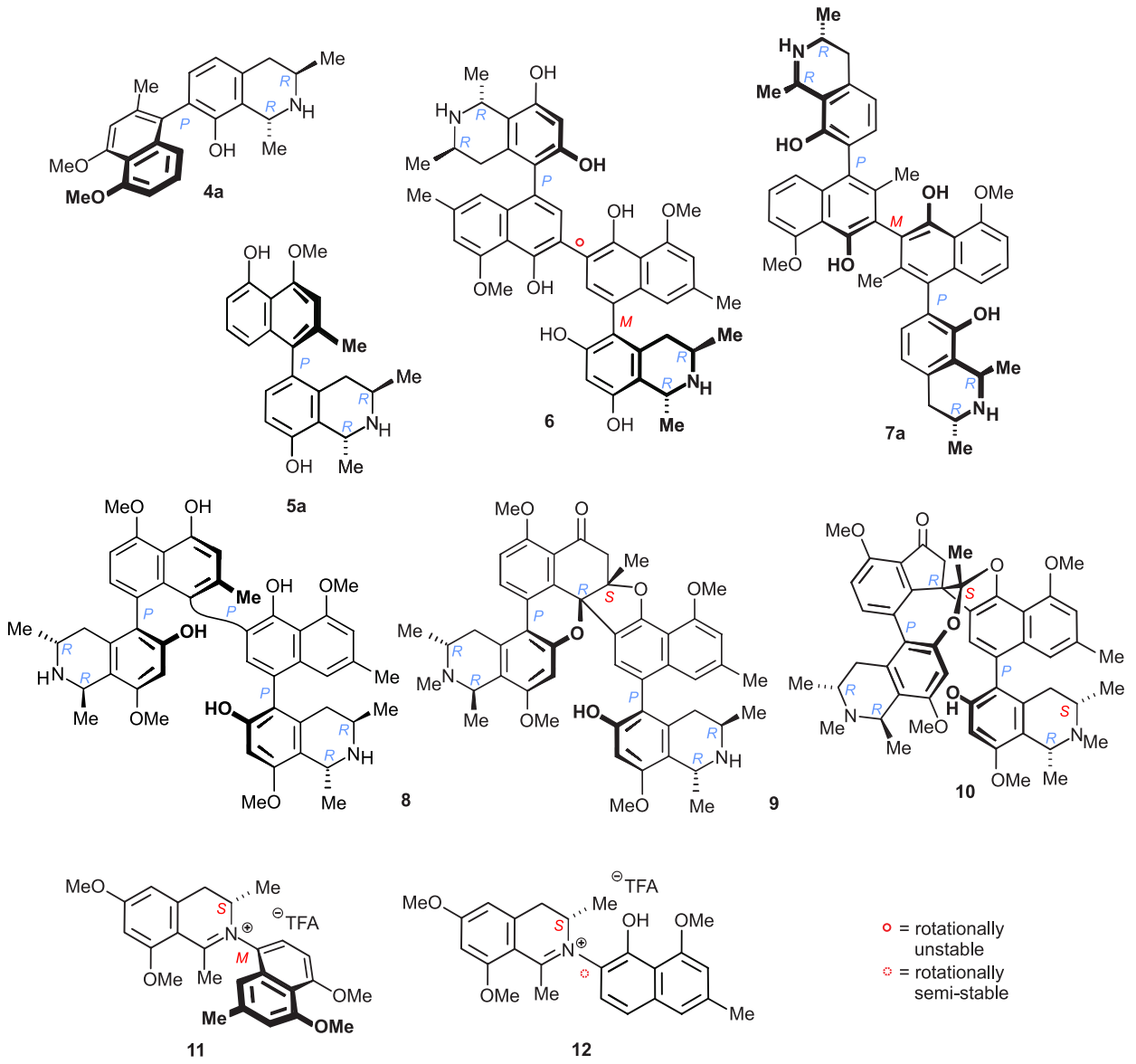


Figure 2. Structures of *C*,*C*- or *N*,*C*-coupled naphthylisoquinolines: dioncophyllines A (**4a**) and C (**5a**), michellamine B (**6**), jozimine A_2 (**7a**), mbandakamine A (**8**), cyclombandakamine A_1 (**9**), spirombandakamine A_1 (**10**) as well as ancistrocladinium A (**11**) and B (**12**).

In view of the intriguing antiplasmodial and anticancer activities of naphthylisoquinoline alkaloids, the present thesis was devoted to the following aims (Figure 3):

- Establishment of a short synthetic route to the dioncophyllines C (**5a**)[24] and C_2 (**13a**)[34], to dioncophyllidine C (**14b**), and to further potentially antiplasmodial 5,1'-coupled naphthylisoquinolines.
- Total synthesis of the 7,8'-linked natural product 5'-*O*-methyldioncophylline D (**15**),[44] which had shown cytotoxic activity against lymphoblastic leukemia and multiple myeloma cell lines.[34] Likewise envisaged was the preparation of **15** for activity testings against further cancer cell lines.
- Elaborating a first synthetic access to the anti-pancreatic cancer compound ancistrolikokine E_3 (**16a**) in order to provide larger quantities of this compound required for in vivo testing.
- Synthesis of dioncophylline E (**17**) and 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**), the latter one being required for the synthesis of the full series of the dimeric jozimine A_2 atropisomers next to the highly antiplasmodial parent compound jozimine A_2 (**7a**)[26].

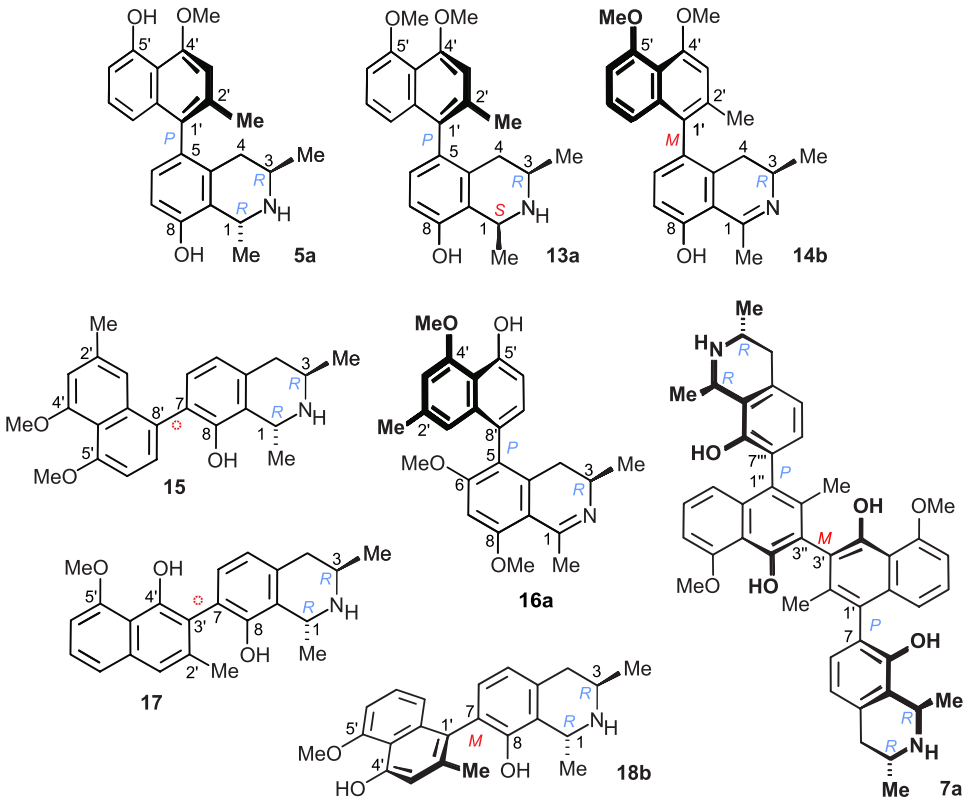


Figure 3. Target compounds of the present thesis: dioncophyllines C (**5a**) and C_2 (**13a**), dioncophyllidine C (**14b**), 5'-*O*-methyldioncophylline D (**15**), ancistrolikokine E_3 (**16a**), dioncophylline E (**17**), 4'-*O*-demethyldioncophylline A (**18b**), and jozimine A_2 (**7a**).

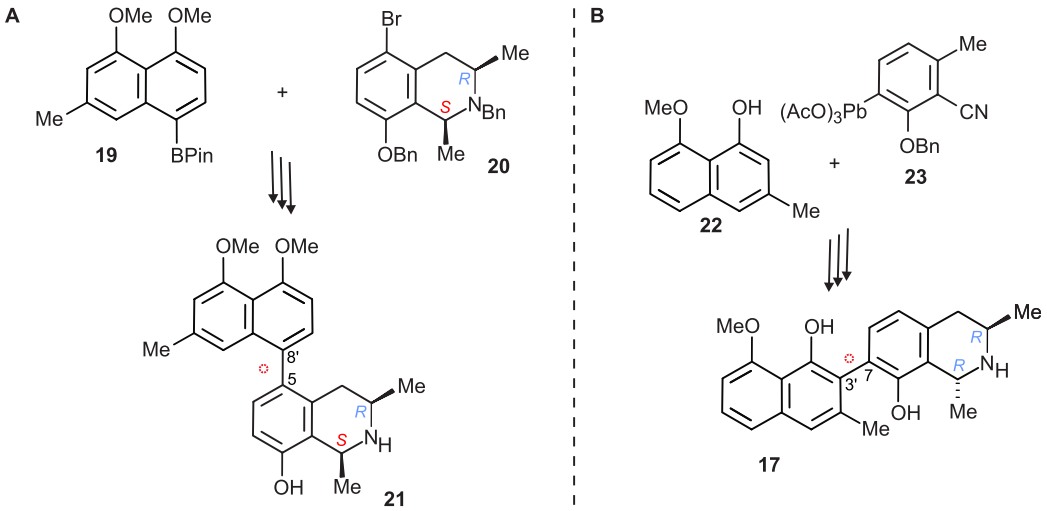
To avoid doublings, more detailed information on why exactly a certain molecule was of scientific interest and, thus, worth synthesizing is given in the corresponding chapters.

In the following two chapters a brief introduction to the different approaches to the stereoselective synthesis of naphthylisoquinoline alkaloids is given.

2 Intermolecular Biaryl-Bond-Forming Reactions in Naphthylisoquinoline Synthesis

With the monomeric *C*,*C*-coupled naphthylisoquinolines being the by far largest group among this class of natural products a plethora of total syntheses have been devoted to their preparation and all naturally occurring coupling types have been achieved synthetically meanwhile. In naphthylisoquinoline synthesis the formation of the biaryl axis is usually the key step. Whether the axis in the respective target compound is freely rotating or rotationally hindered, then resulting in a stereogenic element, has a major impact on how the naphthalene and isoquinoline halves can be joined to one another synthetically.

Regarding the synthesis of naphthylisoquinolines with a configurationally unstable axis the most challenging aspect of the biaryl bond formation is the endeavor to obtain regioselectivity for the coupling step. For this purpose, the naphthalene and the isoquinoline portions are usually functionalized in the respective coupling positions. The synthesis of dioncophylline F (**21**), applying the Suzuki-Miyaura coupling[34] (Scheme 1A), and the one of dioncophylline E (**17**), incorporating the Pinhey-Barton *ortho*-arylation[45] (Scheme 1B), are two recent examples. As most naphthylisoquinoline alkaloids possess a rotationally hindered biaryl axis the synthesis of the configurationally unstable ones is not further addressed here.



Scheme 1. A) Synthesis of dioncophylline F (**21**) by Suzuki-Miyaura coupling. B) Synthesis of dioncophylline E (**17**) by the Pinhey-Barton *ortho*-arylation.

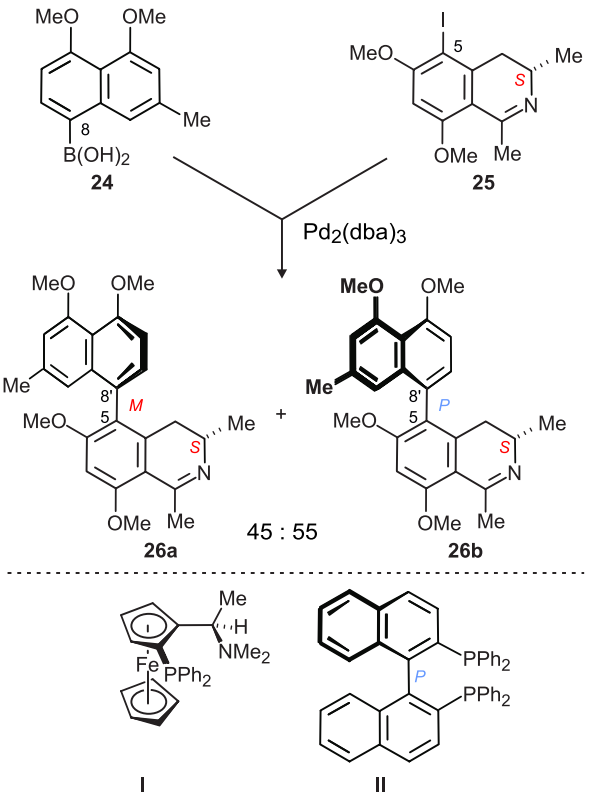
The synthesis of naphthylisoquinoline alkaloids with a configurationally stable axis is more demanding than the preparation of those bearing a configurationally unstable one. For most direct biaryl coupling reactions growing steric hindrance at the axis leads to decreased yields while problems of achieving good atropo-selectivities increase. Regarding the stereoselective formation of the biaryl axis, the intermolecular coupling approaches usually rely on inherent stereo-induction, in case the stereogenic centers are present in the isoquinoline part, or from planar-chiral elements as likewise internal asymmetric inductors, or on chiral metal catalysts as external inductors.

Among the isolated *C*,*C*-coupled monomeric naphthylisoquinoline alkaloids the 5,8'-coupled are the most common ones. Therefore, a multitude of synthetic approaches have been specifically designed for this coupling type. In comparison to most other representatives of this natural product class, 5,8'-coupled naphthylisoquinoline alkaloids have a biaryl axis that is less sterically crowded and the respective coupling positions are electronically favored. Accordingly, a transition metal-catalyzed cross-coupling reaction to build up the biaryl axis in these compounds is feasible.

An apparently easy way to the stereoselective formation of rotationally hindered biaryl axes is to apply a chiral ligand to those reactions. In terms of reaction economy this approach is favorable over others in which the coupling partners themselves first have to be modified in order to induce any stereoselectivity.

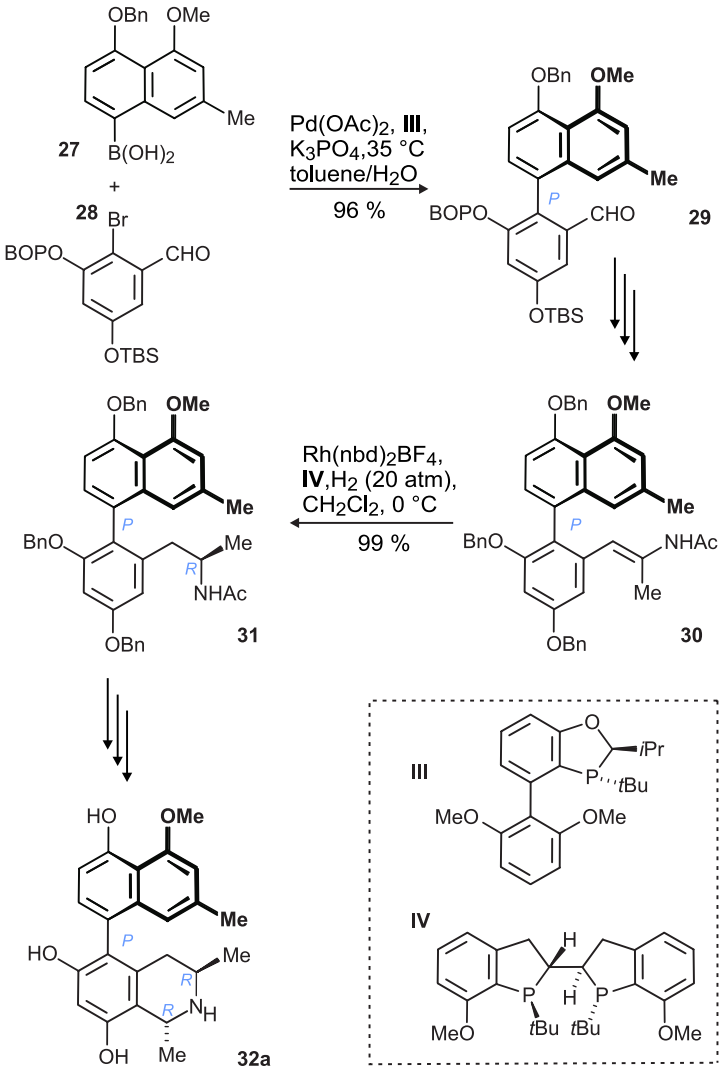
As evident from the synthesis of korupensamine A (**32a**) (Scheme 3) by Hoye via a non-atroposelective Suzuki-Miyaura coupling (not shown here), which resulted in a diastereomeric ratio of 56:44, there is very little inherent stereo-induction to be expected from the chiral isoquinoline substrate.[46-48] This finding was further solidified by the Suzuki-Miyaura coupling of naphthalene **24** with isoquinoline **25** to form the dihydronaphthylisoquinoline alkaloid ancistrotanzanine B (**26a**) and its atropisomer ancistroealaine A (**26b**) with a diastereomeric ratio of 45:55 in favor of the *P*-configured isomer **26b** (Scheme 2).[49] But, adding chiral ligands like **I**[50] or **II** or their corresponding enantiomers to the coupling reaction led to different diastereomeric ratios. With a diastereomeric ratio of 75:25 (*M*:*P*), the best conditions were to use a mixture of toluene

and water, $NaHCO_3$ as the base, $Pd_2(dba)_3$ as the catalyst and the ligands (R_c,S_p)-**I** and (*P*)-**II** resulting in a coupling yield of 38% and 50%, respectively. Surprisingly, no matter which enantiomer was used, the formation of the *M*-atropisomer was always favored. In an analogous approach the effect of chiral ligands on the Suzuki coupling to form 5-*epi*-4'-*O*-demethylancistrobertsonine C was investigated, yielding very similar results, i.e. little stereoselectivity for intermolecular coupling reaction of a naphthylboronic acid and a chiral dihydroisoquinoline.[51]



Scheme 2. Synthesis of ancistrotanzanine B (**26a**) and its atropisomer ancistroealaine A (**26b**) by an asymmetric Suzuki-Miyaura coupling.

More recently, Tang *et al.* elaborated a synthetic pathway to korupensamines A (**32a**) and B (**32b**) via Suzuki-Miyaura coupling by adding a chiral ligand in catalytic quantities to the reaction medium, resulting in a remarkable enantiomeric excess (Scheme 3).[52] Here, the coupling took place between the naphthalene moiety **27** and a monocyclic precursor **28**, which was later transformed into the corresponding isoquinoline half in korupensamine A (**32a**).



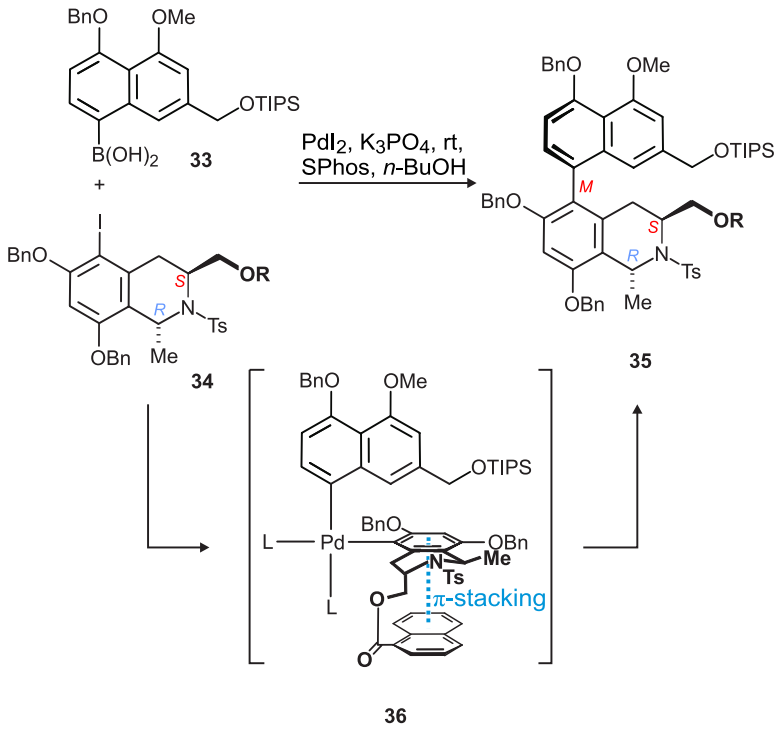
Scheme 3. Enantioselective formation of the biaryl bond and diastereoselective construction of the isoquinoline portion in korupensamine A (**32a**) by applying the chiral phosphine ligands **III** and **IV**, respectively.

While screening the influence of different chiral ligands and protective groups on the enantioselectivity of the coupling reaction, **III** emerged to be the most efficient ligand and bis(2-oxo-3-oxazolidinyl)phosphinyl (BOP) the best-fitting protecting group.

Applying this knowledge to the coupling, the biaryl **29** was obtained in an enantiomeric excess of 93%. The stereogenic center at C-3 was introduced by asymmetric hydrogenation of **30** with a rhodium catalyst in combination with chiral ligand **IV**, which furnished acetamide **31** in a good diastereomeric ratio of 92:8 leading to the envisaged **32a** over a few more steps. In an identical way korupensamine B (**32b**), the atropisomer to **32a**, was

synthesized by simply substituting the chiral ligand **III** by its enantiomer, whereas the following steps remained the same. In consideration of the fact that all stereoinformation in this synthesis was incorporated by applying the ligands **III** and **IV** in catalytical quantities, this approach to the directed synthesis of naphthylisoquinoline alkaloids is highly efficient and economic.

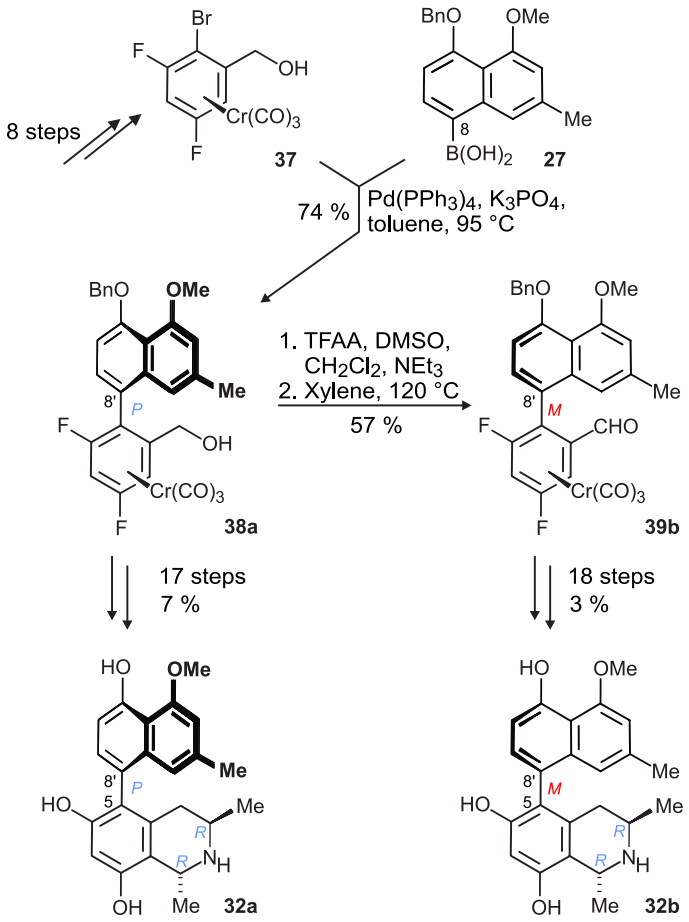
In a different attempt, korupensamine B (**32b**) was synthesized by Lipshutz and co-workers, again based on a Suzuki-Miyaura coupling, which in this case was performed intramolecularly, fixed by chelation as a tool to construct the biaryl axis selectively (Scheme 4).[53] The basic principle that was followed in this approach was to functionalize the isoquinoline coupling partner **34** at its methyl group next to the stereogenic center at C-3. A substituent that enables π-stacking interactions with the transition metal during the cross coupling was chosen, hoping to induce a good central-to-axial chirality transfer. Further, the naphthalene portion **33** was equipped with a bulky group, which was intended to influence the coupling selectivity by effectively shielding one of the diastereotopic coupling sites. The best results for this reaction were obtained by applying the catalytic system of PdI_2, SPhos, and K_3PO_4 in *n*-BuOH furnishing **35** in 72% yield in a diastereomeric ratio of 92:8. It was speculated that the diastereoselectivity was based on the intramolecular π-stacking between the electron-rich isoquinoline and electron-poor aryl ester of **34** leading to an orientation of the isoquinoline as illustrated in **36**. Therefore, the naphthalene part in **36** was in an orientation which positioned the bulky OTIPS group in such a way that steric interaction with the ligands in the square-planar coordination sphere around the metal was avoided. Reductive elimination of the biaryl from this intermediate gave the *M*-configured atropisomer **35**. More recently, in a collaboration of B. Lipshutz, D. Aue, and our group the synthesis of *O*,*N*-dimethylhamatine following a very similar approach under mild Negishi coupling conditions has been published.[54]



Scheme 4. Internal asymmetric induction in the synthesis of korupensamine B (**32b**) by utilizing the π-stacking capability of a naphthoic ester, shielding the bottom face of the isoquinoline part.

A further elegant approach, which furnished both atropisomers, korupensamine A (**32a**) and B (**32b**), starting from one and the same precursor, was elaborated by Uemura (Scheme 5).[55-58] The method is based on the Suzuki-Miyaura coupling of a planar-chiral η^6-polysubstituted arene chromium complex **37**, where the tricarbonyl chromium function effectively blocks one side of the arene ring giving rise to excellent stereoselectivities for the cross-coupling step with **27**. Starting with the formation of the thermodynamically less stable *syn*-biaryl chromium complex **38a**, by coupling boronic acid **27** with **37** under kinetic conditions, it was anticipated to later access the thermodynamically stable *anti*-isomer **39b** after oxidation to the corresponding aldehyde by bond rotation upon heating. In first attempts Uemura and co-workers discovered that depending on the nature of the biaryl chromium complex inversion of the planar chirality came from the stereoselective migration of the tricarbonyl chromium fragment and not as desired from the rotation about the central bond. It was evidenced that electron-withdrawing groups such as the fluorine substituents in **37** have a stabilizing effect on the *syn*-biaryl chromium complex, and upon

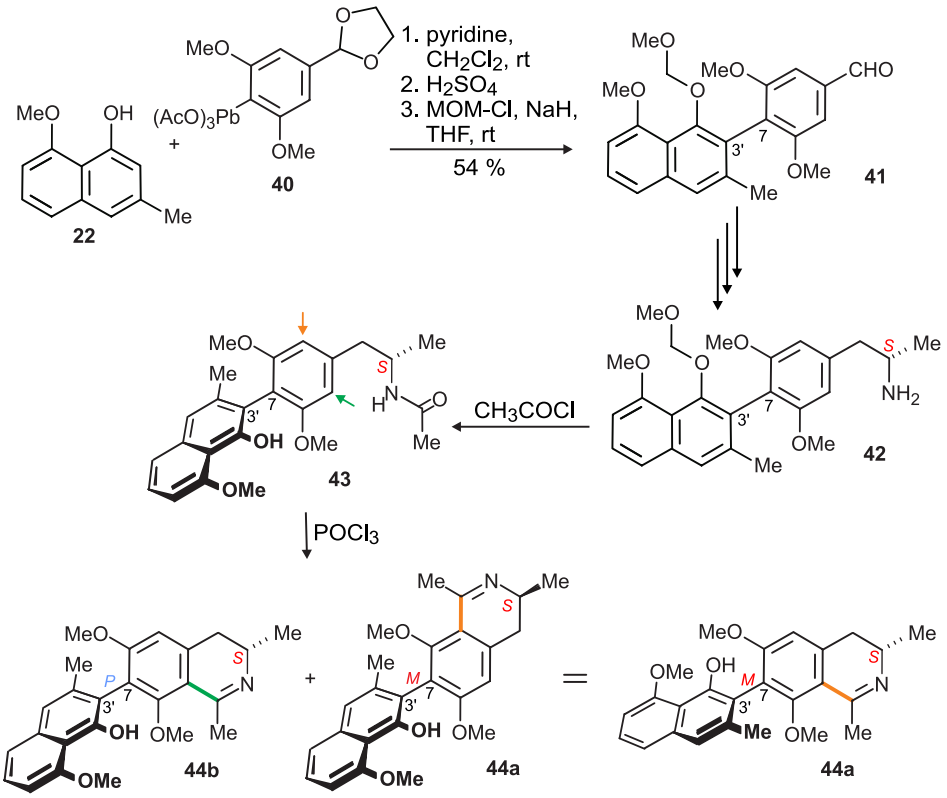
subjecting **38a** to thermal isomerization the anticipated stereo-inversion by bond rotation was observed. With the molecules **38a** and **39b** in hand, the total synthesis of **32a** and **32b** was completed in 7% and 3% yield over 17 and 18 steps, respectively. Advantageous to this method are the high yields and selectivities for the coupling step and the accessibility to both atropisomers from the same precursor. Anyhow, drawbacks are the toxicity of the chromium compounds and the relatively tedious synthesis of the required enantiomerically pure [(arylhalide)$Cr(CO)_3$] complex like **37**. In a comparable approach, Uemura and co-workers synthesized unnatural *O*,*O*-dimethylkorupensamine A.[58, 59]



Scheme 5. Diastereoselective synthesis of korupensamines A (**32a**) and B (**32b**) via planar-chiral chromium arene complexes **38a** and **38b**.

In a synthesis most similar to the one of dioncophylline E (**17**),[45] Morris also synthesized the rotationally hindered 7,3'-coupled ancistrocladidine (**44a**) and its atropisomer **44b** before (Scheme 6).[60, 61] The synthesis of the two compounds seemed rewarding since the

unusual 7,3'-coupling type was at the time of their publication not yet accessible by any other synthetic means. Interestingly and in comparison to the previously described approaches, here only one of the two coupling moieties **22** and **40** was functionalized at its respective coupling position. This was possible as the Pinhey-Barton *ortho*-arylation was the biaryl-bond-forming reaction leading to full regioselectivity yielding the – however - achiral **41**. The secondary amine **42** was accessed over several more steps including a Katsuki-Sharpless epoxidation and a Mitsonobu reaction for the stereoselective introduction of the amine. This functionality was acetylated to give the central but not axially chiral **43**. In course of the Bischler-Napieralski cyclization the axis became a stereogenic element yielding a mixture of ancistrocladidine (**44a**) and its atropisomer **44b**. In this case the simultaneous formation of the two atropisomers **44a**/**44b** was based on the lacking regioselectivity of the cyclization of the axially 'prochiral' **43**. This reaction was equally likely taking place at either one of the diastereotopic carbons (indicated by the orange and green arrows in Scheme 6) of **43**. Considering the 'fixed' axial orientation as indicated in the structure **43**, cyclization at the carbons with the orange and the green arrows gave **44a** and **44b**, respectively. It is remarkable that by applying the Pinhey-Barton reaction for the coupling step the steric constraints induced by the four *ortho*-substituents were overcome and there were no regioselectivity problems for the biaryl coupling step. More recently, in a PhD thesis prepared in the group of Morris a new yet highly similar approach to 7,3'- and 5,3'-linked naphthylisoquinolines has been elaborated replacing the very toxic lead reagent by a bismuth compound.[62] Nevertheless, an atroposelective formation of either **44a** or **44b** would be highly desirable, making this nice method even more appealing. The directed joint total synthesis of the 7,3'-coupled alkaloids ancistrocladidine (**44a**) and ancistrotectorine (**75**) by our group by the lactone method (Scheme 11), as described below, incorporates both regio- and stereoselectivity even for these sterically demanding compounds.[63]

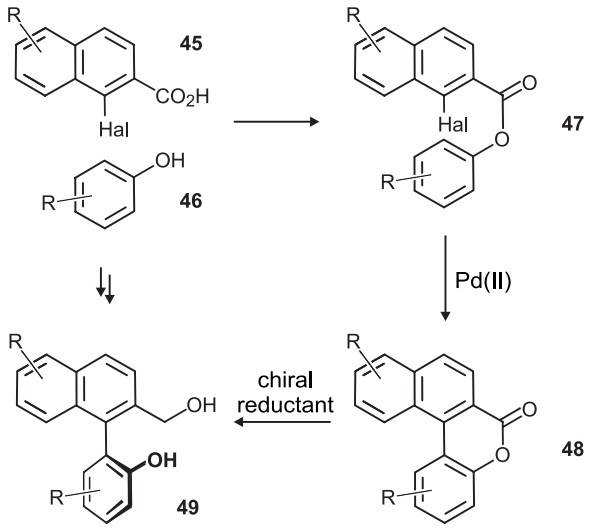


Scheme 6. Non-atroposelective synthesis of ancistrocladidine (**44a**) and its atropisomer (**44b**) via the *ortho*-arylation approach. The orange and green arrows indicate the diastereotopic carbons which were attacked in the Bischler-Napieralski cyclization, yielding either **44a** or **44b**.

3 The Lactone Method

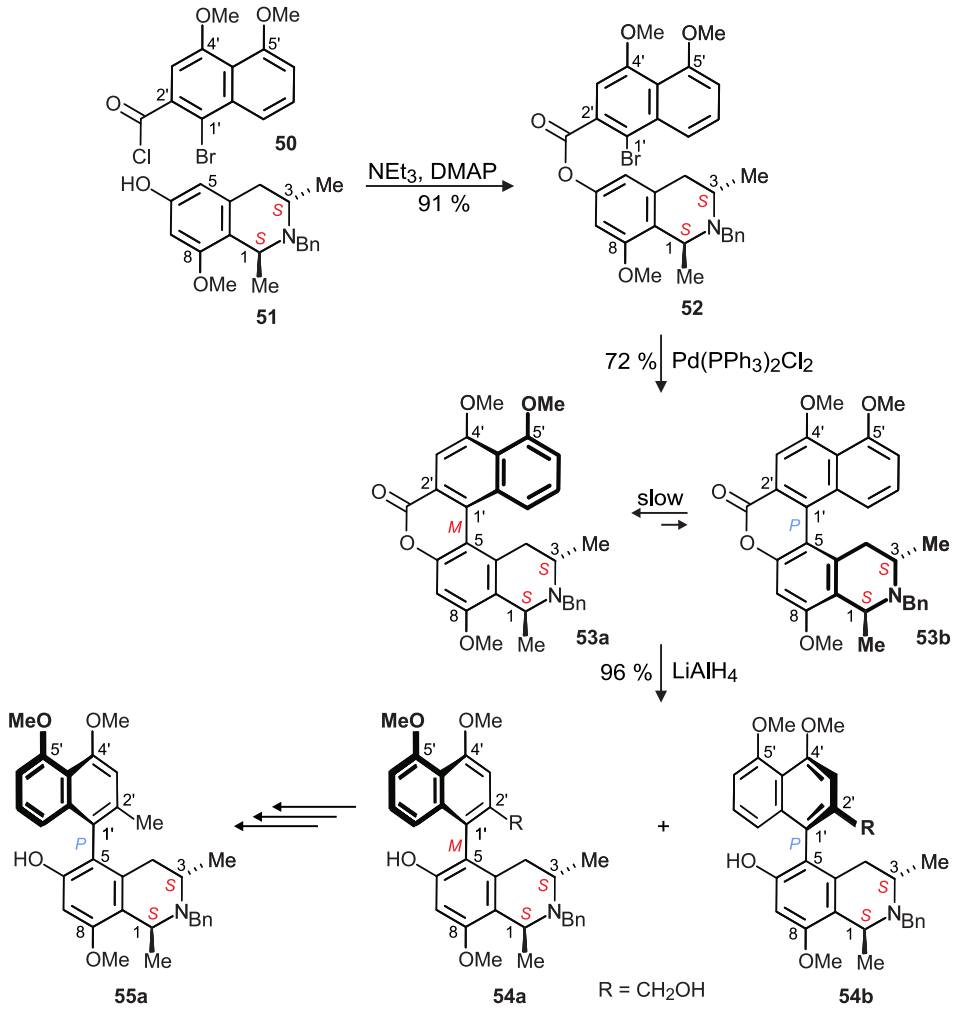
The previously described methods are either based on the principle of an atropo-diastereodivergent or atroposelective biaryl coupling reaction or on non-selective ones forming both atropisomers at the same time. The 'lactone method', by contrast, separates the biaryl-bond-forming step from the stereo-induction, resulting in very good chemical and optical yields. This concept was developed in our research group especially for the synthesis of naphthylisoquinoline alkaloids, but has meanwhile found application in further fields of organic synthesis.[64-67]

Scheme 7 exemplarily illustrates the overall idea behind the lactone method. In a first reaction the coupling building blocks **45** and **46** are linked to one another by an ester bond. Usually, for electronic reasons concerning the ensuing biaryl bond formation, the molecular half that is functionalized by a halogen is also the one which carries a carboxy function. The two arenes of **47** are prefixed in an intramolecular Pd-catalyzed coupling to give the lactone **48**. This reaction proceeds highly regioselectively guided by the position of the halogen and the attack of the carbon in *ortho*-relation to the phenol functionality. All atoms of the six-membered lactone ring are sp^2-hybridized, but anyhow this molecule is not flat and thus achiral but rather helically distorted and hence chiral, but has a low rotational barrier. Thus, the lactone **48** occurs as a mixture of its two rapidly interconverting atropisomers. Out of this equilibrium, by adding chiral hydride,[68-72] nitrogen,[73, 74] or oxygen[75] nucleophiles, the lactone can be opened stereoselectively following the principle of a dynamic kinetic resolution. Scheme 7 exemplarily shows the ring opening of **48** with a chiral reducing agent to give the axially chiral biaryl **49**. As this kinetic resolution is dynamic, the formed atropisomer is obtained in a high enantio- or diastereomeric purity, in an up to quantitative yield. A more detailed analysis of the stereoelectronic and stereochemical effects that play a role in the diastereoselective ring opening of a lactone using a chiral hydride-transfer reagent is given in Chapter 7.3 using the synthesis of 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) as an example.



Scheme 7. The concept of the lactone method.

The total synthesis of the natural product ancistrocladine (**55a**) was the first to profit from the lactone method as the biaryl-bond-forming step (Scheme 8).[76] As in most cases where this method was used in naphthylisoquinoline synthesis, here the lactone was formed by prefixing a halogenated naphthoic acid **50** to an isoquinoline **51** with a free hydroxy function to form the ester **52** and subsequent transition-metal catalyzed biaryl coupling yielding **53a**/**53b**. The regioselectivity of this reaction was determined by the halogen at C-1' and the *ortho*-carbon at C-5 relative to the phenolic function at C-6. In this synthesis the first ring opening of the lactone, with its slowly interconverting **53a**/**53b** was done with the achiral reductant $LiAlH_4$ yielding the atropisomers **54a** and **54b** in a ratio of 70:30 in favor of **54a** that represented the equilibrium of **53a**/**53b**. After resolution, isomer **54a** was subjected to further reactions to obtain ancistrocladine (**55a**). In follow-up experiments, by influencing the equilibrium of **53a**/**53b**, the diastereomeric ratio of the reductive ring opening was further improved by thermodynamically controlling the reaction. Changing the substituent at the lactone's nitrogen from benzyl to $COCF_3$ the isoquinoline half became more rigid. This led to an even further pronounced thermodynamic difference between the two helimers and to an equilibrium (dr = 95:5) almost completely shifted to the side of the ancistrocladine precursor. This thermodynamic control is applicable to configuratively rather stable lactones, i.e. their two helimeric forms interconvert slowly.

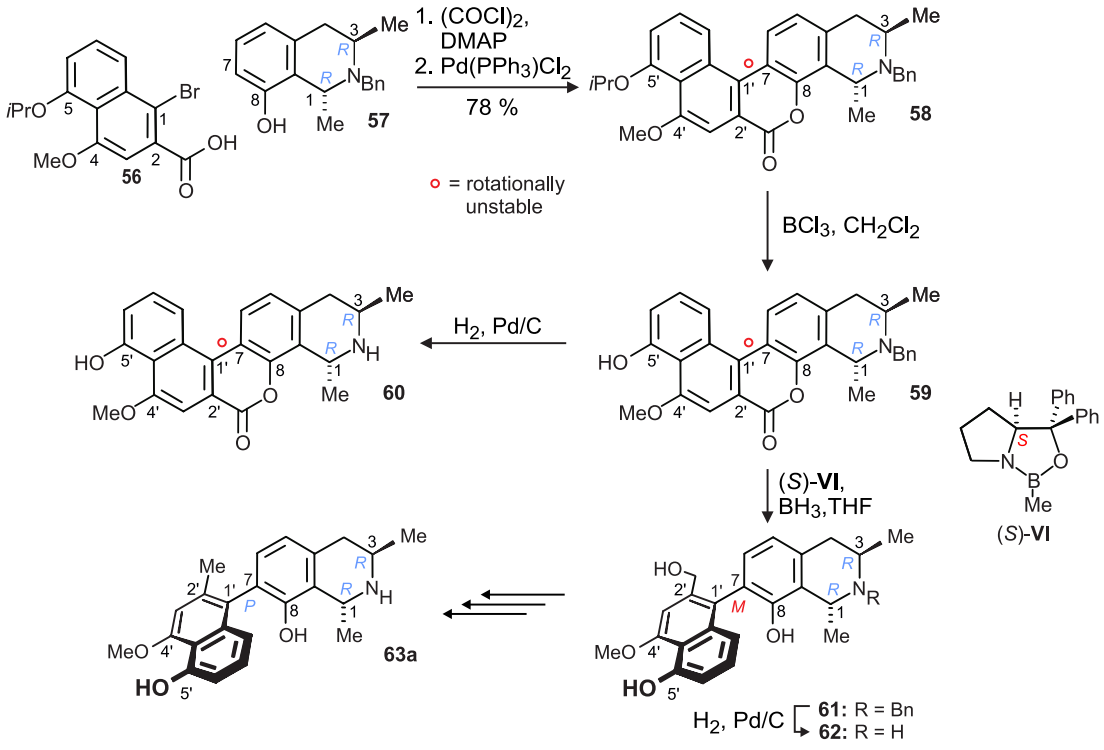


Scheme 8. The total synthesis of ancistrocladine (**55a**).

In order to achieve good diastereomeric ratios for lactones with a low rotational barrier, i.e. their two helimeric forms interconvert rapidly, the ring opening has to be done kinetically controlled.

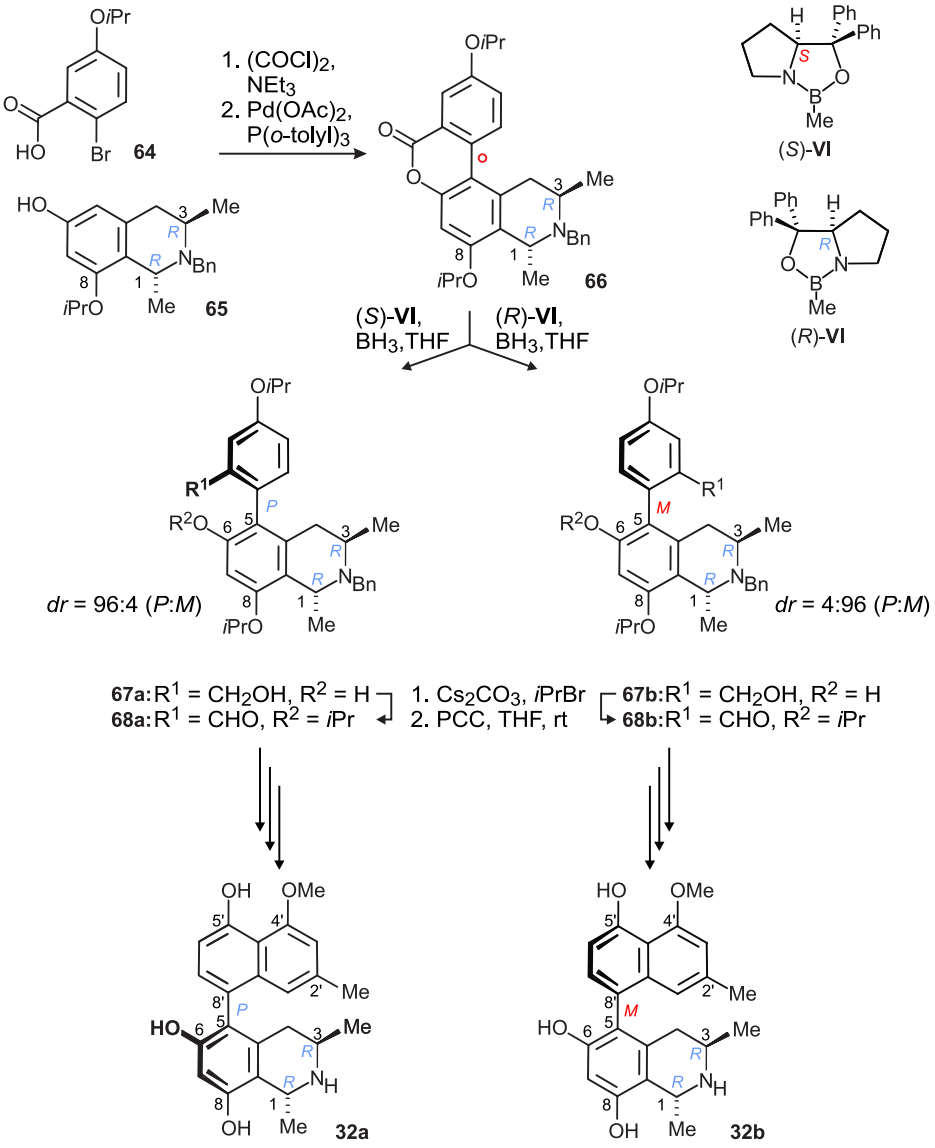
This kinetically controlled ring opening of a configuratively unstable lactone was impressively demonstrated in the joint synthesis of the three 7,1'-coupled natural products, dioncolactone A (**60**), dioncopeltine A (**62**), and 5'-*O*-demethyldioncophylline A (**63a**) (Scheme 9).[77] The overall synthesis started with the linkage of **56** and **57**. Subsequent intramolecular biaryl bond linkage gave the lactone **58**. Removal of the isopropyl group at O-5' of **58** yielded **59** and after a second deprotection the first natural product of this synthesis, dioncolactone A (**60**), was obtained. The lactone **59** was configuratively unstable.

The two helimers of **59** interconverted rapidly and therefore the addition of an achiral reductant might have furnished the two ring-opened atropisomers with low or even no diastereoselectivity. Thus, in the case of **59** the previously mentioned dynamic kinetic resolution was applied using the chiral hydride-transfer reagent mixture (*S*)-**VI**[50]/BH_3. The preferred coordination of (*S*)-**VI**/BH_3 to only one of the two helimers of **59**, and, based on stereoelectronic reasons, the selective attack of the hydride ion from one of the two diastereotopic faces of only one of the two interconverting isomers of the lactone yielded the secondary alcohol **61** with a *de* of 90% (for a detailed explanation on the diastereoselective ring opening of a lactone see Chapter 7.3). Removal of the *N*-benzyl protective group gave dioncopeltine A (**62**). Starting from intermediate **61**, after a few more steps the third natural product in this synthesis was obtained, 5'-*O*-demethyldioncophylline A (**63a**).



Scheme 9. The total synthesis of dioncolactone A (**60**), dioncopeltine A (**62**), and 5'-*O*-demethyldioncophylline A (**63a**).

For the two syntheses described above the carboxy function of the lactone, which gave a secondary alcohol upon reductive ring opening, was transferred into the methyl group at C-2' of the targeted naphthylisoquinolines. So, a structural precondition required by the lactone method is the presence of a carbon substituent *ortho* to the axis. While this circumstance is given for many naphthylisoquinolines, this is, at first glance, not the case for the prominent group of 5,8'-coupled representatives. But, looking at the structure of the korupensamines A (**32a**) and B (**32b**) more closely there is in fact a C_1 unit in *ortho*-position next to the biaryl axis, namely C-1'. Based on this idea, a concept was developed in which this C_1 unit was extended to the second ring of the naphthalene half of korupensamines A (**32a**) and B (**32b**) (Scheme 10).[78] The total synthesis of **32a** and **32b** started with the esterification and the intramolecular biaryl coupling of benzoic acid **64** with the isoquinoline **65** to give **66**. The coupling proceeded regioselectively at C-5 of the isoquinoline. The cleavage of the lactone led to relatively high diastereoselectivities (**67a**/**67b** = 17:83 for L-selectride) even when using achiral hydride-transfer reagents. In order to access the less favored *P*-isomer **67a**, attempts were made to overcome the inherent asymmetric induction of **66** in a diastereo-divergent ring opening reaction by an external stereo-induction coming from chiral hydride-transfer reagents. Using the chiral reductant BINAL-H, however, the inherent stereo-induction of **66** was still so strong that the *M*-configured **67b** remained the predominant isomer (**67a**/**67b** = 33:67 for (*M*)-BINAL-H and 56:54 for (*P*)-BINAL-H). Only upon reduction with Corey's oxazaborolidine-borane system[79] the selectivity was shifted to the *P*-atropisomer **67a** (**67a**/**67b** = 94:6 for (*R*)-**VI**·BH_3 and 4:96 for (*S*)-**VI**·BH_3). The phenolic hydroxy function in **67a**/**67b** was protected and the primary alcohol function was oxidized to form the corresponding aldehydes **68a** and **68b**, from which the naphthalene portion was build up in a few more steps to give korupensamines A (**32a**) and B (**32b**), respectively.

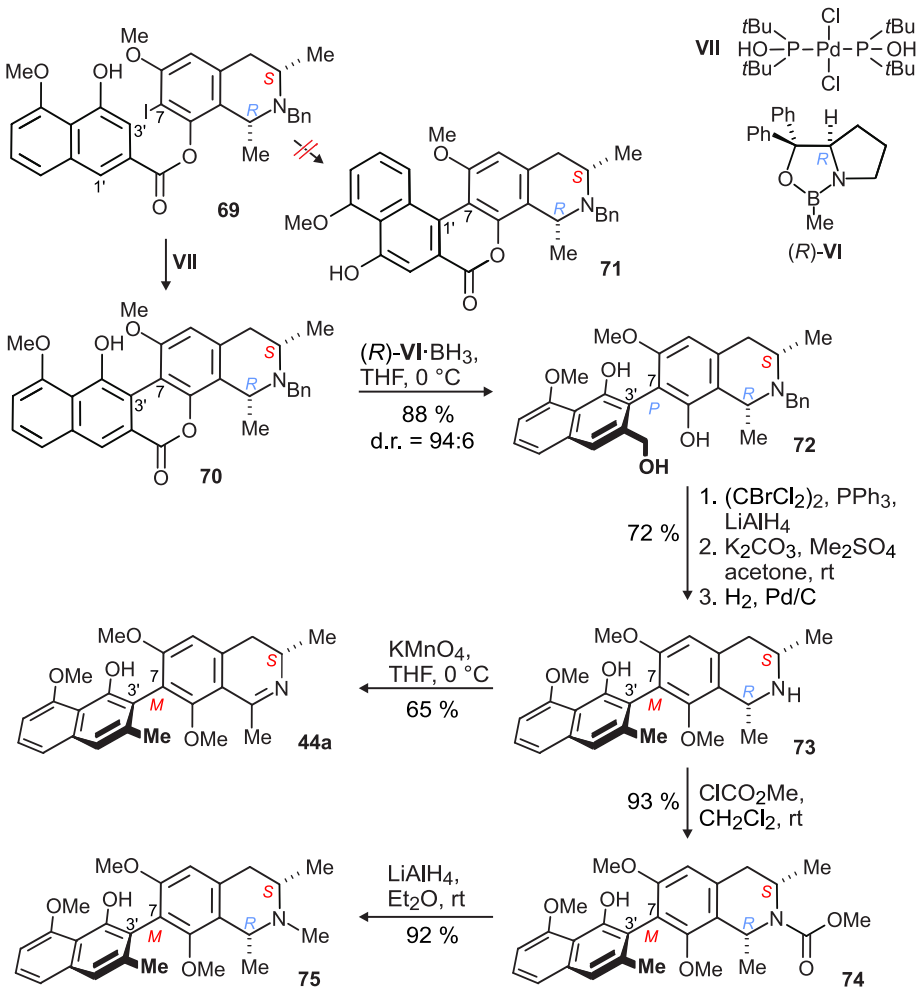


Scheme 10. The total synthesis of korupensamines A (**32a**) and B (**32b**).

A further application that underscores the efficiency of the lactone method is the synthesis of ancistrocladidine (**44a**) and ancistrotectorine (**75**) (Scheme 11).[63] Morris' synthesis of ancistrocladidine (**44a**) had taken advantage of a site-directed biaryl bond formation using an aryllead triacetate (Scheme 6).[60, 61] In our own total synthesis, a modified version of the lactone method was applied.[80, 81] As described above, for our intermolecular coupling step only one of the two involved aromatic rings has to be activated and this is usually the naphthoate (or benzoate) portion, which is functionalized by a bromine or, better, by an iodine substituent. Applying this general concept to the total synthesis of ancistrocladidine

(**44a**) and ancistrotectorine (**75**), no formation of coupling product was observed. This was surprising since a too high degree of steric hindrance could not be the reason for this reaction to fail since comparable lactone syntheses, e.g. the one of ancistrocladine (**55a**), had been accomplished overcoming much higher steric hindrance. Therefore, apparently the unfavorable electronic properties at C-3' hindered the reaction. Taking the synthesis of benanomycin[80] as a role model, an inverse activation concept was applied, in which the halogen was not located next to the carboxyl function but rather at the phenolic side of the ester. Accordingly, by attaching an iodine substituent in the isoquinoline portion of **69** the coupling problem was overcome. The coupling of ester **69** to form lactone **70** itself was performed using catalyst **VII**. In principle, an assumed disadvantage to this synthetic approach was that by attaching the halogen to C-7 of the isoquinoline in the coupling reaction a competition of C-1' and C-3' in the naphthalene portion had to be taken in to account yielding **71** and the desired **70**, respectively. But, presumably due to steric reasons, virtually no undesired 1'-coupling product **71** was formed.

Atroposelective ring opening was accomplished by applying (*R*)-**VI**/BH_3, which gave the best selectivity among all tested achiral and chiral reducing agents, yielding **72** in 88% with a high external asymmetric induction (*M*:*P* = 6:94 for (*R*)-**VI**/BH_3 and conversely 94:6 for (*S*)-**VI**/BH_3). Selective methylation of the OH function at C-8 and reductive removal of the benzylic hydroxy function in **72** furnished the joint precursor **73** for **44a** and **75**. By oxidation of **73** with potassium permanganate, ancistrocladidine (**44a**) and by selective *N*-methylation over two steps, via the carbamate **74**, ancistrotectorine (**75**) was obtained. Compared to the work of Morris et al. (as described above)[60, 61] and typical of the lactone method, this approach is more convergent since the isoquinoline and the naphthalene moieties are synthesized independently from one another and are then linked at the stage of the ester. But most importantly the *M*- as well as the *P*-atropisomer is accessible selectively in high diastereomeric ratios and any material of the undesired isomer can be recycled back to the lactone.



Scheme 11. Total synthesis of ancistrocladidine (**44a**) and ancistrotectorine (**75**).

In summary, concerning the synthesis of naphthylisoquinoline alkaloids with configurationally stable axes and chiral biaryls in general, the lactone method is a very efficient and extensively investigated strategy. Its benefits are, among others, its highly convergent nature where the coupling building blocks already comprise all substituents and stereoinformation prior to the coupling reaction itself, its high regioselectivity in the formation of the axis with good to excellent yields even in the case of sterically demanding substrates, and, most importantly, its capability to selectively acquire both atropisomers from a joint late-stage precursor applying the principle of a dynamic kinetic resolution. Whether this or another method was used for the synthesis of the natural products syntheses described in this thesis is discussed in the respective chapters.

4 New Synthetic Pathway to 5,1'-coupled Dioncophyllaceae-Type Naphthylisoquinolines

Isolated from the roots of the West African liana *Triphyophyllum peltatum*, dioncophylline C (**5a**) became one of the 'star' compounds in the field of naphthylisoquinoline alkaloids.[24, 82] In a broad series of bioactivity testings against the pathogens causing leishmaniasis, trypanosomiasis,[31] and malaria[83-86], **5a** often stood out among others. The potency of **5a** against the cause of *Malaria tropica*, *Plasmodium falciparum*, is exceptional as it is one of the highest ever found for any monomeric naphthylisoquinoline, both of natural and of synthetic origin.[87] With this pronounced antiplasmodial activity, dioncophylline C (**5a**) even made the progression from in vitro to in vivo testings against the murine *P. berghei* parasite.[85] In these experiments parasitemia was decreased after a single oral dose and a cure was observed after a 4-day Peters[88] suppressive test.

Despite major advancements in the field of naphthylisoquinoline isolation from plant material in the past three decades, dioncophylline C (**5a**) remained the only 5,1'-coupled Dioncophyllaceae-type alkaloid to be obtained from natural sources for more than 20 years. Just recently, two new representatives of this class have been found, the *cis*-configured dioncophylline C_2 (**13a**)[34] from *Ancistrocladus ileboensis* and the closely related dihydro analog dioncophyllidine C (**14b**) from *Ancistrocladus abbreviatus* (Figure 4). While **13a** showed distinct antiplasmodial activity too,[34] **5a** remained the most potent compound while **14b** has not yet been tested.

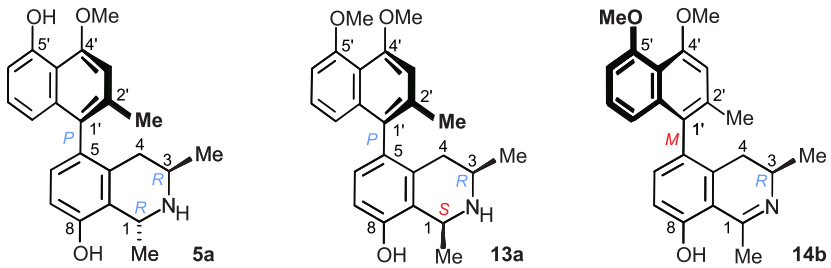


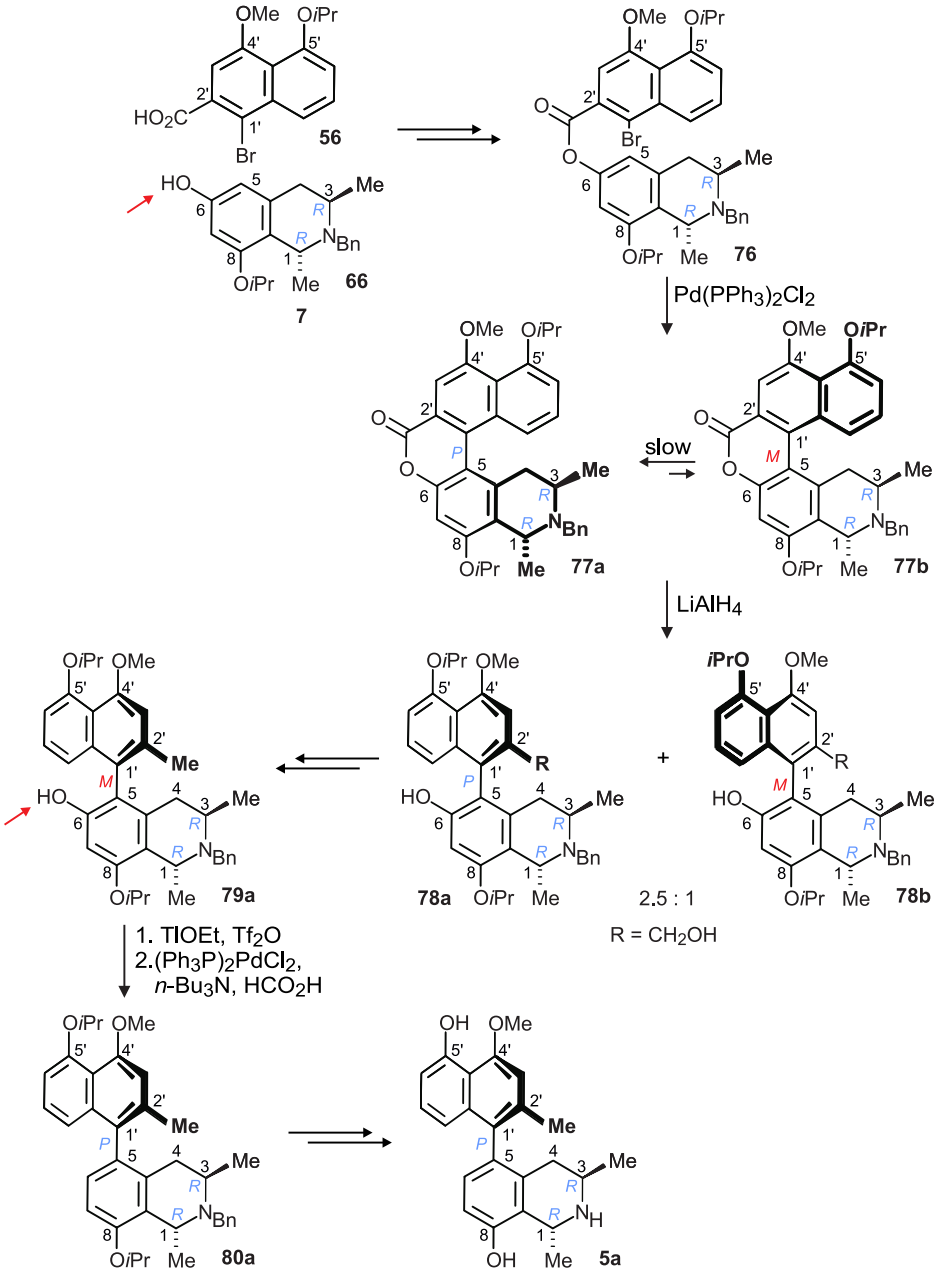
Figure 4. The natural 5,1'-coupled Dioncophyllaceae-type naphthylisoquinolines dioncophylline C (**5a**), dioncophylline C_2 (**13a**), and dioncophyllidine C (**14b**).

Due to these interesting biological activities an easily applicable synthetic path towards dioncophylline C (**5a**) which should be transferable to the synthesis of the two other known natural products **13a** and **14b** and to further closely related as yet non-natural analogs was envisaged. In this regard, the synthesis either by the lactone method or by an intermolecular coupling was feasible.

In previous work, dioncophylline C (**5a**) had already been subject to a successful total synthesis including the above described lactone method as the key step, the biaryl bond formation (Scheme 12).[82] It was closely related to the one of the Ancistrocladaceae-type naphthylisoquinoline ancistrocladine (**55a**) (see Scheme 8). But, here a Dioncophyllaceae-type alkaloid was synthesized. This means that the configuration at C-3 of **5a** is *R* and more importantly there is no oxygen function at C-6 of the isoquinoline subunit. This might seem to be an insignificant difference, but in fact this heavily impacted the total synthesis of **5a** by this method.

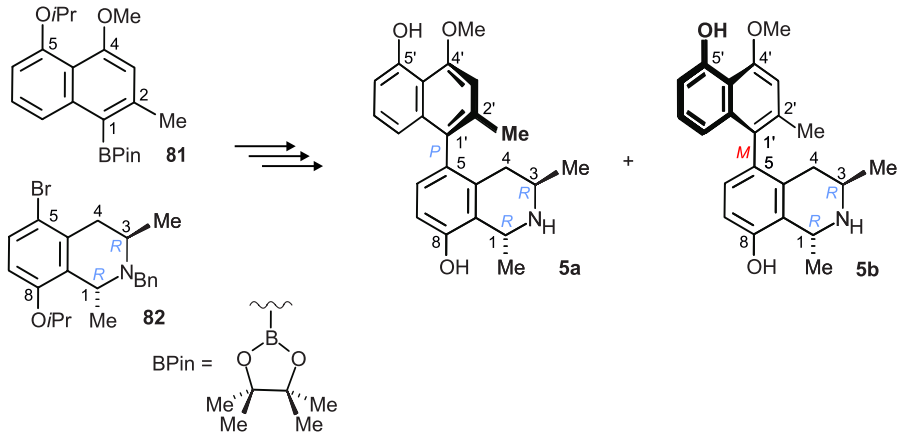
A fundamental obligation of this approach is that in the isoquinoline half **66** there must be a free oxygen (here at C-6) in an *ortho*-position in respect to the planned biaryl axis. This oxygen was required to link **66** to the naphthalene **56** to construct the ester **76**, the direct precursor to the lactone **77a**/**77b**. Thus, even if there is no oxygen functionality in the final product at C-6 it still was mandatory for the total synthesis of **5a**. The ring opening of **77a**/**77b** was done with the achiral reductant $LiAlH_4$ leading to a ratio of 2.5:1 **78a**:**78b** in favor of the desired diastereomer **78a**. An in-depth explanation for the found diastereomeric ratio and an improved thermodynamically controlled synthesis which further improved the selectivity of this reaction is given in the PhD thesis of Dr. Weirich.[89] In molecule **79a** the disadvantageous nature of the oxygen function at C-6 was evident as it obviously had to be removed later on by activating the OH-function with an *O*-triflate followed by reductive cleavage. Most unpleasantly, regarding this activation in the published synthesis of **5a**, a highly toxic thallium base was necessary as others failed. This base of course should be substituted by non-toxic alternatives if the total synthesis of **5a** and its analogs was to be repeated by this approach. Finally, removal of the protective groups in **80a** yielded the natural product dioncophylline C (**5a**).

In terms of diastereoselective formations of biaryl axes in naphthylisoquinoline synthesis the lactone method remains the 'gold standard' and, thus, usually is the method of choice whenever one distinct atropisomer is desired. If this approach was to be repeated, the ring opening of the lactone should be done with chiral reducing agents to see whether under kinetically controlled conditions the *M*-atropisomer **5b** can be accessed selectively.



Scheme 12. Total synthesis of dioncophylline C (**5a**) by applying the lactone method.

Within the present thesis, the synthesis of all three known natural dioncophylline-C-type naphthylisoquinoline alkaloids next to closely related synthetic analogs was envisaged. Therefore, a synthetic approach was desirable which comprised as few (linear) synthetic steps as possible while at the same time yielding as many different target compounds as possible. These two requirements were planned to be fulfilled by including a highly convergent intermolecular coupling into the overall synthesis with the biaryl bond formation at a late stage. By omitting diastereoselectivity in the biaryl coupling reaction, two target compounds, the two atropo-diastereomers, were expected to be formed at once. The Suzuki-Miyaura coupling is a highly advanced well optimized method and more recently even sterically crowded biaryl axes were made accessible by this approach.[90-97] Thus, this reaction was a good starting point for a new synthetic pathway to 5,1'-coupled naphthylisoquinolines. In detail, the plan was to couple a naphthyl boronic acid ester to a halogenated isoquinoline, e.g. **81** to **82**, to obtain dioncophylline C (**5a**) (Scheme 13). There are known atroposelective intermolecular biaryl-bond-forming reactions in naphthylisoquinoline synthesis (see Chapter 2), but either the diastereomeric ratios and yields of the bond formation cannot compete with the ones achieved by the lactone method or/and include modifications of the coupling building blocks, which have to be removed later on. Therefore, the coupling was planned to be done without any external diastereo-induction leading to the two possible atropo-diastereomers in a ratio representing the inherent stereo-induction from the chiral isoquinoline subunit, which was expected to be small.



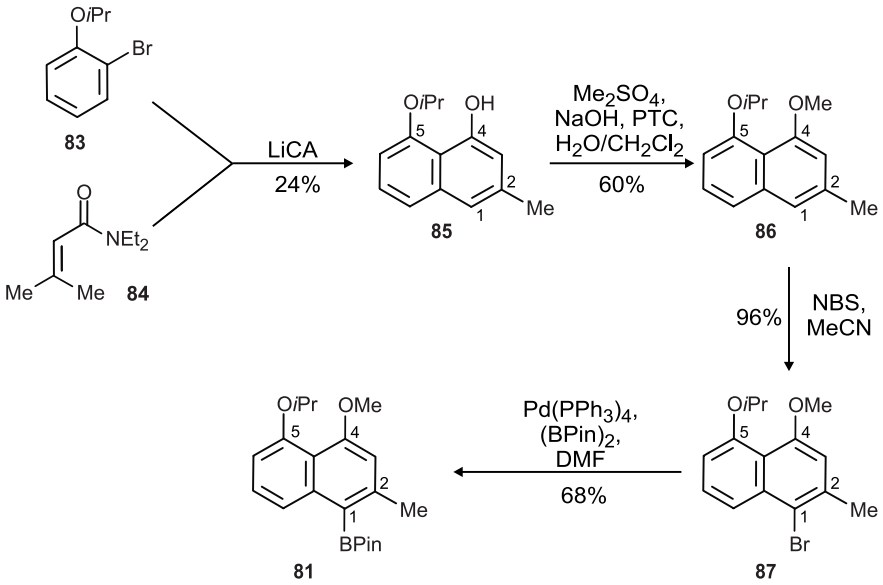
Scheme 13. General concept of synthesizing 5,1'-coupled naphthylisoquinolines by Suzuki-Miyaura cross coupling, here exemplarily for dioncophylline C (**5a**) and its atropisomer **5b**.

4.1 Total Synthesis of Dioncophylline C and its Atropisomer

For the total synthesis of dioncophylline C (**5a**) via the Suzuki-Miyaura coupling first the naphthalene moiety **81** and the isoquinoline **82** had to be prepared. The isopropyl and the benzyl protective groups in **81** and **82**, which are not present in the final products **5a** and **5b**, were introduced to enable the coupling reaction as previous work had shown that free hydroxy or amine functions can negatively impact the resulting yields.[98] The two particular protective groups were chosen as they had already been introduced and cleaved successfully in the atroposelective first total synthesis of dioncophylline C (**5a**) (Scheme 12), as achieved by our group earlier.[82, 89]

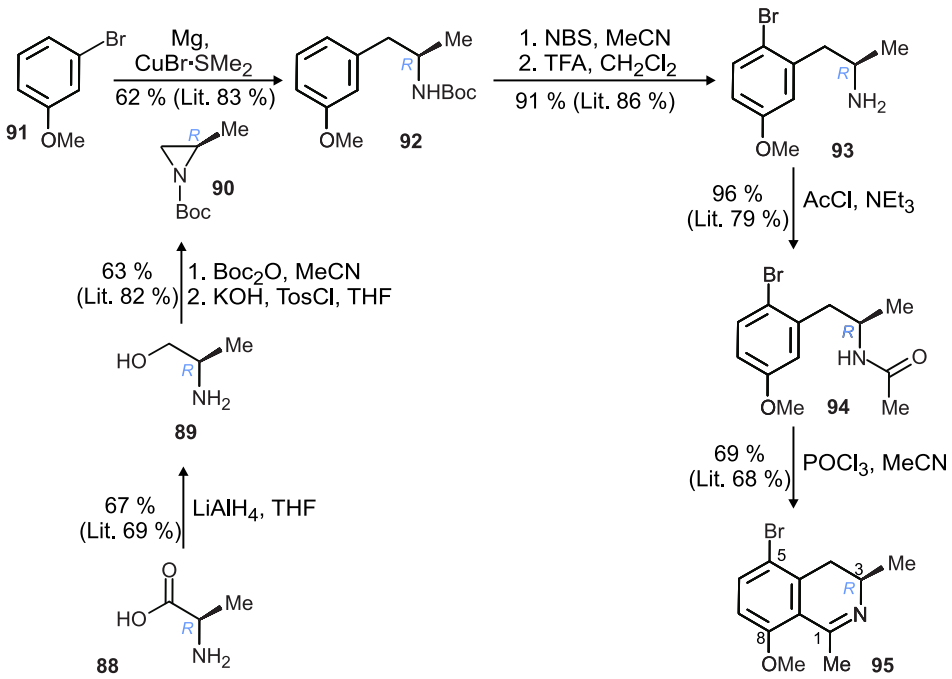
The synthesis of the boronic ester **81** was based on a method first described by Watanabe[99] and had already been applied successfully in the total synthesis of other naphthylisoquinolines.[34, 100, 101] It started with the reaction of 2-isopropoxy bromobenzene (**83**) with acryl amide **84** and lithiumcyclohexylisopropylamid (LiCA) building up the carbon skeleton of naphthalene **85** (Scheme 14). By adding dimethyl sulfate in a phase-transfer catalyzed reaction, the hydroxy function of **85** was methylated to yield **86**. Regioselective bromination at C-1 was accomplished by treatment of **86** with NBS to give **87**. Palladium-catalyzed borylation generated the naphthyl boronate ester **81** as needed for the planned coupling reaction. The reaction time for this last step in building up **81** was highly important as exceeding this time led to decomposition by hydrodeboronation.[95]

This problem is well known for arylboronic acids with sterically hindered or electron-withdrawing substituents.[93, 97, 102]



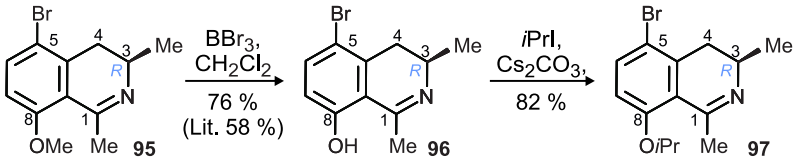
Scheme 14. Synthesis of the naphthoic boronate ester **81**.

The isoquinoline **82** was synthesized via the so-called aziridine route established by Hoye's group[48] and further improved by our research group (Scheme 15).[100] The synthesis started with the formation of the *tert*-butyloxycarbonyl (Boc) protected aziridine **90** from D-alanine (**88**) by reduction, Boc protection of **89**, and subsequent cyclization. Aziridine **90** was opened regioselectively with the Grignard reagent formed from 3-bromo anisole **91** to yield **92**. The phenyl group of **92** was brominated and acidic deprotection led to **93**. The amine was acetylated to give **94** and Bischler-Napieralski cyclization yielded dihydroisoquinoline **95**.



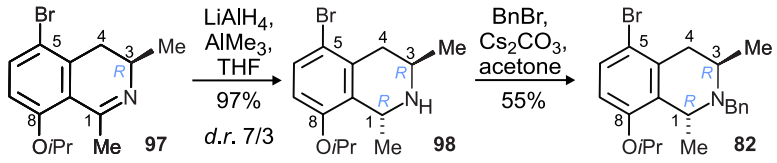
Scheme 15. Synthesis of dihydroisoquinoline **95**.[87]

The methoxy function of **95** was removed with BBr_3 yielding **96** and an isopropyl group was introduced to give **97** (Scheme 16).



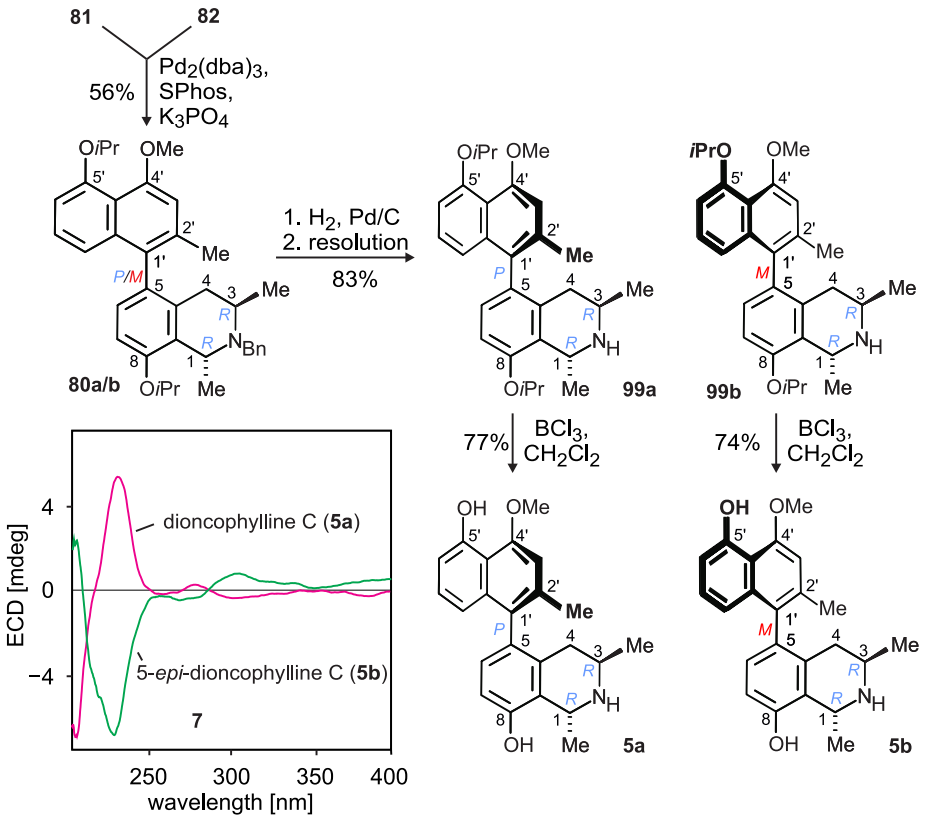
Scheme 16. Introducing the *O*-isopropyl protective group to give **97**.[87]

Dihydroisoquinoline **97** was subjected to diastereoselective reduction using $LiAlH_4$ and $AlMe_3$ yielding the anticipated *trans*-configured 1,3-dimethyl-1,2,3,4-tetrahydro-isoquinoline **98** (Scheme 16). As this procedure is well established in our group with diastereomeric ratios of up to 24:1,[76] it was highly surprising that here only ratios of 7:3 were obtained (Scheme 17). The resulting amine was protected with benzyl bromide concluding the synthesis of the isoquinoline moiety **82**.



Scheme 17. Diastereoselective reduction and *N*-benzyl protection.

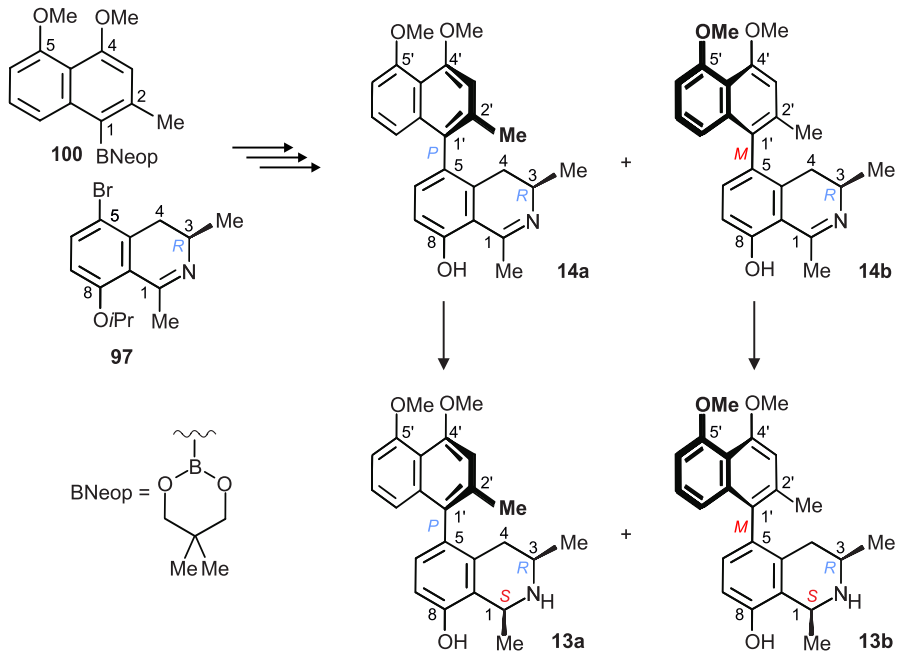
The coupling reaction of **81** to **82** proceeded with 56% yielding **80a** and **80b** by using conditions that had been applied successfully to the published total synthesis of dioncophylline F (**21**, in Scheme 1), but had been developed particularly for this synthesis here (Scheme 18).[34] The benzyl protective group in **80a** and **80b** was removed hydrogenolytically and the diastereomers **99a** and **99b** were resolved by preparative HPLC. The peak that eluted first was assigned (by NMR and ECD spectroscopy) to be the *M*-atropisomer and the second peak to be the *P*-configured atropisomer. Compounds **99a** and **99b** were formed as a 1:1-mixture (as assigned by analytical HPLC). The *O*-isopropyl group was removed with boron trichloride to yield dioncophylline C (**5a**) and its as yet unnatural atropisomer, 5-*epi*-dioncophylline C (**5b**), confirming the applicability of this newly established synthetic path to 5,1'-coupled Dioncophyllaceae-type naphthylisoquinolines.



Scheme 18. Final steps in the synthesis of **5a** and **5b** and their ECD spectra.

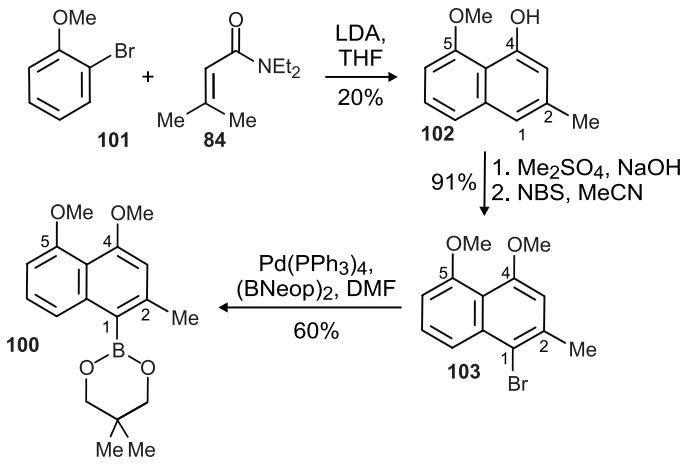
4.2 Total Synthesis of Dioncophyllidine C and Dioncophylline C_2

The planned joint synthesis of dioncophyllidine C (**14b**) and dioncophylline C_2 (**13a**) and their atropisomers, **14a** and **13b**, respectively, was closely related to the one of dioncophylline C (**5a**) as described above. It merely differed in the coupling building blocks **100** and **97** (Scheme 19). Compounds **13a**/**13b** were planned to be obtained by diastereoselective reduction of **14a**/**14b**. While **97** had already been an intermediate in the total synthesis of **5a** and **5b**, the naphthyl boronate ester **100** had to be synthesized '*de novo*'. In contrast to the synthesis of **5a** and **5b** here a more reactive boronic acid neopentylglycol ester was used instead of the previously described pinacol ester.[103, 104]



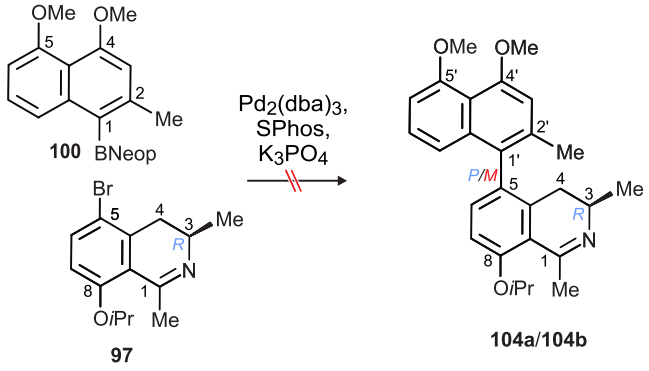
Scheme 19. Planned synthesis of dioncophyllidine C (**14a**) and dioncophylline C_2 (**13a**), and their atropisomers **14b** and **13b**, respectively.

The naphthalene **100** was synthesized starting from the commercially available 2-bromoanisole (**101**), which reacted with acryl amide **84** to obtain naphthol **102** (Scheme 20). Methylation of O-4 of **102** and regioselective bromination yielded **103**. Finally, borylation gave **100**. While the synthesis of **100** was very similar to the one of its pinacol ester analog **81**, the stability of the two differed a lot. For **81** no decomposition was observed even after exposure to air and light while being dissolved in any desirable solvent over an extended period of time. On the other hand, **100** decomposed within seconds depending on which solvent was used. Over the course of the project naphthyl boronic acid neopentylglycol esters, such as **100**, turned out to be stable in toluene, hexane, diethyl ether, ethyl acetate, or acetonitrile as the solvent, but gradually decomposed in methanol and even decomposed instantly in dichloromethane or chloroform.



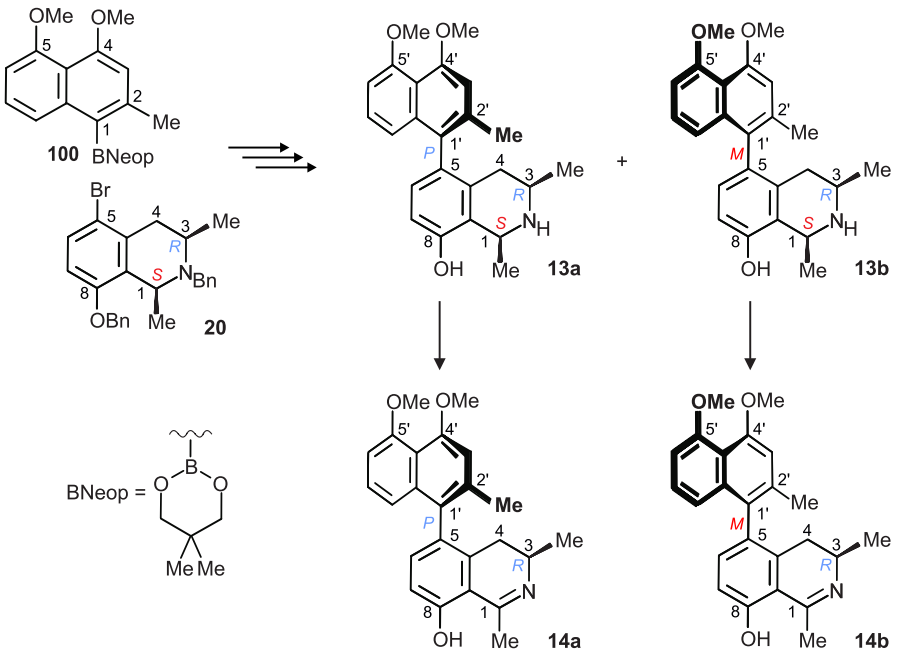
Scheme 20. Synthesis of naphthalene **100**.

Subjecting **100** and **97** to the coupling conditions previously applied to the synthesis of dioncophylline C (**5a**) and 5-*epi*-dioncophylline C (**5b**) only decomposition of the starting materials was observed, but no formation of the desired products **104a**/**104b** (Scheme 21). Presumably, due to the different electronic nature of dihydro- compared to tetrahydroisoquinolines the oxidative addition of the Pd-catalyst into the aryl halogen bond was hampered leading to the overall failure of the coupling reaction.



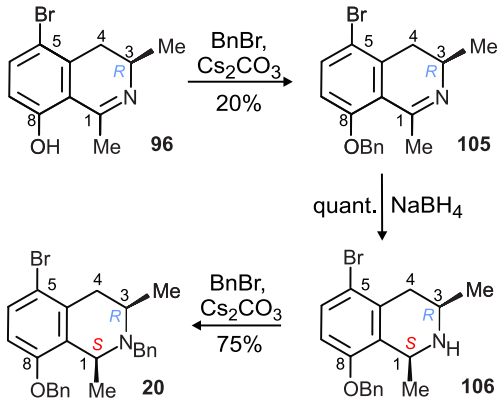
Scheme 21. Failed coupling attempt *en route* to dioncophyllidine C (**14a**).

Thus, the biaryl coupling reaction of the tetrahydroisoquinoline **20** to the same naphthyl boronate ester **100**, which had already been used in our failed coupling attempt, was investigated (Scheme 22). Accordingly, the new plan was to synthesize **13a** and **13b** first and to transfer them into **14a** and **14b** by oxidation.



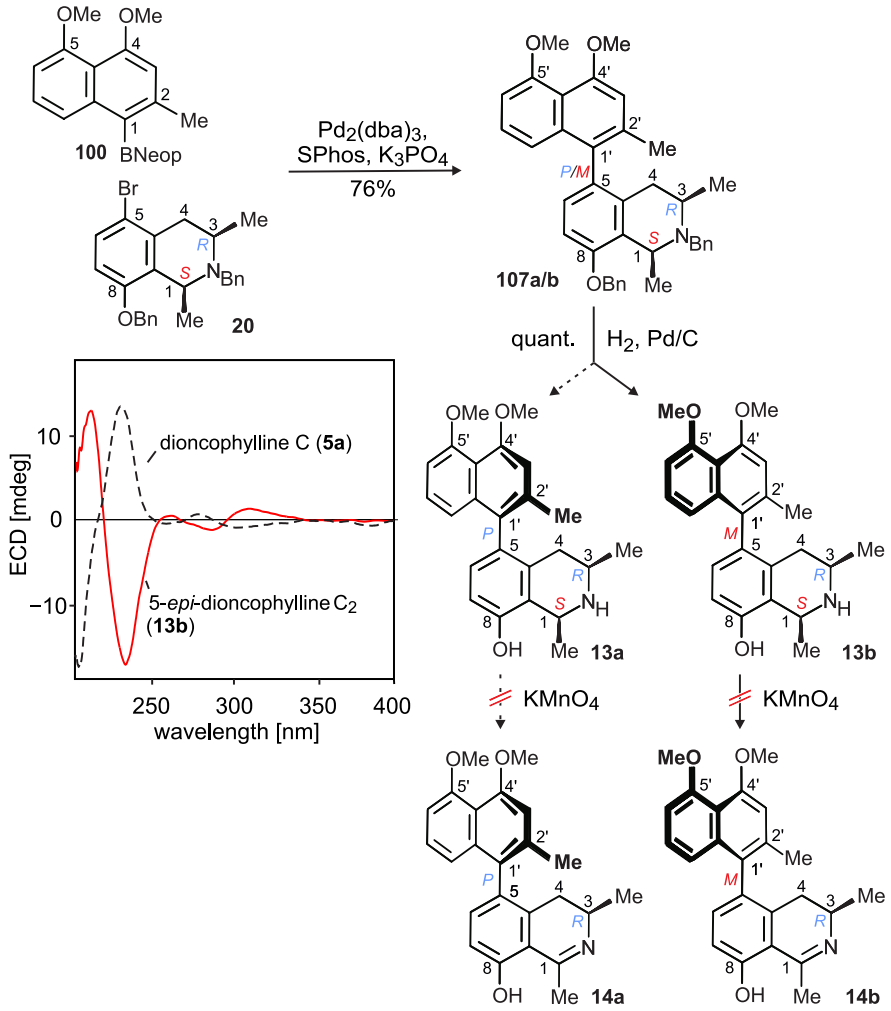
Scheme 22. Planned revised synthesis of dioncophyllidine C (**14a**) and dioncophylline C_2 (**13a**), and their atropisomers.

Starting from the 8-hydroxydihydroisoquinoline **96**, which had been an intermediate in the synthesis of dioncophylline C (**5a**) and 5-*epi*-dioncophylline C (**5b**), **20** was obtained over three steps by *O*-benzylation yielding **105**, reduction to the *cis*-configured **106** using $NaBH_4$ as the reductant, and finally *N*-benzylation (Scheme 23). For this purpose, the same protective groups were chosen for the free oxygen and nitrogen functions, in order to be removed simultaneously later.



Scheme 23. Synthesis of the tetrahydroisoquinoline **20**.

The coupling of **100** and **20** went smoothly with a yield of 76% (Scheme 24). This improved yield compared to the one of the previously described coupling leading to **5a**/**5b** (56%) was attributed to the increased reactivity of the neopentylglycol boronate ester compared to the respective pinacol ester.



Scheme 24. Synthesis of 5-*epi*-dioncophylline C_2 (**13b**), its ECD spectrum, and the failed synthesis of dioncophyllidine C (**14b**).

While the diastereomeric ratio of **107a**/**107b** was expected to be circa 1:1, astonishingly, with a ratio of 80:20, **107b** was the main product (as assigned by ECD and HPLC analysis of the follow-up compounds mixture **13b**/**13a**). This was highly interesting as it showed a high degree of inherent stereo-induction of the *cis*-configured tetrahydroisoquinoline **20** in this coupling reaction (Figure 5). To exclude any other reasons for this finding other than

the different stereochemical nature of *cis*-configured compared to the *trans*-configured tetrahydroisoquinolines described above, the coupling reaction was repeated with the *trans*-1-epimer of **20**, and no pronounced diastereoselectivity for the coupling reaction yielding **108a** and **108b** was observed (see Chapter 4.3).

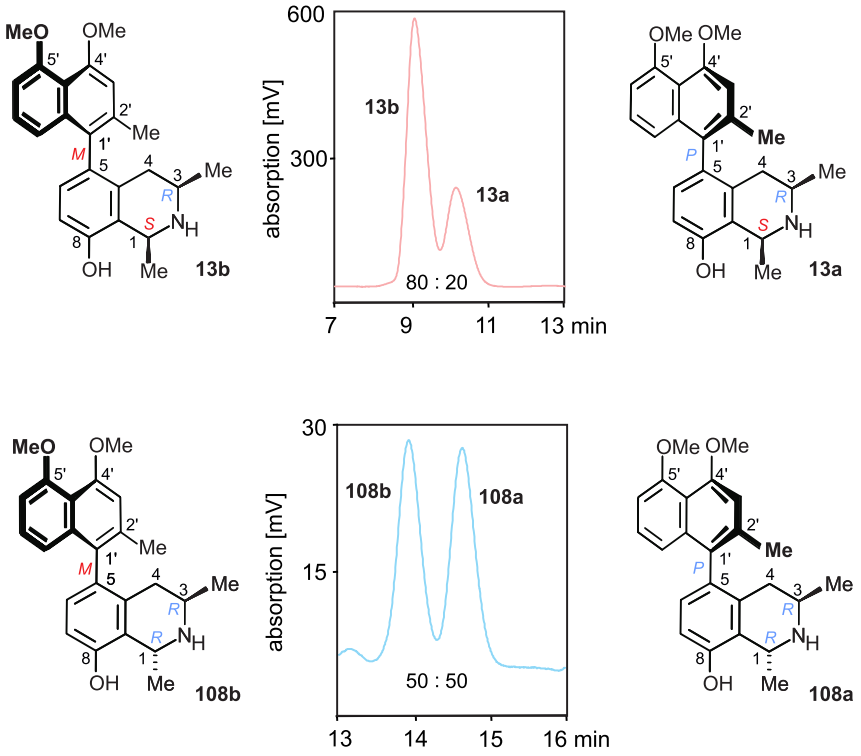


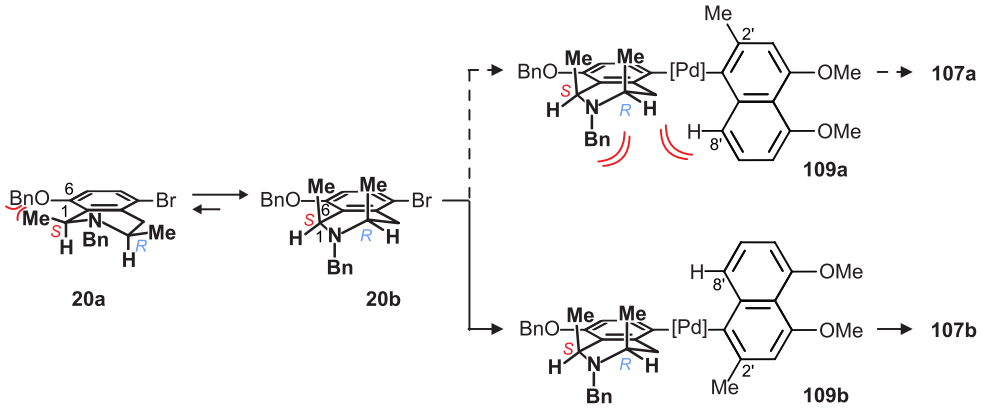
Figure 5. Evaluation of the diastereoselectivity in the formation of the *cis*-configured **13a**/**13b** and the *trans*-configured biaryls **108a**/**108b** by comparing their HPLC chromatograms.

Scheme 25 is intended to give an explanation for the found selectivity for the coupling of **100** and **20** leading to **107b** with a high selectivity. The azacyclohexene ring in **20** exist in two different conformers **20a** and **20b**, which are in an equilibrium and interconvert into one another by a ring flip inversion similar to the one found for cyclohexane. In contrast to *trans*-configured terahydroisoquinolines, in the case of *cis*-configured ones usually this equilibrium is on the side of the conformer with the 1,3-methyl groups in an axial orientation,[105] as found in **20b**. This might be surprising as one would usually assume that due to the repulsive transannular interaction between the 1,3-diaxial methyl groups **20a** should be thermodynamically favored over **20b**. This 'inverted' equilibrium arises from the

oxygen substituent in 8-position of the annulated benzene ring. In the case of conformer **20a** the equatorially oriented methyl group at C-1 has a strong steric repulsion to this oxygen function at C-8 which leads to **20b** being favored over **20a**. This effect is evident from NMR as for the *cis*-configured tetrahydroisoquinolines there is a distinct NOE interaction between Me-1 and Me-3 and usually no significant one for H-1 and H-3 suggesting that conformer **20b** with the two axial methyl groups in close proximity and the equatorial protons far apart is the predominant species. While in principle there is no fixed stereogenic center at the nitrogen of the azacyclohexene ring it is most likely that for steric reasons the *N*-benzyl substituent will be oriented axially in order to avoid steric repulsion from the vincinal methyl groups. This orientation of the *N*-benzyl group is assumed to be the reason for the atropo-diastereoselectivity in the coupling reaction of **100** and **20**.

For reasons of simplicity and comprehensibility in Scheme 25, intermediates **109a** and **109b** were depicted without any ligand or ligands bound to the palladium catalyst. In the catalytic cycle of the Suzuki-Miyaura coupling the diastereomeric **109a** and **109b** are present after the oxidative addition and the transmetalation right before the reductive elimination will take place. As evident from the obtained diastereoselectivity for the coupling reaction of **100** and **20** the two intermediates **109a** and **109b** cannot be equally kinetically favored. For **109a** it was assumed that there is a pronounced repulsion between the axial *N*-benzyl and the proton at C-8' of the naphthalene. On the other side, for **109b** there is the methyl group at C-2' of the naphthalene. While the three protons of the methyl group in **109b** can avoid steric collision with the *N*-benzyl as they can rotate freely, the proton at C-8' in **109a** points directly towards it and cannot escape from this position because of the sp^2-hybridization of C-8'. This repulsion between H-8' and the *N*-benzyl group leads to **109b** being energetically favored over **109a** resulting in the selective formation of the coupling product **107b** from **109b** while little formation of **107a** was observed. This is an interesting finding and while virtually in agreement with published work[53, 106] it is still important to see that more in-depth investigations on this coupling and its diastereomeric ratio are required and that, while being plausible, all thoughts on the

origin of the selectivity are mere assumptions which need quantum-chemical calculations and further synthetic experiments in order to be confirmed.



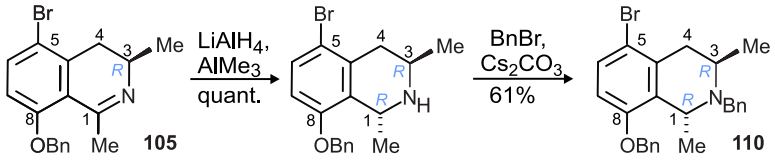
Scheme 25. Possible reasons for the selectivity of the coupling reaction forming **107a** and **107b**.

Anyhow, while initially aiming for both atropisomers **13a** and **13b**, deprotection of **107b** yielded the non-natural **13b** (Scheme 24). First experiments on the synthesis of **14b** by oxidation of **13b** with $KMnO_4$ were not yet successful and more in-depth investigations on the appropriate reaction conditions are still necessary. Anyhow, a highly interesting new insight on the diastereoselectivity of the Suzuki-Miyaura coupling of *cis*-configured tetrahydroisoquinolines to a naphthyl boronate ester to form 5,1'-coupled naphthylisoquinolines was obtained. This approach might serve as a nice addition to the synthesis of these dioncophylline-C-type compounds by the lactone method, where the opposite atropo-diastereoselectivity, i.e. the *P*-isomer is favored over *M*, was found.[82] Anyhow, there are of course more experiments required to validate the diastereoselectivity of this reaction and to see whether it can be transferred to other coupling systems or not.

4.3 Total Synthesis of Non-Natural Dioncophylline C Analogs

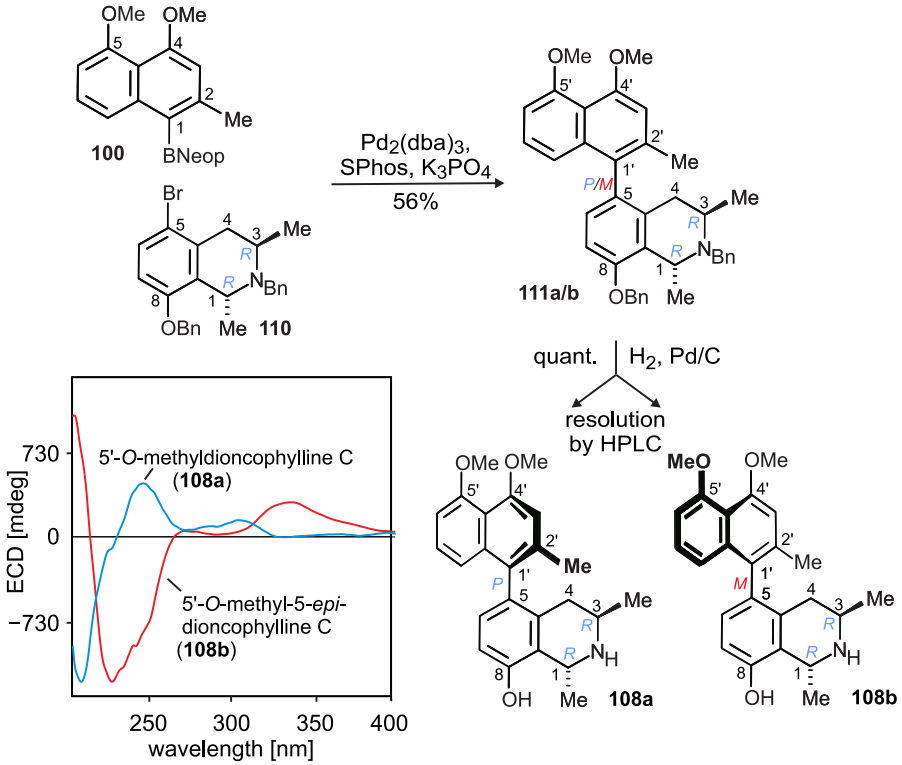
Alongside the natural compounds **5a**, **13a**, **14b**, and their non-natural atropisomers, the synthesis of further related non-natural 5,1'-coupled naphthylisoquinolines was planned. As briefly mentioned above, after obtaining the surprising diastereoselectivity of the coupling reaction leading to **107b** the reaction was repeated substituting the *cis*-configured isoquinoline **20** by the *trans* diastereomer to see if there is still any distinct selectivity.

Starting from **105** by reduction with $LiAlH_4$ and $AlMe_3$ and subsequent *N*-benzylation yielded **110** was obtained (Scheme 26).



Scheme 26. Synthesis of isoquinoline **110**.

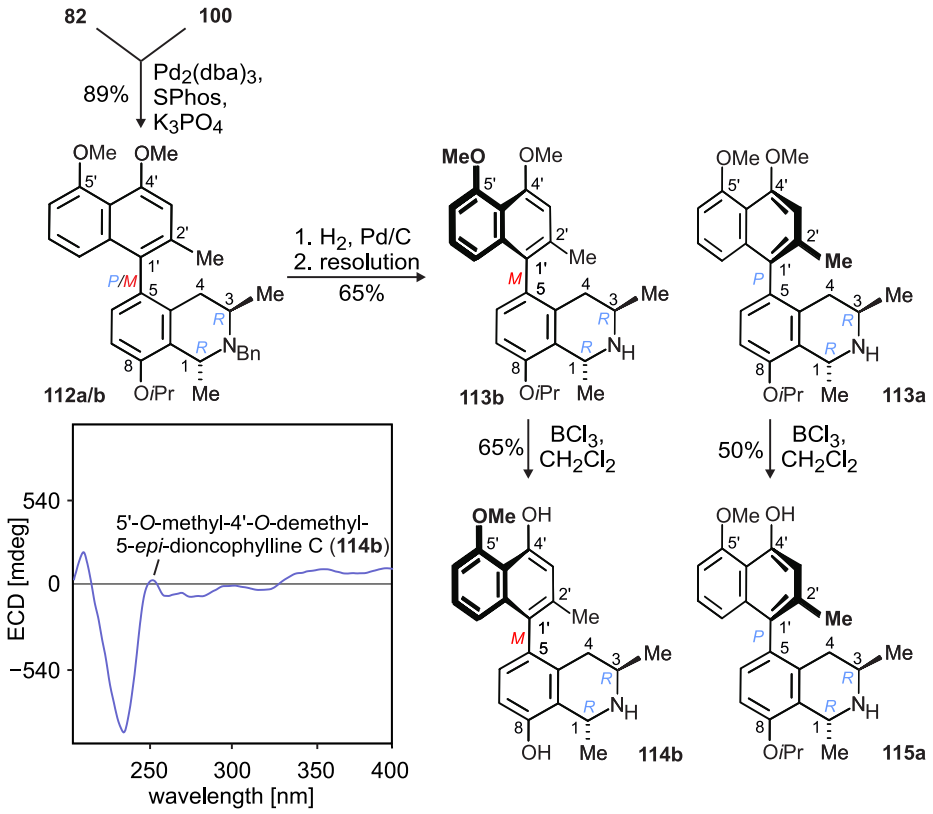
For the coupling reaction with **110** the boronic acid neopentylglycol ester **100** was used (Scheme 27). Here we obtained the two diastereomeric products **111a** and **111b** as the expected 1:1 mixture. This finding solidifies the assumption that the *cis*-configuration of **20** had a crucial impact on the diastereoselectivity in the formation of **107b**, as mentioned above (Figure 5). The benzyl groups in **111a** and **111b** were removed by hydrogenolytic cleavage and the isomers were resolved by preparative HPLC to obtain the target compounds **108a** and **108b** in a pure form.



Scheme 27. Synthesis of the as yet non-natural naphthylisoquinolines **108a** and **108b** and their ECD spectra.

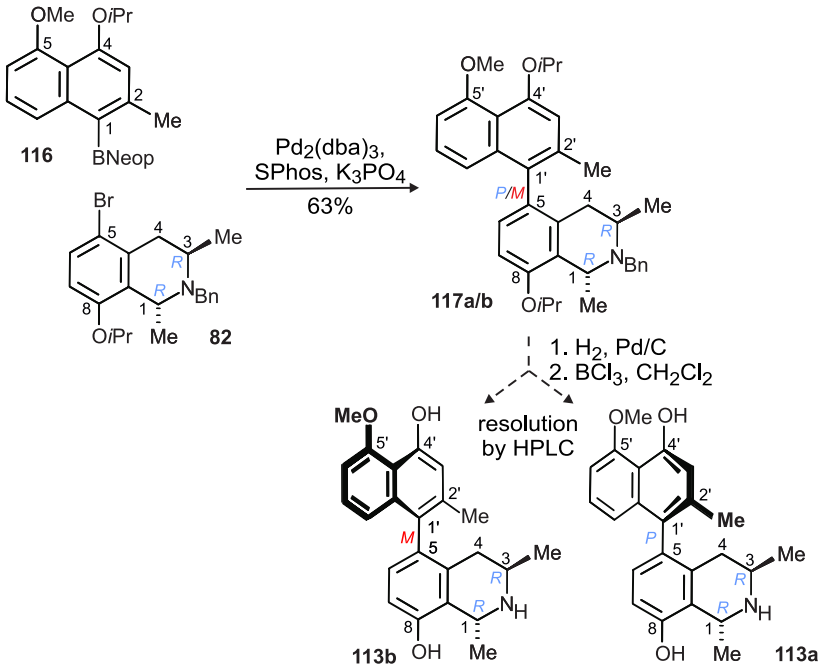
Since the parent compound dioncophylline C (**5a**) had shown good activity against *Babaesia canis* in vitro, the naphthylisoquinolines **108a** and **108b** were also tested on their inhibitory activity against *Babaesia canis* and scored values moderate as in the case of **108a** (IC_{50} = 37.0 μM) or very weak as for **108b** (IC_{50} = 140 μM) compared to dioncophylline C (**5a**) (IC_{50} = 0.87 μM).[107] This significant difference in activity of the two atropo-diastereomers **108a** and **108b** underlines the impact of axial chirality on the biological potential of naphthylisoquinoline alkaloids.

In an early phase of this project some investigations on the cleavage of the protective groups bound to our synthetic dioncophylline C analogs were conducted. The isoquinoline **82** was coupled to the boronic acid pinacol ester **100** (Scheme 28). After removal of all protective groups from **112a**/**112b**, the envisaged target compounds were **108a** and **108b**. But, after removing the *N*-benzyl group, resolving the isomers on HPLC, and trying to get rid of the isopropyl group at O-8 by treating **113b** with BCl_3, it was found that the methyl at O-4' (as assigned by the NOE interaction between H-6' and the methyl at O-5') was split of selectively next to the isopropyl group at O-8 yielding **114b**. The regioselective removal of the methyl at O-4' in presence of the methyl group at O-5'was surprising. A possible explanation was connected to the O-4' in **113b** being in a *para* relation to the biaryl axis. Accordingly, for electronic reasons, either the attack of BCl_3 on the methoxy function at C-4' was favored over the respective attack on the methoxy function at C-5' or the negative charge at O-4' resulting after removal of the methyl group was stabilized better and more evenly distributed over the entire biaryl system than a negative charge at O-5'. In the deprotection of **113a** compound **115a** was obtained, again, with the methyl group at O-4' missing but with the isopropyl group still present. This meant that the methyl group was even abstracted before the isopropyl group. The formation of **114b** was not all too disappointing as it was a planned target molecule anyhow.



Scheme 28. Synthesis of the non-natural 5'-*O*-methyl-4'-*O*-demethyl-5-*epi*-dioncophylline C (**114b**).

The initial plan was to synthesize **114b** alongside its atropisomer **114a** by coupling **82** to **116** (its synthesis is very similar to the one of **81** and **100** and, thus, is described in the experimental section only). While the coupling reaction was accomplished yielding **117a**/**117b**, the separation on preparative HPLC and removal of the protective groups was not completed during the preparation of this thesis.



Scheme 29. Incomplete synthesis of **113a** and **113b**.

4.4 Antiplasmodial Activtities of Selected 5,1'-coupled Dioncophyllaceae-Type Naphthylisoquinolines

In a cooperation with the research groups of L.-M. Birkholtz, V. Maharaj, and T. Egan, a selection of the above described synthesized 5,1'-coupled Dioncophyllaceae-type naphthylisoquinolines, **5a**, **5b**, and **113b**, together with other compounds were part of an attempt to advance this class of compounds with their outstanding antiplasmodial activities in a hit-to-lead strategy.[108] After the in vitro activities of **5a**, **5b**, and **113b** were assessed against the drug-sensitive intra-erythrocytic asexual *P. falciparum* (NF54) strain by applying a SYBR Green I fluorescence assay by P. Moyo from the Birkholtz group,[109] they were also screened against the multidrug-resistant W2 strain and no less than seven further drug-resistant strains and clinical isolates from Africa (Figure 6). All three compounds showed sub- or micromolar potency against selected strains. Interestingly, regarding the NF54 strain, dioncophylline C (**5a**) (IC_{50} = 0.038 µM) was similarly potent as **113b** (IC_{50} = 0.042 µM), which differed from **5a** by its inverted methoxy-hydroxy pattern in the naphthalene portion and by the configuration at the biaryl axis. However, compounds **5a** and **113b** were approximately five times more active than **5b** (IC_{50} = 0.234 µM), the

actual atropo-diastereomer of **5a**. Moreover, the compounds **5a**, **5b**, and **113b** were tested and exhibited minimal to no cytotoxicity against HepG2 cells.

A

Antiplasmodial activities

in vitro screening results (IC_{50} or EC_{50} values in nm)

P. falciparum Strain	**5a**	**5b**	**113b**	Chloroquine
NF54	38.4	234	41.5	13.0
W2	112	556	138	383
K1	43.6	355	55.6	157
Dd2	29.7	248	59.7	63.3
7G8	21.7	131	10.2	41.1
HB3	30.3	139	16.3	10.6
cytotox. HepG2	21200	>50000	25000	37000

Dioncophylline C (**5a**) and the synthetic analogs show good *in vitro* results both, against drug-sensitive and drug-resistant strains of *P. falciparum*, the parasite causing *malaria tropica*.

B

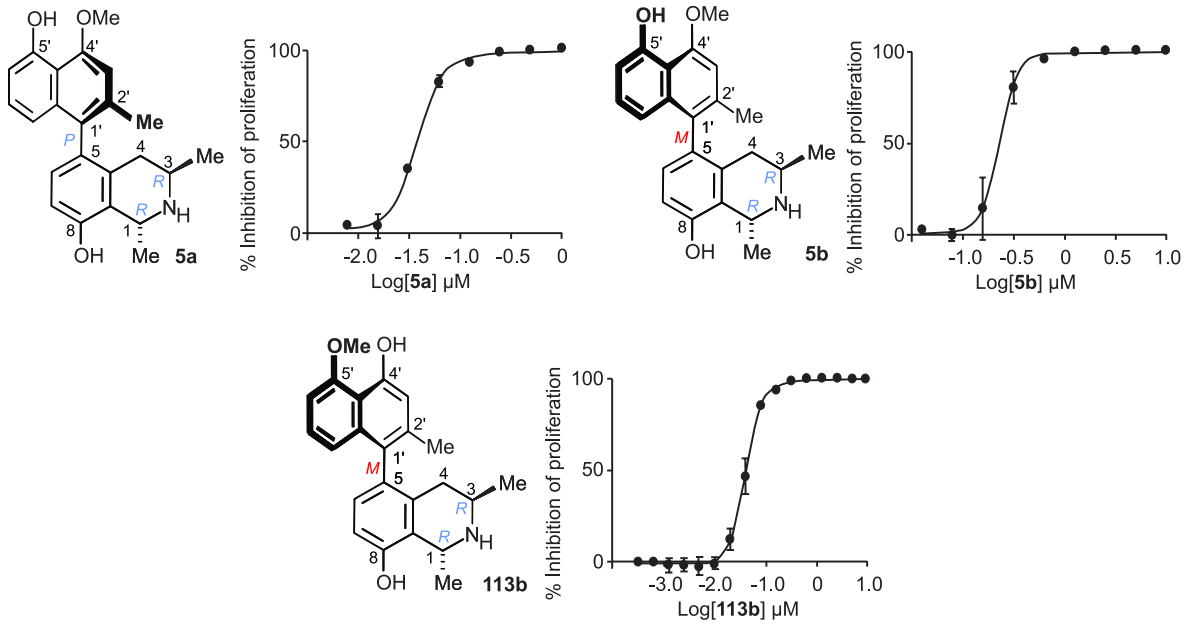


Figure 6. A) Antiplasmodial activities of **5a**, **5b**, and **113b** against drug-sensitive and drug-resistant *P. falciparum* strains. B) Inhibitory curves of **5a**, **5b**, and **113b** against the NF54 strain. These tests were done by the group of L.-M. Birkholtz.

In previous work, dioncophylline C (**5a**) had been found to form a complex with hem,[110] which led to the hypothesis that the inhibition of the formation of β-hematin might be partially responsible for its activity. In order to validate this assumption, the in vitro inhibition of β-hematin formation was investigated by our cooperation partners for **5a** and its regioisomer **113b**, which based on their structural similarity should hit the same target as **5a**. And indeed, in an in vitro experiment the two compounds inhibited the formation of β-hematin (IC_{50} = 19.9 µM for **5a** and 46.6 µM for **113b**) in the range of the reference drug, which was used in this assay, chloroquine (IC_{50} = 13.9 µM).

In solubility and microsomal stability assays[111-113] done by the group of T. Egan dioncophylline C (**5a**) was prioritized due to its high potency against asexual parasites and due to its gamete activity. Its atropisomer **5b** was also included into these experiments to investigate to what degree stereochemical attributes of a compound influence its solubility or microsomal stability. The compounds **5a** and **5b** displayed good kinetic solubilities in PBS at pH 6.5. While dioncophylline C (**5a**) showed good microsomal stability incubated with human, mouse, or rat microsomes, the atropo-diastereomer **5b** exhibited weak stability upon exposure to rat and mouse microsomes.

In the overall study, dioncophylline C (**5a**) was the most promising entity as it continuously maintained good activity across all stages and demonstrated good kinetic solubility and microsomal stability.

5 Synthesis of 5'-*O*-Methyldioncophylline D and Biotinylation for Target Identification Experiments

5'-*O*-Methyldioncophylline D (**15**), a representative of the rarely found 7,8'-coupled Dioncophyllaceae-type naphthylisoquinoline alkaloids, was isolated from two different plants, *Triphyophyllum peltatum* and *Ancistrocladus ileboensis* (Figure 7).[34, 44] During previous work on callus cultures of *T. peltatum*, **15** was difficult to isolate as it coeluted with the well-known dioncophylline A (**4a**) and was present merely as a trace compound in the chemotaxonomic profile of this plant.[114] Only after optimization of the isolation protocol it was accessible at all. The main reason for the struggle during the isolation work was the fact that due to the lack of sufficient steric hinderance around the biaryl axis, 5'-*O*-methyldioncophylline D (**15**) is configurationally unstable, meaning that the two atropisomeric forms interconvert at room temperature, resulting in the appearance of two peaks in the chromatogram recorded on an HPLC system. This is a highly interesting feature as it is found only for a small number of natural naphthylisoquinolines, the Dioncophyllaceae-type dioncophyllines B (**118**),[115] E (**17**),[116] and F (**21**)[34] and, in the field of Ancistrocladaceae-type alkaloids, only the *N*,*C*-coupled ancistrocladinium B (**12**)[30] (Figure 7).

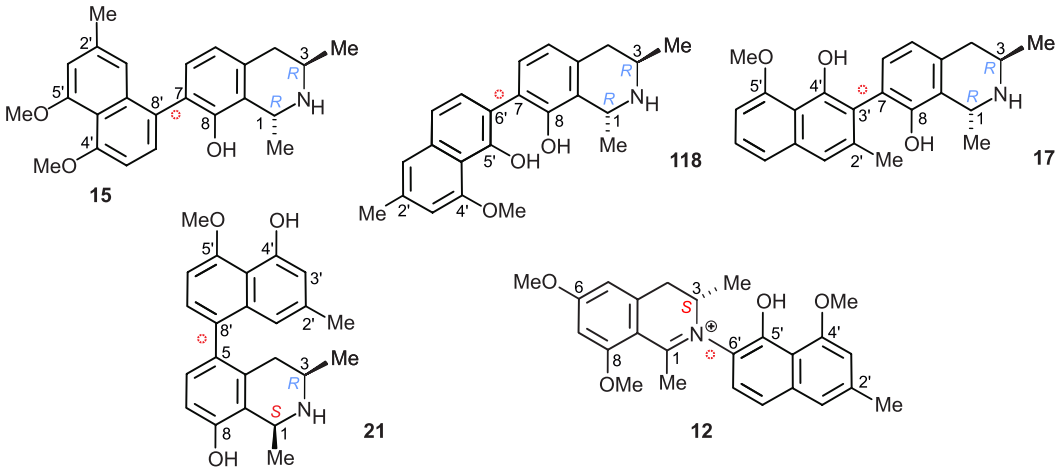
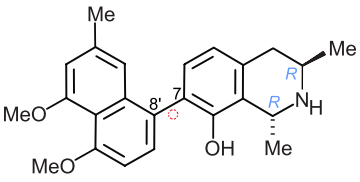
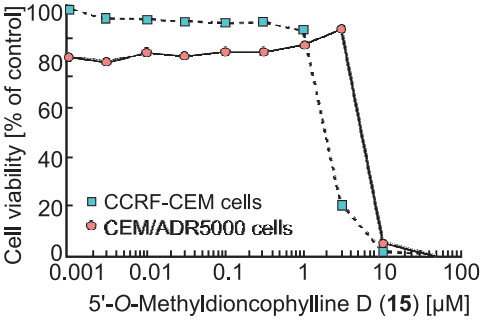


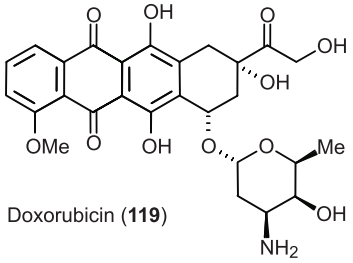
Figure 7. Overview of the natural configuratively unstable naphthylisoquinoline alkaloids 5'-*O*-methyldioncophylline D (**15**), dioncophylline B (**118**), E (**17**), and F (**21**) and ancistrocladinium B (**12**).

Compound **15** displayed cytotoxic activity against the drug-sensitive lymphoblastic CCRF-CEM leukemia cell lines yielding exceptional results in the range of the standard antileukemic drug doxorubicin (**119**) and in particular against a multidrug-resistant subline, CEM/ADR5000 (Figure 8).[34] Moreover, it was active against multiple myeloma INA-6 cells and against the malaria parasite *P. falciparum*. This biological potency of 5'-*O*-methyldioncophylline D (**15**) made it an interesting substrate for further bioactivity testing and a valuable target for total synthesis and synthetic modification for target identification experiments.



5'-*O*-Methyldioncophylline D (**15**)

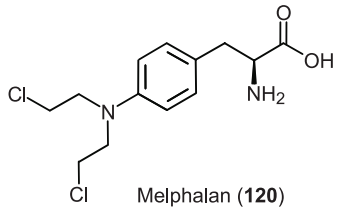




Doxorubicin (**119**)

IC_{50} Values (µM) of Human Lymphoblastic CCRF/CEM and Multidrug-Resistant CEM/ADR5000 Leukemia Cells

compound	CCRF-CEM	CEM/ADR5000	degree of resistance
119	0.017±0.002	3.007±11.81	1769
15	1.857±0.140	5.31±0.37	2.9



Melphalan (**120**)

EC_{50} Values (µM) of INA-6 Multiple Myeloma Cells and Peripheral Mononuclear Blood Cells

compound	INA-6	PMBCs
120	2.0±0.7	3.0±0.5
15	2.6±0.3	19±1.0

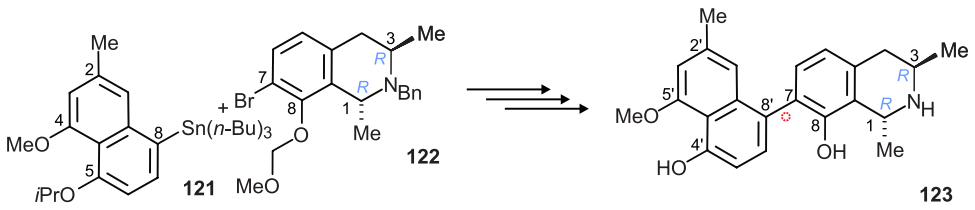
Figure 8. Activity of 5'-*O*-methyldioncophylline D (**15**) against human lymphoblastic and multiple myeloma cells in comparison to the standard drugs doxorubicin (**119**) and melphalan (**120**), respectively.[34]

5.1 First Total Synthesis of 5'-*O*-Methyldioncophylline D

Regarding the total synthesis of 5'-*O*-methyldioncophylline D (**15**), an intermolecular formation of the configurationally unstable biaryl axis in **15** as the key step seemed

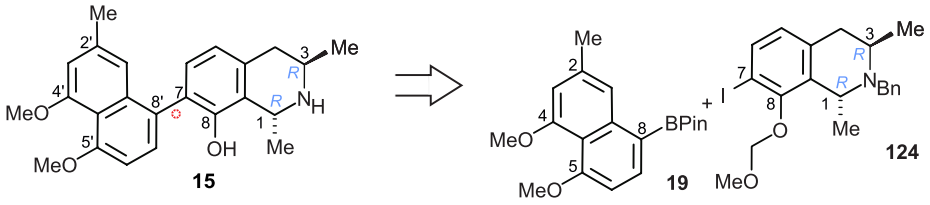
favorable. This approach was highly convergent and the two major advantages of the previously described alternative intramolecular formation of axes by the lactone method, the stereoselective construction of aryl-aryl bonds and the potential to overcome highest steric loads next to the axis, were obviously of minor importance here.

In previous work, the parent compound dioncophylline D (**123**) had been synthesized in order to confirm the structure of a new natural product, which was initially believed to be 7,8'-coupled (Scheme 30).[117] Comparing the data set of the synthetic compound with that of the one isolated from plant material revealed that the biaryl linkage in the natural product had been incorrectly assigned to be between C-7 and C-8' whereas it actually was located between C-7 and C-6', being named dioncophylline B (**118**).[118] Accordingly, dioncophylline D (**123**) is a naphthylisoquinoline of synthetic origin only as it has not yet been isolated from plant material. The key step of its synthesis was the coupling of tin compound **121** to the halogenated isoquinoline **122** in a Stille coupling (Scheme 30). While this fact supported the idea of an intermolecular formation of the biaryl axis in the synthesis of 5'-*O*-methyldioncophylline D (**15**), applying the Stille coupling, which requires highly toxic stannanes, was avoided.



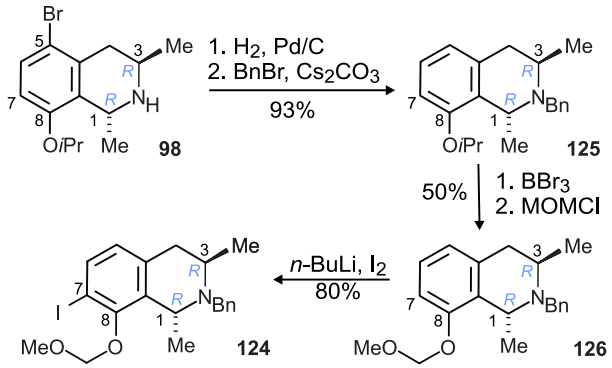
Scheme 30. Synthesis of dioncophylline D (**123**) applying the Stille coupling as the biaryl-bond-forming key step.

As the Suzuki-Miyaura reaction had been used successfully in the syntheses of the dioncophylline C derivatives (see Chapter 4), its application to the biaryl-bond-forming step in the synthesis of the 7,8'-compound **15** by coupling **19** to **124** seemed an attractive option (Scheme 31).



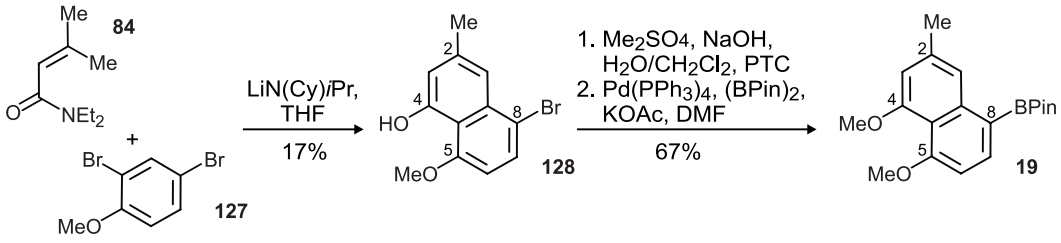
Scheme 31. Retrosynthetic cleavage of the biaryl bond in 5'-*O*-methyldioncophylline D (**15**) with a Suzuki-Miyaura reaction in mind.

One synthetic principle of our research group is to have one joint late-stage precursor which will be further functionalized according to its planned use at the latest-possible stage. In various syntheses described in this thesis the isoquinoline **98**, which had already been used in the construction of the dioncophylline C derivatives (Chapter 4), was this key intermediate. Accordingly, the isoquinoline building block **124**, as required for the synthesis of 5'-*O*-methyldioncophylline D (**15**), was obtained after no more than five steps starting from compound **98**. For this purpose, first, the bromine substituent at C-5 of **98** was removed under hydrogenolytic conditions and the secondary amine was benzyl-protected yielding **125** (Scheme 32). The isopropoxy function of the tetrahydroisoquinoline **125** was removed with boron tribromide and the resulting free hydroxy function was protected with methoxymethyl chloride to yield compound **126**. Despite the known high toxicity of methoxymethyl chloride, it was used anyhow as it so far is the only reported protective group in naphthylisoquinoline synthesis that enables so-called directed *ortho*-metalation (DoM)[117-119] reactions required to halogenate compound **126** regioselectively at C-7 (instead of the normally favored C-5) to give the anticipated coupling precursor **124**.



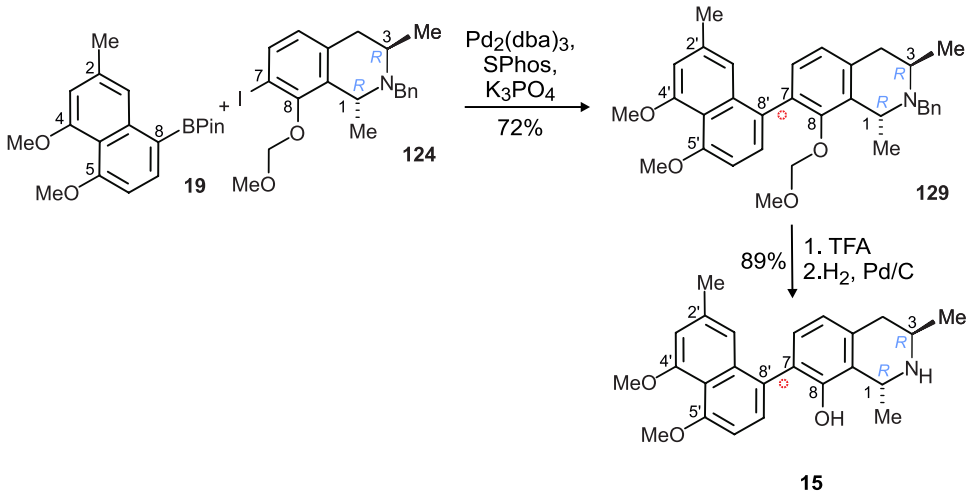
Scheme 32. Synthesis of the isoquinoline building block **124**.

The naphthalene portion was synthesized according to a previously described protocol for the synthesis of the 5,8'-coupled dioncophylline F (**21**),[34] starting with the reaction of compound **84** and **127** yielding the 8-bromonaphthol **128**, which was methylated at O-4 by phase transfer catalysis. The bromine was substituted by a boronic acid ester in a transition-metal catalyzed reaction to give coupling building block **19** (Scheme 33).



Scheme 33. Synthesis of the boronic acid ester **19**.[34]

The coupling of **19** to **124** forming **129** proceeded smoothly at 72% yield (Scheme 34). Removal of the protective groups over two steps furnished the desired natural product 5'-*O*-methyldioncophylline D (**15**).



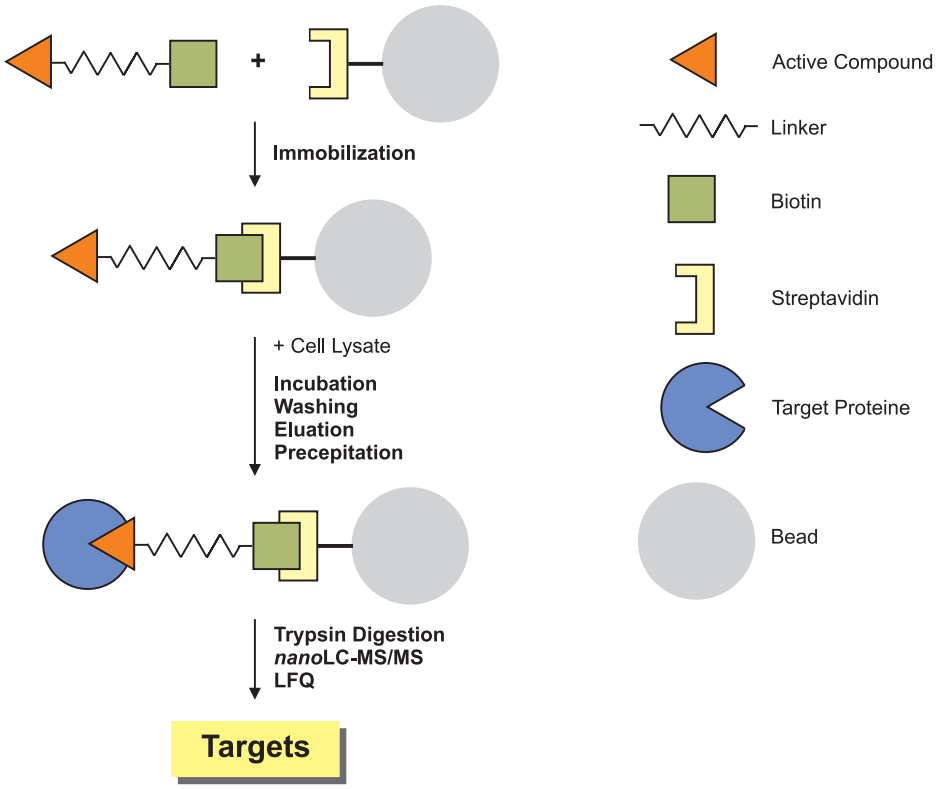
Scheme 34. Coupling and deprotection steps in the synthesis of 5'-*O*-methyldioncophylline D (**15**).

5.2 Biotinylation of 5'-*O*-Methyldioncophylline D

5'-*O*-Methyldioncophylline D (**15**) showed good values against both, lymphoblastic leukemia and multiple myeloma cells.[34] Therefore, a synthetic approach to functionalize this natural product in order to make it applicable to target identification experiments was envisaged.

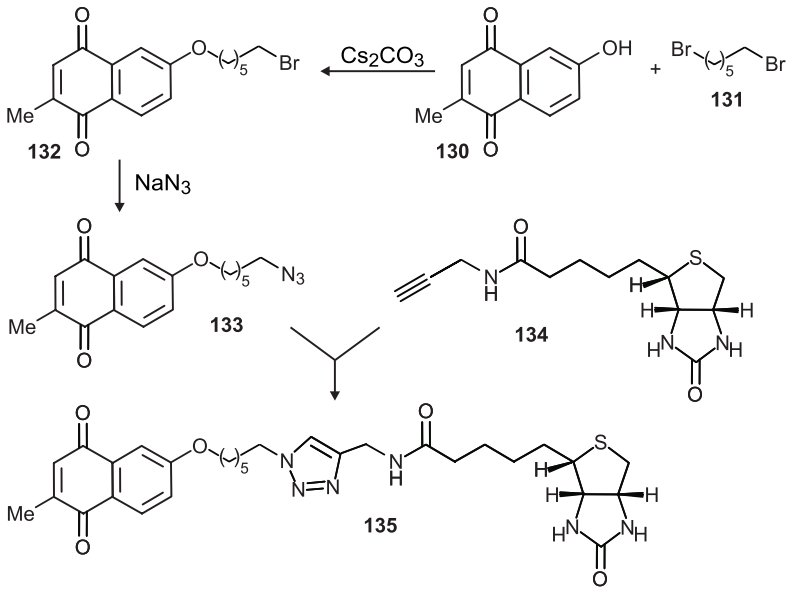
Scheme 35 gives an overview on the key points of target-identification procedures.[33] The relevant active compound is bound to a molecular entity (here biotin) via a linker, which can bind in the form of non-covalent bonds to a respective counter entity (here streptavidin), which is, in turn, attached to an appropriate resin or bead.[33] The modified activated compound is then immobilized by binding to the respective resin or bead. Cell lysate of the targeted cell line is then incubated with the compound-bead complex. Now the target proteins from the cell lysate will bind to the active compound, which is still immobilized by the linkage to the bead. All non-binding material can be removed easily by washing the bead. With the protein-compound-linker-bead complex in hand, the next step is the trypsin-mediated digestion of the proteins.[33] The resulting mixture of peptide fragments is subjected to mass spectrometric analysis providing masses, which can be compared to those of a library of proteins elucidating the targeted proteins that are bound to the respective bioactive compound.[120] From this information insights on the mode of action of the compound can be obtained.

In the attempt to functionalize 5'-*O*-methyldioncophylline D (**15**) the introduction of a biotin linker to **15** was chosen which will bind to a bead equipped with streptavidin. In previous work from our research group this method had already led to significant results.[33, 121-123] Before starting the synthesis, the reported modifications of a non-natural naphthoquinone **130**[33, 122] and of a naphthylisoquinoline, dioncophylline A (**4a**),[123] were examined and evaluated regarding their applicability to 5'-*O*-methyldioncophylline D (**15**) as the substrate.



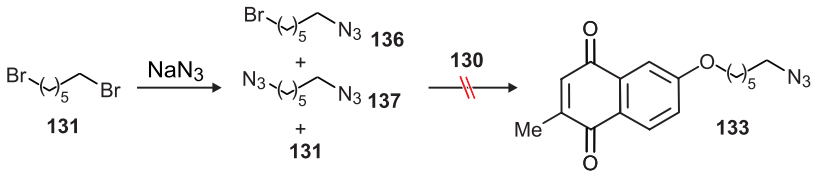
Scheme 35. Key steps of the target identification procedure.

The linkage of the naphthoquinone **130** to biotin by a Huisgen-click reaction started with the nucleophilic substitution of 1,6-dibromohexane (**131**) with the quinone **130**. The bromide at the alkyl chain of **132** was then replaced by an azide functionality to give **133**. This unit was coupled to a previously functionalized biotin derivative **134** by the Huisgen-click reaction to give **135**. As the yield of this reaction is usually high and there is no formation of any byproduct,[124] it was planned to be include into the functionalization approach of 5'-*O*-methyldioncophylline D (**15**). Anyhow, a major disadvantage to the synthetic path to **135** was that the nucleophilic substitution of the naphthoquinone **130** with the dibromide **131** with two equally electrophilic positions also led to the formation of the doubly substituted product (not shown here) leading to the loss of the immensely precious and tedious-to-synthesize compound **130**.



Scheme 36. Synthetic approach to the biotinylation of quinone **130**.

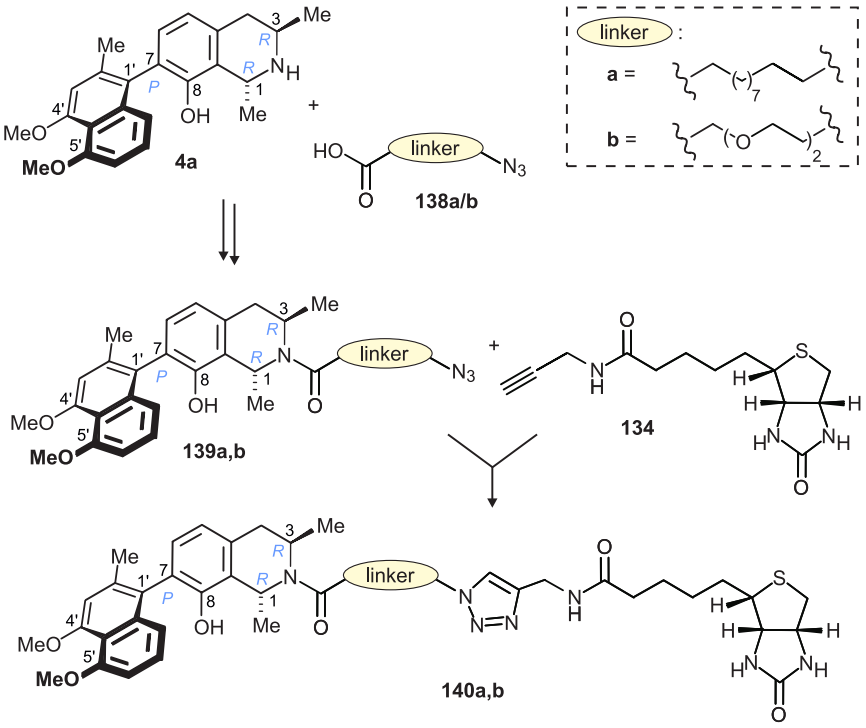
In a previous attempt of synthesizing the intermediate **133**, 1,6-dibromohexane (**131**) had been substituted by an azide functionality to give **136** (Scheme 37). This was favorable as then the less expensive NaN_3, in comparison to precious **130**, was the nucleophile which would undergo either mono- or disubstitution. But this approach had the difficulty of controlling the competing mono- and disubstitution at **131** as there was no possibility to follow the reaction process, neither by TLC nor by HPLC, thus, resulting in an inseparable mixture of the starting material **131** and the monoazide **136** and the diazahexane **137**, which upon reacting with the hydroxyquinone **130** did not lead to satisfying results.



Scheme 37. Failed synthesis of quinone **133**.

The successful biotinylation of dioncophylline A (**4a**) also included the click chemistry into the linkage of the natural product with the biotin marker (Scheme 38).[123] In comparison to the synthesis described above, here the much longer linkers **138a** and **138b** were used. As the nitrogen in dioncophylline A (**4a**) was picked as the site of linkage, **138a** and **138b** were

bound to the natural product by the formation of an amide bond to give **139a** and **139b**. Since the linkers only comprise one electrophilic carboxylate function, there was no disubstitution possible, in contrast to the linkage using dibromohexane (**131**), as described above. The coupling of functionalized biotin **134** and the dioncophylline-A-linker complexes **139a**/**139b** was again done by Huisgen-click reaction to yield **140a**/**140b**.

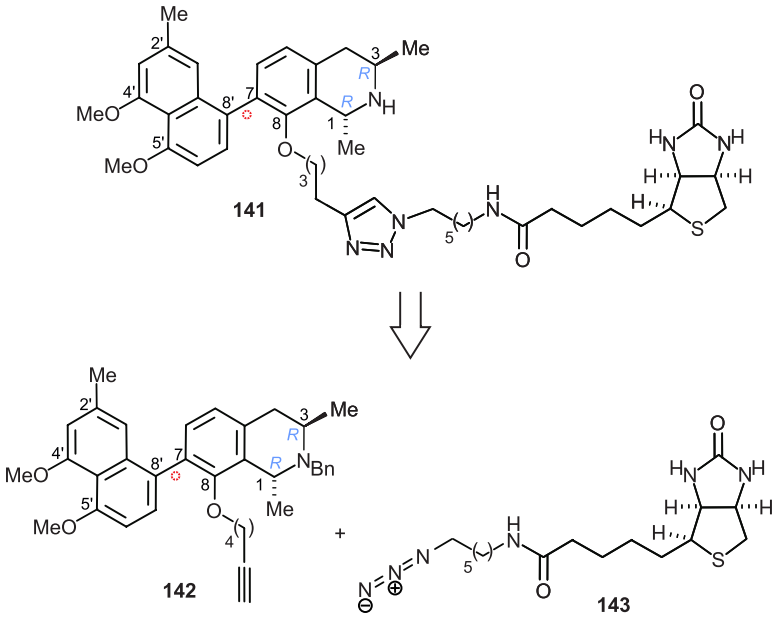


Scheme 38. Biotinylation of dioncophylline A (**4a**).

Based on the evaluation of the two biotinylations successfully achieved by our research group, the following outlines for the functionalization of 5'-*O*-methyldioncophylline D (**15**) were decided:

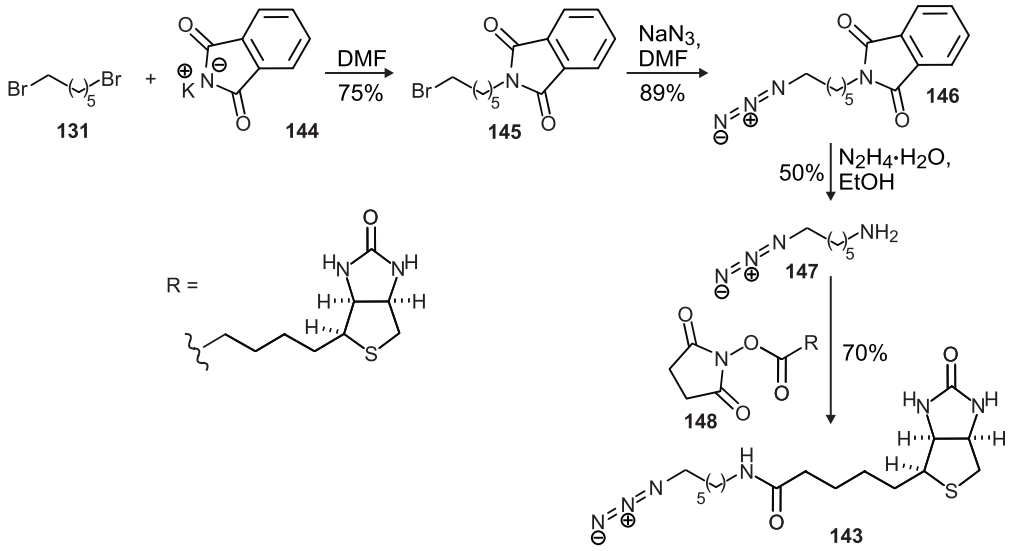
1. The Huisgen-click reaction was required to be the key step of the synthesis.
2. The synthesis had to be convergent, i.e. in particular as few syntheses as possible should include the natural product.
3. Any chances of product loss due to doubly reacting substrates had to be excluded.

Taking these principles into consideration, the biotinylation of 5'-*O*-methyldioncophylline D (**15**) to give **141** was planned to include the Huisgen-click reaction but here the positions of the alkyne was shifted to the side of the natural product in **142** and the one of the azide to the biotin linker **143**, in order to avoid loss of the most precious 5'-*O*-methyl-dioncophylline D (**15**) from doubly reacting with dibromohexane (**131**) (Scheme 39).



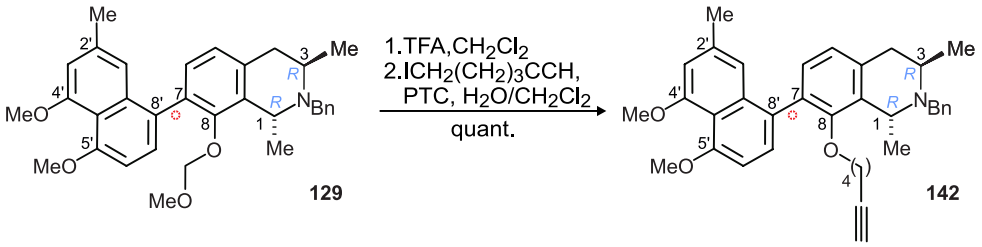
Scheme 39. Retrosynthetic analysis of the anticipated biotinylated natural product **141**.

The synthesis of **143** and especially the introduction of the azide functionality was done in a more elegant way compared to syntheses using dibromohexane (**131**) and NaN_3 (see Scheme 37). In this new approach, substituting one bromide of dibromohexane (**131**) with potassium phthalimide (**144**) in a Gabriel synthesis led to **145** (Scheme 40). In comparison to the aforementioned approach, it was possible to follow the reaction progress of the substitution by TLC leading to the formation of the anticipated monosubstituted compound **145** as the main compound at good yields. Now, with only one electrophilic position left in **145** the introduction of the azide function succeeded efficiently giving **146**. The amino group in compound **147** was set free by subjecting imide **146** to hydrolysis with hydrazine in ethanol. The last step in the synthesis of the azide-functionalized biotin was the formation of the amide bond by treating **147** with the activated biotin derivative **148**.



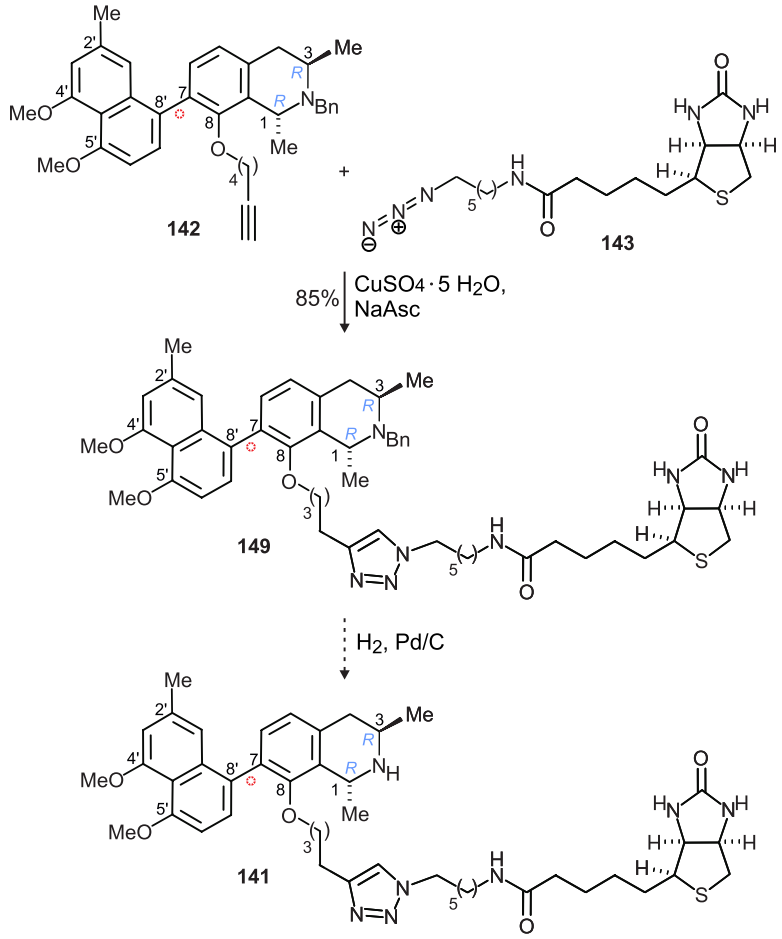
Scheme 40. Synthesis of the biotin azide **143**.

The functionalization of 5'-*O*-methyldioncophylline D (**15**) started from the building block **129**, which had been part of the total synthesis of the genuine natural product (Chapter 5.1). The MOM protective group in **129** was removed and the free hydroxy function was alkylated with commercially available 6-iodo-1-hexyne leading to the targeted modified naphthylisoquinoline **142** ready to be subjected to the click reaction with the biotin azide **143** (Scheme 41).



Scheme 41. Deprotection and alkynylation of **129**.

The Huisgen-click reaction was done using the original conditions published by Sharpless with sodium ascorbate as the base, $CuSO_4$ as the Cu(I) provider, and a mixture of *t*BuOH and H_2O as solvent (Scheme 42).[125] The reaction itself proceeded smoothly with a good yield at a low scale and the formation of compound **149** was evidenced by mass spectrometric analysis.



Scheme 42. Final steps in the synthesis of **141**.

As much more material would have been required to proceed to the target identification investigations but as only limited amounts of the relevant building block **98** essential for the preparation of precursor **124** were available and further were needed for the synthesis of more desirable compounds as described later, the final step, i.e. the removal of the benzyl protective group, was not done in the course of the present thesis. Anyhow, this advanced synthesis clearly has to be considered as a proof of concept and further established a highly original and useful synthetic path to an azide-functionalized biotin building block, which certainly will be very useful for similar experiments and investigations.

6 First Synthetic Access to Ancistrolikokine E_3

Based on previous work,[126] my colleague, Shaimaa Ali Fayez, isolated a large series of 5,8'-coupled naphthylisoquinolines from the twigs of the Central African liana *Ancistrocladus likoko*, which differed from one another in terms of their oxygenation patterns, degree of hydrogenation, and their axial and central configurations, both Ancistrocladaceae- and hybrid-type alkaloids.[35, 38, 127] Among them was ancistrolikokine E_3 (**16a**), which at first sight might not seem too extraordinary. But due to its exceptional bioactivity, it is now considered as one of the 'star' compounds from our research group (Figure 9). In a highly fruitful interdisciplinary collaboration between the staff around Prof. Awale in Japan and our group in the search for molecules with activities against PANC-1 human pancreatic cancer cells, ancistrolikokine E_3 (**16a**) stood out among the others because of its high potency.[38]

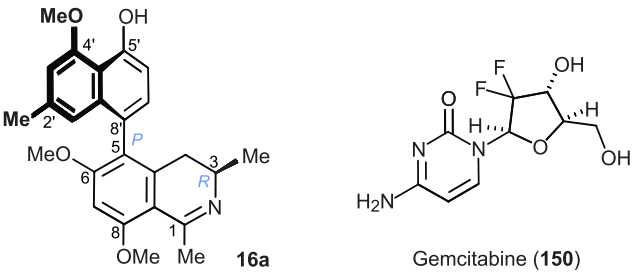


Figure 9. Structure of ancistrolikokine E_3 (**16a**).

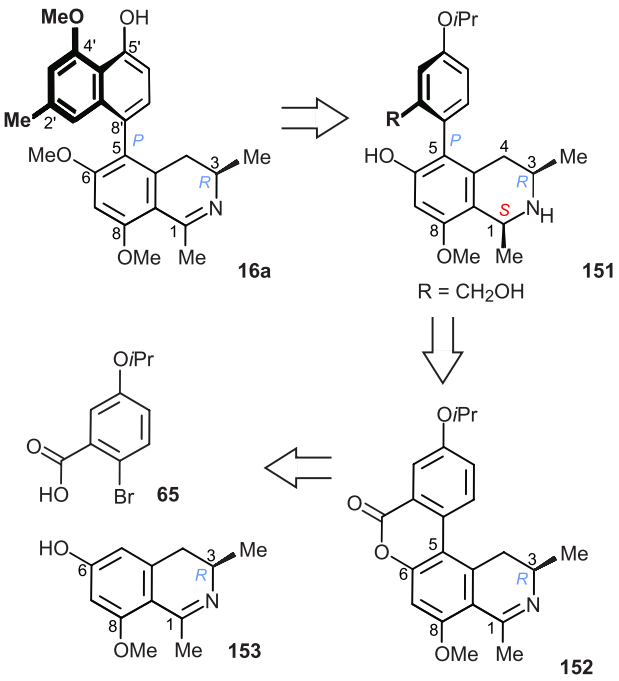
Pancreatic cancer is hard to prognose, has a high mortality rate, and patients who are suffering from it have to expect a short survival time, and, thus, it can be considered as one of the most aggressive forms of cancer.[128, 129] Surgical removal of the tumor effected tissue is the only potentially curative treatment, whereas this therapy is applicable solely to a minor portion of patients who suffer from this disease.[130] The standard drug which is currently being applied treating pancreatic cancer is gemcitabine (**150**), but chemo- and radiotherapy have little positive impact.[131] In search of novel therapeutic approaches, the before-mentioned collaboration was focused on finding alkaloids with a so-called anti-austerity activity. Austerity, i.e. the tolerance of cells to survive in a nutrient-deprived environment, is a possible target for anti-cancer therapy.[132] Tumor growth leads to certain

metabolic conditions, like the deficiency of nutrients, in which the progression of cancer is not hampered, as one might expect. As a matter of fact, the resulting rising metabolic stress leads to mutagenesis, which even further contributes to the proliferation of the tumor. Thus, a new possible approach in treating pancreatic cancer is to target nutrient-deprived cancer cells. The anti-austerity activity of a series of compounds from our group has recently been tested in a screening.[20, 37, 39] Among the tested alkaloids, ancistrolikokine E_3 (**16a**) had the highest activity against PANC-1 human pancreatic cancer cells and, thus, in-depth mechanistic studies, e.g. its effect on the morphology of cancer cells, inhibition of cell migration, and colonization of pancreatic cancer cells, were done and aspects of its signaling pathway were elucidated.[133] For further investigations, such as in vivo experiments, large quantities of the test compound were required. As only small quantities were available from plant material, a synthetic pathway to ancistrolikokine E_3 (**16a**) was envisaged, granting 'unlimited' access to this intriguing natural product.

While there was a plethora of synthetic pathways to access 5,8'-coupled naphthylisoquinoline alkaloids,[32, 46-49, 52, 57, 78] both with an inter- or intramolecular coupling reaction as key step, there were two approaches which seemed particularly promising for the total synthesis of ancistrolikokine E_3 (**16a**). On the one hand, there was the lactone method, the most commonly applied strategy in the synthesis of representatives of this intriguing class of compounds and of numerous other biaryl natural products. On the other hand, there was the Suzuki-Miyaura coupling approach, which had already been applied successfully within the frame of the present thesis in the synthesis of 5,1'- and 7,8'-coupled naphthylisoquinolines, as described above.

The general retrosynthetic plan for ancistrolikokine E_3 (**16a**) by the lactone method is depicted in Scheme 43. Most noticeable in comparison to the total synthesis of 5,1'- or 7, 1'-linked naphthylisoquinolines by this method was the fact that for the 5,8'-fused representatives the naphthalene portion had to be build up 'post'-coupling.[18, 78] This circumstance led to a less convergent, thus, more linear overall synthesis. Still, following this approach highly crowded coupling sites had been made accessible for biaryl linkages and by separating the construction of the axis itself from the stereo-induction step, most

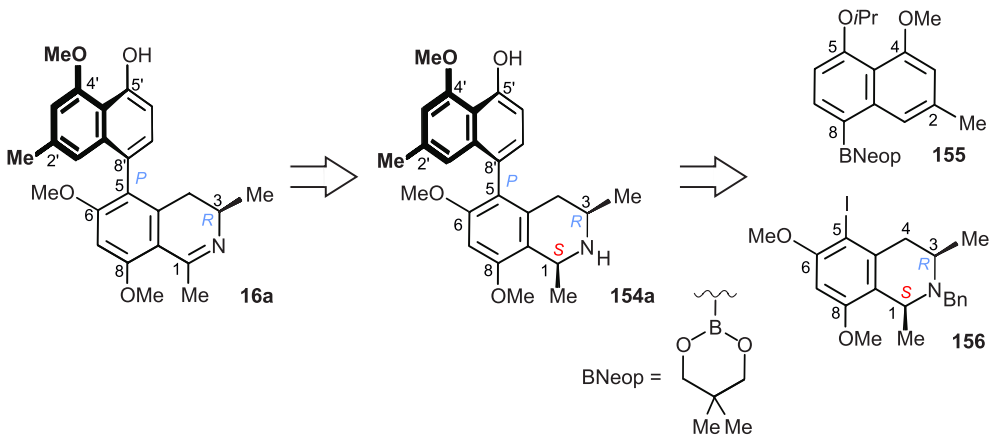
remarkable results have been obtained, both in terms of coupling yields and diastereoselectivities. Another important aspect regarding the synthesis of **16a** by this approach was that after coupling **65** and **153** to give the lactone **152** with a dihydroisoquinoline half in the southern part of the molecule (as depicted in Scheme 43) it would be inevitably reduced to give the phenyl tetrahydroisoquinoline **151** (presumably *cis*-configured) in the course of the stereoselective ring opening and, thus, an oxidation at a later stage would become necessary. This planned approach counted an overall of 23 steps (not shown here).



Scheme 43. Retrosynthetic analysis of ancistrolikokine E_3 (**16a**) based on the lactone method.

The major disadvantage of the retrosynthetic plan for ancistrolikokine E_3 (**16a**) using the intermolecular Suzuki-coupling approach was obviously the assumed lack of diastereoselectivity in the biaryl-bond-forming step between **155** and **156** (Scheme 44). If at all any preference of one of the two diastereomers over the other would be found, it would result solely from an inherent stereo-induction from the chiral isoquinoline building block **156**, which had been found to have little or no influence on the diastereomeric ratio in comparable syntheses.[32, 46, 47, 49] And, even if there was any selectivity in the coupling

step, only quantum-chemical calculations could have predicted whether it would be in favor of the desired atropisomer **154a** or not. While the lactone method can handle sterically crowded coupling sites, the intermolecular approaches frequently fail. With three substituents next to the coupling positions (two in **156** and one in **155**) here the steric constraints on the linkage were assumed to be moderate or maybe demanding. Anyhow, following this approach ancistrolikokine E_3 (**16a**) would be synthetically accessible within 11 or 8 steps - depending on whether a tetrahydro- or dihydroisoquinoline moiety was subjected to the coupling reaction - starting from precursors readily available in our research group and 20 or 16 steps starting from commercially available compounds. Further, molecule **16b** was not only the atropisomer to ancistrolikokine E_3 (**16a**), but the previously isolated natural product ancistrobonsoline A_2,[134] which had also shown activity against cancer cells in previous investigations. As this approach included fewer steps and would yield two active natural products at a time, it was chosen over the one with the lactone method.



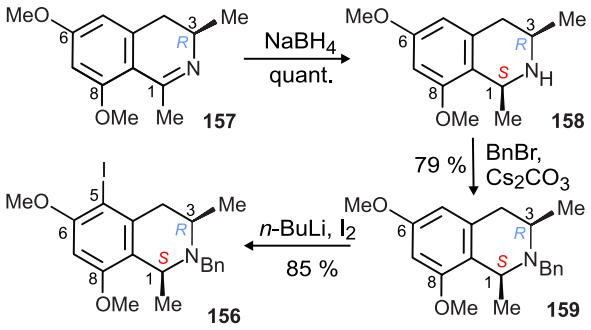
Scheme 44. Retrosynthetic analysis of ancistrolikokine E_3 (**16a**) with the Suzuki-Miyaura coupling as a key step.

6.1 Total Synthesis of Ancistrolikokine E_3 and Ancistrobonsoline A_2

Based on the retrosynthetic analysis, described above, ancistrolikokine E_3 (**16a**) was to be synthesized by the Suzuki-Miyaura coupling of either a dihydroisoquinoline or the tetrahydroisoquinoline **156** with the naphthylboronic acid ester **155**. In previous attempts of synthesizing the dihydro analog of dioncophylline C, dioncophyllidine C (**14b**), by

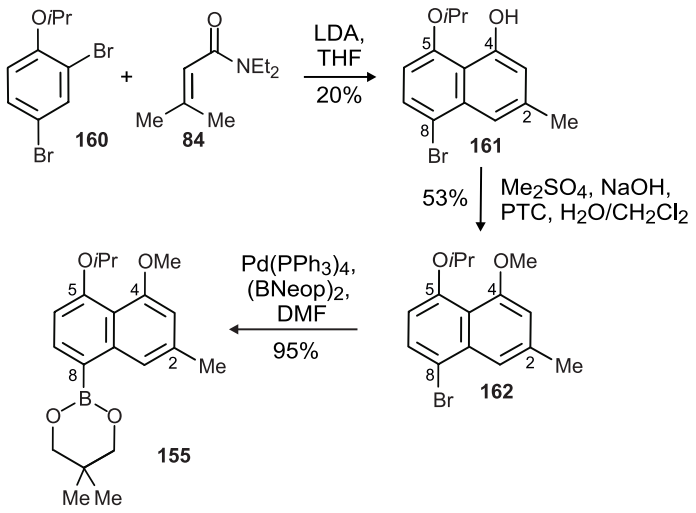
coupling a dihydroisoquinoline to a naphthylboronic acid ester it had turned out that this reaction only led to decomposition of the starting materials and to no formation of the anticipated coupled compound (see Chapter 4.2). Therefore, in a first attempt of synthesizing ancistrolikokine E_3 (**16a**) the benzyl-protected *cis*-configured tetrahydroisoquinoline **156** was to be subjected to a Suzuki-Miyaura coupling.

The synthesis of **156** started from the known precursor **157**[135] by diastereoselective reduction with $NaBH_4$ to the respective *cis*-configured tetrahydroisoquinoline **158** (Scheme 45), which was protected with benzyl bromide to give **159**. After regioselective iodination at C-5 the coupling building block **156** was obtained.



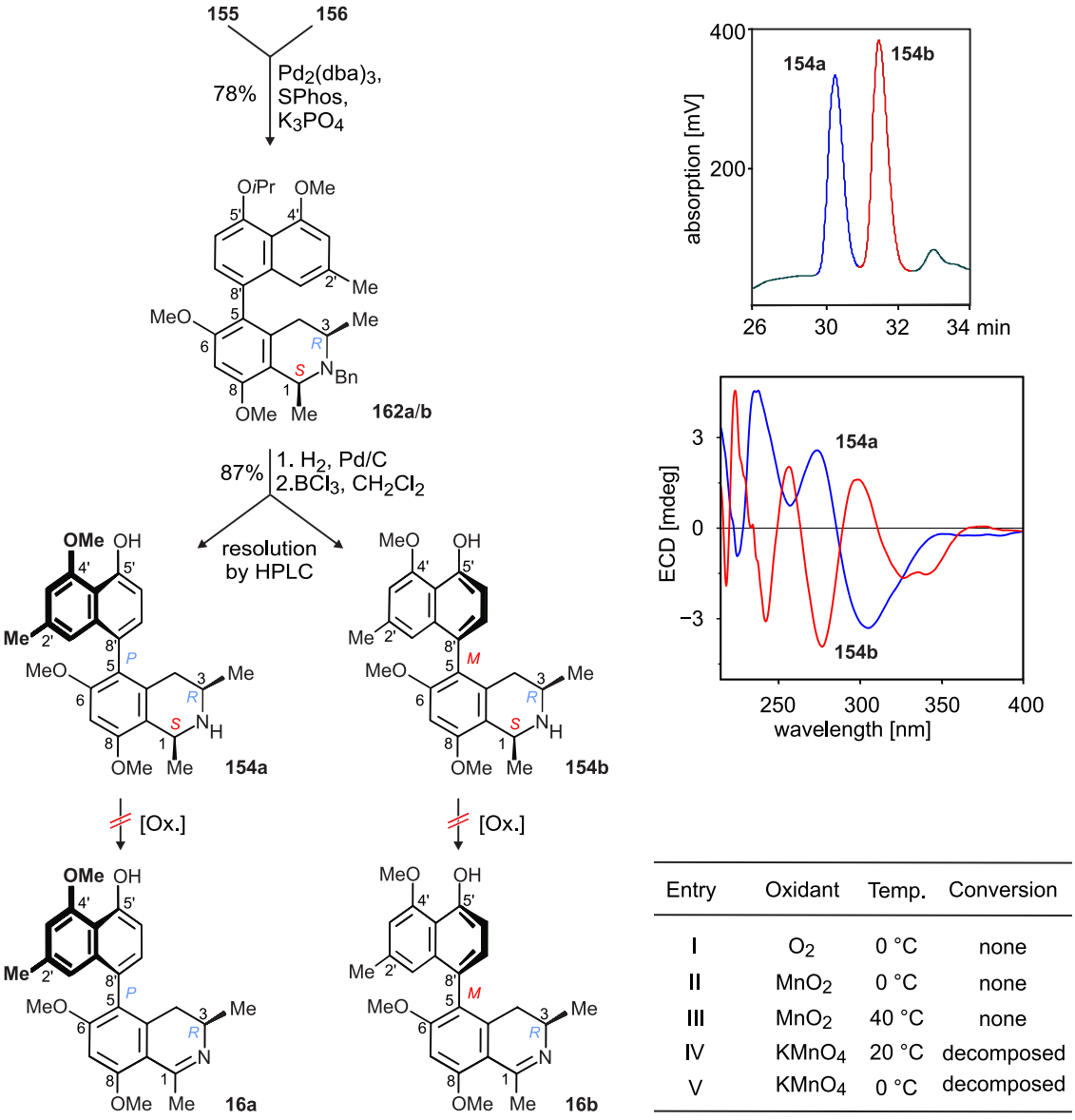
Scheme 45. Synthesis of the tetrahydroisoquinoline **156**.

The naphthylboronic acid ester **155** with its coupling function in the 8-position of the naphthalene was synthesized in a similar way as the ones described above, in particular as the one used in the synthesis of 5'-*O*-methyldioncophylline D (**15**). It began with the *O*-isopropylation of the commercially available 2,4-dibromophenol giving **160** (Scheme 46), which was subjected to the reaction with **84** to yield naphthol **161** with the bromide already in the appropriate 8-position. After phase-transfer catalyzed methylation of the free hydroxy function giving **162**, the bromide was substituted by a boronic acid ester via a palladium-catalyzed transmetalation yielding the second required building block for the planned Suzuki-Miyaura coupling, compound **155**.



Scheme 46. Synthesis of the boronic acid ester **155**.

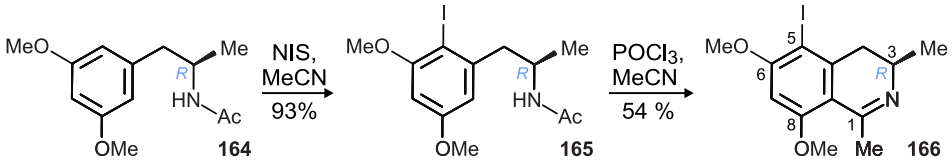
Subjecting isoquinoline **156** and naphthyl boronic acid ester **155** to the coupling conditions which had previously been optimized for the synthesis of the 7,8'-coupled 5'-*O*-methyldioncophylline D (**15**), this reaction led to a remarkable 78% yield of the anticipated atropisomeric mixture of the naphthyltetrahydroisoquinolines **163a** and **163b** in a 1:1 ratio as assigned by ^{1}H NMR (Scheme 47). After removal of the *N*-benzyl function by hydrogenolysis and deprotection of the isopropyl group with BCl_3, the two atropisomers **154a** and **154b** were resolved by reverse phased HPLC. The *cis*-configuration in the isoquinoline halves of **154a** and **154b** was introduced intentionally, instead of *trans*, as previous investigation had shown that *cis*-configured 1,3-dimethyltetrahydroisoquinolines are more easily oxidized to the respective dihydroisoquinolines than the *trans*-configured ones.[136-138] Surprisingly, neither bubbling oxygen through a solution[139] of **154a** and **154b** in methanol nor subjecting the molecules **154a** and **154b** to MnO_2 under various reaction conditions led to the formation of any product. Thus, the oxidation conditions previously described in the total synthesis of ancistrocladidine (**44a**) (Scheme 11) were applied.[63] While the starting material was consumed within seconds, no formation of the product but only decomposition was observed, even under mild conditions. It was assumed that the free hydroxy functions in molecules **154a** and **154b** might be the reasons for this reaction to fail.



Entry	Oxidant	Temp.	Conversion
I	O_2	0 °C	none
II	MnO_2	0 °C	none
III	MnO_2	40 °C	none
IV	$KMnO_4$	20 °C	decomposed
V	$KMnO_4$	0 °C	decomposed

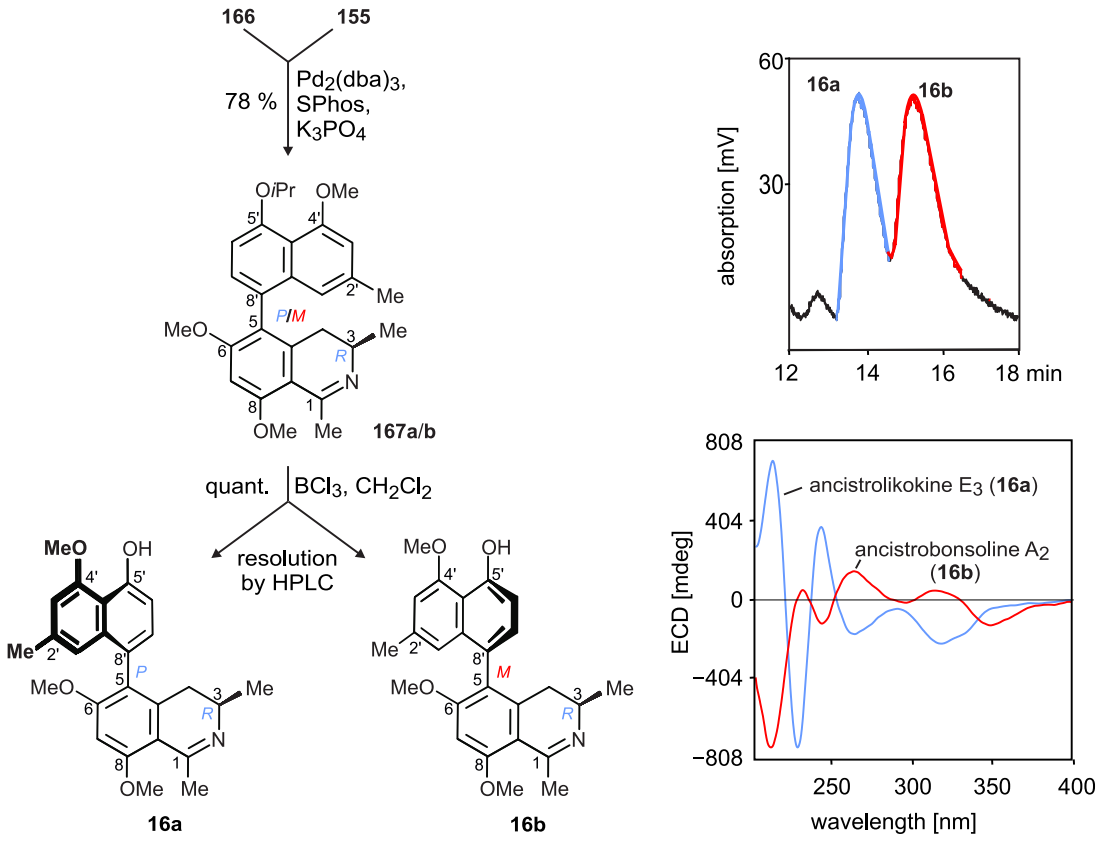
Scheme 47. Coupling reaction to form **154a** and **154b**, their ECD spectra and resolution by HPLC, and failed oxidation to give **16a** and **16b**.

In parallel to the oxidation attempts, the synthesis of ancistrolikokine E_3 (**16a**) by coupling the iodine-functionalized dihydroisoquinoline **166** was investigated. The construction of building block **166** started from the known precursor **164**, which was iodinated with NIS yielding the iodo acetamide **165** in good yield. Compound **165** was subjected to Bischler-Napieralski cyclization to obtain the anticipated dihydroisoquinoline **166** (Scheme 48).



Scheme 48. Synthesis of the dihydroisoquinoline **166**.

As this approach was most similar to the failed one described above, in which the tetrahydroisoquinoline was used in the coupling reaction, the required naphthyl boronic acid ester **155** fortunately remained the same. In spite of the previous bad experience regarding the coupling of dihydroisoquinoline building blocks in the synthesis of dioncophyllidine C (**14b**) (see Chapter 4.2), the palladium-catalyzed biaryl linkage between **155** and **166** proceeded with astonishingly good yield of 78% giving **167a** and **167b** (Scheme 49). Finally, after removing the *O*-isopropyl functions in **167a** and **167b** with BCl_3, the atropisomeric natural products ancistrolikokine E_3 (**16a**) and ancistrobonsoline A_2 (**16b**) were resolved by reverse phased preparative HPLC. This was the first successful synthesis of the highly active and extensively investigated ancistrolikokine E_3 (**16a**), making larger quantities of this exceptional secondary metabolite accessible in comparably few steps, as required for currently ongoing in vivo studies.



Scheme 49. Successful synthesis of ancistrolikokine E_3 (**16a**) and ancistrobonsoline A_2 (**16b**) and their ECD spectra.

7 Total Synthesis of Jozimine A_2 and its Atropisomers

A major portion of the synthetic work described in the present thesis was devoted to the total synthesis of the dimeric jozimine A_2 (**7a**) and all of its possible atropisomers, i.e. the jozibrevines A (**7b**), B (**7c**), and C (**7d**), which are genuine natural products, and **7e** and **7f**, which have not been isolated from plant sources yet (Figure 10). Even after the isolation and synthesis of over 200 naphthylisoquinoline alkaloids, jozimine A_2 (**7a**) remains the most potent representative of this natural product class in terms of its bioactivity against *P. falciparum* and has, thus, always been an attractive target for total synthesis.[26, 140, 141]

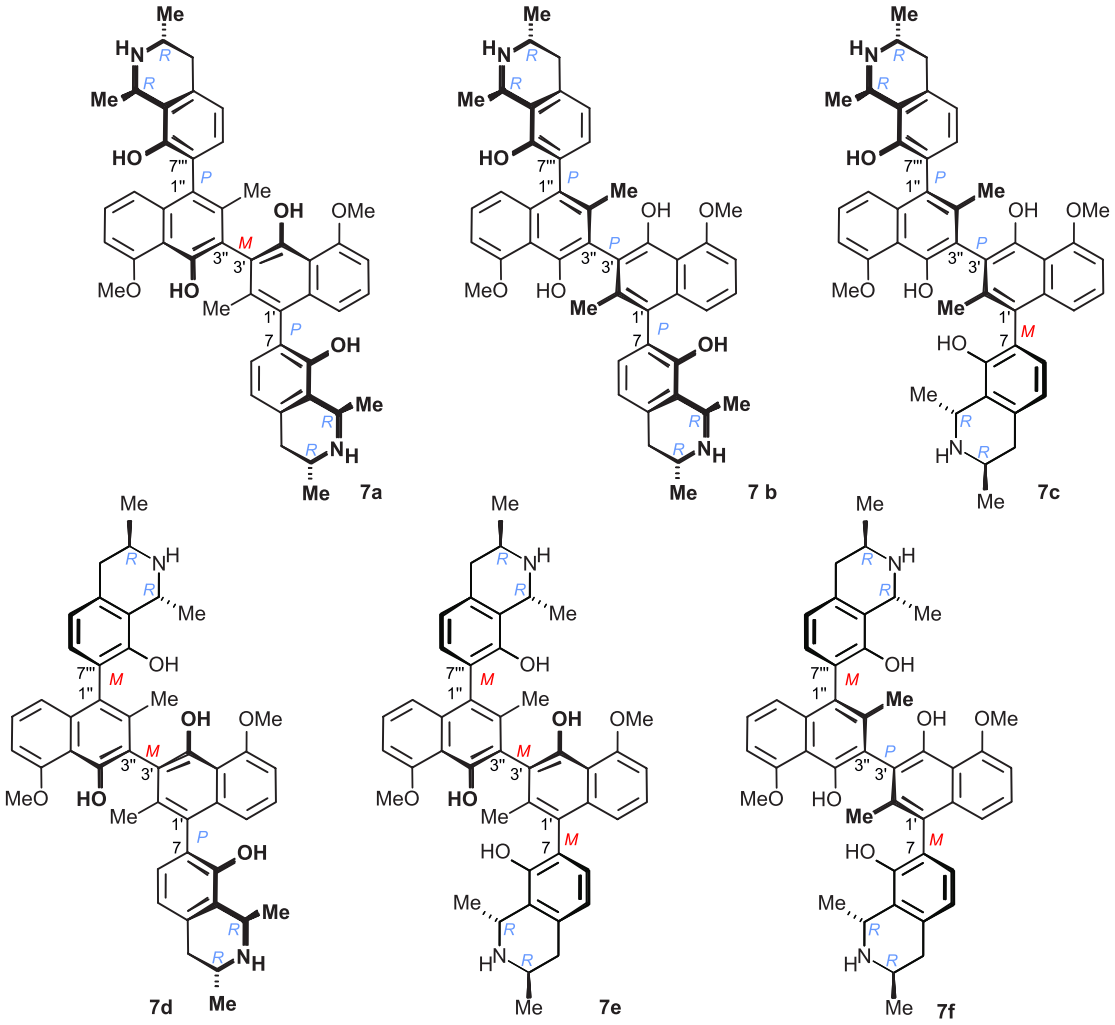
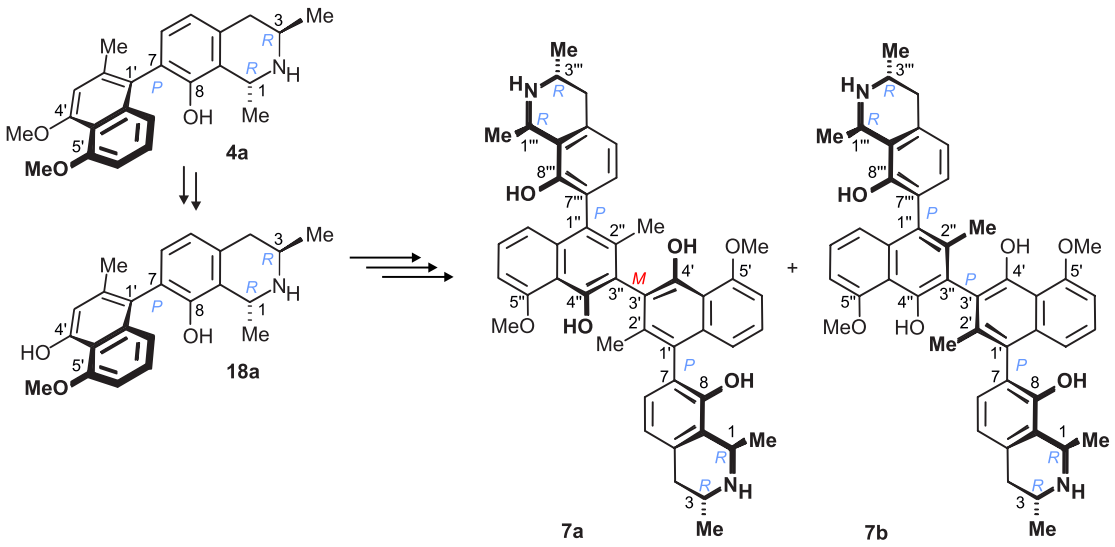


Figure 10. All six possible jozimine-A_2-type atropisomers, jozimine A_2 (**7a**), the jozibrevines A (**7b**), B (**7c**), and C (**7d**), and the as yet unnatural **7e** and **7f**.

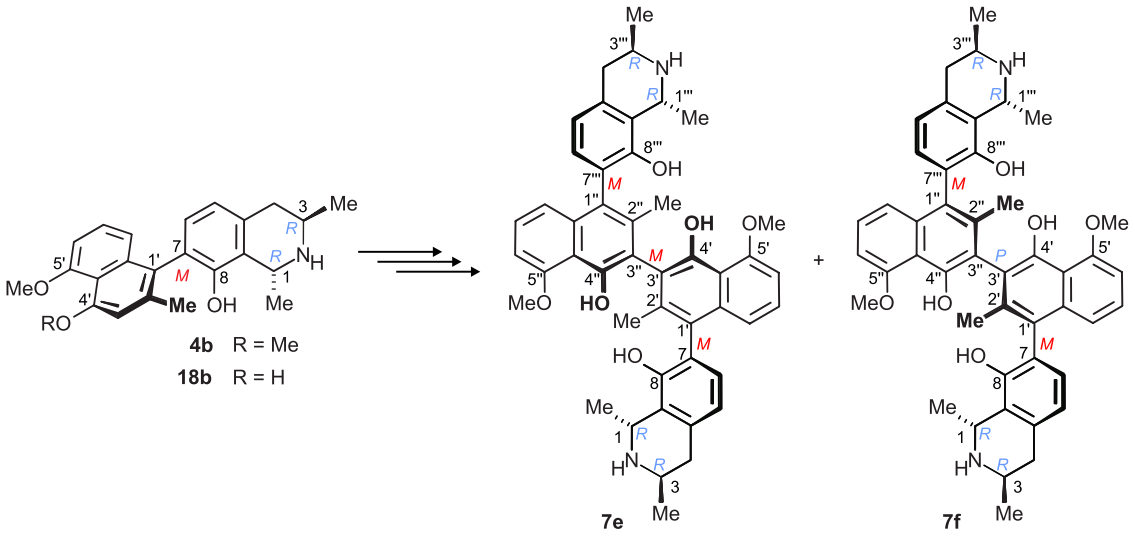
More recently, three new jozimine-A_2-type dimers, **7b**, **7c**, and **7d** have been isolated from the West African shrub *Ancistrocladus abbreviatus*, alongside with the parent compound **7a**.[21] They showed comparably good antiplasmodial activities in the submicromolar range.[21] In addition to their potency against *Plasmodium falciparum*, the parasite causing *Malaria tropica*, these compounds are remarkable considering their intriguing structure comprising four stereogenic centers and three consecutive rotationally hindered and, thus, chiral biaryl axes. Since all of the as yet found atropisomers of jozimine A_2 (**7a**) displayed pronounced antiplasmodial activities, a completion of the series to obtain all possible atropo-diastereomers by synthetic means was a fascinating and promising goal.

In previous work, different research groups elaborated synthetic approaches towards dimeric naphthylisoquinolines.[46, 52, 142-144] Thus, our research group developed a synthesis of jozimine A_2 (**7a**) and its 3'-epimer, jozibrevine A (**7b**), by linking two monomeric 4'-*O*-demethyldioncophylline A (**18a**) subunits in a non-stereoselective phenol-oxidative homo-coupling (Scheme 50).[26, 140, 141] In this thesis, the synthesis of the full series of isomers was planned to be accomplished based on this phenol-oxidative coupling by homo-coupling of the respective monomeric alkaloids, **18a** and **18b**, and by their cross-coupling. In the published work the *P*-configured dioncophylline A (**4a**) was the starting material for the synthesis of **7a** and **7b**. Dioncophylline A (**4a**) itself is a natural product readily available by isolation from plant material, but it has also been synthesized by our group.[145]



Scheme 50. Previously reported total synthesis of jozimine A_2 (**7a**) and its 3'-epimer jozibrevine A (**7b**).[26, 140, 141]

For the planned total synthesis of the other four of all six jozimine-A_2-type atropisomers **7c**, **7d**, **7e**, and **7f** either the *M*-configured 7-*epi*-dioncophylline A **4b** or even better 4'-*O*-demethyl-7-*epi*-dioncophylline A **18b** were required to access the homo-coupled **7e** and **7f** (Scheme 51) and also the hetero-coupled **7c** and **7d**. In the end, large efforts were directed towards obtaining **18b** synthetically, which itself is a natural product but appears in the chemotaxonomic profile of several plants merely as trace compound making a semi-synthetic approach to the dimers, i.e. starting from **18b** itself, less favorable. In the following section, both, total- and semi-synthetic approaches to 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**), are described.

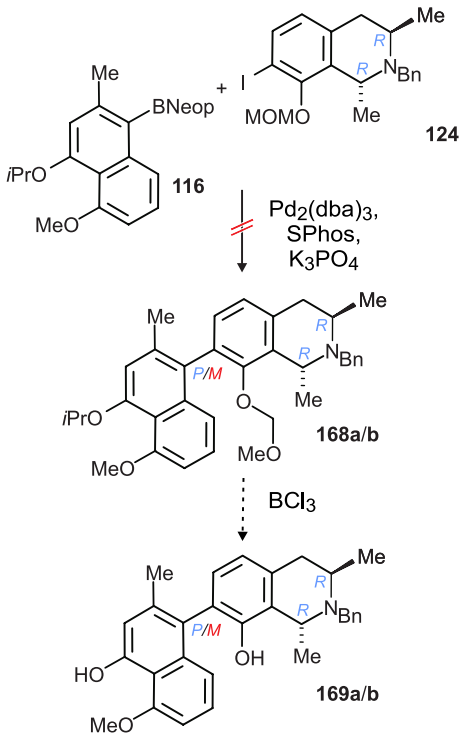


Scheme 51. Planned total synthesis of **7e** and **7f**.

7.1 Attemped Synthesis of 4'-*O*-Demethyl-7-*epi*-dioncophylline A by Suzuki-Miyaura Coupling

The synthesis of the full series of jozimine-A_2-type dimers required the atropisomeric monomers **18a** and **18b**. It was evident that in the hetero-coupling of these two molecular halves to obtain the mixed dimers **7c**/**7d** the formation of the homo-dimers **7a**/**7b** and **7e**/**7f** would be equally favored, resulting in the formation of a probably statistical mixture of all desired compounds. Thus, a first synthetic approach was directed towards an atropisomeric mixture of **169a** and **169b**, the *N*-benzyl protected forms of the natural products **18a** and **18b**, by a non-diastereoselective intermolecular biaryl coupling. With the coupling building blocks **124** and **116** at hand, forming the biaryl bond between these two moieties was attempted, but no formation of the anticipated product mixture **168a**/**168b** was observed, only decomposition of the starting materials (Scheme 52). This was rather surprising taking into account that the formation of the sterically more hindered dioncophylline C (**5a**) and analogs was successful applying this method (Chapter 4). Further, the completed synthesis of 5'-*O*-methyldioncophylline D (**15**) (Chapter 5.1), which was similar to the one attempted here except for the fact that the methyl group in the naphthalene portion was 'shifted' to a position next to the axis, was astonishing. Presumably, the lability of the iodo function and the methoxy methyl protective group were, in particular, responsible for the decomposition of the isoquinoline unit **124** on the one side and accordingly the lack of an appropriate aryl

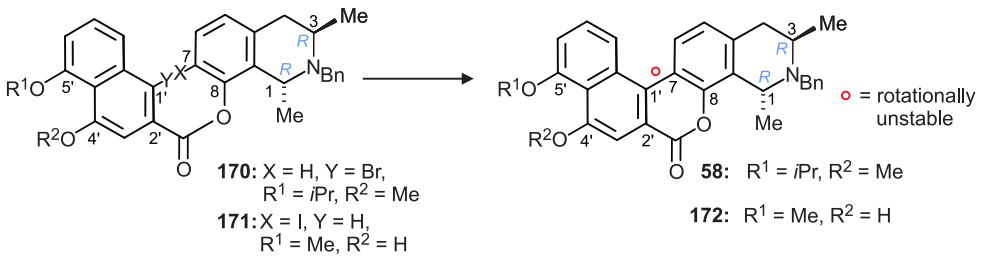
halogen for the Pd-catalyzed coupling led to the hydrodeboronation of the anyhow 'vulnerable' boronic acid ester **116** on the other. As the intermolecular hetero-coupling failed, the formation of **18b** was planned to be done using the lactone method.



Scheme 52. Attempted Suzuki-Miyaura coupling to obtain the atropdiastereomeric mixture **169a**/**169b**.

7.2 Synthesis of the Lactones *en route* to 4'-*O*-Demethyl-7-*epi*-dioncophylline A and Dioncophylline E

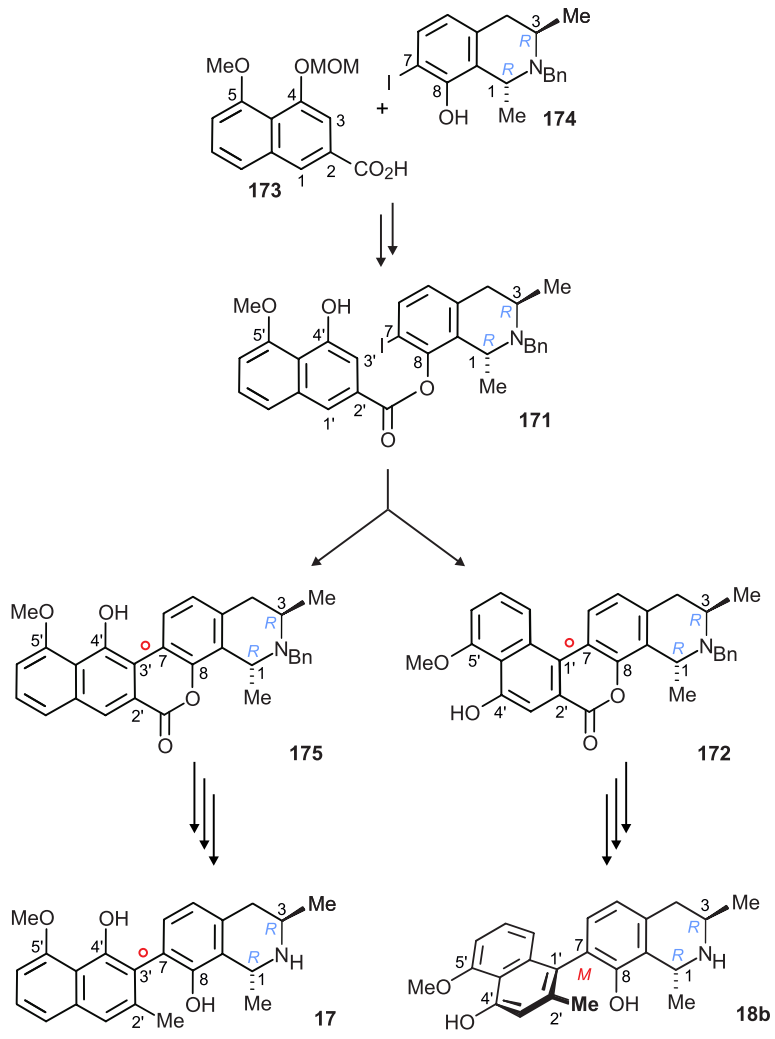
In previous work, two approaches to dioncophylline-A-type naphthylisoquinoline alkaloids had been elaborated both included the highly efficient lactone method and differed from one another in terms of the biaryl-bond forming key step. In the total synthesis of 5'-*O*-demethyldioncophylline A (**63a**) (see Chapter 3; Scheme 9), the normal activation concept for the lactone method to yield **58** was applied meaning that in ester **170** the halogen was located in the naphthalene portion next to the carboxyl function. In the synthesis of 4'-*O*-demethyldioncophylline A (**18a**),[141] an inverse activation concept to yield **172** was followed, i.e. the halogen-aryl bond was in the isoquinoline half of **171**.



Scheme 53. Application of a normal- and an inverse-activation variant of the lactone method in the planned synthesis of 5'-*O*-demethyldioncophylline A (**63a**) and 4'-*O*-demethyldioncophylline A (**18a**), respectively.

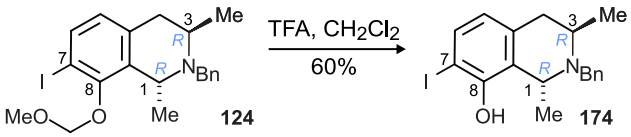
In principle, both methods could have been applied to the synthesis of **18b** but in the end the inverse one was applied as it had been successfully used in the synthesis of the atropisomer to the desired compound **18b** before. Further, the direct precursor **124** to an 7-iodo functionalized isoquinoline unit **174** (Scheme 54) was available from previous experiments (Chapter 5.1) and the synthesis of the non-halogenated naphthoic acid ester **173** (Scheme 54) comprised four steps less than the one of the respective 1-bromo analog **56** (see Scheme 9). An additional benefit to this synthetic approach was that along with the desired 7,1'-coupled compound the 7,3'-linked dioncophylline E (**17**) would have been formed as a highly valuable side product (Scheme 54). The synthesis of **17** had been accomplished by this method previously, but checking for its reproducibility, contributing spectra to the data set required for publication, and providing further material of the scarce compound **17** for bioactivity tests made this approach a rewarding goal.

The first steps in the synthesis of 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) and dioncophylline E (**17**), the linkage of **173** and **174** to form ester **171**, were identical (Scheme 54). Only after the lactone formation of **172** and **175** the two paths diverged into different directions leading to the desired products. The overall synthesis started with the formation of **173** and **174**.



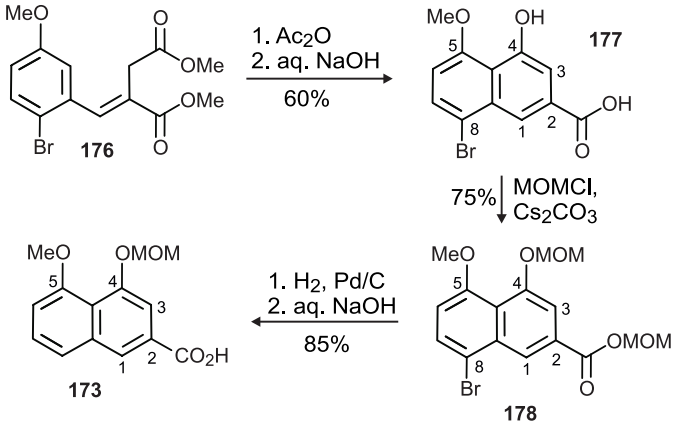
Scheme 54. Synthetic plan for the preparation of dioncophylline E (**17**) and 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**).

Starting from the previously mentioned building block **124**, isoquinoline **174** was obtained in only one reaction step in good yield by removal of the MOM protective group at O-6 by treating **124** with trifluoroacetic acid in CH_2Cl_2 (Scheme 55).



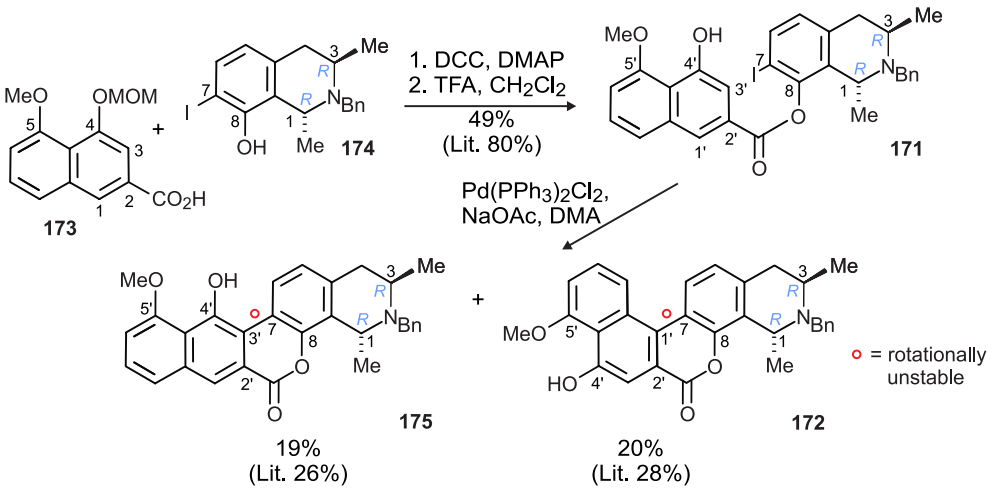
Scheme 55. Synthesis of isoquinoline **174**.

The synthesis of naphthoic acid **173** started from the known[146-148] precursor **176** (Scheme 56). By heating **176** in acetic anhydride and saponification during the workup process, molecule **177** was obtained. Under basic conditions, the resulting hydroxy naphthoic acid **177** was treated with MOM-Cl leading to the doubly protected ester **178**. The bromine, which had been necessary for controlling the regioselectivity of the ring closure, was removed hydrogenolytically and the ester function was saponified to yield the free acid **173**.



Scheme 56. Synthesis of naphthoic acid **173**.

With the building blocks **173** and **174** at hand, the ester **171** was formed by activation of the carboxylic function in **173** with DCC and the Steglich catalyst, DMAP, and subsequent addition of **174** (Scheme 57). To enhance the reactivity of the ester towards the palladium-catalyzed coupling the hydroxy group in the naphthoic acid was freed from its protective group and the resulting hydroxy iodo ester **171** was subjected to the intramolecular biaryl bond formation leading to the two anticipated lactones **172** and **175**, used for the synthesis of 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) and dioncophylline E (**17**), respectively. The yields obtained were only partially in agreement with the ones that had been reported previously.[141] The following reactions to the natural products **18b** and **17** are described separately in the next chapters.



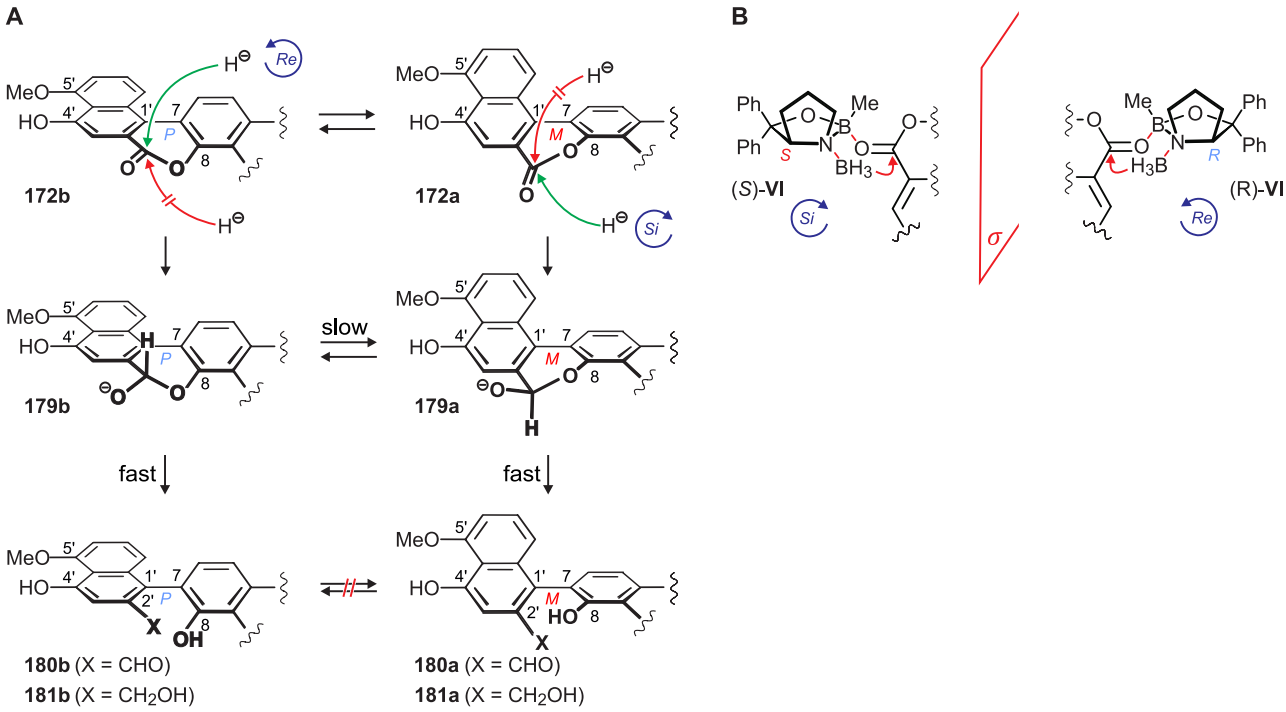
Scheme 57. Synthesis of the lactones **175** and **172**.[141]

7.3 Total Synthesis of 4'-*O*-Demethyl-7-*epi*-dioncophylline A

The lactone method, as a powerful tool for the construction of biaryl axes, can be used to obtain either of two possible atropo-diastereomers from one joint late-stage precursor. The stereochemical principles of the kinetically controlled ring opening of a lactone with a chiral reductant are described in the following section, with the synthesis of 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) as a typical example (Scheme 58).

The lactone **172** is present in form of two conformers, more accurately speaking, in the form of the two helimers[149] **172a** and **172b** (Scheme 58A). At room temperature the two forms **172a** and **172b** interconvert, as the rotational barrier at the biaryl axis is comparably low. This is an important precondition required for a dynamic kinetic resolution to be successful. Considering a case where an achiral reducing agent is being used, e.g. $LiAlH_4$, there are in principle four different possible trajectories for the hydride ion to attack the electrophilic carboxylate, two for each helimer, either from above or below the plane of the carboxylic function. But, for stereoelectronic reasons, only attacks leading to the hemiacetal **179a** and **179b** with the 'hydride' in an axial orientation are allowed (green arrows in Scheme 58) and those with an equatorial orientation are forbidden (red arrows in Scheme 58).[150] This is an important fact as this is the reason why upon treatment with a reductant one distinct helimer reacts to only one distinct hemiacetal. In a fast reaction the hemiacetals

179a and **179b** rearrange to the respective aldehydes **180a** and **180b**, which are subsequently reduced by a second equivalent of the reducing agent to each give one single atropisomer, either **181a** or **181b**. Using achiral reducing agents, for configuratively unstable lactones, such as **172a** and **172b**, the selectivity for the attack of the hydride on the different diastereotopic faces of the carboxy function is further influenced by the impact of stereogenic centers in the proximity of the reaction site. For enantiomeric lactones, on the other side, the reduction of none of the helimers is favored over the other, resulting in the formation of a racemate.



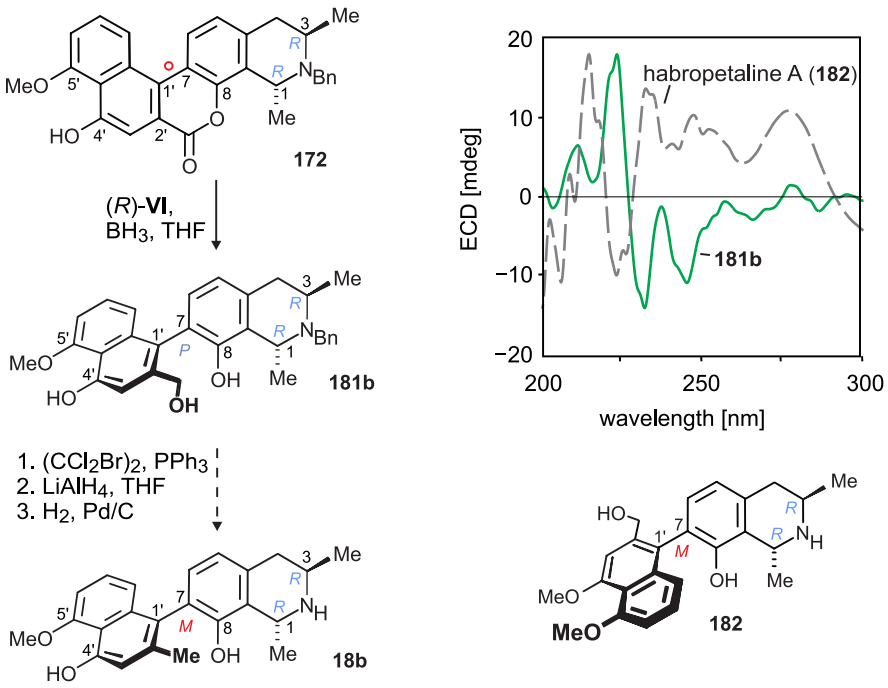
Scheme 58. The kinetically controlled ring opening of a lactone with a chiral reductant.

Using the chiral oxazaborolidine system, consisting of either the enantiomerically pure CBS catalyst, (*R*)-**VI** or (*S*)-**VI**, and diborane, as the reducing agent, there is a pronounced differentiation between helimer **172a** and **172b** (Scheme 58B). The coordination between the CBS catalyst, diborane, and the sp^2-hybridized oxygen of the carboxy function of the lactone, as shown in Scheme 58B, determines from which particular diastereotopic face the attack of the hydride will take place, the *Re*- or the *Si*-face.[79, 151, 152] Considering the *R*-configured CBS catalyst (*R*)-**VI**, only the attack from the *Re*-face is possible. Taking into

account that the hydride must approach the lactone in an axial trajectory, only helimer **172b** will react under these conditions leading to the formation of the *P*-configured ring-opened biaryl **181b**. And *vice versa*, (*S*)-**VI**/BH_3 will selectively reduce helimer **172a** yielding the *M*-configured biaryl **181a**, which is in agreement with previous work.[63, 78]

Taking this insight into account, it was decided to first assess which one of the CBS enantiomers, (*R*)-**VI** or (*S*)-**VI**, in theory was required to obtain the *M*-configured 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) and then to compare the predicted outcome of the reaction with the results from the experiment. Accordingly, the reduction using (*R*)-**VI** which should lead to the *P*-configured secondary alcohol **181b** was done, yielding the *M*-configured **18b** after two more steps.

The experiment showed that the prediction was correct (Scheme 59). Adding (*R*)-**VI** and diborane to a solution of lactone **172** in THF at room temperature led to the formation of **181b** in favor of the anticipated *P*-configured atropo-diastereomer. The configuration at the axis was assigned by comparing the ECD spectra of **181b** with that of the closely related natural product habropetaline A (**182**) (Scheme 59). As the ECD curves of **181b** and **182** were opposite to one another it was clear that the axial configuration also had to be opposite.



Scheme 59. Diastereoselective ring opening of **172**.

The last steps of the synthesis of the natural product **18b** would have been the substitution of the hydroxy function at the methylene unit at C-2' with a bromide by an Appel-type reaction using an efficient reagent developed in our group, $(CBrCl_2)_2$, as the source of the halogen, the reductive removal of this halogen using $LiAlH_4$, and the removal of the *N*-benzyl protective group by hydrogenolysis to give 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**). These last steps have not been completed during this thesis. Anyhow a semi-synthetic access to **18b** was successfully elaborated as discussed in Chapter 7.5.

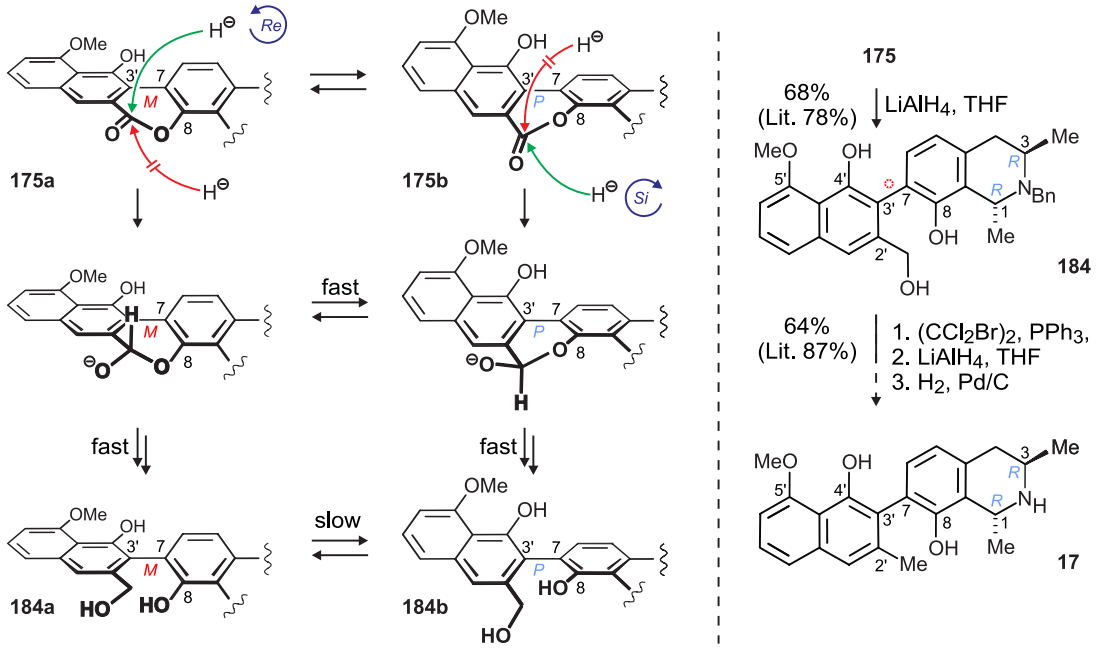
7.4 Total Synthesis of Dioncophylline E

Dioncophylline E (**17**) was planned to be synthesized analogously to the above described 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) whereas here no chiral reductant had to be used for the ring opening reaction, due to the configurational instability.

And still, it would have been interesting to apply the CBS catalysts, (*R*)-**VI** or (*S*)-**VI**, for the ring cleavage to demonstrate the strong stereoinductive potency of the lactone method demonstrating that even configurationally semi-stable compounds can be accessed in an atropisomerically pure form, which will then at room temperature interconvert to give the

respective atropodiastereomeric mixture over a certain period of time. This equilibration process was planned to be followed by analytical HPLC in combination with a UV detector. Unfortunately, first experiments showed that tedious chromatographic work up would have been required before passing any sample through the HPLC, as (*R*)-**VI**/BH_3 had an overwhelmingly high absorption suppressing any peaks connected to the ring opened product. This workup would have included many parameters, e.g. acidity of silica gel, loss of traces of one atropisomer on the column, thermal 'stress' upon warming the product-containing fractions to remove the solvent, and of course the time required for the chromatography itself, upon which the overall procedure would have become somewhat of a 'black box' method, resulting in a diastereomeric ratio that would not necessarily reflect the actual diastereomeric ratio of the stereoselective reductive cleavage of the lactone. Thus, despite being highly interesting, this experiment in the end was excluded from the present work.

Nevertheless, based on the above-mentioned principles for the kinetically controlled stereoselective reduction of a lactone (Chapter 7.3), the outcome of the ring opening of **175** using either (*R*)- or (*S*)-**VI** was elaborated (Scheme 60). If the attack of the hydride-transferring agent took place from the *Re*-face, i.e. when the *R*-configured **VI** is being used, the *M*-atropisomer **184a** would be the predicted main product. Accordingly, using (*S*)-**VI**, the *Si*-face would be attacked by the hydride, leading to the *P*-configured **184b**. Again, even if the selectivity was likely to be found when performing these syntheses, the main products (*M*)-**184a** and (*P*)-**184b**, using (*R*)- and (*S*)-**VI**, respectively, will interconvert at room temperature due to the low rotational barrier at the stereogenic axis.



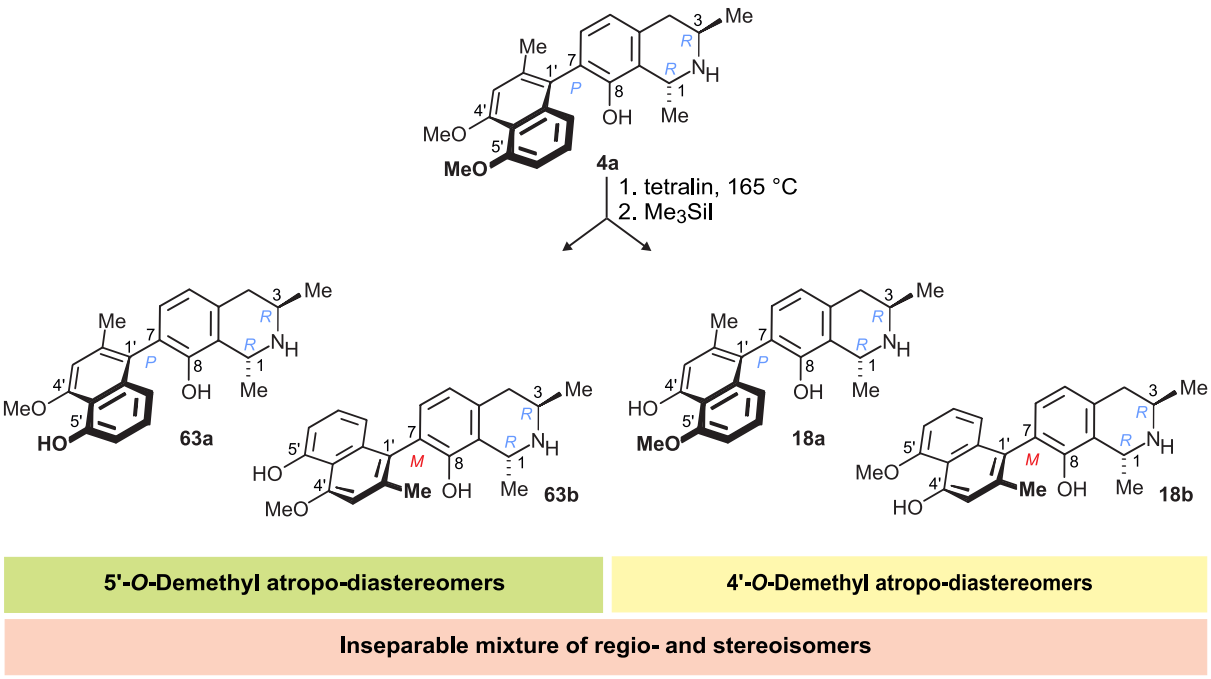
Scheme 60. Synthesis of dioncophylline E (**17**) and stereodifferentiation between the different diastereotopic faces in terms of the hydride attack.

To perform the experiments described above, much more material of **175** would have been required and in-depth time-consuming optimization of the sample preparation for HPLC analysis would have been necessary, thus, the actual synthetic ring opening was done using $LiAlH_4$ in THF following the method described in the literature yielding **184**. The secondary alcohol in **184** was transferred into a methyl group by first replacing the hydroxy function with a bromide and then reductively substituting it with a hydride, as confirmed by mass spectrometry. The final step, the removal of the benzyl protective group using H_2 and Pd/C, yielding the highly desired dioncophylline E (**17**) was not completed.

7.5 Semi-synthesis of 4'-*O*-Demethyl-7-*epi*-dioncophylline A

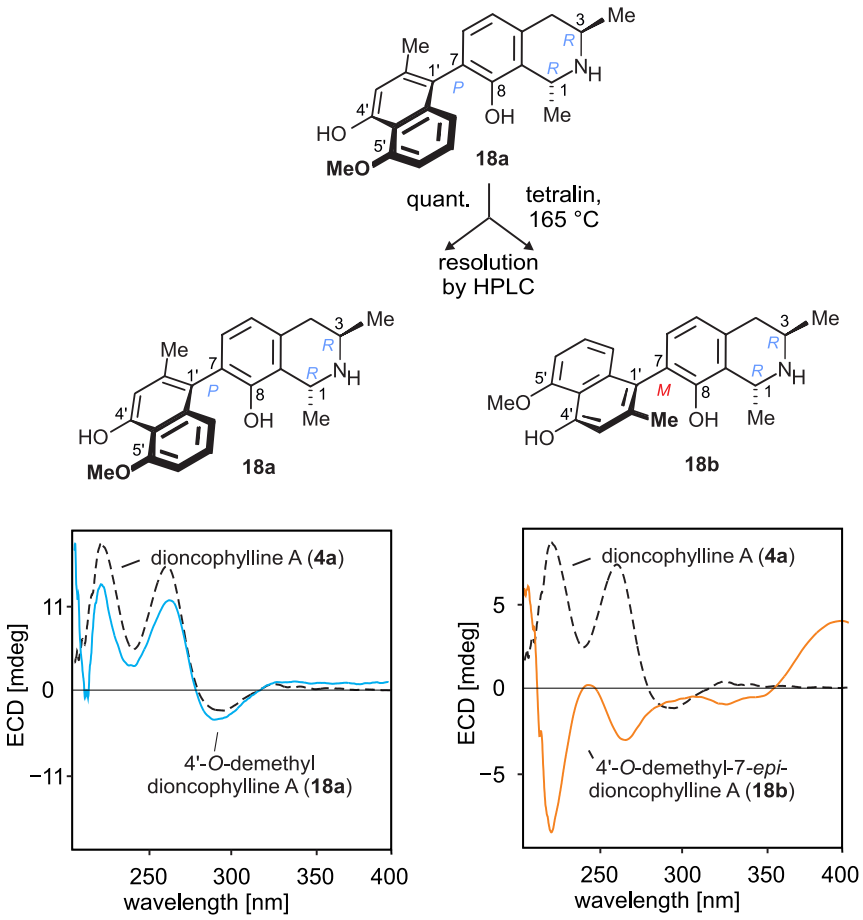
Although the total synthetic approach to 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) was almost completed, it was clear that this by no means can be the method of choice to provide sufficient quantities of **18b** for the synthesis of the jozimine-A_2-type dimers. Thus, it was additionally planned to access **18b** by thermic atropisomerization of the readily available dioncophylline A (**4a**) from plant material. In a first experiment **4a** was heated to 165 °C in the high-boiling solvent tetralin, which resulted in an isomerization at the axis of the

natural product yielding **4a** and 7-*epi*-dioncophylline A (**4b**) in a 1:1 ratio (Scheme 61). After only one step, the removal of the methyl group of O-4' in the naphthalene portion using iodo trimethyl silane, the anticipated natural product **18b** was formed. As this demethylation reaction was not regioselective, besides the atropisomer 4'-*O*-demethyldioncophylline A (**18a**) the two regioisomeric atropisomers 5'-*O*-demethyldioncophylline A (**63a**) and 5'-*O*-demethyl-7-*epi*-dioncophylline A (**63b**) were formed. Unfortunately, this mixture was inseparable on HPLC as the anticipated **18b** coeluted with 5'-*O*-demethyldioncophylline A (**63a**).



Scheme 61. Joint synthesis of **63a**, **63b**, **18a**, and **18b** resulting in an inseparable mixture.

Therefore, the approach had to be modified slightly, doing the demethylation of dioncophylline A (**4a**) first, then separating the regioisomers **18a** and **63a**, followed by the thermic atropisomerization of **18a** (Scheme 62). Now, **18a** and **18b** were nicely resolvable by HPLC on a preparative scale. Anyhow, for the formation of the hetereo-dimers **7c** and **7d** (see Figure 10), the mixture of **18a** and **18b** could be used without the need of resolving the atropisomers.



Scheme 62. Atropisomerization of **18a** by heating.

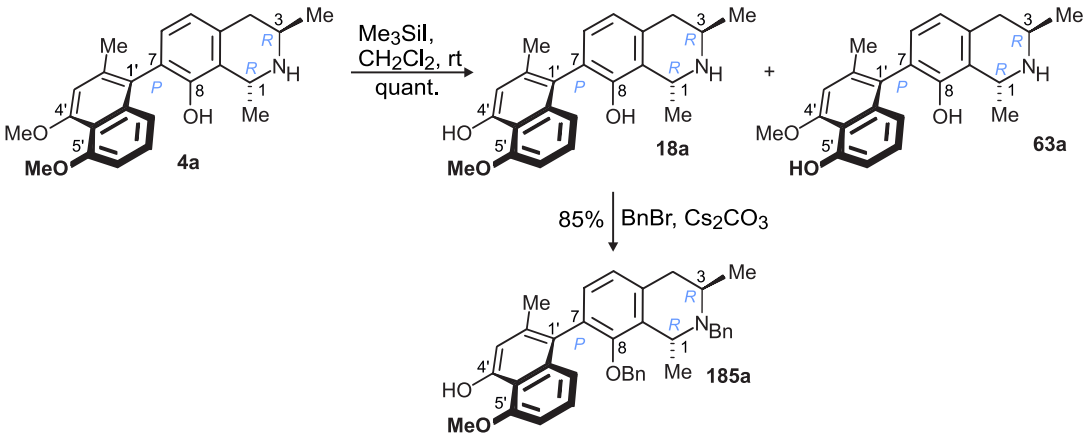
It was fascinating to see that on the one hand the complex monomer **18b** could be accessed in a remarkable total synthetic approach over 31 steps and on the other hand by using a compound provided from plant sources over no more than two steps. With this semi-synthetic approach elaborated, enough material to start with the dimerization experiments was available.

7.6 Synthesis of the Complete Series of Atropisomeric Jozimine-A_2-Type Dimers

As a starting point in synthesizing the full series of jozimine-A_2-type dimers the repetition of the published synthetic protocol for the total synthesis of jozimine A_2 (**7a**) seemed most reasonable.[26, 140, 141] Starting from dioncophylline A (**4a**), 4'-*O*-demethyldioncophylline A (**18a**) was synthesized next to 5'-*O*-demethyldioncophylline A (**63a**) by treatment with Me_3SiI.

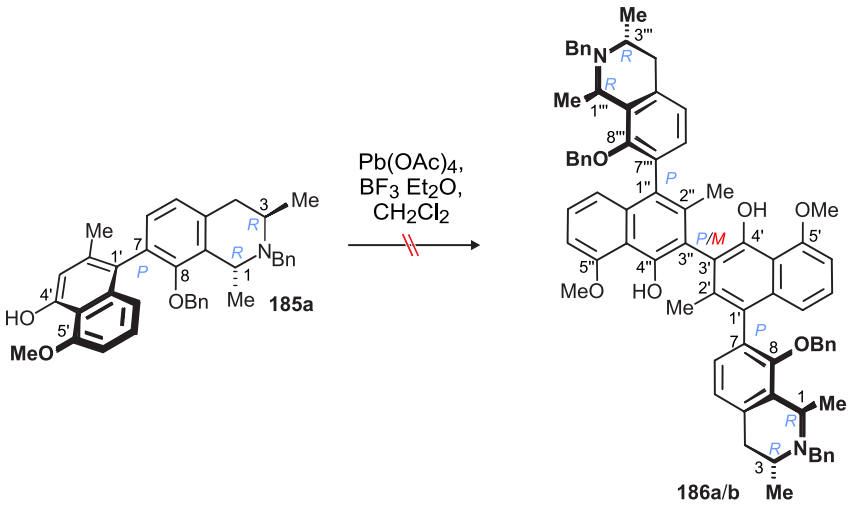
Beforehand, an attempt of removing the methyl group at O-4' selectively was done by subjecting **4a** to BCl_3. The assumption that the deprotection might proceed regioselectively was based on a finding in the synthesis of a dioncophylline C derivative, where, despite being less prone to deprotection, a methoxy function at C-4' and *para* to the biaryl axis was removed selectively with BCl_3 in the presence of a more reactive isopropoxy function at C-8 (Chapter 4.3) next to another methoxy function at C-5' giving **115a** (Scheme 28). As the methoxy group at C4' of **4a** was the targeted functionality and happened to be *para* to the biaryl axis, it was envisaged that treatment with BCl_3 would again lead to a regioselective demethylation, but at low temperature no reaction occurred. Anyhow, further investigations on finding proper reaction conditions applying BCl_3 seemed rewarding as the treatment with Me_3SiI resulted in a 1:1 mixture of the regioisomers **18a** and **63a**, which had to be resolved tediously by HPLC

After resolution, 4'-*O*-demethyldioncophylline A (**18a**) was bisbenzylated at N-2 and O-8 to give **185a**. The published work[26, 141] stated that this bisbenzylation was required as otherwise the upcoming phenol-oxidative coupling reaction would not proceed as the free hydroxy function at C-8 would not allow the reaction to take place. The selective bisbenzylation at N-2 and O-8 while sparing the OH-group at C-4', which was required for the oxidation reaction, worked out nicely and following the reaction progress by analytical HPLC and comparison of the retention times of the peaks of the isolated products to the ones of the reaction mixture proved that at first the nitrogen and then the oxygen function was protected, as expected.



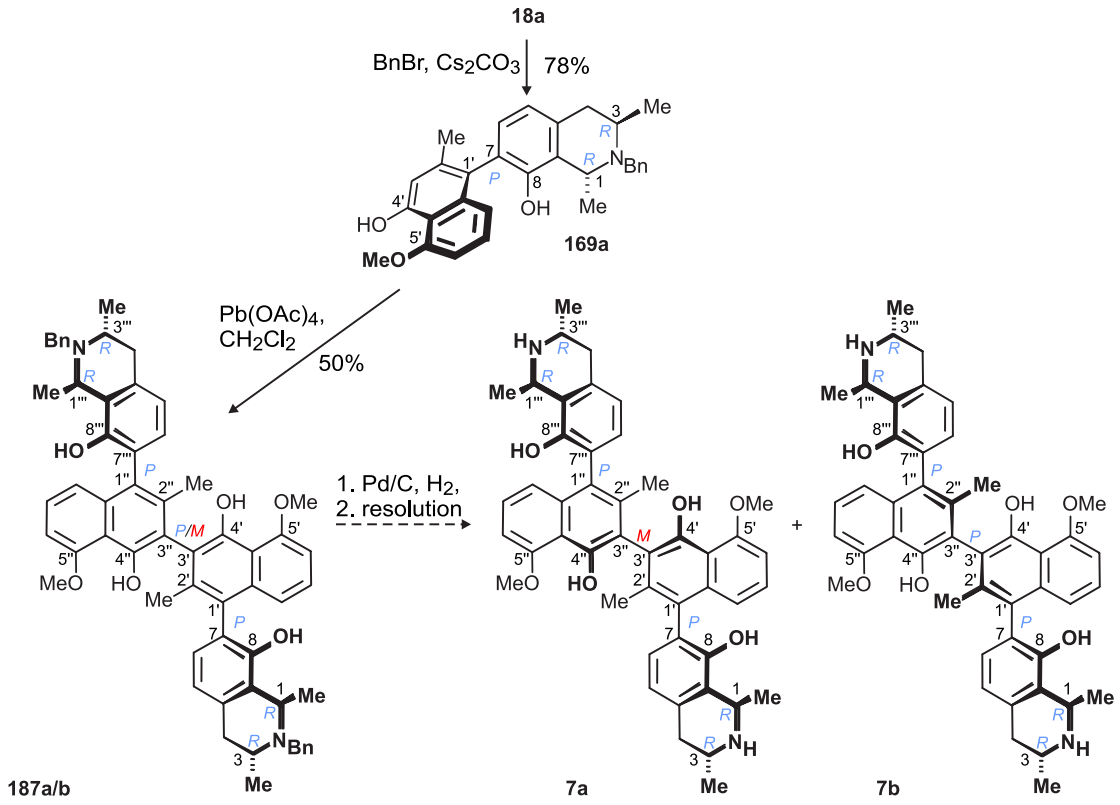
Scheme 63. *O*-Demethylation of dioncophylline A (**4a**) and bisbenzylation of 4'-*O*-demethyldioncophylline A (**18a**).

Compound **185a** was subjected to the optimized published[26, 141] oxidation conditions. Surprisingly, only decomposition of the starting material was observed. Therefore, a screening of various reaction conditions was done following the reaction by analytical HPLC, but still decomposition was observed always but once when a minimal peak in mass spectrometry hinted at the presence of the anticipated products **186a**/**186b**. This frustrating outcome in repeating an already published synthesis led to the reconsideration of all aspects of the coupling reaction. The attention soon fell on the additive $BF_3{\cdot}EtO_2$. This chemical had been used extensively in published phenol-oxidative couplings.[18, 26, 141, 144] Still, no statement on why this harsh chemical had been added to the reaction mixture in the first place had been given. Further, $BF_3{\cdot}EtO_2$ is known to be used as a deprotecting agent for phenolic benzoxy functions, just like the one at C-8 of compound **185a**.[153, 154] With these facts in mind it was decided to pass on $BF_3{\cdot}EtO_2$ as an additive in the coupling and to attempt the reaction with the mono-*N*-benzylated compound **169a** (Scheme 65).



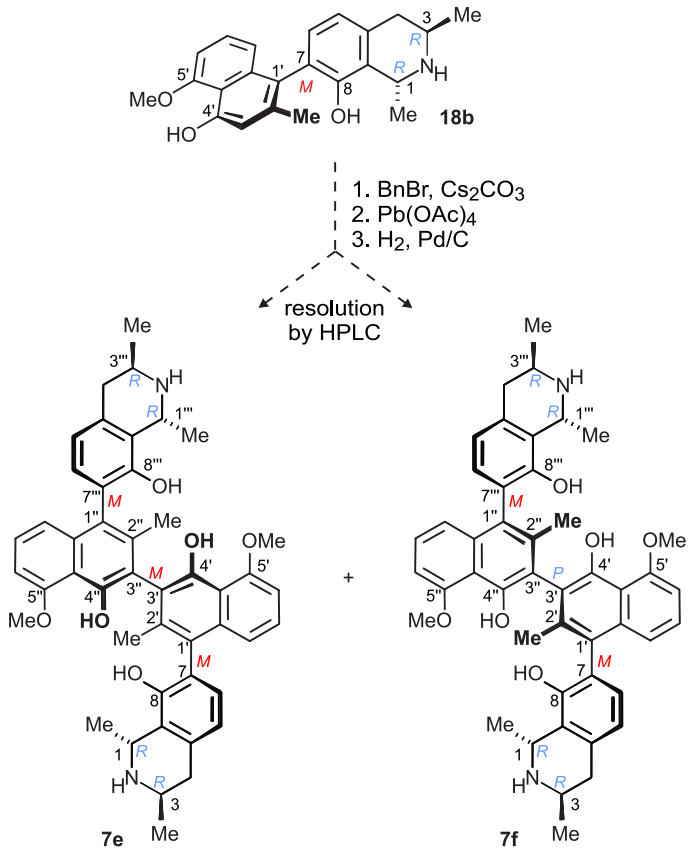
Scheme 64. Failed phenol-oxidative coupling reaction in the synthesis of **185a**/**185b**.

The synthesis of the mono-*N*-benzylated **169a** was achieved using the same conditions as for the synthesis of **185a** but reducing the equivalents of benzyl bromide added and decreasing the reaction temperature. Finally, the phenol-oxidative coupling of **169a** proceeded leading to the formation of **187a**/**187b** in 50% yield. These two small amendments, using **169a** instead of **185a** and passing on $BF_3{\cdot}EtO_2$, almost doubled the coupling yield in comparison to the published one.[26, 141] Moreover, during the reaction, the starting material was not fully consumed, so there is still some potential for optimization. And while this hurdle was taken in parallel to finalizing the present thesis, the deprotection of **187a**/**187b**, the resolution of **7a** and **7b**, and the overall synthesis of **7c**/**7d**/**7e**/**7f** was not accomplished in the course of this PhD thesis.

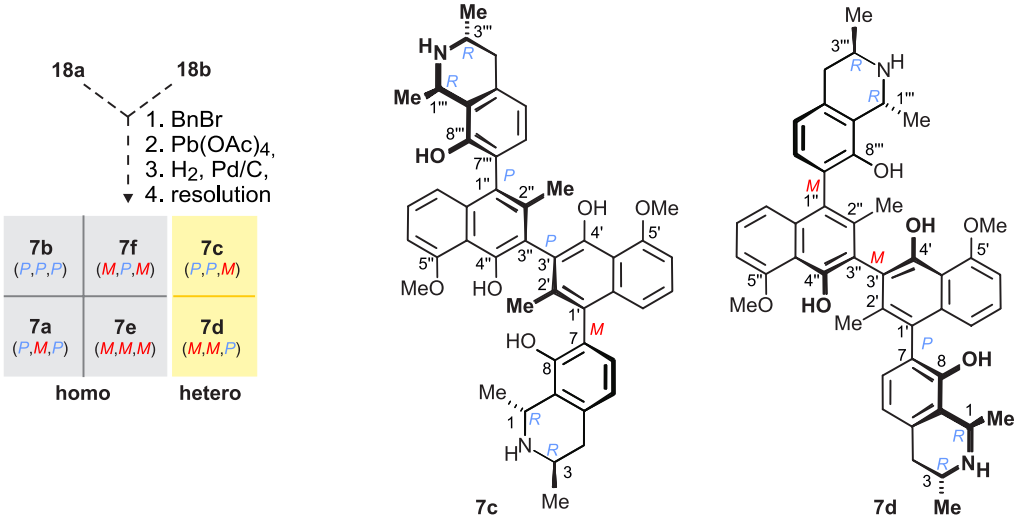


Scheme 65. Biaryl bond formation by phenol-oxidative coupling after mono-benzylation of **169a**.

Anyhow, with the established syntheses of the required coupling building blocks **169a** and **169b** starting from readily available dioncophylline A (**4a**) and with the optimized coupling conditions, the synthesis of all six jozimine-A_2-type dimers **7a**/**7b**, the homo-dimers **7e**/**7f** as depicted in Scheme 66 and the hetero-dimers **7c**/**7d** next to the homo-dimers as depicted in Scheme 67 might still be completed.



Scheme 66. Synthesis of **7e** and **7f**.



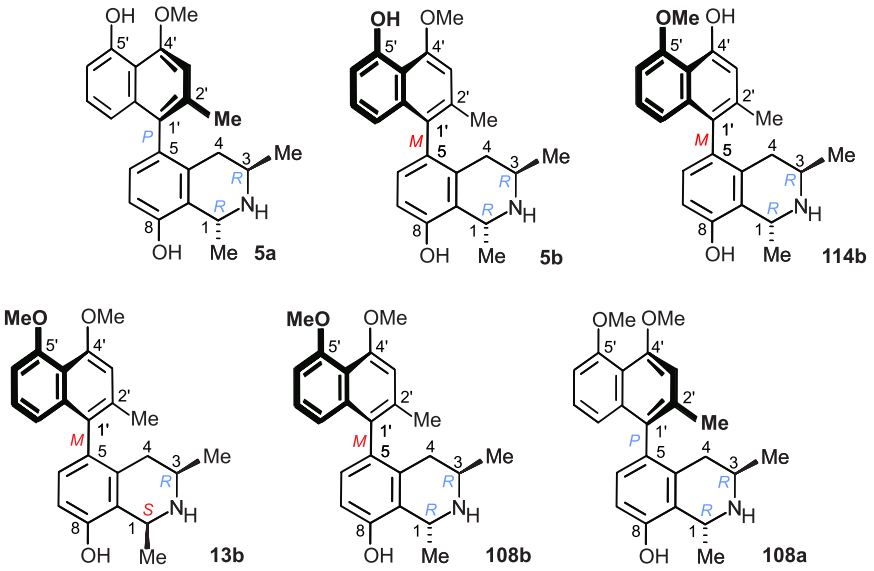
Scheme 67. Planned synthesis of the hetero-dimers **7c** and **7d** and of the homo-dimers **7a**/**7b**/**7e**/**7f**.

8 Summary

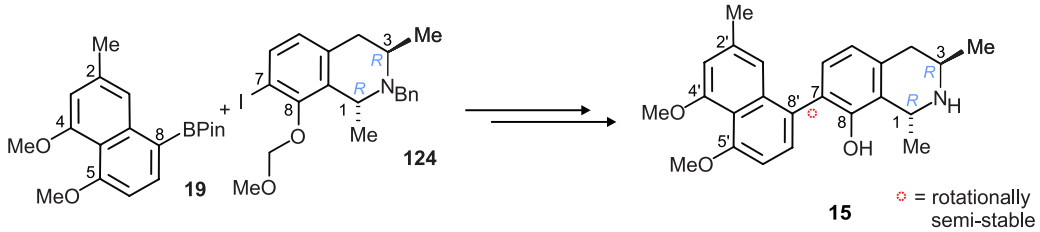
The current Covid-19 pandemic and its worldwide major impact on people's health, economic and social life underlines the importance of drug discovery and development. Our research group focusses on the isolation, structural elucidation, and synthesis of bioactive natural products, among others, the naphthylisoquinoline alkaloids from tropical lianas. This intriguing class of compounds comprises representatives with activities against, e.g. *P. falciparum*, the cause of *Malaria tropica*, against the neglected disease leishmaniasis, and, as discovered more recently, against different types of cancer cells. Based on the high potency of theses extraordinary secondary metabolites, this thesis was devoted to the total synthesis of bioactive natural products and closely related analogs.

In detail, the results of the present work are listed as follows:

- A new synthetic access to 5,1'-coupled Dioncophyllaceae-type naphthylisoquinolines closely related to the highly active antiplasmodial dioncophylline C (**5a**) by a Suzuki-Miyaura coupling has been elaborated. New insight into the diastereoselectivity in the formation of the stereogenic biaryl axis were obtained. A total of six compounds - among them their parent compound, dioncophylline C (**5a**) - have been synthesized and their full structures were confirmed spectroscopically. Three of them were part of an in-depth study on their antiplasmodial activity against drug-sensitive and drug-resistant strains of *P. falciparum* and compared well with the most commonly applied drug, chloroquine, without showing significant cytotoxicities. In a further study, two of the six synthesized target compounds were tested against the dog-pathogenic parasite *Babesia canis* but merely showed moderate or weak activities.

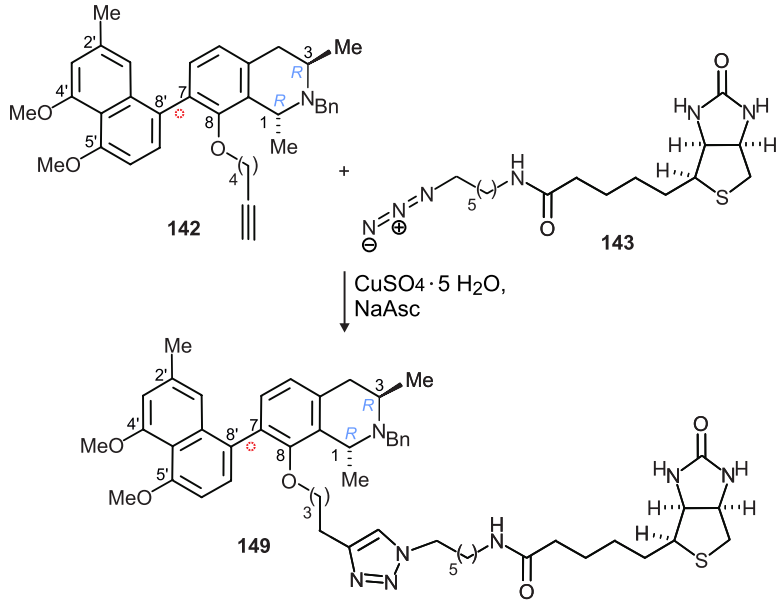


- The total synthesis of the 7,8'-coupled naphthylisoquinoline alkaloid 5'-*O*-methyldioncophylline D (**15**) was completed. This compound had shown good activities against lymphoblastic leukemia cell lines. But, as its isolation from plant material is particularly difficult, a synthetic access seemed highly rewarding. Further, the synthesis demonstrated the applicability of this highly powerful Suzuki-Miyaura coupling method without the need of any toxic reagents in comparison to the former synthetic approach towards 7,8'-coupled Dioncophyllaceae-type naphthylisoquinoline alkaloids by the Stille coupling.

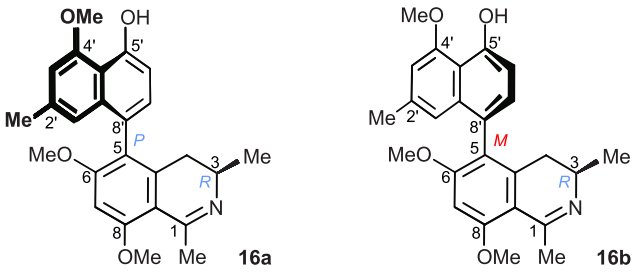


- A straightforward protocol for the biotinylation of compounds by click chemistry was elaborated and its applicability was exemplarily proven by the functionalization

of 5'-*O*-methyldioncophylline D (**15**) to give **149**. This should prove to be an efficient method for labeling experiments for target identification investigations.

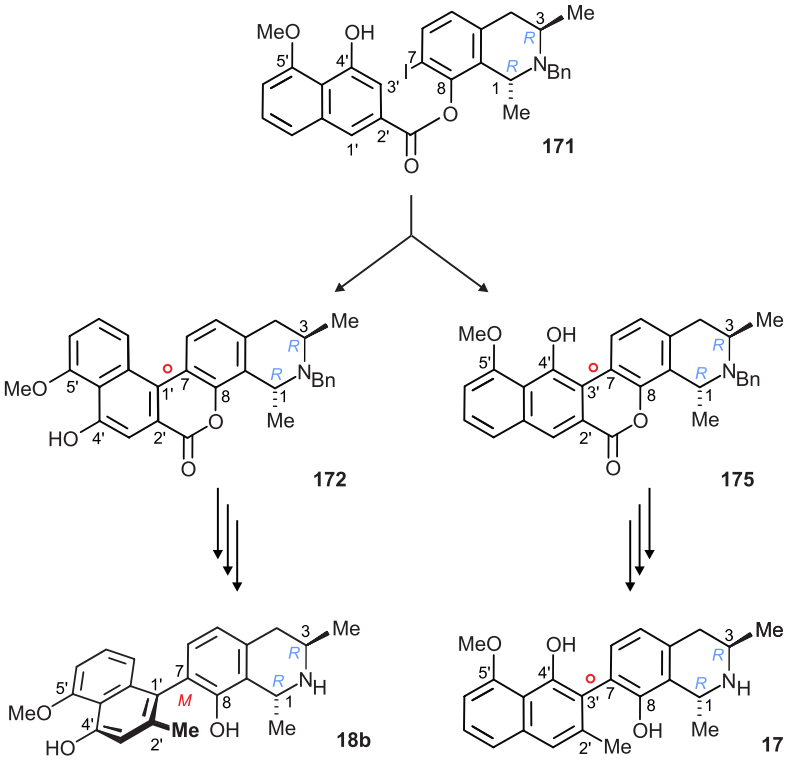


- The first synthetic access to the highly potent and thoroughly investigated anti-pancreatic cancer compound ancistrolikokine E_3 (**16a**) has been accomplished. During its synthesis the natural product ancistrobonsoline A_2 (**16b**) was formed as a precious side product. Following this newly designed synthetic protocol larger quantities of ancistrolikokine E_3 (**16a**) were made accessible, i.e. an amount large enough even for in vivo experiments, which are currently ongoing.

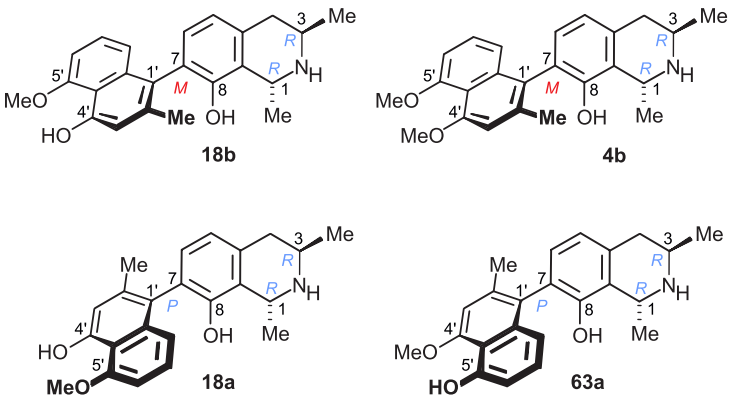


- The total synthesis of 4'-*O*-methyl-7-*epi*-dioncophylline A (**18b**) by the lactone method over 31 steps was completed except for the last two steps. In addition, the

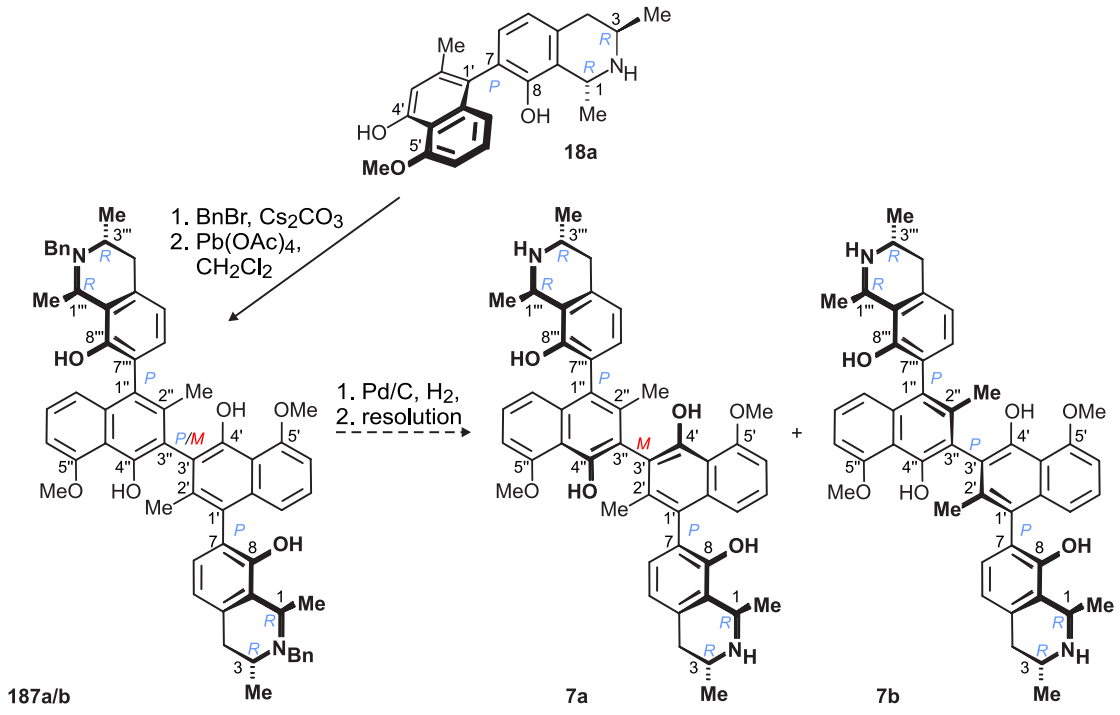
synthesis of dioncophylline E (**17**) was repeated as published and completed except for the last deprotection step.



- A new semi-synthetic access to 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) comprising no more than two steps - in contrast to the total synthesis, which incorporates 31 steps - starting from readily available dioncophylline A (**4a**) was elaborated. Additionally, the natural products 7-*epi*-dioncophylline A (**4b**), 4'-*O*-demethyldioncophylline A (**18a**), and 5'-*O*-demethyldioncophylline A (**63a**) were obtained.



- The published total synthesis of jozimine A_2 (**7a**) by phenol-oxidative homo-coupling of 4'-*O*-demethyldioncophylline A (**18a**) was repeated. As the coupling reaction did not proceed under the published conditions, new ones were elaborated reproducibly increasing the yield of **187a**/**187b** from 30% to 50%. The last steps of the planned synthesis of jozimine A_2 (**7a**) and of all its possible atropisomers were not completed.



In summary, a total of 15 naphthylisoquinoline alkaloids and closely related analogs were synthesized comprising representatives of four different coupling types with distinct

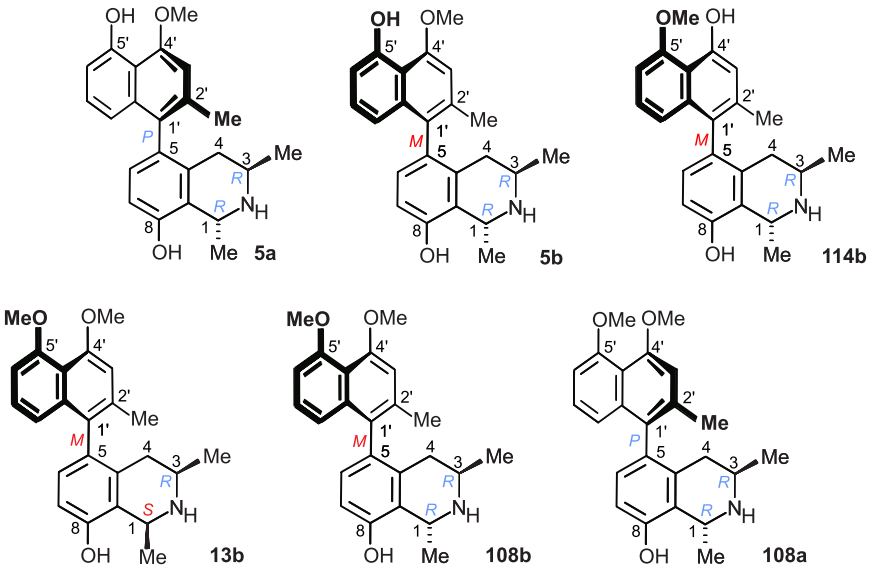
antiplasmodial activity and cytotoxicity against lymphoblastic leukemia and pancreatic cancer cell lines.

9 Zusammenfassung

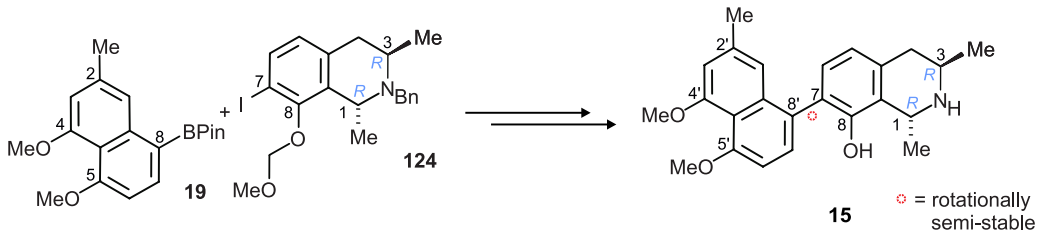
Die gegenwärtige Covid-19-Pandemie, ihr massiver Einfluss auf die Gesundheit und das wirtschaftliche und soziale Leben der Bevölkerung zeigt auf, wie wichtig nach wie vor die Medikamentenforschung und Wirkstofffindung ist. Unser Arbeitskreis befasst sich mit der Isolierung, Strukturaufklärung und Synthese bioaktiver Naturstoffe, unter anderem mit den sogenannten Naphthylisochinolin-Alkaloiden. Diese bemerkenswerte Substanzklasse enthält Wirkstoffe mit Aktivitäten gegen *P. falciparum*, den Erreger der *Malaria tropica*, gegen Leishmaniose und, wie erst kürzlich entdeckt, Wirkstoffe mit Aktivität gegenüber Zelllinien verschiedener Krebsarten. Aufgrund der hohen Wirksamkeit dieser außergewöhnlichen Sekundärmetabolite wurde die vorliegende Doktorarbeit auf die Totalsynthese bioaktiver Naphthylisochinoline und davon abgeleiteter Derivate ausgerichtet.

Im Detail wurden die folgenden Ergebnisse erzielt:

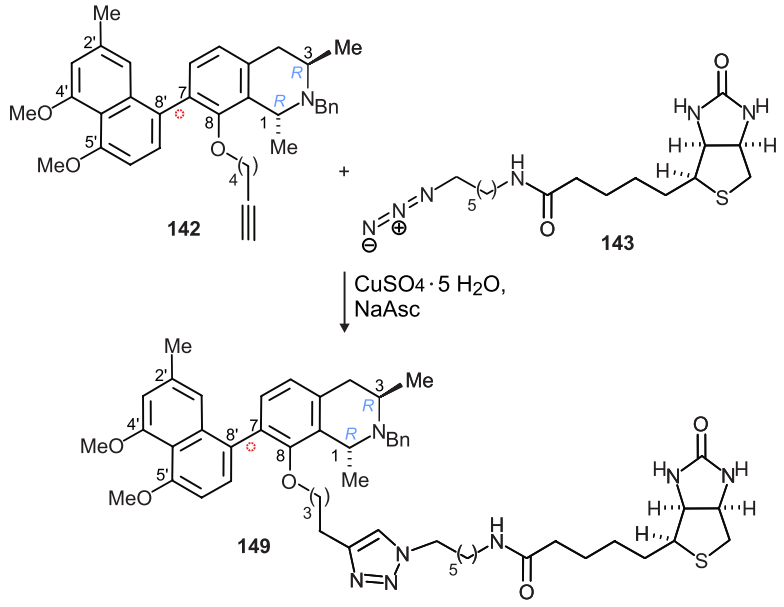
- Ein neuer synthetischer Zugang zu 5,1'-gekuppelten Dioncophyllaceae-Typ-Naphthylisochinolinen, deren Struktur vom höchstantiplasmodialen Dioncophyllin C (**5a**) abgeleitet war, mittels Suzuki-Miyaura-Kupplung wurde etabliert. Dabei konnten neue Erkenntnisse hinsichtlich der intrinsischen Stereoinduktion der chiralen Kupplungsbausteine auf das Atropisomeren-Verhältnis der Kupplungsreaktion gewonnen werden. Insgesamt wurden somit sechs Verbindungen – unter anderem auch die Leitstruktur, Dioncophyllin C (**5a**) – synthetisiert und anhand spektroskopischer Daten vollständig strukturell aufgeklärt. Drei dieser Verbindungen waren Teil einer detaillierten Studie zu deren antiplasmodialer Aktivität gegenüber Arzneimittel-resistenten *P. falciparum*-Stämmen und erzielten dabei Werte im Bereich des Arzneistoffs Chloroquin. In einer weiteren Studie wurden zwei der Zielverbindungen auf ihre Aktivität gegenüber *Babesia canis*, dem Erreger der Hundemalaria, untersucht, lieferten jedoch nur mäßige bis schwache Werte.



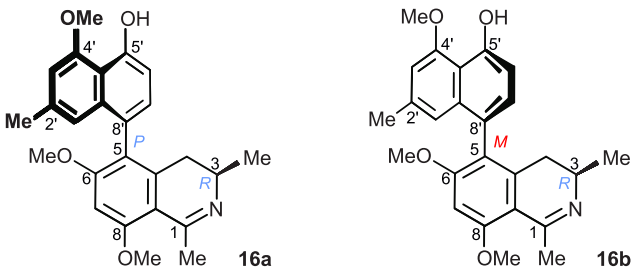
- Die Totalsynthese des 7,8'-gekuppelten 5'-*O*-Methyldioncophyllins D (**15**), welches in vorherigen Studien Aktivität gegenüber Krebszellen gezeigt hatte, wurde erfolgreich abgeschlossen. Die Verbindung zeigte gute zytotoxische Aktivität gegenüber lymphatischen Leukämiezellen, da sie jedoch mittels Isolierung nur schwer zu erhalten ist, war ein synthetischer Zugang wünschenswert.



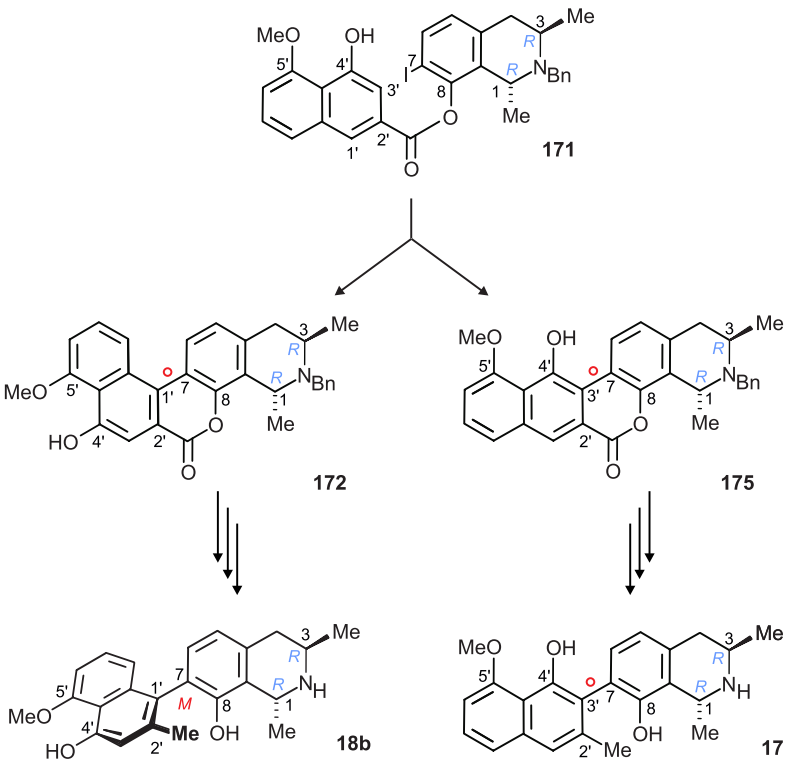
- Es wurde ein neues Protokoll zur einfachen Biotinylierung von Verbindungen mittels Click-Chemie ausgearbeitet und am Beispiel von 5'-*O*-Methyldioncophylline D (**15**) erfolgreich auf seine Anwendbarkeit in der Synthese von **149** getestet. Dieses Syntheseprotokoll sollte sich als hilfreich bei künftigen Drug-Target-Untersuchungen erweisen.



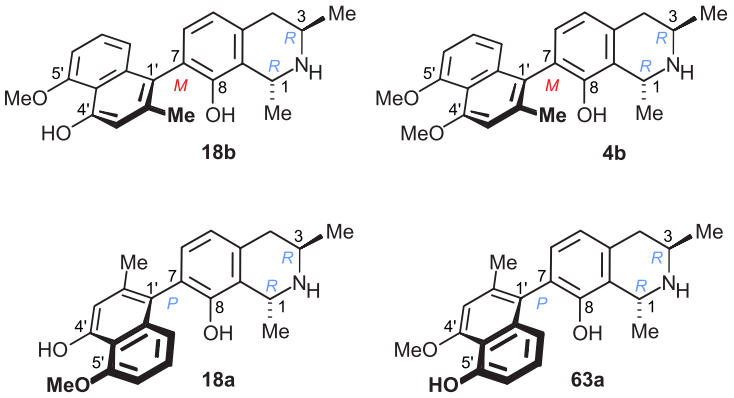
- Der erste Totalsynthese zu dem hochaktiven und gut erforschten Ancistrolikokin E_3 (**16a**) wurde erfolgreich abgeschlossen. Dieser Naturstoff zeichnet sich durch seine Wirksamkeit gegenüber Pankreaskrebszellen aus. Bei der Synthese fiel als Nebenprodukt der ebenfalls aktive Naturstoff Ancistrobonsolin A_2 (**16b**) an. Im Rahmen dieser Arbeit wurden größere Mengen an Ancistrolikokin E_3 (**16a**) hergestellt, ausreichend für gegenwärtig stattfindende In-vivo-Experimente.



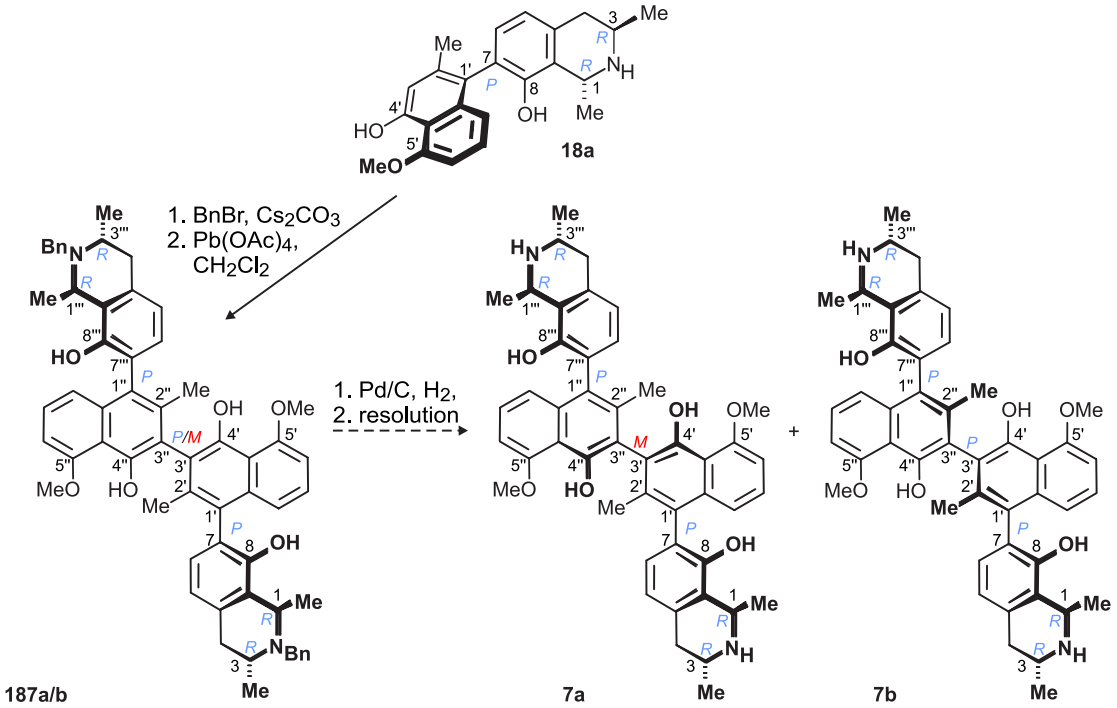
- Die 31-stufige Totalsynthese von 4'-*O*-Demethyl-7-*epi*-dioncophyllin A (**18b**) mittels des Lacton-Konzepts wurde bis auf die letzten zwei Stufen erfolgreich abgeschlossen. Darüber hinaus wurde die publizierte Synthese von Dioncophyllin E (**17**) auf ihre Reproduzierbarkeit hin untersucht und bis auf den letzten Entschützungsschritt fertiggestellt.



- 4'-*O*-Demethyl-7-*epi*-dioncophyllin A (**18b**) wurde in einer zweistufigen Semisynthese ausgehend von Dioncophyllin A (**4a**) auf Basis einer Atropisomerisierungs-Reaktion hergestellt. Zusätzlich dazu wurden die Naturstoffe 7-*epi*-Dioncophyllin A (**4b**), 4'-*O*-Demethyldioncophyllin A (**18a**) und 5'-*O*-Demethyldioncophyllin A (**63a**) synthetisiert.



- Die publizierte Synthese von Jozimin A_2 (**7a**) mittels phenoloxidativer Homokupplung von 4'-*O*-Demethyldioncophyllin A (**18a**) wurde auf ihre Reproduzierbarkeit hin untersucht. Da unter Anwendung der publizierten Bedingungen keine Kupplung stattfand, wurden neue Reaktionsbedingungen entwickelt, die wiederholt zu einer Steigerung der Kupplungsausbeute von **187a**/**187b** auf 50% führten im Vergleich zu den 30% der publizierten Kupplung. Die letzten Schritte der geplanten Synthese von Jozimin A_2 (**7a**) und dessen Atropisomeren wurden im Rahmen dieser Arbeit nicht erfolgreich abgeschlossen werden.



Zusammenfassend wurden im Laufe dieser Arbeit 15 Naphthylisochinolin-Alkaloide und nahverwandte Derivate mit antiplasmodialer Aktivität und Wirksamkeit gegenüber Leukämie- und Pankreaskrebs-Zelllinien synthetisiert.

EXPERIMENTAL SECTION

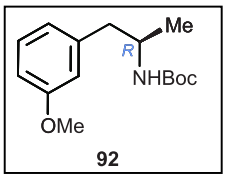
General Methods: All melting points were measured on a Thermovar-Kofler heating plate microscope by Reichert and have not been corrected. Optical rotation values were obtained with a polarimeter P-1020 of *Jasco* at the sodium-D line (λ = 589 nm). Infrared spectra were recorded on a spectrometer FT-IR-410 by *Jasco* equipped with an ATR support. The intensities of the absorption bands are illustrated by the following abbreviations: s = strong, m = medium, w = weak. All spectra were acquired at room temperature. All ^{1}H und ^{13}C NMR spectra were recorded on spectrometers of the type Bruker Avance III HD 400. Processing of the spectra was done with the software packages of 'Topspin'. Chemical shifts are given in units of the δ scale and are calibrated on the trace proton signals of the used deuterated solvents for ^{1}H NMR spectra and the ^{13}C signals of the solvents for ^{13}C spectra. For ^{1}H NMR: δ ($CDCl_3$) = 7.26 ppm; δ (CD_3OD) = 3.31 ppm; δ (acetone-d_6) = 2.05 ppm; and for ^{13}C NMR: δ ($CDCl_3$) = 77.2 ppm; δ (CD_3OD) = 49.2 ppm; δ (acetone-d_6) = 29.8 ppm. Spin multiplicities are given by the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet. Coupling constants are given in Hertz (Hz). Electronic-ionization (EI) mass spectra were measured on a *Finnigan* MAT-8200 spectrometer at ionization potentials of 70 eV. The values in parentheses correspond to the intensities of the corresponding signals in relation to the base peak (I = 100 %). Electron spray ionization (ESI) mass spectra were recorded on a *Bruker* Daltonics micOTOF focus. The samples were dissolved in MeOH prior to the measurement. The progress of reactions was monitored by thin layer chromatography using *Merck* aluminum foil silica gel 60 F_{254} plates. Detection was carried out by irradiation and consequent fluorescence quenching at 254 nm or excitation at 366 nm. For column chromatography silica gel from *Merck* (0.063−0.2 mm) was used. Silica gel was deactivated by addition of 7.5 % ammonia. Analyses of samples by HPLC were performed on a system of *Jasco* consisting of: pump PU-2080, degassing unit DG-2080, auto sampler AS-2050, mixer LG-2080, and diode array detector MD-1510. Experiments were carried out either on a Chromolith Performance RP-18 column (*Merck*), on a XSelect HSS PFP column (*Waters*), or on a Symmetry C18 column (*Waters*). All solvents were distilled prior to use. Water for the

HPCL system was purified with a Milli-Q unit of *Merckmillipore* and degassed. Acetonitrile, methanol, and trifluoroacetic acid for HPLC were used without further purification. All the other chemicals that were employed for synthesis were purchased from *Sigma-Aldrich*, *Alfa Aesar*, *Merck*, *VWR,* or *Acros Organics* and were used without further purification.

Synthesis of Dioncophylline C and C_2, and of Dioncophyllidine C and Alanolgs

(*R*)-3-(*N*-*tert*-Butoxycarbonyl-2'-aminopropyl)-anisole (92):

All reactions were performed under an N_2 atmosphere.



A 250 mL flask was charged with Mg (1.72 g, 2.5 equiv., 70.8 mmol). 3-bromoanisole (**91**) (7.91 g, 5.31 mL, 1.5 equiv., 42.5 mmol) in 25 mL abs. THF was added dropwise. The reaction started immediately. The mixture was refluxed for 3 h, it was cooled to 0 °C before $CuBr{\cdot}SMe_2$ (1.16 g, 0.2 equiv., 5.66 mmol) was added. The solution was stirred for 30 min at this temperature, then aziridine **90** (4.44 g, 1.0 equiv., 28.3 mmol) dissolved in 10 mL abs. THF was added. The reaction mixture was stirred for 1 h at room temperature. Addition of an aqueous saturated solution of NH_4Cl at 0 °C quenched the reaction. The black solution was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtrated, and concentrated in vacuo. The brownish-green crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 5:1) to yield **92** (4.60 g, 17.4 mmol, 62%) as a colorless solid.

Yield: 4.60 g (17.4 mmol, 62%); Lit. 83%.[87]

M.p. 79 °C (CH_2Cl_2/*n*-hexane); Lit. 79 °C (CH_2Cl_2/*n*-hexane).[87]

$[\alpha]_D^{24}$ = -7(*c* = 0.09, MeOH). Lit. $[\alpha]_D^{25}$ = +10 (*c* = 0.09, $CHCl_3$).[87]

IR (ATR): $\tilde{\nu}$ = 3367 (w), 2974 (w), 1682 (s), 1589 (w), 1523 (s), 1458 (m) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (d, *J* = 7 Hz, 3H, CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 2.73 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.91 (s, 1H, NH), 6.72 (s, 1H, Ar-H), 6.74-6.77 (m, 2H, Ar-H), 7.20 (t, *J* = 8 Hz, 1H, Ar-H) ppm.

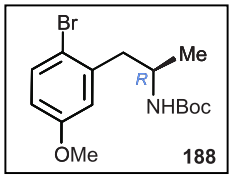
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 1.13, 20.3, 28.5, 43.1, 47.4, 55.2, 111, 115, 122, 129, 139, 155, 160 ppm.

MS (EI = 70 eV): *m/z* (%) = 265 (3) $[M]^+$, 209 (1), 149 (14), 144 (40), 122 (27), 121 (22), 88.1 (28), 57.1 (100), 44.1 (82).

HRMS (ESI, positive) calcd. for $C_{15}H_{23}NNaO_3$ $[M + Na]^+$ 288.15701; found 288.15779.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[87]

(*R*)-4-Bromo-3-(*N*-*tert*-butoxycarbonyl-2'-aminopropyl)-anisole (188):



To a cooled (0 °C) solution of anisole **92** (6.55 g, 1.0 equiv., 24.7 mmol) in 100 mL MeCN, *N*-bromosuccinimide (NBS) (4.41 g, 1.0 equiv., 24.7 mmol) was added. The mixture was stirred 48 h at room temperature. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 15:1) to yield **188** (7.82 g, 22.7 mmol, 92%) as a colorless solid.

Yield: 7.82 g (22.7 mmol, 92%). Lit. 91%.[87]

M.p. 114 °C (CH_2Cl_2/*n*-hexane). Lit. 114 °C (CH_2Cl_2)[87]

$[\alpha]_D^{24}$ = -37 (*c* = 0.11, MeOH). Lit. $[\alpha]_D^{25}$ = -36 (*c* = 0.10, MeOH).[87]

IR (ATR): $\tilde{\nu}$ = 3305 (w), 2969 (w), 1681 (s), 1589 (w), 1462 (m), 1346 (w) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (d, *J* = 7 Hz, 3H, CH_3), 1.58 (s, 9H, $C(CH_3)_3$), 2.85 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 4.01 (m, 1H, CH), 4.45 (s, 1H, NH), 6.65 (dd, *J* = 9 Hz, 3 Hz, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 7.40 (d, *J* = 9 Hz, 1H, Ar-H) ppm.

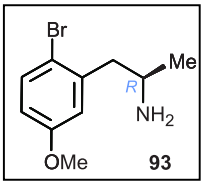
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.9, 28.5, 43.0, 47.1, 55.6, 77.4, 114, 116, 117, 133, 139, 155, 159 ppm.

MS (EI = 70 eV): *m/z* (%) = 264 (2), 227 (6), 201 (13), 144 (48), 88.0 (40), 57.1 (100), 44.1 (95).

HRMS (ESI, positive) calcd. for $C_{15}H_{22}BrNNaO_3$ $[M + Na]^+$ 366.06753; found 366.06784.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[87]

(*R*)-3-(2'-Aminopropyl)-4-bromoanisole (93):



To a cooled (0 °C) solution of **188** (3.50 g, 1.0 equiv., 10.2 mmol) in 70 mL CH_2Cl_2, trifluoroacetic acid (11.6 g, 7.78 mL, 10.0 equiv., 102 mmol) was added dropwise and the mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo. The brownish oil was dissolved in water. HCl (10%) was added until the solution turned acidic. It was washed with *n*-hexane. The aqueous phase was basified with a 1 N NaOH solution and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtrated, and concentrated in vacuo to yield **93** (2.46 g, 10.1 mmol, 99%) as a colorless oil.

Yield: 2.46 g (10.1 mmol, 99%). Lit 95%.[87]

$[\alpha]_D^{24}$ = -7 (*c* = 0.09, MeOH). Lit. $[\alpha]_D^{25}$ = +10 (*c* = 0.10, $CHCl_3$).[87]

IR (ATR): $\tilde{\nu}$ = 2958 (w), 2839 (w), 1578 (m), 1466 (s), 1242 (s), 1161 (m) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (d, *J* = 6 Hz, 3H, CH_3), 1.47 (s, 2H, NH_2), 2.71 (m, 2H, CH_2), 3.27 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 6.64 (dd, *J* = 8 Hz, 4 Hz, 1H, Ar-H), 6.77 (d, *J* = 4 Hz, 1H, Ar-H), 7.41 (d, *J* = 8 Hz, 1H, Ar-H) ppm.

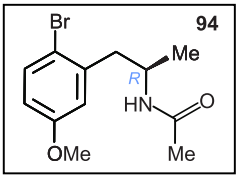
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.6, 46.8, 47.2, 55.4, 113, 115, 117, 134, 140, 159 ppm.

MS (EI = 70 eV): *m/z* (%) = 244 (17) $[M]^+$, 227 (43), 199 (100), 164 (11), 148 (40), 44.1 (46).

HRMS (ESI, positive) calcd. for $C_{10}H_{15}BrNO$ $[M + H]^+$ 244.03315; found 244.03328.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[87]

(*R*)-4-Bromo-3-(*N*-acetyl-2'-aminopropyl)-anisole (94):



To a cooled (0 °C) solution of **93** (2.28 g, 1.0 equiv., 9.34 mmol) in 50 mL CH_2Cl_2, triethylamine (1.13 g, 1.55 mL, 1.2 equiv., 11.2 mmol) and acetyl chloride (806 mg, 0.73 mL, 1.1 equiv., 10.3 mmol) were added. The mixture was stirred for 90 min at room temperature. Water

was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo to yield **94** (2.55 g, 8.92 mmol, 96%) as a colorless solid.

Yield: 2.55 g (8.92 mmol, 96%). Lit. 79%.[87]

M.p. 115 °C (CH_2Cl_2). Lit. 138 °C (CH_2Cl_2/MeOH).[87]

$[\alpha]_D^{24} = +19$ ($c = 0.10$, MeOH). Lit. $[\alpha]_D^{25} = +3$ ($c = 0.09$, $CHCl_3$).[87]

IR (ATR): $\tilde{\nu}$ = 3309 (m), 3074 (w), 2962 (w), 1632 (s), 1543 (s), 1450 (m), 1373 (m), 1304 (m), 1238 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.20 (d, J = 7 Hz, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.89 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 4.31 (m, 1H, CH), 5.48 (s, 1H, NH), 6.65 (dd, J = 9 Hz, 3 Hz, 1H, Ar-H), 6.80 (d, J = 3 Hz, 1H, Ar-H), 7.41 (d, J = 9 Hz, 1H, Ar-H) ppm.

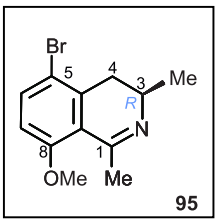
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.7, 23.5, 42.1, 46.6, 55.6, 114, 115, 117, 133, 139, 159, 170 ppm.

MS (EI = 70 eV): *m/z* (%) = 286 (1) $[M]^+$, 228 (25), 206 (37), 148 (5), 86.1 (55).

HRMS (ESI, positive) calcd. for $C_{12}H_{16}BrNNaO_2$ $[M + Na]^+$ 308.02566; found 308.02549.

The obtained spectroscopic data were in agreement with those reported in the literature.[87]

(*R*)-5-Bromo-8-methoxy-1,3-dimethyl-3,4-dihydroisoquinoline (95):



To a solution of **94** (1.15 g, 1.0 equiv., 4.02 mmol) in 120 mL MeCN, $POCl_3$ (3.84 g, 2.29 mL, 6.0 equiv., 25.1 mmol) was added dropwise. The reaction mixture was refluxed for 24 h with stirring, then it was cooled to 0 °C and water was added cautiously. By adding 1 N NaOH the solution was basified. After extraction with CH_2Cl_2 the organic phase was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/NEt_3, 99:1) to yield **95** (736 mg, 2.75 mmol, 69%) as a brown solid.

Yield: 736 mg (2.75 mmol, 69%). Lit. 68%.[87]

M.p. 75 °C (CH_2Cl_2). Lit. 75 °C (CH_2Cl_2).[87]

$[\alpha]_D^{24}$ = -69 (*c* = 0.10, MeOH). Lit. $[\alpha]_D^{25}$ = +80 (*c* = 0.80, $CHCl_3$).[87]

IR (ATR): $\tilde{\nu}$ = 2966 (w), 1608 (m), 1570 (m), 1458 (s), 1373 (w), 1277 (s), 1111 (m), 1061 (s), 798 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.41 (d, *J* = 8 Hz, 3H, CH_3), 2.22 (dd, *J* = 16 Hz, 13 Hz, 1H, CH_2), 2.44 (d, *J* = 1 Hz, 3H, CH_3), 2.91 (dd, *J* = 16 Hz, 4 Hz, 1H, CH_2), 3.30 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 6.76 (d, *J* = 9 Hz, 1H, Ar-H), 7.49 (d, *J* = 9 Hz, 1H, Ar-H) ppm.

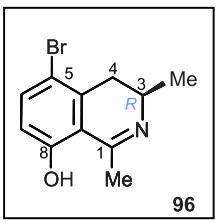
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 27.4, 34.3, 51.5, 55.8, 112, 114, 122, 135, 140, 157, 163 ppm.

MS (EI = 70 eV): *m/z* (%) = 267 (100), 252 (63), 239 (20), 237 (16), 188 (13), 173 (30), 132 (13), 115 (19), 77.1, (12).

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[87]

(*R*)-5-Bromo-8-hydroxy-1,3-dimethyl-3,4-dihydroisoquinoline (96):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of **95** (1.41 g, 1.0 equiv., 5.26 mmol) in 30 mL abs. CH_2Cl_2, a 1 M solution of BBr_3 in CH_2Cl_2 (13.1 mL, 2.5 equiv., 13.1 mmol) was added dropwise. The solution was stirred at room temperature over the weekend. To get rid of excess BBr_3 methanol was added carefully at 0 °C. The solvent was removed under reduced pressure. Column chromatography (SiO_2, CH_2Cl_2/MeOH, 12:1) to yielded **96** (1.02 g, 4.06 mmol, 76%) as a yellow solid.

Yield: 1.02 g (4.06 mmol, 76%). Lit. 58%.[87]

M.p. 209 °C (CH_2Cl_2/MeOH).

$[\alpha]_D^{24}$ = +16 (*c* = 0.08, MeOH).

IR (ATR): $\tilde{\nu}$ = 3250 (w), 2923 (m), 1585 (m), 1419 (m), 1284 (m), 710 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.54 (d, J = 7 Hz, 3H, CH_3), 2.73 (dd, J = 17 Hz, 10 Hz, 1H, CH_2), 3.00 (s, 3H, OCH_3), 3.13 (dd, J = 17 Hz, 5 Hz, 1H, CH_2), 3.94 (m, 1H, CH), 6.81 (d, J = 9 Hz, 1H, Ar-H), 7.43 (d, J = 9 Hz, 1H, Ar-H) ppm.

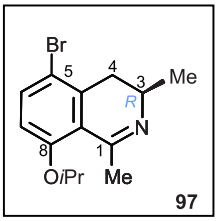
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.6, 24.4, 29.8, 34.8, 48.2, 109, 115, 122, 136, 141, 170, 175 ppm.

MS (EI = 70 eV): *m/z* (%) = 253 (100), 238 (26), 225 (23), 211 (5), 173 (8), 159 (21), 131 (17), 103 (11), 77.1 (13).

HRMS (ESI, positive) calcd. for $C_{11}H_{13}BrNO_2$ $[M + H]^+$ 254.01750; found 254.01673.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[87]

(*R*)-5-Bromo-8-isopropoxy-1,3-dimethyl-3,4-dihydroisoquinoline (97):



To a solution of **96** (200 mg, 1.0 equiv., 787 µmol) in 70 mL acetone, Cs_2CO_3 (641 mg, 2.5 equiv., 1.97 mmol) and isopropyl iodide (535 mg, 314 µL, 4.0 equiv., 3.15 mmol) was added. While stirring for 24 h, the suspension changed from yellow to colorless. It was filtered and concentrated under reduced pressure. Column chromatography (SiO_2, CH_2Cl_2/MeOH, 17:1) yielded **97** (190 mg, 642 µmol, 82%) as a brown oil.

$[\alpha]_D^{24}$ = -55 (c = 0.09, MeOH).

IR (ATR): $\tilde{\nu}$ = 2969 (w), 2927 (w), 2873 (w), 1612 (m), 1569 (w), 1454 (m), 1373 (m), 1273 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (dd, J = 10 Hz, 6 Hz, 6H, $CH(CH_3)_2$), 1.41 (d, J = 7 Hz, 3H, CH_3), 2.21 (dd, J = 16 Hz, 14 Hz, 1H, CH_2), 2.46 (s, 3H, CH_3), 2.91 (dd, J = 16 Hz, 4 Hz, 1H, CH_2), 3.30 (m, 1H, CH), 4.60 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.74 (d, J = 9 Hz, 1H, Ar-H), 7.45 (d, J = 9 Hz, 1H, Ar-H) ppm.

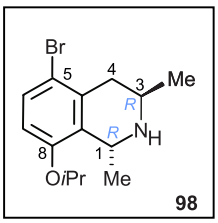
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0, 22.1, 22.2, 34.4, 51.5, 70.9, 113.6, 113.7, 122, 135, 140, 155, 164 ppm.

MS (EI = 70 eV): *m/z* (%) = 296 (14) $[M]^+$, 295 (80), 255 (62), 254 (100), 252 (96), 238 (29), 225 (23).

HRMS (ESI, positive) calcd. for $C_{14}H_{19}BrNO$ $[M + H]^+$ 296.06445; found 296.06437.

(1*R*,3*R*)-5-Bromo-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (98):

All reactions were performed under an N_2 atmosphere.



To a cooled (-78 °C) solution of **97** (632 mg, 1.0 equiv., 2.13 mmol) in 30 mL abs. THF, $LiAlH_4$ (284 mg, 3.5 equiv., 7.45 mmol) and a 2 M solution of $AlMe_3$ in *n*-hexane (3.72 mL, 3.5 equiv., 7.45 mmol) were added. The solution was stirred for 90 min at -78 °C, 1 h at -40 °C and 90 min at -20 °C before NaF (9.50 g, large excess) was added to quench the unreacted $AlMe_3$. At -20 °C water was added very carefully. The sluggish mixture was filtrated. The filtrate was extracted with CH_2Cl_2, the obtained solid from the filtration was dissolved in aq. HCl (10%) and also extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) to yield **98** as a diastereomeric mixture of 7/3 in favor of the desired *trans*-configured diastereomer (611 mg, 2.06 mmol, 97%). No full separation of the obtained diastereomeric mixture succeeded.

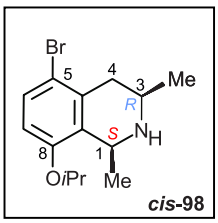
dr: 7/3, *trans*/*cis*.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, J = 6 Hz, 3H, CH_3), 1.33 (dd, J = 6 Hz, 3 Hz, 6H, $CH(CH_3)_2$), 1.45 (d, J = 7 Hz, 3H, CH_3), 2.30 (dd, J = 11 Hz, 17 Hz, 1H, CH_2) 2.87 (m, 1H + 1H, CH_2, CH) 4.42 (q, J = 7 Hz, 1H, CH), 4.53 (sept, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.58 (d, J = 8 Hz, 1H, Ar-H), 7.33 (d, J = 8 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.8, 22.0, 22.1, 22.2, 37.7 42.3, 47.7, 69.7, 111, 115, 130, 131, 134, 153 ppm.

(1*S*,3*R*)-5-Bromo-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (*cis*-98):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of **97** (400 mg, 1.0 equiv., 1.35 mmol) in 10 mL abs. MeOH, $NaBH_4$ (153 mg, 3.0 equiv., 4.05 mmol) was added and it was stirred for 2 h at 0 °C. The mixture was quenched by the addition of water, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo to yield *cis*-**98** (399 mg, 1.34 mmol, 99%) as a yellow oil.

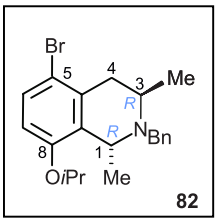
$[\alpha]_D^{24}$ = -108 (*c* = 0.09, MeOH).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (d, *J* = 6 Hz, 3H, CH_3), 1.35 (dd, *J* = 21 Hz, 6 Hz, 6H, $CH(CH_3)_2$), 1.46 (d, *J* = 6 Hz, 3H, CH_3), 2.26 (dd, *J* = 16 Hz, 11 Hz, 1H, CH_2) 2.85 (m, 1H + 1H, CH_2, CH) 4.28 (q, *J* = 6 Hz, 1H, CH), 4.52 (sept, *J* = 6 Hz, 1H, $CH(CH_3)_2$), 6.59 (d, *J* = 9 Hz, 1H, Ar-H), 7.33 (d, *J* = 9 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0, 22.3, 22.4, 22.6, 39.9, 48.3, 50.2, 69.9, 112, 116, 130, 132, 137, 154 ppm.

HRMS (ESI, positive) calcd. for $C_{14}H_{21}BrNO$ $[M + H]^+$ 298.08010; found 298.07982.

***N*-Benzyl-(1*R*,3*R*)-5-bromo-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (82):**



To a solution of a *trans*/*cis*-diastereomeric mixture of **98** (70:30, at this level not resolvable) (71.0 mg, 1.0 equiv., 238 µmol) in 10 mL of acetone, Cs_2CO_3 (194 mg, 2.5 equiv., 595 µmol) and benzyl bromide (102 mg, 70.7 µL, 2.5 equiv., 595 µmol) were added. Stirring was continued overnight at room temperature, then the suspension was filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 20:1, 1% NEt_3) to yield the diastereomerically pure **82** (51.0 mg, 131 µmol, 55%) as a colorless powder.

$[\alpha]_D^{24}$ = +28 (*c* = 0.09, MeOH).

IR (ATR): $\tilde{\nu}$ = 2997 (w), 1565 (m), 1455 (m), 1250 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (d, J = 6 Hz, 3H, $CH(CH_3)_2$), 1.25 (d, J = 6 Hz, 3H, $CH(CH_3)_2$), 1.29 (d, J = 7 Hz, 3H, CH_3), 1.32 (d, J = 7 Hz, 3H, CH_3), 2.43 (dd, J = 18 Hz, 12 Hz, 1H, CH_2) 2.65 43 (dd, J = 18 Hz, 4 Hz, 1H, CH_2), 3.17 (d, J = 14 Hz, 1H, CH_2), 3.51 (m, 1H, CH), 3.82 (d, J = 14 Hz, 1H, CH_2), 3.95 (q, J = 7 Hz, 1H, CH), 4.45 (sept, J = 10 Hz, 1H, $CH(CH_3)_2$), 6.61 (d, J = 9 Hz, 1H, Ar-H) 7.21-7.38 (m, 6H, Ar-H) ppm.

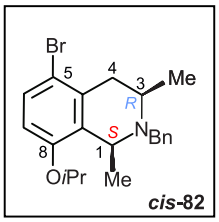
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.7, 20.0, 22.0, 22.1, 33.1, 45.8, 49.8, 51.9, 70.0, 112, 116, 127, 128, 129, 130, 131, 135, 141, 155 ppm.

MS (EI = 70 eV): *m/z* (%) = 372 (100), 330 (25), 293 (5), 240 (2), 159 (3).

HRMS (ESI, positive) calcd. for $C_{21}H_{27}BrNO$ $[M + H]^+$ 388.12705; found 388.12795.

_N_-Benzyl-(1*S*,3*R*)-5-bromo-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (*cis*-82):

To a solution of ***cis*-98** (399 mg, 1.0 equiv., 1.34 mmol) in 10 mL acetone, Cs_2CO_3 (1.09 g, 2.5 equiv., 3.34 mmol) and benzyl bromide (572 mg, 397 µL, 2.5 equiv., 3.34 mmol) were added. After stirring overnight at room temperature, the suspension was filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 20:1, 1% NEt_3) to yield *cis*-**82** (149 mg, 0.38 mmol, 29%) as a brown oil.



$[\alpha]_D^{24}$ = +44 (c = 0.10, MeOH).

IR (ATR): $\tilde{\nu}$ = 2998 (w), 2325 (w), 1443 (w), 1276 (m), 1260 (m), 750 (s) cm^{-1}.

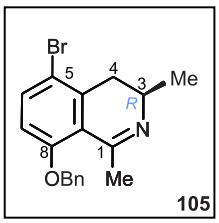
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (m, 6H, $CH(CH_3)_2$), 1.26 (d, J = 6 Hz, 3H, CH_3), 1.29 (d, J = 6 Hz, 3H, CH_3), 2.53 (dd, J = 16 Hz, 8 Hz, 1H, CH_2), 2.83 (m, 1H, CH), 2.97 (dd, J = 16 Hz, 5 Hz, 1H, CH_2), 3.69 (d, J = 14 Hz, 1H, CH_2), 3.86 (d, J = 14 Hz, 1H, CH_2), 4.19 (q, J = 7 Hz, 1H, CH), 4.45 (sept, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.60 (d, J = 9 Hz, 1H, Ar-H) 7.21-7.38 (m, 6H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 22.2, 22.3, 22.7, 29.8, 36.2, 52.5, 52.9, 59.0, 70.1, 111, 115, 127, 128, 129, 130, 132, 136, 141, 153 ppm.

MS (EI = 70 eV): *m/z* (%) = 372 (92), 330 (24), 293 (4), 282 (7), 240 (8), 159 (4), 91.1 (100).

HRMS (ESI, positive) calcd. for $C_{21}H_{27}BrNO$ $[M + H]^+$ 388.12705; found 388.12738.

(*R*)-5-Bromo-8-benzoxy-1,3-dimethyl-3,4-dihydroisoquinoline (105)



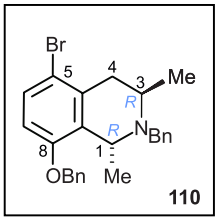
A solution of (*R*)-5-bromo-8-hydroxy-1,3-dimethyl-3,4-dihydro-isoquinoline (**96**) (5.12 g, 1.0 equiv., 20.2 mmol), 300 mL acetone, Cs_2CO_3 (16.4g, 2.5 equiv., 50.4 mmol), and benzyl bromide (8.62 mg, 5.98 mL, 2.5 equiv., 50.4 mmol) was stirred under reflux for 24 h. The solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1 + 1% Net_3) to yield **105** (1.37 g, 3.98 mmol, 20%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (d, J = 7 Hz, 3H, CH_3), 2.09 (dd, J = 16 Hz, 13 Hz, 1H, CH_2), 2.31 (d, J = 2 Hz, 3H, CH_3), 2.79 (dd, J = 16 Hz, 4 Hz, 1H, CH_2), 3.17 (m, 1H, CH), 4.96 (s, J = 6 Hz, 1H, OCH_2), 6.68 (d, J = 9 Hz, 1H, Ar-H), 7.21-7.29 (m, 5H, Ar-H), 7.34 (d, J = 9 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.2, 27.8, 34.5, 51.7, 71.2, 113, 115, 122, 127.2, 127.8, 128.5, 128.9, 135, 136, 140, 156, 163 ppm.

(1*R*,3*R*)-*N*-Benzyl-5-bromo-8-benzoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (110)

All reactions were performed under an N_2 atmosphere.



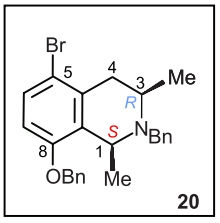
To a cooled (-78 °C) solution of **105** (200 mg, 1.0 equiv., 587 µmol) in 30 mL of abs. THF, $LiAlH_4$ (77.2 mg, 3.5 equiv., 2.03 mmol) and a 2 M solution of $AlMe_3$ in *n*-hexane (2.03 mL, 3.5 equiv., 2.03 mmol) were added. The stirred solution was allowed to reach room temperature over 2 h. At -20 °C an excess of NaF (5 g) was added to destroy the unreacted $AlMe_3$. Water was added very carefully at -20 °C. The resulting thick sludge was dissolved in diluted HCl (10%) and extracted with CH_2Cl_2. The organic phases were combined, dried over

$MgSO_4$, filtrated, and concentrated in vacuo. The resulting oil was dissolved in acetone and K_2CO_3 (203 mg, 2.5 equiv. 1.47 mmol) and 180 µL of benzyl bromide (251 mg, 2.5 equiv., 1.47 mmol) were added. This mixture was stirred for 48 h at room temperature. The solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1 + 1% Net_3) to yield **110** (156 mg, 3.57 mmol, 61%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (d, J = 7 Hz, 6H, CH_3), 2.58 (dd, J = 16 Hz, 8 Hz, 1H, CH_2), 2.88 (m, 1H, CH_2), 3.01 (dd, J = 16 Hz, 5 Hz, 1H, CH_2), 3.70 (d, J = 14 Hz, 1H, CH_2), 3.88 (d, J = 14 Hz, 1H, CH_2), 4.31 (q, J = 7 Hz, 1H, CH), 5.00 (s, 2H, CH_2), 6.61 (d, J = 9 Hz, 1H, Ar-H) 7.23-7.41 (m, 11H, Ar-H) ppm.

_N_-Benzyl-(1_S_,3_R_)-5-bromo-8-benzoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (20):

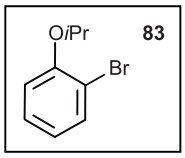
All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of (3*R*)-5-bromo-8-benzoxy-1,3-dimethyl-3,4-dihydro-isoquinoline (**105**) (200 mg, 1.0 equiv., 580 µmol) in 8 mL MeOH, $NaBH_4$ (43.9 mg, 2.0 equiv., 1.16 mmol) was added while stirring for 4 h. The mixture was quenched by the addition of water, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. Without further purification the resulting residue was dissolved in acetone and benzylbromide (198 mg, 2.0 equiv., 1.16 mmol) and Cs_2CO_3 (378 mg, 2.0 equiv., 1.16 mmol) were added. This mixture was stirred overnight at room temperature. The solvent was removed and the crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1 + 1% NEt_3) to yield **20** (190 mg, 435 µmol, 75%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (m, 6H, CH_3), 2.58 (dd, J = 16 Hz, 8 Hz, 1H, CH_2), 2.88 (m, 1H, CH_2), 3.01 (dd, J = 16 Hz, 5 Hz, 1H, CH_2), 3.68 (d, J = 14 Hz, 1H, CH_2), 3.88 (d, J = 14 Hz, 1H, CH_2), 4.31 (q, J = 7 Hz, 1H, CH), 5.00 (s, 2H, CH_2), 6.71 (d, J = 9 Hz, 1H, Ar-H) 7.23-7.41 (m, 11H, Ar-H) ppm.

2-Isopropoxybromobenzene (83):



To a solutio of 2-bromophenol (24.2 g, 16.3 mL, 1.0 equiv., 140 mmol) in 600 mL acetone, Cs_2CO_3 (114 g, 2.5 equiv., 0.35 mol) and isopropyl iodide (95.2 g, 56.0 mL, 4.0 equiv., 0.56 mol) were added. The mixture was stirred at room temperature for 5 h. It was filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, EtOAc/cyclohexane, 1:7) to yield **83** (28.5 g, 133 mmol, 95%) as a colorless oil.

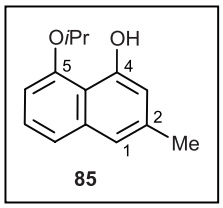
IR (ATR): $\tilde{\nu}$ = 3050 (w), 2996 (w), 1573 (s), 1474 (m), 1279 (s), 1256 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 4.55 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.80-6.84 (m, 1H, Ar-H), 6.92 (dd, J = 8 Hz, J = 2 Hz, 1H, Ar-H), 7.20-7.25 (m, 1H, Ar-H), 7.37 (m, 2H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.2, 72.3, 114, 116, 122, 128, 134, 155 ppm.

5-Isopropoxy-4-hydroxy-2-methylnaphthalene (85):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of *N*-cyclohexylisopropylamine (28.0 g, 32.6 mL, 3.5 equiv., 198 mmol) a 1.6 M solution of *n*-BuLi in *n*-hexane (135 mL, 3.8 equiv., 215 mmol) was added dropwise. The solution was stirred for 90 min at room temperature. The sluggish mixture was diluted with 60 mL abs. THF and cooled to -78 °C. A solution of **84** (8.80 g, 1.0 equiv., 56.7 mmol) in 30 mL abs. THF was added dropwise. After stirring at -78 °C for 2 h, **83** (28.0 g, 2.3 equiv., 130 mmol) was added. The solution was allowed to warm to room temperature over 48 h, upon which the solution turned black. At 0 °C the mixture was quenched by adding a saturated solution of aq. NH_4Cl and a 10% aq. HCl solution. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, the combined organic phases were washed with water, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 17:1) to yield **85** (2.98 g, 13.8 mmol, 24%) as a brown oil.

IR (ATR): $\tilde{\nu}$ = 3346 (w), 2976 (w), 1620 (m), 1600 (m), 1458 (s), 1372 (s), 1066 (s) cm[1].

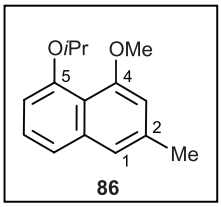
^{1}H NMR (400 MHz, acetone-d_6): δ = 1.52 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 2.41 (s, 3H, CH_3), 5.00 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$),6.66 (d, J = 2 Hz, 1H, Ar-H), 6.95 (dd, J = 7 Hz, J = 2 Hz, 1H, Ar-H), 7.12 (s, 1H, Ar-H), 7.30-7.37 (m, 2H, Ar-H) 9.63 (s, 1H, Ar-OH) ppm.

^{13}C NMR (acetone-d_6, 100 MHz): δ = 21.3, 21.8, 73.1, 107, 111.9, 112.1, 118, 121, 127, 137.9, 137.8, 154.7, 155.3, ppm.

MS (EI = 70 eV): *m/z* (%) = 216 (18) $[M]^+$, 192 (15), 174 (100), 150 (11), 128 (9), 91.1 (2), 65.1 (2), 43.1 (3).

HRMS (ESI, positive) calcd. for $C_{14}H_{16}NaO_2$ $[M + Na]^+$ 239.10425; found 239.10496.

5-Isopropoxy-4-methoxy-2-methylnaphthalene (86):



86

Compound **85** (2.98 g, 1.0 equiv., 13.8 mmol), sodium hydroxide (13.8 g, 25.0 equiv., 0.34 mmol), benzyltributylammonium chloride (2.58 g, 0.6 equiv., 8.27 mmol) were dissolved in 50 mL CH_2Cl_2. The solution was cooled to 0 °C and 10 mL H_2O were added. While stirring at this temperature, Me_2SO_4 (12.2 g, 9.15 mL, 7.0 equiv., 96.5 mmol) was added dropwise. The solution was stirred 48 h at room temperature. After separation, the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:1) to yield **86** (1.89 g, 8.22 mmol, 60%) as a brown solid.

M.p. 48 °C (CH_2Cl_2/*n*-hexane).

IR (ATR): $\tilde{\nu}$ = 3050 (w), 2973 (w), 1573 (s), 1454 (m), 1373 (s), 1277 (s) cm^{-1}.

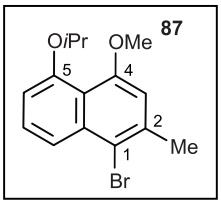
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.46 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 2.50 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.57 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.71 (s, 1H, Ar-H), 6.92 (dd, J = 7 Hz, J = 2 Hz, 1H, Ar-H), 7.23 (m, 1H, Ar-H), 7.37 (m, 2H, Ar-H) ppm.

^{13}C NMR (CD_3OD, 100 MHz): δ = 22.6, 23.2, 57.6, 75.4, 111, 115, 120, 122, 123, 128, 138, 140, 156, 159 ppm.

MS (EI = 70 eV): *m/z* (%) = 230 (39) $[M]^+$, 188 (100), 173 (31), 145 (34), 115 (18), 91 (3), 63 (3), 43 (5).

HRMS (ESI, positive) calcd. for $C_{15}H_{18}NaO_2$ $[M + Na]^+$ 253.11990; found 253.12009.

1-Bromo-5-isopropoxy-4-methoxy-2-methylnaphthalene (87):



To a solution of **86** (1.87 g, 1.0 equiv., 8.12 mmol) in 40 mL MeCN, NBS (1.45 g, 1.0 equiv., 8.12 mmol) was added. Complete conversion was obtained after 15 min of stirring at room temperature. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:2) to yield **87** (2.42 g, 7.80 mmol, 96%) as a colorless solid.

M.p. 64 °C (CH_2Cl_2/*n*-hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (d, *J* = 6 Hz, 6H, $CH(CH_3)_2$), 2.58 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.52 (sep, *J* = 6 Hz, 1H, $CH(CH_3)_2$), 6.72 (s, 1H, Ar-H), 6.94 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H, Ar-H), 7.43 (m, 1H, Ar-H), 7.94 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H, Ar-H) ppm.

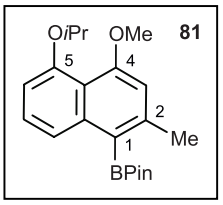
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.2, 24.7, 56.6, 73.4, 110, 113, 116, 121, 128, 130, 136, 137, 155, 156 ppm.

MS (EI = 70 eV): *m/z* (%) = 308 (35) $[M]^+$, 267 (96), 266 (100). 251 (42), 223 (24), 187 (9), 144 (10), 128 (29), 115 (25).

HRMS (ESI, positive) calcd. for $C_{15}H_{17}BrNaO_2$ $[M + Na]^+$ 331.03041; found 331.02962.

5-Isopropoxy-4-methoxy-2-methylnaphthyl-1-boronic acid pinacol ester (81):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of **87** (640 mg, 1.0 equiv., 2.07 mmol), $Pd(PPh_3)_4$ (76.3 mg, 0.1 equiv., 207 µmol), KOAc (1.22 g, 6.0 equiv., 12.4 mmol) and $(BPin)_2$ (1.31 g, 2.5 equiv., 5.17 mmol) in 20 mL abs. DMF was stirred at 150 °C for 1 h 30 min. It was passed through a short pad of Celite, concentrated in vacuo, and purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 8:1) to yield **81** (500 mg, 1.41 mmol, 68%) as a colorless powder.

M.p. 116 °C (CH_2Cl_2/*n*-hexane).

IR (ATR): $\tilde{\nu}$ = 2973 (w), 1593 (s), 1297 (s), 1100 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (m, 18H, $(OC(CH_3)_2)_2$ + $CH(CH_3)_2$), 2.48 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 4.62 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.68 (s, 1H, Ar-H), 6.84 (d, J = 8 Hz, 1H, Ar-H), 7.93 (d, J = 8 Hz, 1H, Ar-H), 8.15 (m, 1H, Ar-H) ppm.

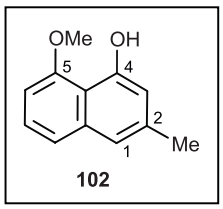
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.9, 22.3, 24.7, 25.2, 56.4, 73.3, 77.4, 83.3, 83.6, 109, 113, 120, 121, 126 ppm.

MS (EI = 70 eV): *m/z* (%) = 356 (35) $[M]^+$, 314 (100), 241 (22), 214 (22), 171 (9), 83.1 (4).

HRMS (ESI, positive) calcd. for $C_{21}H_{29}BNaO_4$ $[M + Na]^+$ 379.20511; found 379.20473.

5-Methoxy-4-hydroxy-2-methylnaphthalene (102):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of *N*-cyclohexylisopropylamine (42.2 g, 49.0 mL, 3.5 equiv., 299 mmol) a solution of *n*-butyllithium in *n*-hexane (200 mL, c = 1.6 M, 3.8 equiv., 321 mmol) was added dropwise. The solution was stirred for 90 min at room temperature. The resulting sludge was dissolved in 150 mL abs. THF. At -78 °C a solution of **84** (13.0 g, 1.0 equiv., 83.7 mmol) in 30 mL abs. THF was added dropwise. After stirring at -78 °C

for 2 h 2-bromoanisole (36.0 g, 2.3 equiv., 193 mmol) was added. The solution was warmed to room temperature over 48 h. At 0 °C the mixture was quenched by adding an aqueous saturated solution of NH_4Cl followed by the addition of an aq. 10% HCl solution. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with water, dried over $MgSO_4$, filtrated, and concentrated in vacuo. After column chromatography (SiO_2, *n*-hexane/Et_2O, 17:1), all product containing fractions were combined, concentrated, and recrystallized from a mixture of CH_2Cl_2 and *n*-hexane to yield **102** (3.23 g, 17.1 mmol, 20%) as colorless crystals.

Yield: 3.23 g (17.1 mmol, 20%). Lit. 35%.[100]

M.p. 61 °C (CH_2Cl_2/*n*-hexane). Lit. 89 °C (petroleum ether/ethyl acetate).[100]

IR (ATR): $\tilde{\nu}$ = 3359 (w), 2931 (w), 1581 (m), 1438 (m), 1369 (s), 1273 (s) cm^{-1}.

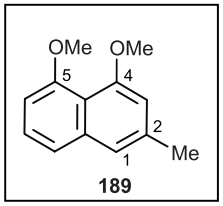
^1H NMR ($CDCl_3$, 400 MHz): δ = 2.42 (s, 3H, CH_3), 4.04 (s, 3H, OCH_3), 6.70 (dd, J = 8 Hz, 1 Hz, 1H, Ar-H), 6.72 (d, J = 1 Hz, 1H, Ar-H), 7.09 (s, 1H, Ar-H), 7.26 (m, 1H, Ar-H), 7.32 (dd, J = 8 Hz, 1H, Ar-H), 9.23 (s, 1H, Ar-OH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.8, 56.1, 103, 112, 113, 118, 121, 126, 137, 138, 154, 156 ppm.

MS (EI = 70 eV): *m/z* (%) = 188 (100) $[M]^+$, 173 (33), 145 (51), 127 (9), 115 (14), 94.0 (5).

The obtained physical and spectroscopic data are in agreement with those reported in the literature.[100]

4,5-Dimethoxy-2-methylnaphthalene (189):



189

To a solution of **102** (1.00 g, 1.0 equiv., 5.31 mmol), NaOH (5.31 g, 25 equiv., 133 mmol), tributylbenzylammonium chloride (994 mg, 0.6 equiv., 3.19 mmol) in 30 mL CH_2Cl_2, 5 mL H_2O and Me_2SO_4 (4.69 g, 3.53 mL, 7.0 equiv., 37.2 mmol) were added at 0 °C. The solution turned yellow. It was stirred at room temperature over the weekend. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined

organic phases were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 1:1) yielded **189** (916 mg, 4.53 mmol, 91%) as a colorless solid.

Yield: 916 mg (4.53 mmol, 91%). Lit. 81%.[100]

IR (ATR): $\tilde{\nu}$ = 2850 (w), 2195 (m), 1256 (m), 1200 (m), 1097 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.47 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.69 (d, J = 2 Hz, 1H, Ar-H), 6.78 (dd, J = 7 Hz, 2 Hz, 1H, Ar-H), 7.19 (s, 1H, Ar-H), 7.94-7.35 (m, 2H, Ar-H) ppm.

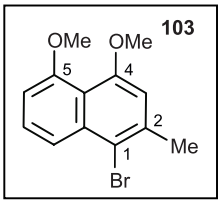
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.9, 56.4, 56.5, 105, 108, 116, 120.1, 120.4, 127, 136, 137, 156.9, 157.1 ppm.

MS (EI = 70 eV): *m/z* (%) = 202 (100) $[M]^+$, 187 (3), 159 (8), 129 (33), 115 (12).

HRMS (ESI, positive) calcd. for $C_{13}H_{14}NaO_2$ $[M + Na]^+$ 225.08860; found 225.08888.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[100]

1-Bromo-4,5-methoxy-2-methylnaphthalene (103):



To a solution of **189** (916 mg, 1.0 equiv., 4.53 mol) in 40 mL MeCN, NBS (806 mg, 1.0 equiv., 4.53 mmol) was added at room temperature. After stirring for 5 min, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:1) to yield **103** (1.27 g, 4.53 mmol, 100%) as a colorless solid.

Yield: 1.27 g (4.53 mmol, 100%). Lit. 87%.[100]

M.p. 103 °C (CH_2Cl_2/*n*-hexane). Lit. 56 °C (petroleum ether/ethyl acetate).[100]

IR (ATR): $\tilde{\nu}$ = 2946 (w), 2838 (w), 1457 (m), 1349 (s), 1218 (s), 1110 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.58 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.88 (d, J = 8 Hz, 1H, Ar-H), 7.47 (dd, J = 8 Hz, 8 Hz, 1H, Ar-H), 7.92 (dd, J = 9 Hz, 1 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.8, 56.7, 106, 109, 115, 120, 128, 136, 137, 156, 157 ppm.

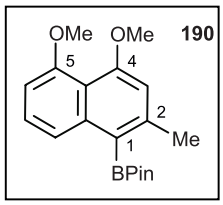
MS (EI = 70 eV): *m/z* (%) = 280 (100) $[M]^+$, 237 (4), 209 (16), 186 (28), 158 (31), 128 (31).

HRMS (ESI, positive) calcd. for $C_{13}H_{13}BrNaO_2$ $[M + Na]^+$ 302.99911; found 302.99887.

The obtained spectroscopic data were in agreement with those reported in the literature.[100]

4,5-Dimethoxy-2-methylnaphthyl-1-boronic acid pinacol ester (190):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of **103** (795 mg, 1.0 equiv., 2.83 mmol), $Pd(PPh_3)_4$ (327 mg, 0.1 equiv., 283 µmol), KOAc (1.67 g, 6.0 equiv., 17.0 mmol) and $(BPin)_2$ (1.08 g, 1.5 equiv., 4.24 mmol) in 25 mL abs. DMF was stirred at 150 °C for 1 h 15 min. The solvent was removed and the resulting residue was dissolved in Et_2O and passed through a short pad of Celite. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1) to yield **190** (663 mg, 2.00 mmol, 71%) as a colorless solid. As a side product, 4,5-dimethoxy-2-methylnaphthalene (**189**) was isolated and recycled.

M.p. 97 °C (*n*-hexane/Et_2O).

IR (ATR): $\tilde{\nu}$ = 2973 (w), 1581 (s), 1461 (m), 1376 (m), 1307 (s), 1257 (s), 1130 (s) cm^{1}.

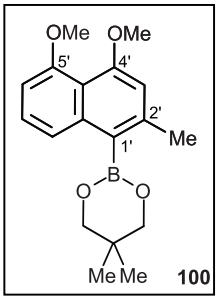
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.46 (s, 12H, $B(OC(CH_3)_2)_2$) 2.57 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.78 (d, J = 8 Hz, 1H, Ar-H), 7.32 (dd, J = 8 Hz, 8 Hz, 1H, Ar-H), 7.67 (dd, J = 8 Hz, 1 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0, 24.7, 25.2, 56.2, 56.5, 83.9, 105, 109, 116, 120, 127, 141, 143, 157, 158 ppm.

MS (EI = 70 eV): *m/z* (%) = 328 (100) $[M]^+$, 255 (15), 228 (19), 155 (9), 141 (6), 83.2 (2).

4,5-Dimethoxy-2-methylnaphthyl-1-boronic acid neopentyl ester (100):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.

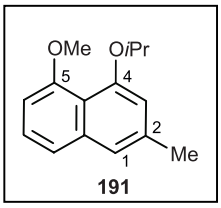


A mixture of 1-bromo-4,5-dimethoxy-2-methylnaphthalene (**103**) (100 mg, 1.0 equiv., 35.4 µmol), $Pd(PPh_3)_4$ (40.9 mg, 0.1 equiv., 35.5 µmol), KOAc (200 mg, 6.0 equiv., 2.05 mmol) and $(BNeop)_2$ (200 mg, 2.5 equiv., 88.5 µmol) in 6 mL abs. DMF was stirred overnight at 110 °C. After concentration under reduced pressure, the crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1) to yield **100** (67.2 mg, 21.4 µmol, 60%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 6H, CH_3) 2.54 (s, 3H, CH_3), 3.88 (s, 4H, CH_2), 3.94 (m, 6H, OCH_3), 6.66 (s, 1H, Ar-H), 6.76 (d, J = 7 Hz, 1H, Ar-H), 7.30-7.33 (m, 1H, Ar-H) 7.54 (d, J = 8.4 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.6, 22.5, 56.3, 56.5, 72.4, 72.6, 73.1, 73.3, 76.8, 104, 109, 116, 120, 126, 141 ppm.

4-Isopropoxy-5-methoxy-2-methylnaphthalene (191):



A solution of **102** (500 mg, 1.0 equiv., 2.66 mmol), isopropyl iodide (1.06 mL, 1.81 g, 4.0 equiv., 10.6 mmol), and Cs_2CO_3 (2.16 g, 2.5 equiv., 6.64 mmol) in 10 mL acetone was stirred for 48 h at room temperature. The suspension was filtered over a Celite pad, eluted with CH_2Cl_2, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 1:1) to yield **191** (445 mg, 1.94 mmol, 73%) as a colorless solid.

M.p. 51 °C (*n*-hexane/CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 2973 (w), 1577 (m), 1442 (w), 1369 (s), 1272 (s), 1088 (s) cm^{-1}.

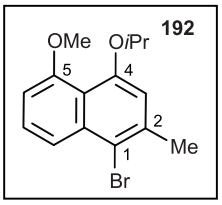
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 2.44 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.53 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.74 (m, 1H, Ar-H), 6.77 (d, J = 2 Hz, 1H, Ar-H), 7.21 (m, 1H, Ar-H), 7.29 (d, J = 1 Hz, 1H, Ar-H) 7.29 (s, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.8, 22.3, 56.4, 73.3, 106, 116, 118, 120.5, 121, 126, 136, 138, 155, 157 ppm.

MS (EI = 70 eV): *m/z* (%) = 230 (40) $[M]^+$, 188 (100), 173 (32), 145 (34), 115 (15), 91.1 (3), 77.1 (2), 41.1 (4).

HRMS (ESI, positive) calcd. for $C_{15}H_{18}NaO_2$ $[M + Na]^+$ 253.11990; found 253.11915.

1-Bromo-5-methoxy-4-isoporpoxy-2-methylnaphthalene (192):



To a solution of **191** (425 mg, 1.0 equiv., 1.85 mmol) in 10 mL MeCN, NBS (329 mg, 1.0 equiv., 1.85 mmol) was added. The mixture was stirred at room temperature for 15 min. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:1) to yield **192** (491 mg, 1.59 mmol, 86%) as a yellow solid.

M.p. 69 °C (CH_2Cl_2/*n*-hexane).

IR (ATR): $\tilde{\nu}$ = 2969 (w), 1585 (m), 1454 (m), 1354 (s), 1257 (s), 1215 (m), 1103 (s) cm^{1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 2.56 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.53 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.84 (m, 1H, Ar-H), 7.43 (dd, J = 8 Hz, 1 Hz, 1H, Ar-H) 7.29 (s, 1H, Ar-H) ppm.

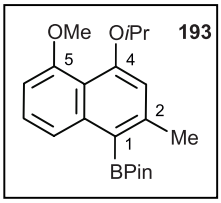
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.2, 24.6, 56.5, 73.5, 106, 116.1, 116.4, 119, 120, 128, 136, 137, 154, 157 ppm.

MS (EI = 70 eV): *m/z* (%) = 310 (36) $[M]^+$, 266 (100), 251 (31), 223 (21), 187 (9), 128 (27).

HRMS (ESI, positive) calcd. for $C_{15}H_{17}BrNaO_2$ $[M + Na]^+$ 331.03041; found 331.03019.

4-Isopropoxy-5-methoxy-2-methylnaphthyl-1-boronic acid pinacol ester (193):

All reactions were performed under an N_2 atmosphere. The solvent had been degassed, prior to use.



A solution of **192** (200 mg, 1.0 equiv., 647 µmol), $Pd(PPh_3)_4$ (74.8 mg, 0.1 equiv., 64.7 µmol), KOAc (381 mg, 6.0 equiv., 3.88 mmol) and $(BPin)_2$ (246 mg, 1.5 equiv., 970 µmol) in 15 mL abs. DMF was stirred at 150 °C overnight. The solvent was removed, the residue was dissolved in Et_2O and passed through a short pad of Celite. The crude product was purified by column chromatography (SiO_2, n-hexane/Et_2O, 4:1) to yield **193** (185 mg, 520 µmol, 80%) as a colorless solid.

M.p. 74 °C (*n*-hexane/Et_2O).

IR (ATR): $\tilde{\nu}$ = 2978 (w), 1581 (m), 1457 (w), 1303 (s), 1257 (m), 1203 (w), 1115 (s) cm^1.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (s, 12H, $B(OC(CH_3)_2)_2$), 1.39 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 2.43 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.52 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.74 (m, 1H, Ar-H), 7.20 (m, 1H, Ar-H) 7.28 (d, J = 1Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H) ppm.

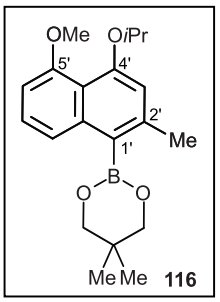
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.8, 22.3, 24.7, 56.4, 73.3, 83.4, 106, 116, 118, 120.5, 121.1, 126, 136, 138 ppm.

MS (EI = 70 eV): *m/z* (%) = 356 (42) $[M]^+$, 314 (100), 241 (13), 214 (22), 127 (4).

HRMS (ESI, positive) calcd. for $C_{21}H_{29}BNaO_4$ $[M + Na]^+$ 379.20511; found 379.20554.

4-Isopropoxy-5-methoxy-2-methylnaphthyl-1-boronic acid neopentylglycol ester (116):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



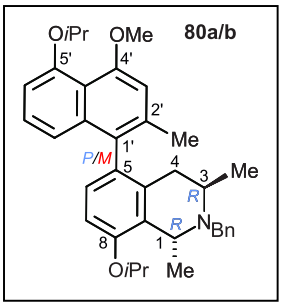
A solution of **192** (515 mg, 1.0 equiv., 1.67 mmol), $Pd(PPh_3)_4$ (192 mg, 0.1 equiv., 167 µmol), KOAc (1.67 g, 6.0 equiv., 17.0 mmol) and $(BNeop)_2$ (564 mg, 1.5 equiv., 2.50 mmol) in 10 mL abs. DMF was stirred at 110 °C for 24 h. The solvent was removed, the resulting residue was dissolved in Et_2O and passed through a short pad of Celite. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1) to yield **116** (383 mg, 1.15 mmol, 69%) as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.46 (s, 12H, $B(OC(CH_3)_2)_2$) 2.57 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.78 (d, J = 8 Hz, 1H, Ar-H), 7.32 (dd, J = 8 Hz, 8 Hz, 1H, Ar-H), 7.67 (dd, J = 8 Hz, 1 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0, 24.7, 25.2, 56.2, 56.5, 83.9, 105, 109, 116, 120, 127, 141, 143, 157, 158 ppm.

_N_-Benzyl-(1_R_,3_R_)-5-(5'-isopropoxy-4'-methoxy-2'-methylnaphthyl)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (80a/b):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of naphthalene **81** (36.8 mg, 1.0 equiv., 175 µmol), isoquinoline **82** (40.0 mg, 1.0 equiv., 103 µmol), K_3PO_4 (87.5 mg, 4.0 equiv., 412 µmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 16.9 mg, 0.4 equiv., 41.2 µmol), and $Pd_2(dba)_3$ (9.43 mg, 0.1 equiv., 10.3 µmol) in 3 mL of abs. toluene was stirred for 48 h at 100 °C. Then the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with water. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 6:1) to yield **80a/b** (31.1 mg, 57.7 µmol, 56%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96-1.37 (m, 20H, 6 x CH_3 + CH_2), 2.05 (s, 3H, CH_3), 3.17 (d, J = 14 Hz, 1H, CH), 3.33 (m, 1H, CH), 3.64 (m, 1H, CH), 3.91 (s, 3H, OCH_3), 4.00 (m, 1H, CH), 4.50 (m, 2H, 2 x $CH(CH_3)_2$), 6.79-7.30 (m, 11H, 11 x Ar-H) ppm.

MS (EI = 70 eV): *m/z* (%) = 528 (12), 429 (51), 356 (39), 314 (100), 214 (22).

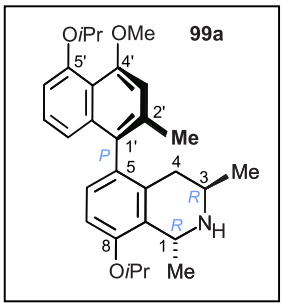
HRMS (ESI, positive) calcd. for $C_{36}H_{44}NO_3$ $[M + H]^+$ 538.33157; found 538.33085.

(1_R_,3_R_)-5-(5'-Isopropoxy-4'-methoxy-2'-methylnaphthyl)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (99a/b):

80a/b (40.0 mg, 1.0 equiv., 74.5 µmol) and Pd/C (79.1 mg, 1.0 equiv., 10% Pd, 7.45 µmol) were stirred in MeOH under an H_2 atmosphere for 2 h. The suspension was filtrated over Celite. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 16:1) to yield **99a/b** (27.8 mg, 62.1 µmol, 83%) as a yellow oil. The atropo-diastereomers were separated by preparative HPLC on an XSelect HSS PFP HPLC column using an isocratic system consisting of the solvents A (H_2O + 0.05% TF) and B (MeOH + 0.05%

TFA) at 5 mL min^{-1}: 0 min: 60% of B, 19 min: 90% of B, 21 min: 100% of B, 24 min: 100% of B, 25 min: 60% of B, 28 min: 60% of B.

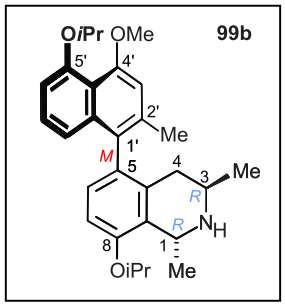
^{1}H NMR (MeOD, 400 MHz): δ = 1.26 (d, J = 6.4 Hz, 3H, CH_3), 1.41 (d, J = 2.3 Hz, 3H, CH_3), 1.42 (d, J = 2.4 Hz, 3H, CH_3), 1.45 (d, J = 5.9 Hz, 3H, CH_3), 1.48 (d, J = 6.0 Hz, 3H, CH_3), 1.72 (d, J = 6.8 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3) 2.21 (dd, J = 17.9 Hz, 11.8 Hz, 1H, CH_2), 2.55 (dd, J = 18.0 Hz, 4.9 Hz, 1H, CH_2), 3.78 (m, 1H, CH), 4.00 (s, 3H, OCH_3), 4.60 (sep, J = 6.1, 1H, CH), 4.85 (sep, J = 5.96 Hz, 1H, CH), 4.88 (q, 1H, CH), 6.73 (dd, J = 8.4 Hz, 1.0 Hz, 1H, Ar-H), 6.93 (s, 1H, Ar-H) 6.94 (dd, J = 9.0 Hz, 0.8 Hz, 1H, Ar-H), 7.11 (m, 2H, Ar-H), 7.20 (dd, J = 8.4 Hz, 7.7 Hz, 1H, Ar-H) ppm.



^{13}C NMR (MeOD, 100 MHz): δ = 17.0, 17.8, 19.4, 20.9, 20.9, 21.0, 31.4, 43.5, 55.3, 70.0, 73.0, 108.9, 110.6, 112.1, 118.6, 122.3, 126.1, 130.9, 131.4, 134.1, 136.6, 154.9 ppm.

HRMS (ESI, positive) calcd. for $C_{30}H_{40}NO_3$ $[M + H]^+$ 462.3003; found 462.3013.

^{1}H NMR (MeOD, 400 MHz): δ = 1.28 (d, J = 6.4 Hz, 3H, CH_3), 1.41 (m, 12H, CH_3), 1.72 (d, J = 6.5 Hz, 3H, CH_3), 2.12 (s, 3H, CH_3) 2.31 (dd, J = 18.6 Hz, 10.9 Hz, 1H, CH_2), 2.42 (dd, J = 18.4 Hz, 5.3 Hz, 1H, CH_2), 3.71 (m, 1H, CH), 4.00 (s, 3H, OCH_3), 4.60 (sep, J = 5.9 Hz, 1H, CH), 4.85 (sep, J = 6.2, 1H, CH), 4.89 (q, J = 7.1 Hz, 1H, CH), 6.82 (dd, J = 8.3 Hz, 1.2 Hz, 1H, Ar-H), 6.91 (s, 1H, Ar-H) 6.95 (dd, J = 7.7 Hz, 0.9 Hz, 1H, Ar-H), 7.10 (m, 2H, Ar-H), 7.23 (dd, J = 8.3 Hz, 7.7 Hz, 1H, Ar-H) ppm.



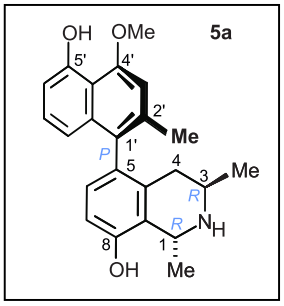
^{13}C NMR (MeOD, 100 MHz): δ = 17.0, 19.2, 20.9, 20.9, 21.0, 31.7, 43.5, 55.4, 70.0, 73.0, 108.8, 118.6, 127.9, 130.9 ppm.

HRMS (ESI, positive) calcd. for $C_{30}H_{40}NO_3$ $[M + H]^+$ 462.3003; found 462.3012.

MS (**93a/b**) (EI = 70 eV): *m/z* (%) = 447 (22) $[M]^+$, 432 (100), 390 (16), 174 (9).

Dioncophylline C (5a):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of **99a** (4.50 mg, 1.0 equiv., 10.1 µmol) in 2 mL abs. CH_2Cl_2 a 1 M solution of BCl_3 in CH_2Cl_2 (5.89 mg, 50.3 µL, 5.0 equiv., 50.3 µmol) was added. This mixture was stirred at 0 °C for 2 h. Cautious addition of water stopped the reaction. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica (SiO_2, CH_2Cl_2/MeOH, 10:1) to yield **5a** (2.90 mg, 7.79 µmol, 77%) as a beige oil.

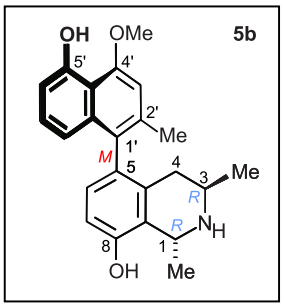
^{1}H NMR (MeOD, 400 MHz): δ = 1.28 (d, J = 6.4 Hz, 3H, CH_3), 1.76 (d, J = 6.4 Hz, 3H, CH_3), 2.13 (s, 3H, CH_3) 2.28 (dd, J = 17.7 Hz, 11.4 Hz, 1H, CH_2), 2.51 (dd, J = 17.8 Hz, 5.2 Hz, 1H, CH_2), 3.72 (m, 1H, CH), 4.15 (s, 3H, OCH_3), 4.89 (q, J = 6.5 Hz, 1H, CH), 6.65 (dd, J = 8.5 Hz, 1.0 Hz, 1H, Ar-H), 6.75 (dd, J = 7.7 Hz, 1.0 Hz, 1H, Ar-H), 6.93 (m, 2H, Ar-H), 7.20 (dd, J = 8.4 Hz, 7.7 Hz, 1H, Ar-H) ppm.

MS (EI = 70 eV): *m/z* (%) = 363 (5) $[M]^+$, 348 (25), 332 (8), 239 (2), 149 (8), 83 (10), 71.1 (13), 57.1 (20), 44.0 (47).

HRMS (ESI, positive) calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.19072; found 364.19073.

5-*epi*-Dioncophylline C (5b):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of **99b** (4.50 mg, 1.0 equiv., 10.1 µmol) in 2 mL abs. CH_2Cl_2 a 1 M solution of BCl_3 in CH_2Cl_2 (5.89 mg, 50.3 µL, 5.0 equiv., 50.3 µmol) was added and the mixture was stirred at 0 °C for 2 h. Water was added and the solvent was removed in vacuo. The crude product was purified by column chromatography on deactivated silica (SiO_2, CH_2Cl_2/MeOH, 10:1) to yield **5b** (2.70 mg, 7.39 µmol, 74%) as a beige oil.

^{1}H NMR (MeOD, 400 MHz): δ = 1.26 (d, J = 6.4 Hz, 3H, CH_3), 1.75 (d, J = 6.8 Hz, 3H, CH_3), 2.16 (s, 3H, CH_3) 2.21 (dd, J = 18.0 Hz, 11.9 Hz, 1H, CH_2), 2.51 (dd, J = 18.0

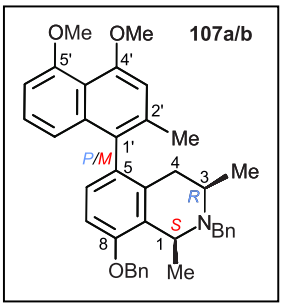
Hz, 4.8 Hz, 1H, CH_2), 3.78 (m, 1H, CH), 4.15 (s, 3H, OCH_3), 4.89 (q, J = 6.8 Hz, 1H, CH), 6.58 (dd, J = 8.4 Hz, 1.0 Hz, 1H, Ar-H), 6.75 (dd, J = 7.7 Hz, 1.0 Hz, 1H, Ar-H), 6.95 (m, 2H, Ar-H), 7.16 (dd, J = 8.4 Hz, 7.7 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 18.9, 20.1, 21.7, 33.6, 57.6, 108.7, 111.4, 115.4, 118.2, 129.6, 132.7, 132.9, 138.2, 155.4 ppm.

MS (EI = 70 eV): *m/z* (%) = 363 (5) $[M]^+$, 348 (25), 332 (8), 239 (2), 149 (8), 83 (10), 71.1 (13), 57.1 (20), 44.0 (47).

HRMS (ESI, positive) calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.19072; found 364.19073.

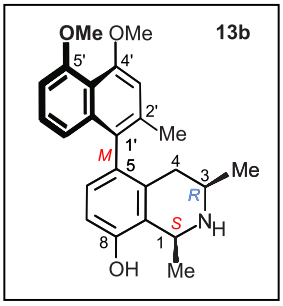
_N_-Benzyl-(1*S*,3*R*)-5-(4',5'-dimethoxy-2'-methylnaphthyl)-8-benzoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (107a/b):



A mixture of the naphthalene precursor **100** (46.8 mg, 1.0 equiv., 149 µmol), the isoquinoline building block **20** (65.0 mg, 1.0 equiv., 149 µmol), K_3PO_4 (126 mg, 4.0 equiv., 596 µmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 24.5 mg, 0.4 equiv., 91.5 µmol), and tris(dibenzylideneacetone)di-palladium(0) ($Pd_2(dba)_3$, 13.6 mg, 0.1 equiv., 14.9 µmol) in 5 mL of dry toluene was stirred for 48 h at 100 °C. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 6:1) to yield a mixture of the protected diastereomeric biaryls **107a/b** (63.5 mg, 187 µmol, 76%) as an orange-colored oil.

HRMS (ESI, positive) calcd. for $C_{38}H_{40}NO_3$ $[M]^+$ 558.3003; found 558.2983.

Dioncophylline C$_2$ and 5-*epi*-dioncophylline C$_2$ (13a/b):



A mixture of **107a/b** (10.0 mg, 1.0 equiv., 17.9 µmol) and Pd/C (10 mg, 10% Pd) was stirred in 6 mL of degassed isopropanol for 4 h under a hydrogen atmosphere. After filtration of the suspension over Celite, the solvent was removed in vacuo to yield **13a/b** (6.60 mg, 17.9 µmol, quant.) as a yellow oil. The atropo-diastereomers

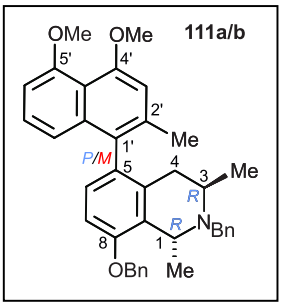
13a and **13b** were resolved on an XSelect HSS PFP HPLC column using an isocratic system consisting of the solvents A (H_2O + 0.5% TFA) and B (MeOH +0.5%TFA) at 5 mL min^{-1} (0 min: 60% of B, 30 min: 60% of B) to yield **13b** as the distinct main product. Fractions containing **13a** still had **13b** as their main component and, thus, no spectral data for **13a** were obtained.

^{1}H NMR (MeOD, 400 MHz): δ = 1.26 (d, J = 6.6 Hz, 3H, CH_3), 1.86 (d, J = 6.7 Hz, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.26-2.34 (m, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.78 (q, J = 6.1 Hz, 1H, CH), 6.84 (dd, J = 8.5 Hz, 0.9 Hz, 1H, Ar-H), 6.89-7.00 (m, 4H, Ar-H), 7.25 (pt, J = 8.4 Hz, 7.9 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 150 MHz): δ = 18.8, 19.4, 21.1, 30.8, 50.9, 52.5, 55.8, 56.8, 57.0, 107.8, 110.2, 115.4, 119.5, 127.8, 129.2, 131.6, 132.1, 135.8, 158.8, 162.8 ppm.

HR-MALDI-MS: calcd. for $C_{24}H_{28}NO_3$ $[M]^+$ 378.2063; found 378.2045.

_N_-Benzyl-(1_R_,3_R_)-5-(4',5'-dimethoxy-2'-methylnaphthyl)-8-benzoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (111a/b):



A mixture of the naphthalene precursor **100** (108 mg, 1.5 equiv., 344 µmol), the isoquinoline building block **110** (100 mg, 1.0 equiv., 229 µmol), K_3PO_4 (194 mg, 4.0 equiv., 915 µmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 37.6 mg, 0.4 equiv., 91.5 µmol), and tris(dibenzylideneacetone)di-palladium(0) ($Pd_2(dba)_3$, 21.0 mg, 0.1 equiv., 34.4 µmol) in 15 mL of dry toluene was stirred for 48 h at 100 °C. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 6:1) to yield a mixture of the protected diastereomeric biaryls **111a/b** (104 mg, 187 µmol, 56%) as an orange-colored oil.

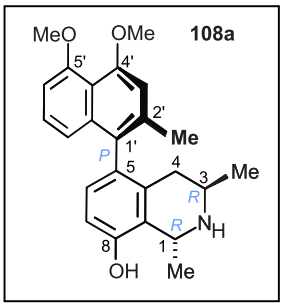
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (3H, d, J = 6.5 Hz, Me-3), 1.65 (3H, d, J = 6.6 Hz, Me-1), 2.14 (3H, s, Me-2'), 2.28 (1H, dd, J = 17.8 Hz, 5.8 Hz, CH_2), 2.51 (1H, dd, J = 19.1 Hz, 5.6 Hz, CH_2), 3.52 (1H, d, J = 9.9 Hz, CH_2), 4.00 (3H, s, OMe), 4.03 (3H, s, OMe), 4.20 (1H, m, CH), 4.48 (1H, d, J = 12.5 Hz, CH_2), 4.70 (1H, q, J = 6.6 Hz,

CH_2), 5.02 (1H, d, J = 11.6 Hz, CH_2), 5.10 (1H, d, J = 11.6 Hz, CH_2), 6.64-7.17 (6H, m, Ar-H), 7.36 (10H, m, Ar-H) ppm.

HRMS (ESI, positive) calcd. for $C_{38}H_{40}NO_3$ $[M]^+$ 558.3003, found 558.2998.

5'-*O*-Methyldioncophylline C (108a) and 5'-*O*-methyl-5-*epi*-dioncophylline C (108b):

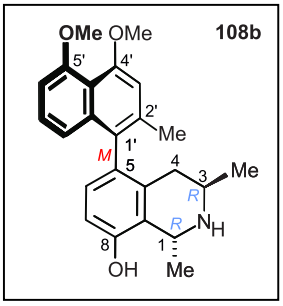
A mixture of **111a/b** (39.0 mg, 1.0 equiv., 69.9 µmol) and Pd/C (15 mg, 10% Pd) was stirred in 6 mL of degassed isopropanol for 4 h under a hydrogen atmosphere. After filtration of the suspension over Celite, the solvent was removed in vacuo to yield **108a/b** (26.4 mg, 69.9 µmol, quant.) as a yellow oil. The atropo-diastereomers **108a** and **108b** were resolved on an XSelect HSS PFP HPLC column using an isocratic system consisting of the solvents A (H_2O + 0.5% TFA) and B(MeOH + 0.5% TFA) at 5 mL min^{-1} (0 min: 60% of B, 30 min: 60% of B).



^{1}H NMR (MeOD, 400 MHz): δ = 1.25 (3H, d, J = 6.4 Hz, Me-3), 1.74 (3H, d, J = 7.1 Hz, Me-1), 2.10 (3H, s, Me-2'), 2.28 (1H, dd, J = 17.9 Hz, 6.4 Hz, H-4_{eq}), 2.33 (1H, dd, J = 11.6 Hz, 5.9 Hz, H-4_{eq}), 3.94 (3H, s, OMe-4'), 3.97 (3H, s, OMe-5'), 6.79 (1H, dd, J = 8.7 Hz, 0.8 Hz, H-8'), 6.88-6.94 (4H, m, H-6, H-7, H-3', H-6'), 7.23 (1H, pt, J = 8.4 Hz, 7.73 Hz, H-7') ppm.

^{13}C NMR (MeOD, 150 MHz): δ = 18.2 (Me-1), 19.4 (Me-3), 20.7 (Me-2'), 33.2 (C-4), 45.2 (C-3), 57.1 (OMe-4' and OMe-5'), 107.2 (C-6), 110.2 (C-3'), 114.8 (C-7), 117.7 (C-1'), 119.2 (C-8'), 122.2 (C-5), 128.1 (C-7') 129.9 (C-2'), 131.2 (C-5), 132.4 (C-6'), 136.4 (C-10'), 137.9 (C-9'), 157.8 (C-4'), 157.9 (C-5'), 158.9 (C-8) ppm.

HR-MALDI-MS: calcd for $C_{24}H_{28}NO_3$ $[M]^+$ 378.2051; found 378.1995.



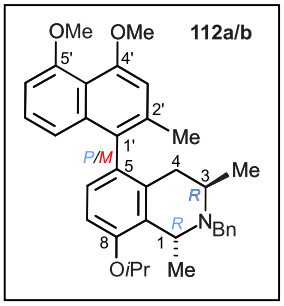
^{1}H NMR (MeOD, 600 MHz): δ = 1.24 (3H, d, J = 6.4 Hz, Me-3), 1.73 (3H, d, J = 6.8 Hz, Me-1), 2.13 (3H, s, Me-2'), 2.17 (1H, dd, J = 14.0 Hz, 11.4 Hz, H-4$_{ax}$), 2.48 (1H, dd, J = 18.0 Hz, 4.8 Hz, H-4$_{eq}$), 3.75 (1H, m, H-3), 3.93 (3H, s, OMe-4'), 3.97 (3H, s, OMe-5'), 6.70 (1H, dd, J = 8.7 Hz, 1.0 Hz, H-8'), 6.87 (1H, d, J = 7.6 Hz, H-6), 6.90 (1H, d, J = 8.2 Hz, H-7), 6.91 (1H, s, H-3'), 6.94 (1H, d, J = 8.2 Hz, H-6'), 7.19 (1H, pt, J = 8.1 Hz, 8.1 Hz, H-7') ppm.

^{13}C NMR (MeOD, 150 MHz): δ = 18.2 (Me-1), 19.3 (Me-3), 21.0 (Me-2'), 32.9 (C-4), 45.2 (C-3), 48.1 (C-1), 57.1 (OMe-4' and OMe-5'), 107.1 (C-6), 110.3 (C-3'), 114.7 (C-7), 117.1 (C-1'), 119.4 (C-8'), 121.8 (C-5), 127.9 (C-7'), 129.9 (C-2'), 131.7 (C-5), 132.4 (C-6'), 135.8 (C-10'), 137.8 (C-9'), 157.8 (C-5'), 157.9 (C-4'), 159.3 (C-8) ppm.

HRMS (ESI, positive) calcd. for $C_{24}H_{28}NO_3$ $[M]^+$ 378.2051; found 378.2064.

_N_-Benzyl-(1_R_,3_R_)-5-(4',5'-dimethoxy-2'-methylnaphthyl)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (112a/b):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of naphthalene **100** (33.8 mg, 2.0 equiv., 103 µmol), isoquinoline **82** (20.0 mg, 1.0 equiv., 51.5 µmol), K_3PO_4 (43.7 mg, 4.0 equiv., 206 µmol), SPhos (8.46 mg, 0.4 equiv., 20.6 µmol) and $Pd_2(dba)_3$ (4.72 mg, 0.1 equiv., 5.15 µmol) in 3 mL of abs. toluene was stirred for 19 h at 100 °C. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed with water. The crude product was purified by column chromatography (SiO_2, _n_-hexane/Et_2O, 1:1, 1% NEt_3) to yield **112a/b** (23.0 mg, 45.3 µmol, 89%) as a yellow oil.

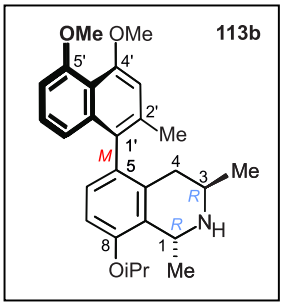
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96-1.41 (m, 14H, 4 x CH_3 + CH_2), 2.00 (d, J = 8 Hz, 1H, CH), 2.14 (s, 3H, CH_3), 3.24 (d, J = 14 Hz, 1H, CH), 3.74 (m, 1H, CH), 3.99 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3) 4.08 (q, J = 7 Hz, 1H, CH), 4.58 (sep, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.79-7.37 (m, 11H, 11 x Ar-H) ppm.

MS (EI = 70 eV): *m/z* (%) = 494 (100), 361 (2), 346 (3), 247 (5), 91 (13).

HRMS (ESI, positive) calcd. for $C_{34}H_{40}NO_3$ $[M + H]^+$ 510.3003; found 510.3004.

(1*R*,3*R*)-5-(4',5'-dimethoxy-2'-methylnaphthyl)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (113a/b):

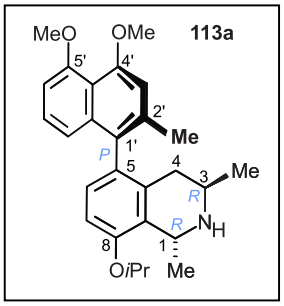
Compounds **112a/b** (5.90 mg, 1.0 equiv., 11.6 µmol) and Pd/C (12.3 mg, 1.0 equiv., 10% Pd, 1.16 µmol) were stirred in 2 mL MeOH under an H_2 atmosphere for 4 h. The suspension was filtrated over Celite. After removal of the solvent in vacuo, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 16:1) to yield **113a/b** (3.15 mg, 7.54 µmol, 65%) as a yellow oil. The atropo-diastereomers were separated by preparative HPLC on an XSelect HSS PFP HPLC column using a system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeOH + 0.05% TFA) at 5 mL min^{-1}: 0 min: 60% of B, 19 min: 90% of B, 21 min: 100% of B, 24 min: 100% of B, 25 min: 60% of B, 28 min: 60% of B.



^{1}H NMR (MeOD, 400 MHz): δ = 1.25 (d, J = 6.4 Hz, 3H, CH_3), 1.46 (d, J = 5.9 Hz, 6H, CH_3), 1.49 (d, J = 5.9 Hz, 6H, CH_3), 1.72 (d, J = 6.8 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3) 2.20 (dd, J = 18.0 Hz, 11.7 Hz, 1H, CH_2), 2.51 (dd, J = 17.8 Hz, 4.9 Hz, 1H, CH_2), 3.79 (m, 1H, CH), 3.96 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.85 (sep, J = 6.2, 1H, CH) 4.88 (q, J = 7.0 Hz, 1H, CH), 6.69 (dd, J = 8.4 Hz, 1.0 Hz, 1H, Ar-H), 6.89 (d, J = 7.1 Hz, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 7.10 (m, 2H, Ar-H), 7.21 (dd, J = 8.4 Hz, 7.8 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 16.9, 17.8, 19.5, 20.9, 21.0, 25.1, 31.4, 43.4, 55.4, 55.5, 67.5, 70.0, 73.0, 105.6, 108.7, 110.6, 116.2, 117.7, 122.3, 126.4, 127.9, 130.9, 131.4, 134.3, 136.3, 153.1, 156.4, 157.4 ppm.

HRMS (ESI, positive) calcd. for $C_{27}H_{34}NO_3$ $[M + H]^+$ 420.2533; found 420.2539.



^{1}H NMR (MeOD, 400 MHz): δ = 1.25 (d, J = 6.4 Hz, 3H, CH_3), 1.41 (d, J = 6.0 Hz, 3H, CH_3), 1.46 (d, J = 6.1 Hz, 3H, CH_3), 1.71 (d, J = 6.8 Hz, 3H, CH_3), 2.09 (s, 3H, CH_3) 2.25 (dd, J = 17.9 Hz, 11.4 Hz, 1H, CH_2), 2.36 (dd, J = 12.8 Hz, 5.2 Hz, 1H, CH_2), 3.69 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.81 (sep, J = 6.1, 1H, CH) 4.85 (q, J = 8.5 Hz, 1H, CH), 6.7 (m, 1H, Ar-H), 6.89 (m, *2*H, Ar-H), 6.94 (s, 1H, Ar-H), 7. 02 (m, 2H, Ar-H), 7.21 (dd, J = 8.2 Hz, 7.8 Hz, 1H, Ar-H) ppm.

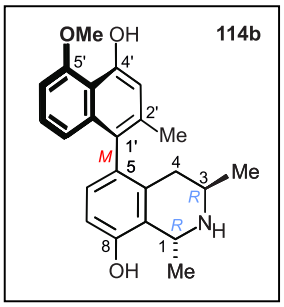
^{13}C NMR (MeOD, 100 MHz): δ = 18.4, 19.3, 20.6, 22.3, 22.4, 28.8, 33.0, 44.9, 56.4, 71.4, 107.2, 110.3, 112.1, 118.9, 123.9, 128.0, 132.5, 136.3, 137.7, 154.6, 157.9, 158.48 ppm.

HRMS (ESI, positive) calcd. for $C_{27}H_{34}NO_3$ $[M + H]^+$ 420.2533; found 420.2543.

MS (**109a/b**) (EI = 70 eV): *m/z* (%) = 419 (23) $[M]^+$, 404 (100), 362 (35), 181 (12), 18.1 (29).

5'-*O*-Methyl-4'-*O*-demethyl-5-*epi*-dioncophylline C (114b):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of **113b** (5.50 mg, 1.0 equiv., 13.1 µmol) in 2 mL abs. CH_2Cl_2 a 1 M solution of BCl_3 in CH_2Cl_2 (3.84 mg, 32.7 µL, 2.5 equiv., 32.7 µmol) was added. The mixture was stirred at 0 °C for 2 h. Cautious addition of water stopped the reaction. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica (SiO_2, CH_2Cl_2/MeOH, 10:1) to yield **114b** (3.20 mg, 8.51 µmol, 65%) as a beige oil.

^{1}H NMR (MeOD, 400 MHz): δ = 1.23 (d, J = 6.4 Hz, 3H, CH_3), 1.71 (d, J = 6.8 Hz, 3H, CH_3), 2.06 (s, 3H, CH_3) 2.15 (dd, J = 18.0 Hz, 11.7 Hz, 1H, CH_2), 2.46 (dd, J = 18.0 Hz, 4.8 Hz, 1H, CH_2), 3.73 (m, 1H, CH), 4.08 (s, 3H, OCH_3), 4.85 (q, J = 4.5 Hz, 1H, CH), 6.70 (dd, J = 8.6 Hz, 0.9 Hz, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 6.86 (d, J = 5.4 Hz,

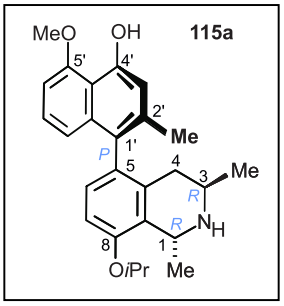
1H, Ar-H), 6.91 (d, *J* = 13.1 Hz, 1H, Ar-H), 7.17 (dd, *J* = 8.5 Hz, 7.8 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 16.7, 17.8, 19.3, 31.5, 43.6, 55.4, 103.2, 112.1, 113.1, 118.6, 120.2, 125.8, 126.7, 130.2, 130.6, 130.9, 135.5, 135.7, 153.1, 153.7, 156.6 ppm.

HRMS (ESI, positive) calcd. for $C_{23}H_{25}NO_3$ $[M]^+$ 363.1829; found 363.1823.

5'-*O*-Methyl-4'-*O*-demethyl-8-*O*-isopropyl-5-dioncophylline C (115a):

All reactions were performed under an N_2 atmosphere.

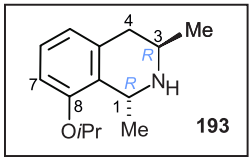


To a cooled (0 °C) solution of **113a** (4.00 mg, 1.0 equiv., 9.53 µmol) in 2 mL abs. CH_2Cl_2 a 1 M solution of BCl_3 in CH_2Cl_2 (2.79 mg, 23.8 µL, 2.5 equiv., 23.8 µmol) was added. The mixture was stirred at 0 °C for 2 h. Cautious addition of water stopped the reaction. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica (SiO_2, CH_2Cl_2/MeOH, 10:1) to yield **115a** (1.80 mg, 4.71 µmol, 50%) as a beige oil.

^{1}H NMR (MeOD, 400 MHz): δ = 1.15 (d, *J* = 6.3 Hz, 3H, CH_3), 1.30 (d, *J* = 5.7 Hz, 3H, CH3), 1.36 (d, *J* = 6.7 Hz, 3H, CH3), 1.61 (d, *J* = 7.2 Hz, 3H, CH_3), 1.94 (s, 3H, CH_3) 2.17 (m, 1H, CH_2), 2.27 (dd, *J* = 17.0 Hz, 5.4 Hz, 1H, CH_2), 3.59 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.75 (m, 2H, 2 x CH), 6.66 (d, *J* = 8.9 Hz, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 6.78 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.97 (m, 2H, 2 x Ar-H), 7.10 (m, 1H, Ar-H) ppm.

Total Synthesis and Biotinylation of 5'-*O*-Methyldioncophylline D

(1*R*,3*R*)-8-Isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (193):



The diastereomeric mixture of tetrahydroisoquinoline **98** (70:30, at this level not resolvable) (3.00 g, 1.0 equiv., 10.1 mmol) and Pd/C (137 mg, 0.1 equiv., 10% Pd, 1.01 mmol) were stirred in 10 mL MeOH under an H_2 atmosphere for 4 h. The suspension was filtrated over Celite to yield **193** (2.21 g, 10.1 mmol, quant., *dr*: 7/3, *trans*/*cis*) as a colorless solid.

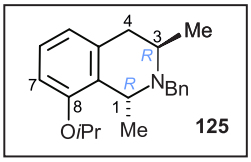
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (dd, J = 6 Hz, 2 Hz, 6H, $CH(CH_3)_2$), 1.77 (d, J = 7 Hz, 3H, CH_3), 1.78 (d, J = 2 Hz, 3H, CH_3), 2.95 (dd, J = 17 Hz, 4 Hz, 1H, CH_2) 3.20 (dd, J = 17 Hz, 12 Hz, 1H, CH_2), 3.77 (m, 1H, CH), 4.58 (sept, J = 6 Hz, 1H, $CH(CH_3)_2$), 4.88 (q, J = 6 Hz, 1H, CH), 6.66 (d, J = 8 Hz, 1H, Ar-H), 6.70 (d, J = 8 Hz, 1H, Ar-H), 7.15 (t, J = 8 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.6, 19.0, 22.2, 22.6, 34.2, 45.2, 48.4, 70.2, 110, 121, 123, 129, 132, 154 ppm.

MS (EI = 70 eV): *m/z* (%) = 204 (100),162 (94), 146 (7), 134 (14), 115 (3), 91 (4), 80 (3), 44.1 (6), 18.1 (23).

HRMS (ESI, positive) calcd. for $C_{14}H_{22}NO$ $[M + H]^+$ 220.1696; found 220.1699.

N-Benzyl-(1*R*,3*R*)-8-isopropoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (125):



A mixture of **193** (262 mg, 1.0 equiv., 1.19 mmol), Cs_2CO_3 (973 mg, 2.5 equiv., 2.99 mmol), and benzyl bromide (510 mg, 355 µL, 2.5 equiv., 2.99 mmol) in 10 mL acetone were stirred for 24 h at room temperature. The suspension was filtered, concentrated in vacuo, and purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 20:1, 1% NEt_3) to yield **125** (345 mg, 1.12 mmol, 93%) as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (d, J = 6 Hz, 3H, $CH(CH_3)_2$), 1.23 (d, J = 6 Hz, 6H, $CH(CH_3)_2$), 1.30 (d, J = 6 Hz, 3H, CH_3), 2.43 (dd, J = 18 Hz, 12 Hz, 1H, CH_2) 2.60 (m, 2 H, CH_2-Ar), 3.25 (d, J = 14 Hz, 1H, CH_2), 3.49 (m, 1H, CH), 3.80 (d, J = 14 Hz,

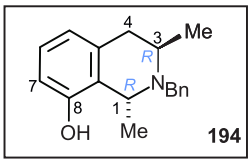
1H, CH_2), 3.94 (q, J = 7 Hz, 1H, CH), 4.45 (sept, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.65 (m, 2H, Ar-H), 7.05 (t, J = 8 Hz, Ar-H) 7.15-7.38 (m, 5H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.1, 22.4, 30.0, 32.4, 45.9, 50.2, 51.9, 69.8, 110, 121, 126, 127, 128, 129, 137, 142, 156 ppm.

HRMS (ESI, positive) calcd. for $C_{21}H_{28}NO$ $[M + H]^+$ 310.2165; found 310.2166.

_N_-Benzyl-(1*R*,3*R*)-8-hydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (194):

All reactions were performed under an N_2 atmosphere.

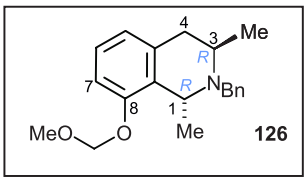


To a cooled (0 °C) solution of **125** (280 mg, 1.0 equiv., 905 µmol) in 11 mL abs. CH_2Cl_2 a 1 M solution of BBr_3 in CH_2Cl_2 (2.26 mL, 2.5 equiv., 2.26 mmol) was added dropwise. The solution was stirred at 0 °C for 2 h. To get rid of excess BBr_3 methanol was added carefully. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 6:1) to yield **194** (171 mg, 642 µmol, 71%) as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (d, J = 6 Hz, 3H, $CH(CH_3)_2$), 1.25 (d, J = 6 Hz, 3H, $CH(CH_3)_2$), 1.29 (d, J = 7 Hz, 3H, CH_3), 1.32 (d, J = 7 Hz, 3H, CH_3), 2.43 (dd, J = 18 Hz, 12 Hz, 1H, CH_2) 2.65 43 (dd, J = 18 Hz, 4 Hz, 1H, CH_2), 3.17 (d, J = 14 Hz, 1H, CH_2), 3.51 (m, 1H, CH), 3.82 (d, J = 14 Hz, 1H, CH_2), 3.95 (q, J = 7 Hz, 1H, CH), 4.45 (sept, J = 10 Hz, 1H, $CH(CH_3)_2$), 6.61 (d, J = 9 Hz, 1H, Ar-H) 7.21-7.38 (m, 6H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.7, 20.0, 22.0, 22.1, 33.1, 45.8, 49.8, 51.9, 70.0, 112, 116, 127, 128, 129, 130, 131, 135, 141, 155 ppm.

_N_-Benzyl-(1_R_,3_R_)-8-_O_-methoxymethylene-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (126):



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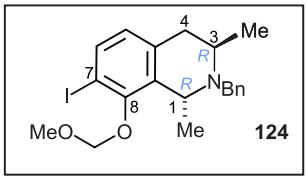
A solution of **194** (143 mg, 1.0 equiv., 534 µmol), Cs_2CO_3 (350 mg, 2.0 equiv., 1.07 mmol), and chloromethoxy methane (51.7 mg, 1.2 equiv., d = 1.06 g/mL, 49.0 µL) in acetone was stirred at room temperature for 2 h. After addition of water, the mixture was extracted into ethyl acetate. The organic phases were combined, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 20:1) to yield **126** (117 mg, 373 µmol, 70%) as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, J = 7 Hz, 3H, CH_3), 1.36 (d, J = 7 Hz, 3H, CH_3), 2.65 (m, 2H, CH_2), 3.30 (d, J = 14 Hz, 1H, CH), 3.34 (s, 3H, OCH_3), 3.52 (m, 1H, CH), 3.86 (d, J = 14 Hz, 1H, CH), 3.99 (m, 1H, CH), 5.11 (s, 2H, CH_2), 6.77 (d, J = 8 Hz, 1H, Ar-H), 6.89 (d, J = 8 Hz, 1H, Ar-H), 7.23-7.38 (m, 5H, Ar-H) ppm.

_N_-Benzyl-(1_R_,3_R_)-7-iodo-8-_O_-methoxymethylene-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (124):

All reactions were performed under an N_2 atmosphere.



124

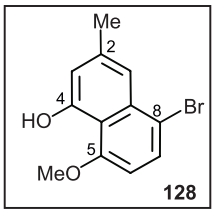
To a cooled (-78 °C) solution of **126** (117 mg, 1.0 equiv., 376 µmol) in 6 mL THF a 1.6 M solution of *n*-BuLi in *n*-hexane (470 µL, 2.0 equiv., 751 µmol) was added dropwise. This mixture was stirred for 2 h at 0 °C. It was cooled to -78 °C and iodine (191 mg, 2.0 equiv., 751 µmol) dissolved in 1 mL THF was added dropwise. After stirring at room temperature for 2 h, methanol was added cautiously. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 20:1) to yield **124** (130 mg, 301 µmol, 80%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, J = 7 Hz, 3H, CH_3), 1.35 (d, J = 7 Hz, 3H, CH_3), 2.62 (m, 2H, CH_2), 3.00 (s, 3H, OCH_3), 3.31 (d, J = 14 Hz, 1H, CH), 3.49 (m, 1H, CH), 3.89 (d, J = 14 Hz, 1H, CH), 4.72 (d, J = 6 Hz, 1H, CH), 5.00 (d, J = 6 Hz, 1H,

CH), 6.65 (d, J = 8 Hz, 1 H, Ar-H), 7.22-7.32 (m, 5H, Ar-H), 7.40 (d, J = 8 Hz, 1 H, Ar-H) ppm.

8-Bromo-5-methoxy-2-methylnaphth-4-ol (128):

All reactions were performed under an N_2 atmosphere.



To a cooled (0 °C) solution of *N*-cyclohexylisopropylamine (20.7 g, 3.5 equiv., 147 mmol) a solution of *n*-butyllithium in *n*-hexane (100 mL, c = 1.6 M, 3.8 equiv., 159 mmol) was added dropwise. The mixture was stirred for 90 min at room temperature. The resulting sludge was dissolved in 150 mL abs. THF. At -78 °C a solution of **84** (6.50 g, 1.0 equiv., 41.8 mmol) in 30 mL abs. THF was added dropwise. After stirring at -78 °C for 2 h, 2,4-dibromo anisole (**127**) (25.6 g, 2.3 equiv., 96.3 mmol) was added. The solution was slowly warmed to room temperature over 48 h. At 0 °C the mixture was quenched by adding an aqueous saturated solution of NH_4Cl followed by the addition of aq. 10% HCl solution. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with water, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 17:1) to yield **128** (1.96 g, 7.12 mmol, 17%) as a yellowish solid.

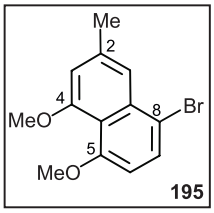
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.47 (s, 3H, CH_3), 4.04 (s, 3H, OCH_3), 6.58 (d, J = 8 Hz, 1H, Ar-H), 6.81 (d, J = 2 Hz, 1H, Ar-H), 7.48 (m, 1H, Ar-H), 7.58 (d, J = 8 Hz, 1H, Ar-H), 9.33 (s, 1H, Ar-OH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.3, 56.6, 104, 114.4, 114.7, 115, 118, 130, 135, 140, 155, 156 ppm.

MS (EI = 70 eV): m/z (%) = 268 (98) $[M]^+$, 266 (100), 253 (44), 251 (46), 225 (43), 223 (44), 187 (4), 144 (15).

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[121]

4,5-Dimethoxy-8-bromo-2-methylnaphthalene (195):



To a cooled (0 °C) solution of **128** (1.00 g, 1.0 equiv., 3.74 mmol), NaOH (3.74 g, 25 equiv., 93.6 mmol), tributylbenzylammonium chloride (700 mg, 0.6 equiv., 2.25 mmol) in 25 mL CH_2Cl_2 and 5 mL H_2O, Me_2SO_4 (3.31 g, 2.50 mL, 7.0 equiv., 26.2 mmol) was added. The solution turned yellow. Stirring was continued overnight at room temperature. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 1:1) yielded **195** (950 mg, 3.38 mmol, 90%) as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.51 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.64 (d, J = 8 Hz, 1H, Ar-H), 6.76 (s, 1H, Ar-H), 7.60-7.64 (m, 2H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 56.8, 56.9, 58.9, 106, 110, 113, 120, 131, 135, 138, 157, 158 ppm.

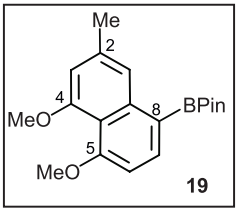
MS (EI = 70 eV): *m/z* (%) = 282 (100) $[M]^+$, 280 (99), 209 (20), 207 (20), 186 (31), 158 (37).

HRMS (ESI, positive) calcd. for $C_{13}H_{13}BrO_2$ $[M]^+$ 280.0093; found 280.0097.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[121]

4,5-Dimethoxy-2-methylnaphthyl-8-boronic acid pinacol ester (19):

All reactions were performed under an N_2 atmosphere. The solvent had been degassed prior to use.



A solution of **195** (450 mg, 1.0 equiv., 1.60 mmol), $Pd(PPh_3)_4$ (185 mg, 0.1 equiv., 160 µmol), KOAc (943 mg, 6.0 equiv., 9.60 mmol) and $(BPin)_2$ (610 mg, 1.5 equiv., 2.40 mmol) in 12 mL abs. DMF. was stirred at 157 °C for 1 h 30 min. The solvent was removed, the resulting residue was dissolved in Et_2O and passed through a short pad of

Celite. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1) to yield **19** (387 mg, 1.18 mmol, 74%) as a colorless solid.

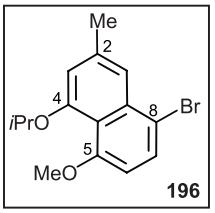
IR (ATR): $\tilde{\nu}$ = 2973 (w), 1581 (s), 1461 (m), 1376 (m), 1307 (s), 1257 (s), 1130 (s) cm^1.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.46 (s, 12H, $B(OC(CH_3)_2)_2$) 2.57 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.78 (d, J = 8 Hz, 1H, Ar-H), 7.32 (dd, J = 8 Hz, 8 Hz, 1H, Ar-H), 7.67 (dd, J = 8 Hz, 1 Hz, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0, 24.7, 25.2, 56.2, 56.5, 83.9, 105, 109, 116, 120, 127, 141, 143, 157, 158 ppm.

MS (EI = 70 eV): *m/z* (%) = 328 (100) $[M]^+$, 255 (15), 228 (19), 155 (9), 141 (6), 83.2 (2).

8-Bromo-4-isopropoxy-5-methoxy-2-methylnaphthalene (196):



A solution of **128** (1.50 g, 1.0 equiv., 2.66 mmol), isopropyl iodide (2.22 mL, 3.80 g, 4.0 equiv., 22.5 mmol) and Cs_2CO_3 (5.00 g, 2.0 equiv., 14.1 mmol) in 20 mL acetone and stirred for 24 h at room temperature. The suspension was filtered over a Celite pad, eluted with CH_2Cl_2, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 4:1) to yield **196** (1.37 g, 4.43 mmol, 79%) as a yellowish solid.

M.p. 130 °C (*n*-hexane/CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 2977 (m), 2930 (w), 1590 (m), 1572 (m), 1084 (s), 646 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 2.49 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 4.53 (m, 1 H, $CH(CH_3)_2$), 6.61 (d, J = 8 Hz, 1 H, Ar-H), 6.84 (s, 1 H, Ar-H), 7.60 (d, J = 8 Hz, 1 H, Ar-H, 7.64 (m, 1 H, Ar-H) ppm.

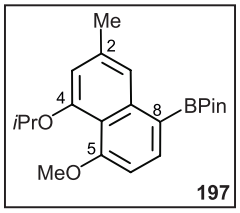
^{13}C NMR (CDCl3, 100 MHz): δ = 22.0, 22.1, 56.3, 73.3, 106, 113, 116, 119, 120, 130, 135, 138, 155, 157 ppm.

MS (EI = 70 eV): *m/z* (%) = 310 (48) [M]+, 266 (100), 251 (43), 223 (29), 128 (39), 187 (11) 115 (35).

HRMS (ESI, positive) calcd. for $C_{15}H_{17}BrO_2$ $[M]^+$ 309.0406; found 309.0482.

5-Methoxy-4-isopropoxy-2-methylnaphthyl-8-boronic acid pinacol ester (197):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of **196** (650 mg, 1.0 equiv., 2.10 mmol), $Pd(PPh_3)_4$ (242 mg, 0.1 equiv., 210 µmol), KOAc (1.24 g, 6.0 equiv., 12.6 mmol) and $(BPin)_2$ (800 mg, 1.5 equiv., 3.15 mmol) in 12 mL abs. DMF was stirred at 157 °C for 1 h 30 min. The solvent was removed, the resulting residue was dissolved in Et_2O and passed through a short pad of Celite. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 8:1) to yield **197** (432 mg, 1.21 mmol, 58%) as a colorless solid.

M.p. 65 °C (*n*-hexane/Et_2O).

IR (ATR): $\tilde{\nu}$ = 2979 (m), 2934 (m), 1620 (m), 1578 (s), 1320 (s), 1084 (s), 696 (m) cm^1.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 1.40 (s, 12 H, BPin), 2.46 (s, 3 H, CH_3), 3.94 (s, 3 H, OCH_3), 4.48 (m, 1 H, $CH(CH_3)_2$), 6.73 (d, J = 8 Hz, 1 H, Ar-H), 6.80 (s, 1 H, Ar-H), 7.92 (d, J = 8 Hz, 1 H, Ar-H), 8.19 (m, 1 H, Ar-H) ppm.

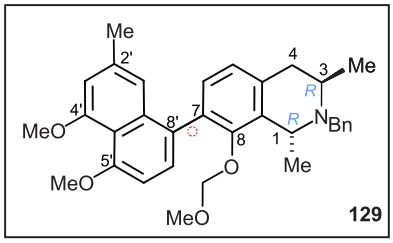
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 22.2, 24.9, 55.8, 73.5, 83.4, 104, 116, 122, 136, 137, 155, 160 ppm.

MS (EI = 70 eV): m/z (%) = 356 (32) $[M]^+$, 315 (20), 314 (100), 241 (22), 214 (13), 171 (7), 84 (8), 18 (12).

HRMS (ESI, positive) calcd. for $C_{21}H_{29}BO_4$ $[M]^+$ 356.2153; found 356.2266.

(1*R*,3*R*)-*N*-Benzyl-7-(4',5'-dimethoxy-2'-methylnaphthyl)-8-*O*-(methoxymethylene)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (129):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.

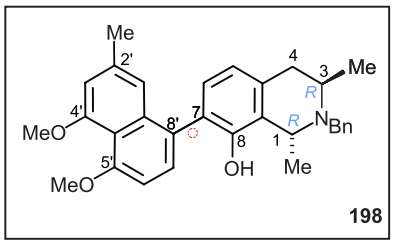


A solution of naphthalene **19** (50.0 mg, 1.2 equiv., 152 µmol), isoquinoline **124** (55.5 mg, 1.0 equiv., 127 µmol), K_3PO_4 (108 mg, 4.0 equiv., 508 µmol), SPhos (20.9 mg, 0.4 equiv., 68.6 µmol) and $Pd_2(dba)_3$ (11.6 mg, 0.1 equiv., 12.7 µmol) in 6 mL abs. toluene was stirred for 48 h at 100 °C. After cooling to room temperature, water was added and the mixture was extracted into CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (Al_2O_3, *n*-hexane/Et_2O, 4:1) to yield the interconverting atropisomers **129** (46.9 mg, 91.8 µmol, 72%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = ^{1}H NMR (MeOD, 400 MHz): δ = 1.40-1.63 (m, 6H, CH_3), 2.23 and 2.40 (s, 3H, CH_3), 2.75 (m, 1H, CH), 3.47 (m, 1H, CH_2), 3.60 (m, 1H, CH), 3.96 (m, 8H, 2 x OCH_3, 2 x CH), 6.66-7.50 (m, 11H, Ar-H) ppm.

HRMS (ESI, positive) calcd. for $C_{33}H_{38}NO_4$ $[M + H]^+$ 512.2795; found 512.28034.

(1*R*,3*R*)-*N*-Benzyl-7-(4',5'-dimethoxy-2'-methylnaphthyl)-8-hydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (198):

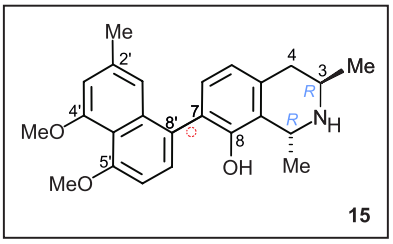


To a solution of **129** (36.0 mg, 1.0 equiv., 70.4 µmol) in 4 mL CH_2Cl_2, trifluoroacetic acid (27.3 mg, 19.0 µL, 4.0 equiv., 281 µmol) was added dropwise. The mixture was stirred at room temperature for 2 h and first turned green and then orange. The solvent was removed under reduced pressure to yield **198** (32.9 mg, 70.4 µmol, quant.) as a orange oil.

^{1}H NMR (MeOD, 400 MHz): δ = 1.40-1.63 (m, 6H, CH_3), 2.23 and 2.40 (s, 3H, CH_3), 2.75 (m, 1H, CH), 3.47 (m, 1H, CH_2), 3.60 (m, 1H, CH), 3.96 (m, 8H, 2 x OCH_3, 2 x CH), 6.66- 7.50 (m, 11H, Ar-H) ppm.

HRMS (ESI, positive) calcd. for $C_{31}H_{34}NO_4$ $[M + H]^+$ 468.2533; found 468.2541.

5'-*O*-Methyldioncophylline D (15):



A mixture of the protected naphthylisoquinoline **198** (10.0 mg, 1.0 equiv., 21.4 µmol) and Pd/C (2.35 mg, 0.1 equiv., 10% Pd, 2.14 µmol) in MeOH was stirred under an H_2 atmosphere for 2 h at room temperature. The suspension was filtered over Celite. The crude product was purified by column chromatography (Al_2O_3, CH_2Cl_2/MeOH, 50:1) to yield **15** (7.23 mg, 19.0 µmol, 89%) as a colorless oil.

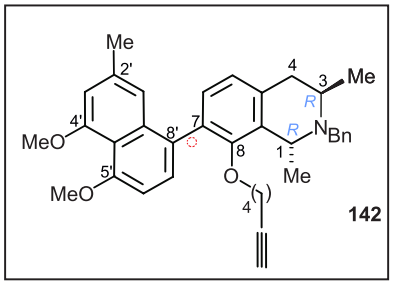
^{1}H NMR (MeOD, 400 MHz): δ = 1.57 (d, J = 6.5 Hz, 3H, CH_3), 1.72 and 1.77 (d, J = 7.0 Hz, 3H, CH_3), 2.31 and 2.34 (s, 3H, CH_3), 2.95 (m, 1H, CH), 2.95 (dd, J = 17.3, 4.6 Hz, 1H, CH_2), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.88 (q, J = 6.5 Hz, 1H, CH), 6.81 (m, 1H, Ar-H) , 6.84 (s, 1H, Ar-H), 6.88 (d, J = 17.8, 1H, Ar-H), 6.96 (dd, J = 8.0, 4.2, 1H, Ar-H), 7.08 (dd, J = 7.8, 3.4, 1H, Ar-H), 7.26 (t, J = 8.4, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.9, 20.6, 22.3, 33.0,43.7, 55.3, 55.5, 105, 108, 117, 118, 119, 119.5, 128, 130, 131, 131.3, 136, 157, 157, 159 ppm.

HRMS (ESI, positive) calcd. for $C_{24}H_{28}NO_3$ $[M]^+$ 378.2064; found 378.2054.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[44]

5'-*O*-Methyl-8-*O*-hex-1''-ynyldioncophylline D (142):

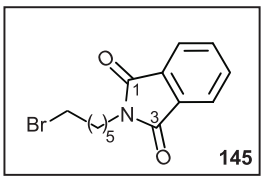


A mixture of naphthylisoquinoline **198** (10.0 mg, 1.0 equiv., 21.4 µmol), Cs_2CO_3 (17.4 mg, 2.5 equiv., 53.5 µmol), and 6-iodohex-1-yn (11.1 mg, 2.5 equiv., 53.5 µmol) in 5 mL acetone was stirred overnight. The suspension was filtered over Celite. The crude product was purified by column chromatography (Al_2O_3, hexane/Et_2O, 3:1) to yield **142** (11.7 mg, 21.4 µmol, quant.) as a colorless oil.

^{1}H NMR (MeOD, 400 MHz): δ = 1.62 (d, J = 6.5 Hz, 3H, CH_3), 1.68 and 1.76 (d, J = 7.0 Hz, 3H, CH_3), 2.30 and 2.44 (s, 3H, CH_3), 3.11-3.41 (m, 6H, CH_2), 3.92 and 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.92-4.00 (m, 2H, OCH_2), 4.42 (m, 1H, CH), 4.65-4.80 (m, 1H, CH), 6.70-7.60 (m, 11H, Ar-H) ppm.

HRMS (ESI, positive) calcd. for $C_{37}H_{42}NO_3$ $[M + H]^+$ 548.1592; found 548.31499.

2-(6'-Bromhexyl)isoindoline-1,3-dione (145):



To a solution of 1,6-dibromohexane **131** (10.3 g, 2.0 equiv., 42.0 mmol) in 20 mL DMF a solution of potassium phthalimide (**144**) (3.90 g, 1.0 equiv., 21.0 mmol) in 25 mL DMF was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica (SiO_2, *n*-hexane/EtOAc, 4:1) to yield **145** (4.90 g, 15.8 mmol, 75%) as a colorless solid.

M.p. 61 °C (*n*-hexane/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2932 (m), 2856 (w), 1769 (m), 1711 (s), 1393 (s), 719 (s) cm^{-1}.

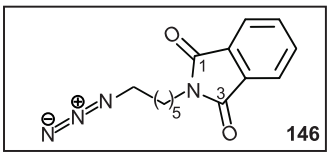
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (m, 2 H, CH_2), 1.48 (m, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 1.85 (m, 2 H, CH_2), 3.39 (t, J = 7 Hz, 2 H, CH_2), 3.69 (t, J = 7 Hz, 2 H, CH_2), 7.71 (m, 2 H, Ar-H), 7.84 (m, 2 H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.0, 27.7, 28.4, 32.6, 33.8, 37.9, 123, 132, 134, 168 ppm.

MS (EI = 70 eV): *m/z* (%) = 311 (25) $[M]^+$, 230 (7), 161 (48), 160 (100), 130 (12), 104 (10), 77 (10), 18 (16).

HRMS (ESI, positive) calcd. for $C_{14}H_{16}BrNO_2$ $[M]^+$ 310.0360; found 310.0432.

2-(6-Azidohexyl)isoindoline-1,3-dione (146):



A solution of **145** (4.50 g, 1.0 equiv., 14.5 mmol) and sodium azide (1.89 g, 2.0 equiv., 29.0 mmol) in 15 mL DMF was stirred at room temperature overnight. Water was added and the mixture was extracted into EtOAc. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography on silica (SiO_2, *n*-hexane/EtOAC, 4:1) to yield **146** (3.51 g, 12.9 mmol, 89%) as a colorless solid.

M.p. 28 °C (*n*-hexane/EtOAc).

IR (ATR): $\tilde{\nu}$ = 2936 (m), 2859 (w), 2092 (s), 1706 (s), 1395 (s), 1052 (s), 717 (s) cm^{-1}.

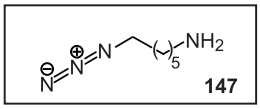
^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (m, 4 H, 2 x CH_2), 1.60 (m, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 3.25 (t, *J* = 6 Hz, 2 H, CH_2), 3.69 (t, *J* = 7 Hz, 2 H, CH_2), 7.71 (m, 2 H, Ar-H), 7.85 (m, 2 H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.6, 26.7, 28.8, 29.0, 38.2, 51.7, 124, 133, 134, 169 ppm.

MS (EI = 70 eV): *m/z* (%) = 272 (3) $[M]^+$, 160 (100), 130 (16), 96 (11), 77 (15), 70 (22), 56 (12), 43 (18).

HRMS (ESI, positive) calcd. for $C_{14}H_{16}N_4O_2$ $[M]^+$ 272.1270; found 272.1343.

6-Azido-1-aminohexane (147):



A solution of **146** (1.00 g, 1.0 equiv., 3.76 mmol) and hydrazine hydrate (760 µL, 4.2 equiv., 15.4 mmol) in 5 mL EtOH was stirred at room temperature for 12 h. The formed solid was removed by filtration. The filtrate was acidified with half-concentrated HCl. The product was extracted into water, basified

with aq. NaOH, and extracted into CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo to yield **147** (262 mg, 1.84 mmol, 50%) as a brown oil.

IR (ATR): $\tilde{\nu}$ = 3297 (m), 2930 (m), 2858 (m), 2090 (s), 1668 (s) cm^{-1}.

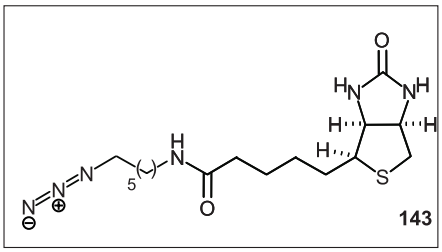
^1H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (m, 6 H, 3 x CH_2), 1.60 (m, 2 H, CH_2), 1.71 (s, 2 H, NH_2), 2.69 (t, J = 7 Hz, 2 H, CH_2), 3.26 (t, J = 7 Hz, 2 H, CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.3, 26.5, 28.7, 36.5, 51.3, 163 ppm.

MS (EI = 70 eV): *m/z* (%) = 142 (1) $[M]^+$, 100 (4), 86 (5), 72 (8), 56 (12), 30 (100).

HRMS (ESI, positive) calcd. for $C_6H_{14}N_4$ $[M]^+$ 142.1213; found 142.1290.

1-((2-Oxo-6-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)hexyl)oxy)pyrrolidine-2,5-dione (143):



A solution of **147** (46.0 mg, 2.0 equiv., 320 µmol), NEt_3 (80.0 mg, 44.0 µL, 5.0 equiv., 800 µmol), and biotin-*N*-hydroxysuccinimide ester **148**[121] (50.0 mg, 1.0 equiv., 160 µmol) in 5 mL DMF was stirred for 72 h. The solvent was removed under reduced pressure and the remaining residue was first purified by column chromatography on silica (SiO_2, CH_2Cl_2/MeOH, 15:1) and then on aluminum oxide (Al_2O_3, CH_2Cl_2/MeOH, 25:1) to yield **143** (40.0 mg, 112 µmol, 70%) as a colorless solid.

IR (ATR): $\tilde{\nu}$ = 3285 (m), 2925 (m), 2855 (m), 2094 (s), 1695 (s), 1212 (m), 653 (s) cm^1.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40-1.80 (m, 18H, CH_2), 2.24 (t, J = 7.6 Hz, 2H, CH_2CON), 2.75 (d, J = 12.8 Hz, 1H, CH), 2.97 (m, 1H, CH), 3.21 (m, 2H, CH_2), 3.32 (t, J = 6.8 Hz, 2H, CH_2N), 4.34 (dd, J = 4.4 Hz, 1H, CH), 4.52 (m, 1H, CH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.5, 25.6, 26.4, 26.5, 28.0, 28.1, 28.7, 29.5, 36.0, 40.5, 51.4, 55.5, 60.4, 62.0, 172, 173 ppm.

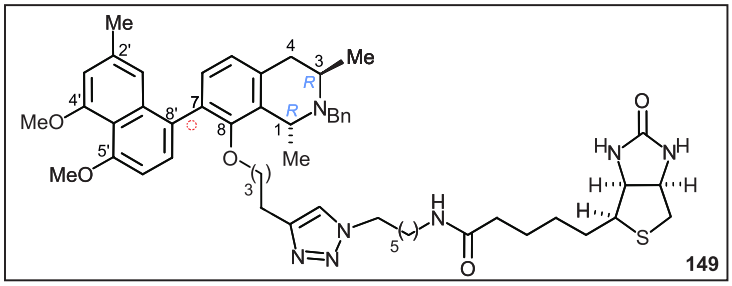
MS (EI = 70 eV): *m/z* (%) = 369 (6), 368 (11) $[M]^+$, 298 (12), 227 (33), 166 (26), 98 (63), 97 (50), 56 (34), 28 (100).

HRMS (ESI, positive) calcd. for $C_{16}H_{28}N_6O_2SNa$ $[M + Na]^+$ 391.1887; found 391.1882.

8-*O*-Biotinylated 5'-*O*-methyldioncophylline D 149:

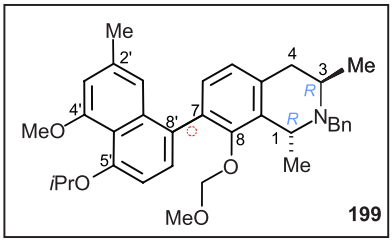
The protected naphthylisoquinoline **142** (2.00 mg, 1.0 equiv., 3.65 µmol), **143** (1.61 mg, 1.0 equiv., 3.65 µmol), sodium ascorbate (1.60 mg, 2.4 equiv., 8.76 µmol), and $CuSO_4$ (1.60 mg, 2.4 equiv., 8.76 µmol), were stirred in a mixture of H_2O and *t*BuOH for 48 h. The suspension was filtered over Celite and the filtrate was concentrated in vacuo to yield **149** (2.80 mg,3.10 µmol, 85%) as a colorless oil.

HRMS (ESI, positive) calcd. for $C_{53}H_{69}N_7O_5S$ $[M + H]^+$ 916.5159; found 916.5115.



(1*R*,3*R*)-2-Benzyl-7-(4-methoxy-7-methyl-5-isopropoxynaphthalene-1-yl)-8-(methoxymethoxy)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (199):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of naphthalene **197** (61.2 mg, 1.0 equiv., 171 µmol), isoquinoline **124** (75.0 mg, 1.0 equiv., 171 µmol), K_3PO_4 (153 mg, 4.0 equiv., 731 µmol), SPhos (28.2 mg, 0.4 equiv., 68.6 µmol) and $Pd_2(dba)_3$ (10.0 mg, 0.1 equiv., 17.1 µmol) in 3 mL abs. toluene was stirred for 96 h at 100 °C. After addition of ice water the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1-2:1) and by HPLC on a chromolith-performance RP-18 column) to yield the interconverting atropisomers **199** (40.0 mg, 74.1 µmol, 43%) as a green oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (m, 6H, 2 x CH_3), 1.80 (m, 6H, 2 x CH_3), 2.30 [2.42] (s, 3H, CH_3), 2.74 [2.82] (s, 3H, OCH_3), 3.11 (m, 1H, CH), 3.23 (m, 1H, CH), 3.74 (m, 1H, CH), 3.96 [3.97] (s, 3H, OCH_3), 4.36 (m, 1H, CH), 4.54-4.62 (m, 2 H, CH + $CH(CH_3)_2$), 4.72 (m, 1H, CH), 6.75-6.82 (m, 4H, Ar-H), 7.06 (m, 1H, Ar-H), 7.20 (m, 1H, Ar-H), 7.37-7.54 (m, 5H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 17.3, 17.4, 22.1, 22.2, 22.3, 22.4, 22.8, 29.5, 29.8, 32.0, 56.2, 73.1, 73.1, 98.5, 105, 105, 115, 115, 117,118, 118,119, 123, 124, 127, 128, 128, 129, 129, 130, 131,133, 135, 155 ppm.

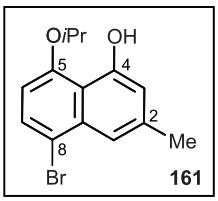
MS (EI = 70 eV): *m/z* (%) = 539 (3) $[M]^+$, 526 (8), 525 (38), 524 (100), 480 (9), 436 (13), 238 (26), 91 (30), 45 (8).

HRMS (ESI, positive) calcd. for $C_{35}H_{41}NO_4$ $[M]^+$ 539.3030; found 539.3105.

Synthesis of Ancistrolikokine E_3 and Ancistrobonsoline A_2

8-Bromo-5-isopropoxy-2-methylnaphthol (161):

All reactions were performed under an N_2 atmosphere.

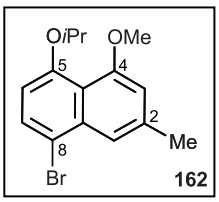


At 0 °C a solution of *n*-butyllithium in *n*-hexane (100 mL, *c* = 1.6 M, 3.6 equiv., 160 mmol) was added dropwise to *N*-diisopropylamine (15.8 g, 3.5 equiv., 156 mmol). The solution was stirred for 90 min at room temperature. The resulting sludge was dissolved in 150 mL abs. THF. At -78 °C a solution of **84** (7.10 g, 1.0 equiv., 46.0 mmol) in 30 mL abs. THF was added dropwise. After stirring at -78 °C for 2 h, 1,3-dibromo-4-isopropoxybenzene (**160**) (30.9 g, 2.3 equiv., 105 mmol) was added. The solution was slowly warmed to room temperature over 48 h. At 0 °C the mixture was quenched with 150 mL of an aqueous saturated solution of NH_4Cl followed by the addition of 100 mL of an aq. 10% HCl solution. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with water, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 17:1) to yield **161** (2.77 g, 9.40 mmol, 20%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.49 (d, *J* = 6.0 Hz, 6H,CH_3), 2.47 (s, 3H, CH_3), 4.82 (sept, *J* = 6.0 Hz, 1H, CH), 6.60 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.77 (d, *J* = 1.4 Hz, 1H, Ar-H), 7.46 (m, 1H, Ar-H), 7.56 (d, *J* = 8.2 Hz, 1H, Ar-H), 9.78 (s, Ar-OH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 73.3, 106.2, 113.2, 114.3, 115.2, 118.0, 129.7, 134.7, 139.6, 154.1, 155.0 ppm.

8-Bromo-4-methoxy-5-isopropoxy-2-methylnaphthalene (162):



To a solution of **161** (2.77 g, 1.0 equiv., 9.40 mmol), sodium hydroxide (9.40 g, 25.0 equiv., 235 mmol), and benzyltributyl-ammonium chloride (1.80 g, 0.6 equiv., 5.70 mmol) in 100 mL CH_2Cl_2 and 30 mL H_2O, Me_2SO_4 (6.30 mL, 8.33 g, 7.0 equiv., 66.0 mmol) was added dropwise at 0 °C. The solution was stirred 48 h at room temperature. After separation, the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried

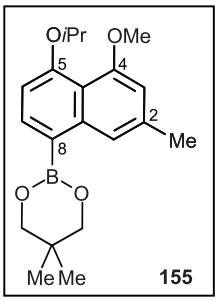
over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:1) to yield **162** (1.55 g, 5.00 mmol, 53%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (d, J = 6.1 Hz, 6H,CH_3), 2.50 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.50 (sept, J = 6.1 Hz, 1H, CH), 6.72 (m, 2H, Ar-H), 7.60 (m, 2H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 22.2, 56.6, 73.3, 109.6, 112.5. 140.0, 119.0, 119.5, 130.5, 135.2, 137.8, 155.1, 157.2 ppm.

4-Methoxy-5-isopropoxy-2-methylnaphthyl-8-boronic acid neopentylglycol ester (155):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of **162** (100 mg, 1.0 equiv., 324 µmol), $Pd(PPh_3)_4$ (37.5 mg, 0.1 equiv., 34.2 µmol), KOAc (191 mg, 6.0 equiv., 1.94 mmol), and $(BNeop)_2$ (181 mg, 2.5 equiv., 809 µmol) in 12 mL abs. DMF was stirred at 100 °C overnight. The solvent was removed, the resulting residue was dissolved in Et_2O and passed through a short pad of Celite. The crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 4:1) to yield **155** (106 mg, 309 µmol, 95%) as a green oil.

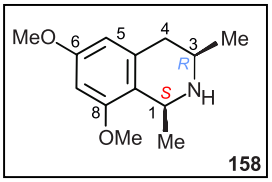
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (s, 6H, CH_3), 1.34 (d, J = 6.0 Hz, 6H,CH_3), 2.42 (s, 3H, CH_3), 3.83 (s, 4H, OCH_2), 3.85 (s, 3H, OCH_3), 4.60 (sept, J = 6.0 Hz, 1H, CH), 6.73 (s, 1H, Ar-H), 6.82 (d, J = 7.9 Hz, 1H, Ar-H), 7.80 (d, J = 7.9 Hz, 1H, Ar-H), 8.10 (m, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.8, 22.2, 22.3, 30.6, 32.3, 56.9, 72.3, 72.9, 109.6, 110.2, 122.4, 136.6, 136.9, 142.2, 158.1, 158.2 ppm.

HRMS (ESI, positive) calcd. for $C_{20}H_{27}BNaO_4$ $[M + Na]^+$ 365.1888; found 365.1895.

(1*S*,3*R*)-Dimethyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (158):

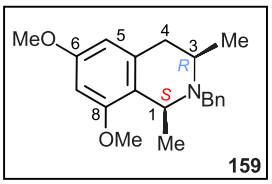
All reactions were performed under an N_2 atmosphere.



A solution of **157** (200 mg, 1.0 equiv., 913 µmol) in 10 mL abs. MeOH was cooled to 0 °C. $NaBH_4$ (87.0 mg, 2.5 equiv., 2.30 mmol) was added to the solution and it was stirred for 2 h at 0 °C. The mixture was quenched by the addition of water, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo to yield the desired diastereomer **158** (202 mg, 913 µmol, quant.) as a brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.20 (d, J = 6.5 Hz, 3H, CH_3), 1.42 (d, J = 6.2 Hz, 3H, CH_3), 2.42 (dd, J = 17.3 Hz, 11.6 Hz, 1H, CH_2), 2.61 (dd, J = 15.2 Hz, 3.4 Hz, 1H, CH_2), 2.85 (m, 1H + 1H, CH_2, CH), 3.76 (s, 6H, OCH_3), 4.20 (q, J = 6.0 Hz, 1H, CH), 6.24 (d, J = 3.0 Hz, 1H, Ar-H), 6.30 (d, J = 2.6 Hz, 1H, Ar-H) ppm.

***N*-Benzyl-(1*S*,3*R*)-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (159):**



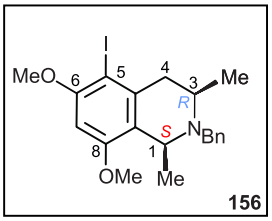
A mixture of **158** (383 mg, 1.0 equiv., 1.73 mmol), Cs_2CO_3 (1.41 g, 2.5 equiv., 4.33 mmol), and benzyl bromide (444 mg, 397 µL, 1.5 equiv., 2.60 mmol) in 30 mL acetone was stirred overnight at room temperature, the suspension was filtered, concentrated in vacuo, and the crude product was purified by column chromatography (SiO_2, *n*-hexane/Et_2O, 20:1, 1% NEt_3) to yield **159** (511 mg, 1.68 mmol, 95%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (m, 6H, $CH(CH_3)_2$), 1.26 (d, J = 6 Hz, 3H, CH_3), 1.29 (d, J = 6 Hz, 3H, CH_3), 2.53 (dd, J = 16 Hz, 8 Hz, 1H, CH_2), 2.83 (m, 1H, CH), 2.97 (dd, J = 16 Hz, 5 Hz, 1H, CH_2), 3.69 (d, J = 14 Hz, 1H, CH_2), 3.86 (d, J = 14 Hz, 1H, CH_2), 4.19 (q, J = 7 Hz, 1H, CH), 4.45 (sept, J = 6 Hz, 1H, $CH(CH_3)_2$), 6.60 (d, J = 9 Hz, 1H, Ar-H) 7.21-7.38 (m, 6H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 22.2, 22.3, 22.7, 29.8, 36.2, 52.5, 52.9, 59.0, 70.1, 111, 115, 127, 128, 129, 130, 132, 136, 141, 153 ppm.

_N_-Benzyl-(1_S_,3_R_)-6,8-dimethoxy-5-iodo-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (156):

All reactions were performed under an N_2 atmosphere.

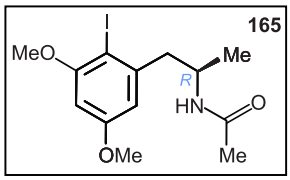


To a solution of **159** (370 mg, 1.0 equiv., 1.19 mmol) in 10 mL THF a 1.6 M solution of *n*-BuLi in *n*-hexane (1.49 mL, 2.0 equiv., 2.38 mmol) was added dropwise at -78 °C. This mixture was stirred for 30 min at 0 °C, iodine (603 mg, 2.0 equiv., 2.38 mmol) dissolved in 3 mL THF was added dropwise at -78 °C. After stirring at room temperature for 30 min, H_2O was added cautiously. The product was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo to yield **156** (483 mg, 1.11 mmol, 93%) as an orange oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (d, J = 7 Hz, 3H, CH_3), 1.19 (d, J = 7 Hz, 3H, CH_3, 2.64 (m, 2H, CH_2), 2.61 (dd, J = 15.2 Hz, 3.4 Hz, 1H, CH_2), 3.64 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.01 (q, J = 7 Hz, 1H, CH), 6.38 (s, 1H, Ar-H), 7.13-7.45 (m, 5H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.2, 23.4, 35.3, 51.5, 53.2, 55.5, 58.6, 60.1, 79.9, 105.9, 125.7, 127.1, 127.6 ppm.

(_R_)-1-Iodo-6-(_N_-acetyl-2'-aminopropyl)-2,4-dimethoxybezene (165):



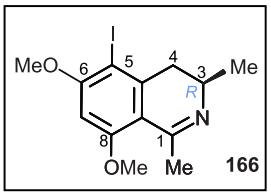
A solution of **164** (1.30 g, 1.0 equiv., 5.48 mmol) and *N*-iodosuccinimide NIS (1.23 g, 1.0 equiv., 5.48 mmol) in 100 mL MeCN was stirred for 24 h at room temperature. The solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 1:5) to yield **165** (1.67 g, 4.60 mmol, 84%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (d, J = 7.2 Hz, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.93 (dd, J = 13.7 Hz, 6.5 Hz, 1H, CH_2), 3.03 (dd, J = 13.7 Hz, 8.0 Hz, 1H, CH_2), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.34 (m, 1H, CH), 6.30 (d, J = 2.6 Hz 1H, Ar-H), 6.49 (d, J = 2.6 Hz 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.7, 46.6, 55.7, 56.6, 56.9, 82.9, 93.7, 97.4, 107.2, 143.4, 158.9, 161.0, 177.6 ppm.

HRMS (ESI, positive) calcd. for $C_{13}H_{18}INNaO_2$ $[M+ Na]^+$ 386.0224; found 386.0210.

(*R*)-5-Iodo-6,8-dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline (166):



To a solution of **165** (2.73 g, 1.0 equiv., 7.52 mmol) in 120 mL MeCN, $POCl_3$ (6.91 g, 4.12 mL, 6 equiv., 45.1 mmol) was added dropwise. The reaction mixture was refluxed and stirred for 2 h. After cooling to 0 °C, water was added cautiously. The solution was basified with 1 N NaOH. After extraction with CH_2Cl_2, the organic phase was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, n-hexane/Et_2O, 4:1, 1% NEt_3) to yield **166** (1.17 g, 3.38 mmol, 45%) as a brown oil.

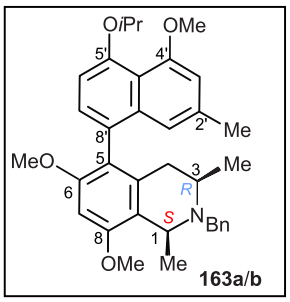
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (d, J = 6.8 Hz, 3H, CH_3), 2.28 (dd, J = 16.2 Hz, 13.0 Hz, 1H, CH_2), 2.44 (d, J = 1.9 Hz, 3H, CH_3), 2.93 (dd, J = 16.0 Hz, 4.6 Hz, 1H, CH_2), 3.30 (m, 1H, CH), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.40 (s, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.9, 26.9, 29.7, 29.8, 40.2, 51.8, 55.8, 56.6, 76.8, 81.7, 94.4, 115.2, 145.2, 159.8, 160.3 ppm.

HRMS (ESI, positive) calcd. for $C_{13}H_{17}INO_2$ $[M]^+$ 346.0299; found 346.0308.

1-*epi*-*N*-Benzyl-6,8-*O*-dimethyl-5'-*O*-isopropylkorupensamines A and B (163a/b):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed



163a/b

Naphthalene **155** (33.8 mg, 2.0 equiv., 103 µmol), isoquinoline **156** (20.0 mg, 1.0 equiv., 51.5 µmol), K_3PO_4 (43.7 mg, 4.0 equiv., 206 µmol), SPhos (8.46 mg, 0.4 equiv., 20.6 µmol) and $Pd_2(dba)_3$ (4.72 mg, 0.1 equiv., 5.15 µmol) were dissolved in 8 mL abs. toluene. This solution was stirred for 48 h at 100 °C. The solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to yield **163a/b** (98.0 mg, 45.3 µmol, 78%) as a green oil.

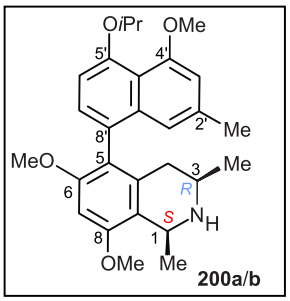
Yield: 23.0 mg (45.3 µmol, 78%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (d, J = 7 Hz, 3H, CH_3), 1.30-1.46 (m, 9H, 3 x CH_3), 2.31 and 2.36 (s, 3H, CH_3), 3.02 (m, *2*H, CH_2), 3.61-3.67 (m, 3H, OCH_3), 3.75 and 3.79 (s, 3H, OCH_3), 3.92 and 3.94 (s, 3H, OCH_3), 4.01 (m, 1H, CH), 4.58 (m, 1H, CH), 6.61 (m, 2H, Ar-H), 6.92 (m, 2H, Ar-H), 7.20-7.58 (m, 6H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.2, 27.4, 35.6, 52.4, 54.9, 55.4, 59.4, 59.7, 71.7, 71.8, 105, 107, 127, 127.9, 128 ppm.

HRMS (ESI, positive) calcd. for $C_{35}H_{41}NO_4$ $[M + H]^+$ 539.3030; found 539.3005.

1-*epi*-6,8-*O*-Dimethyl-5'-*O*-isopropylkorupensamines A and B (200a/b):



200a/b

163a/b (10.0 mg, 1.0 equiv., 18.6 µmol) and Pd/C (12.3 mg, 1.0 equiv., 10% Pd, 11.6 µmol) were stirred in *i*-PrOH under an H_2 atmosphere overnight. The suspension was filtrated over Celite using CH_2Cl_2 as the eluent. The solvent was removed under reduced pressure to yield **200a/b** (7.30 mg, 16.3 µmol, 87%) as a yellow oil.

Yield: 7.30 mg (16.3 µmol, 87%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (d, J = 7 Hz, 3H, CH_3), 1.23 (d, J = 5 Hz, 3H, CH_3),1.38 (m, 6H, 3 x CH_3), 3.62 (m, 2H, CH_2), 3.61-3.80 (m, 9H, 3 x OCH_3), 3.92 (m, 1H, CH), 4.58 (m, 1H, CH), 6.64-7.31 (m, 6H, Ar-H) ppm.

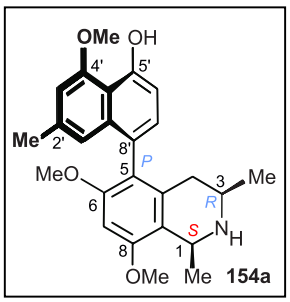
HRMS (ESI, positive) calcd. for $C_{28}H_{34}NO_4$ $[M + H]^+$ 448.2482; found 448.2451.

1-*epi*-6,8-*O*-Dimethylkorupensamines A and B (154a/b):

All reactions were performed under an N_2 atmosphere.

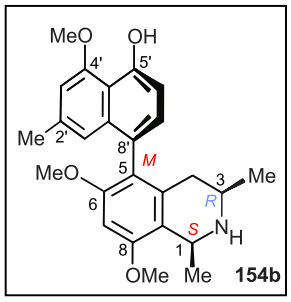
To a solution of **163a/b** (13.3 mg, 1.0 equiv., 29.7 µmol) in 2 mL CH_2Cl_2 a 1 M solution of BCl_3 in CH_2Cl_2 (13.9 mg, 118 µL, 4.0 equiv., 118 µmol) was added at 0 °C and the mixture was stirred at 0 °C for 2 h. Cautious addition of MeOH stopped the reaction. After filtration over Celite, the solvent was removed under reduced pressure to yield **154a/b** (12.0 mg, 29.7 µmol, quant.) as a yellow oil. The atropo-diastereomers were resolved by preparative HPLC on an XSelect column using an isocratic system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeOH + 0.05% TFA): 4.7 mL min^{-1}; 0 min 70% B, 50 min 70% B.

^{1}H NMR (MeOD, 400 MHz): δ = 1.56 (d, J = 7.2 Hz, 3H, CH_3), 1.76 (d, J = 6.5 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.06 (s, 3H, OCH_3), 3.63 (s, 3H, CH_3), 4.09 (s, 3H, OCH_3), 4.74 (q, J = 5.4 Hz, 1H, CH), 6.76 (m, 4H, Ar-H), 7.11 (d, J = 8.5 Hz, 4H, Ar-H) ppm.



HRMS (ESI, positive) calcd. for $C_{25}H_{28}NO_3$ $[M]^+$ 406.2013; found 406.2005.

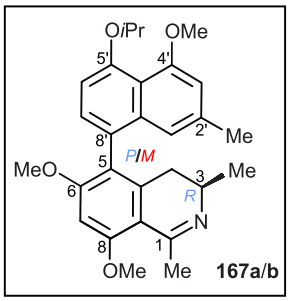
^{1}H NMR (MeOD, 400 MHz): δ = 1.56 (d, J = 7.2 Hz, 3H, CH_3), 1.74 (d, J = 7.3 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.15 (s, 3H, OCH_3), 3.52 (m, 1H, CH), 3.65 (s, 3H, CH_3), 4.10 (s, 3H, OCH_3), 4.74 (q, J = 6.3 Hz, 1H, CH), 6.77 (m, 4H, Ar-H), 7.12 (d, J = 7.3 Hz, 4H, Ar-H) ppm.



HRMS (ESI, positive) calcd. for $C_{25}H_{28}NO_3$ $[M]^+$ 406.2013; found 406.2011.

5'-*O*-Isopropylancistrolikokine E_3 and 5'-*O*-isopropylancistrobonsoline A_2 (167a/b):

All reactions were performed under an N_2 atmosphere. Prior to use, the solvent had been degassed.



A solution of **155** (79.3 mg, 1.0 equiv., 231 µmol), isoquinoline **166** (120 mg, 1.5 equiv., 348 µmol), K_3PO_4 (198 mg, 4.0 equiv., 927 µmol), SPhos (38.0 mg, 0.4 equiv., 92.7 µmol), and $Pd_2(dba)_3$ (21.2 mg, 0.1 equiv., 23.2 µmol) in 8 mL abs. toluene was stirred for 48 h at 100 °C. The solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to yield **167a/b** (98.0 mg, 180 µmol, 78%) as a green oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.42-1.48 (m, 9H, 3 x CH_3), 2.00 (d, J = 8 Hz, 1H, CH), 2.30 and 2.32 (s, 3H, CH_3), 2.99 and 3.00 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.61 (sep, J = 5.9 Hz, 1H, $CH(CH_3)_2$), 6.48-5.30 (m, 2H, 2 x Ar-H), 7.11 (m, 3H, 2 x Ar-H) ppm.

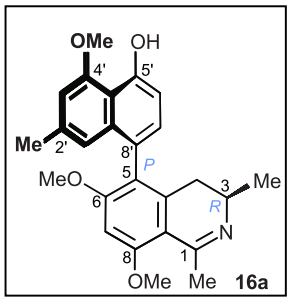
HRMS (ESI, positive) calcd. for $C_{28}H_{34}NO_4$ $[M + H]^+$ 448.2482; found 448.2486.

Ancistrolikokine E_3 (16a) and ancistrobonsoline A_2 (16b):

All reactions were performed under an N_2 atmosphere.

To a solution of **167a/b** (10.0 mg, 1.0 equiv., 22.3 µmol) in 3 mL CH_2Cl_2 a 1 M solution of BCl_3 in CH_2Cl_2 (5.42 mg, 44.7 µL, 2.0 equiv., 44.7 µmol) was added at 0 °C. This mixture was stirred at 0 °C for 1 h. Cautious addition of H_2O stopped the reaction. The solvent was removed in vacuo and the residue was suspended in CH_2Cl_2. After filtration over Celite, the solvent was removed under reduced pressure to yield **16a/b** (9.02 mg, 22.2 µmol, 99%) as an orange oil. The two atropo-diastereomers were resolved by preparative HPLC on an XSelect column using an isocratic system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeOH + 0.05% TFA): 4.7 mL min^{-1}; 0 min 70% B, 50 min 70% B. The faster peak eluting at 15.0 min was identified as ancistrolikokine E_3 (**16a**), the later one at 16.1 min as ancistrobonsoline A_2 (**16b**).

Ancistrolikokine E_3 (**16a**):



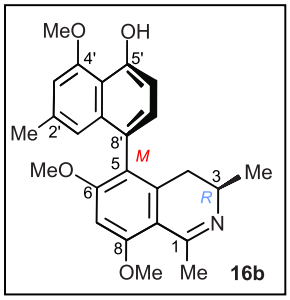
^{1}H NMR (MeOD, 400 MHz): δ = 1.21 (d, J = 6.5 Hz, 3H, CH_3), 2.28 (dd, J = 20.0 Hz, 9.3 Hz 1H, CH_3), 2.31 (s, 3H, CH_3), 2.70 (dd, J = 16.8 Hz, 5.6 Hz 1H, CH_3), 2.83 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.59 (s, 1H, Ar-H), 6.80 (d, J = 7.9 Hz, 1H, Ar-H), 6.82 (s, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 7.07 (d, J = 8.4, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.8, 22.1, 24.9, 32.6, 56.9, 57.0, 95.7, 118.5, 123.2, 130.9 ppm.

HRMS (ESI, positive) calcd. for $C_{25}H_{27}NO_4$ $[M + H]^+$ 405.1935; found 405.1937.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[133]

Ancistrobonsoline A_2 (**16a**):



^{1}H NMR (MeOD, 400 MHz): δ = 1.42 (d, J = 5.7 Hz, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 4.77 (q, J = 6.3 Hz, 1H, CH), 6.65 (s, 1H, Ar-H), 6.79 (d, J = 7.8 Hz, 1H, Ar-H), 6.83 (m, 2H, Ar-H), 7.02 (d, J = 8.0, 1H, Ar-H) ppm.

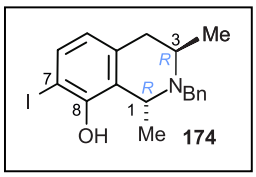
HRMS (ESI, positive) calcd. for $C_{25}H_{28}NO_4$ $[M + H]^+$ 406.2013; found 406.1989.

The obtained physical and spectroscopic data were in agreement with those reported in the literature.[134]

Synthesis of the Lactones *en route* to 4'-*O*-Demethyl-7-*epi*-dioncophylline A and Dioncophylline E

N-Benzyl-(1*R*,3*R*)-7-iodo-8-hydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (174):

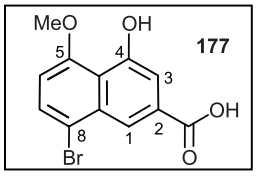
All reactions were performed under an N_2 atmosphere.



To a solution of tetrahydroisoquinoline **124** (300 mg, 1.0 equiv., 685 µmol) in 6 mL CH_2Cl_2, TFA (180 µL, 4.0 equiv., 2.74 mmol) was added dropwise. This mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 8:1) to yield **174** (160 mg, 405 µmol, 60%) as an orange oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (d, J = 9.2 Hz, 3H, CH_3), 1.35 (d, J = 8.4 Hz, 3H, CH_3), 2.60 (m, 2H, CH_2), 3.25 (d, J = 14.3 Hz, 1H, CH), 3.50 (m, 1H, CH), 3.85 (d, J = 14.3 Hz, 1H, CH), 3.99 (q, J = 7.6 Hz, 1H, CH), 6.48 (d, J = 9.2 Hz, 1 H, Ar-H), 7.20-7.38 (m, 5H, Ar-H), 7.42 (d, J = 8.4 Hz, 1 H, Ar-H) ppm.

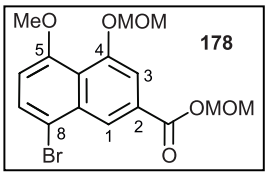
8-Bromo-4-hydroxy-5-methoxy-2-naphthoate (177):



176 (33.2 g, 1.0 equiv., 96.7 mmol) was dissolved in Ac_2O and heated to reflux for 1 h. This mixture was poured onto ice water. The resulting acetic acid was removed in vacuo. The residue was refluxed in a mixture of 30 g NaOH in 250 mL H_2O and 50 mL MeOH for 20 min and poured onto ice cold half-concentrated HCl. The precipitate was collected by filtration and dried under reduced pressure to yield **177** (17.2 g, 58.0 mmol, 60%) as a colorless powder.

^{1}H NMR (DMSO, 400 MHz): δ = 4.04 (s, 3H, OCH_3), 7.04 (d, J = 8.6 Hz, 1H, Ar-H), 7.34 (d, J = 2.0 Hz, 1H, Ar-H), 7.85 (d, J = 8.3 Hz, 1H, Ar-H), 8.24 (d, J = 2.4 Hz, 1H, Ar-H), 9.85 (s, 1H, OH) ppm.

8-Bromo-4-methoxymethoxy-5-methoxy-2-naphthoate methoxymethoxy ester (178):

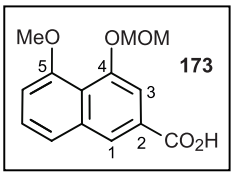


A mixture of **177** (6.00 g, 1.0 equiv., 20.2 mmol), Cs_2CO_3 (16.4 g, 2.5 equiv., 50.5 mmol), and chloromethoxy methane (3.25 g, 2.0 equiv., 40.4 mmol) in 100 mL acetone was stirred overnight. The solvent was removed, the residue was dissolved in CH_2Cl_2 and passed through a pad of Celite. The crude product was purified by column chromatography on silica (SiO_2, *n*-hexane/EtOAc, 2:1) to yield **178** (5.83 g, 15.2 mmol, 75%) as an orange foam.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.53 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 2H, OCH_2), 5.25 (s, 2H, OCH), 6.75 (d, J = 9.1 Hz, 1H, Ar-H), 7.59 (d, J = 2.4 Hz, 1H, Ar-H), 7.55 (d, J = 7.7 Hz, 1H, Ar-H), 8.58 (d, J = 2.4 Hz, 1H, Ar-H) ppm.

5-Methoxy-4-(methoxymethoxy)-2-naphthoic acid (173):

The solvent had been degassed prior to use.

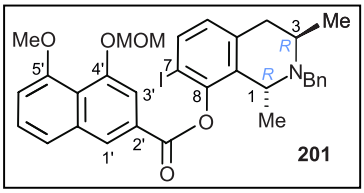


A solution of **178** (5.00 g, 1.0 equiv., 171 µmol) and Pd/C (500 mg) in 50 mL MeOH was stirred under a hydrogen atmosphere overnight. A 1 M solution of aq. NaOH was added and the mixture was heated to reflux for 30 min. After cooling to room temperature, 100 mL CH_2Cl_2 were added and the solution was neutralized by carefully adding a 1 M aq. HCl while stirring. The phases were separated and the organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo to yield **173** (2.89 g, 11.03 mmol, 85%) as a colorless foam.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 13.61 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.31 (s, 2H, OCH_2), 6.98 (d, J = 9.1 Hz, 1H, Ar-H) 7.54 (d, J = 9.4 Hz, 1H, Ar-H), 7.61 (d, J = 1.6 Hz, 1H, Ar-H), 8.29 (d, J = 1.6 Hz, 1H, Ar-H) ppm.

[(1*R*,3*R*)-*N*-Benzyl-7-iodo-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-8-yl]5'-methoxy-4'-methoxymethoxy-2'-naphthoate (201):

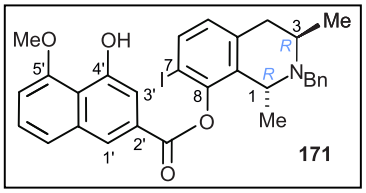
All reactions were performed under an N_2 atmosphere.



A solution of **173** (88.0 mg, 1.1 equiv., 336 µmol), isoquinoline **174** (120 mg, 1.0 equiv., 305 µmol), DCC (139 mg, 2.2 equiv., 671 µmol), DMAP (8.20 mg, 0.2 equiv., 67.1 µmol) in 4 mL abs. CH_2Cl_2 was stirred for 24 h at room temperature. The crude product was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 7:1) to yield **201** (106 mg, 165 µmol, 54%) as a colorless foam.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (d, J = 6.5 Hz, 3H, CH_3), 1.32 (d, J = 6.0 Hz, 3H, CH_3), 2.66 (m, 2H, CH_2), 3.22 (d, J = 13.1 Hz, 1H, CH), 3.52 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 3.69 (q, J = 6.9 Hz, 1H, CH), 3.79 (d, J = 13.1 Hz, 1H, CH), 3.98 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2), 6.84 (d, J = 8.5 Hz, 1H, Ar-H), 6.99 (d, J = 8.1 Hz, 1H, Ar-H), 7.06-7.38 (m, 5H, Ar-H), 7.46 (t, J = 7.0 Hz, 1 H, Ar-H), 7.54 (d, J = 7.8 Hz, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.66 (d, J = 8.2 Hz, 1H, Ar-H) ppm.

[(1*R*,3*R*)-2-Benzyl-7-iodo-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-8-yl]4'-hydroxy-5'-methoxy-2'-naphthoate (171):



Compound **201** (88.0 mg, 1.0 equiv., 138 µmol) was dissolved in 3 mL CH_2Cl_2 and TFA (36.2 µL, 53.6 mg, 4.0 equiv., 552 µmol) was added. This solution was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 6:1) to yield **171** (74.8 mg, 126 µmol, 91%) as a colorless foam.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29-1.37 (m, 6H, 2 x CH_3), 2.59-2.77 (m, 2H, CH_2), 3.11 (d, J = 13.1 Hz, 1H, CH), 3.18-3.30 (m, 1H, CH), 4.08 (m, 5H, 2 x CH, 1 x OCH_3), 6.85 (d, J = 8.5 Hz, 1H, Ar-H), 6.91 (d, J = 8.1 Hz, 1H, Ar-H), 7.06-7.38 (m, 5H, Ar-H), 7.40 (t, J = 8.2 Hz, 1 H, Ar-H), 7.48 (s, 1H, Ar-H), 7.54 (d, J = 8.2 Hz, 1H, Ar-H), 7.67 (d, J = 7.7 Hz, 1H, Ar-H), 8.10 (s, 1H, Ar-H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.7, 29.7, 45.6, 49.7, 51.3, 56.4, 106, 109, 109.8, 117, 122, 123, 126, 127, 128.2, 128.5, 129, 134, 135, 135.8, 143, 155, 156 ppm.

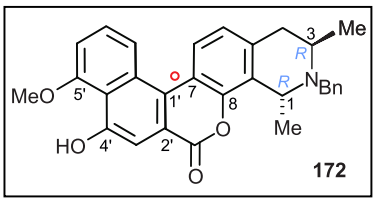
HRMS (ESI, positive) calcd. for $C_{30}H_{29}INO_4$ $[M]^+$ 594.1136; found 594.1098.

Lactone precursors of 4'-*O*-demethyl-7-*epi*-dioncophylline A and dioncophylline E (172/175):

All reactions were performed under an N_2 atmosphere. The solvent had been degassed prior to use.

A solution of **173** (70.0 mg, 1.0 equiv., 138 µmol), NaOAc (38.7 mg, 4.0 equiv., 471 µmol), and $Pd(PPh_3)Cl_2$ in 3 mL abs. DMA was stirred for 24 h at 100 °C. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 4:1) to yield the separated regioisomeric lactones **175** (10.0 mg, 126 µmol, 19%) and **172** (11.0 mg, 126 µmol, 20%) as yellow oils.

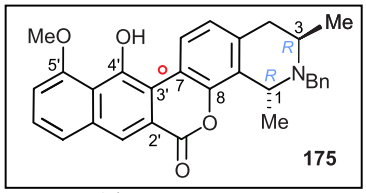
Lactone precursor **172** of 4'-*O*-demethyl-7-*epi*-dioncophylline A:



^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (m, 3H, CH_3), 1.56 (m, 3H, CH_3), 2.77 (m, 2H, CH_2), 3.35 (m, 1H, CH), 3.63 (m, 1H, CH), 4.14 (s, 3H, OCH_3), 4.39 (m, 1H, CH), 7.08 (d, J = 7.3 Hz, 1H, Ar-H), 7.08-7.42 (m, 5H, Ar-H), 7.55 (t, J = 8.9 Hz, 1 H, Ar-H), 7.64 (s, 1H, Ar-H), 8.14 (m, 1H, Ar-H), 8.46 (d, J = 8.9 Hz, 1H, Ar-H) ppm.

HRMS (ESI, positive) calcd. for $C_{30}H_{28}NO_4$ $[M]^+$ 466.2013; found 466.2017.

Lactone precursor **175** of dioncophylline E:



^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.25 (m, 3H, CH_3), 1.60 (m, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.33 (m, 1H, CH), 3.62 (m, 1H, CH), 3.76 (d, J = 13.1 Hz, 1H, CH), 4.17 (s, 3H, OCH_3), 4.36 (m, 1H, CH), 6.98 (d, J = 7.6 Hz, 1H, Ar-H), 7.08 (d, J = 8.7 Hz, 1H,

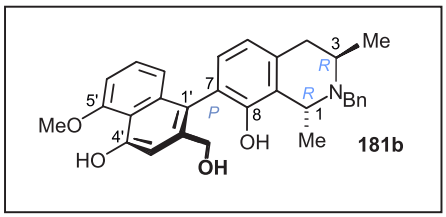
Ar-H), 7.08-7.45 (m, 5H, Ar-H), 7.59 (t, J = 7.6 Hz, 1 H, Ar-H), 7.64 (s, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 8.48 (s, 1H, Ar-H) ppm.

HRMS (ESI, positive) calcd. for $C_{30}H_{28}NO_4$ $[M]^+$ 466.2013; found 466.2000.

Total Synthesis of 4'-*O*-Demethyl-7-*epi*-dioncophylline A

(1*R*,3*R*,7*P*)-*N*-Benzyl-7-(4'-hydroxy-2'-(hydroxymethyl)-5'-methoxynaphthalene-1'-yl)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-8-ol (181b):

All reactions were performed under an N_2 atmosphere.



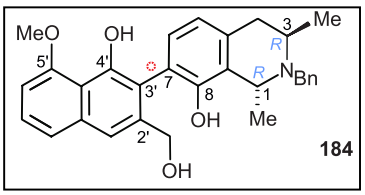
To a solution **174** (4.40 mg, 1.0 equiv., 9.45 µmol) in 1 mL THF a 1 M solution of BH_3 in THF (0.52 mg, 4.0 equiv., 37.8 µmol) and a 1 M solution of (*R*)-**VI** (10.5 mg, 4.0 equiv., 37.8 µmol) were added at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. Addition of H_2O stopped the reaction. The reaction mixture was extracted into CH_2Cl_2, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 4:1) to yield **181b** (3.20 mg, 6.80 µmol, 72%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (d, J = 5.3 Hz, 3H, CH_3), 1.55 (m, 3H, CH_3), 2.78 (m, 2H, CH_2), 3.36 (m, 1H, CH), 3.63 (m, 1H, CH), 4.14 (s, 3H, OCH_3), 4.38 (q, J = 6.2 Hz, 1H, CH), 7.10 (d, J = 7.3 Hz, 1H, Ar-H), 7.30 (m, 5H, Ar-H), 7.54 (t, J = 8.9 Hz, 1 H, Ar-H), 7.64 (s, 1H, Ar-H), 8.14 (m, 1H, Ar-H), 8.46 (d, J = 8.8 Hz, 1H, Ar-H) ppm.

Total Synthesis of Dioncophylline E

(1*R*,3*R*,7*M*/*P*)-2-Benzyl-7-(4'-hydroxy-2'-(hydroxymethyl)-5'-methoxy-naphthalene-3'-yl)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-8-ol (184):

All reactions were performed under an N_2 atmosphere.



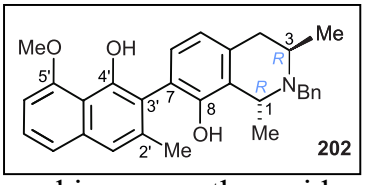
To a solution of **175** (7.90 mg, 1.0 equiv., 16.9 µmol) in 3 mL THF, $LiAlH_4$ (1.93 mg, 3.0 equiv., 171 µmol) was added at 0 °C and the mixture was stirred for 1 h. Cautious addition of H_2O stopped the reaction. The reaction mixture was extracted into CH_2Cl_2, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified

by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 6:1) to yield **184** (5.40 mg, 11.5 µmol, 68%) as a colorless oil.

HRMS (ESI, positive) calcd. for $C_{30}H_{32}NO_4$ $[M]^+$ 470.2326; found 470.2365.

N-Benzyldioncophylline E (202):

All reactions were performed under an N_2 atmosphere.



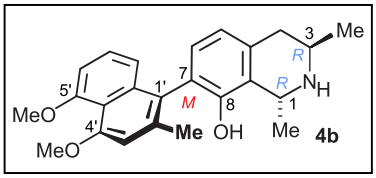
Compound **184** (4.40 mg, 1.0 equiv., 9.37 µmol), PPh_3 (4.92 mg, 2.0 equiv., 18.7 µmol), and $(BrCl_2C)_2$ (6.10 mg, 2.0 equiv., 18.7 µmol) were dissolved in 3 mL CH_2Cl_2 and stirred for 15 min at room temperature. The solvent was removed in vacuo, the residue was dissolved in THF and cooled to 0 C. $LiAlH_4$ (1.00 mg, 3.0 equiv., 28.1 µmol) was added and the mixture was stirred for 30 min. After addition of HCl, the reaction mixture was extracted into CH_2Cl_2, dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 6:1) to yield **202** (2.72 mg, 5.99 µmol, 64%) as a colorless oil.

HRMS (ESI, positive) calcd. for $C_{30}H_{31}NO_3$ $[M + H]^+$ 454.2377; found 454.2395.

Semi-synthesis of 4'-*O*-Demethyl-7-*epi*-dioncophylline A

7-*epi*-dioncophylline A (4b):

All reactions were performed under an N_2 atmosphere.



A degassed solution of dioncophylline A (**4a**) (10.0 mg, 1.0 equiv., 106 µmol) in 0.5 mL tetralin was heated to 165 °C for 4 h. The solvent tetralin was removed by eluting with hexane over a column of deactivated silica gel. The atropo-diastereomeric mixture of **4a**/**4b** was obtained by flushing the column with CH_2Cl_2/MeOH (9:1). The two atropo-diastereomers were resolved by preparative HPLC on an XSelect column using an isocratic system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeOH + 0.05% TFA): 5 mL min^{-1}; 0 min 60% B, 50 min 60% B. The faster eluting peak was identified as the starting material, dioncophylline A (**4a**), the later-eluting one as the anticipated 7-*epi*-dioncophylline A (**4b**).

^{1}H NMR (MeOD, 400 MHz): δ = 1.55 (d, J = 6.8 Hz, 3H, CH_3), 1.72 (d, J = 7.3 Hz, 3H, CH_3), 2.14 (s, 3H, CH_3) 2.94 (dd, J = 17.4 Hz, 11.4 Hz, 1H, CH_2), 3.25 (m, 1H, CH_2), 3.93 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 6.85 (d, J = 8.6 Hz, 1H, Ar-H), 6.92 (m, 3H, Ar-H), 7.12 (pt, J = 7.9 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 16.6, 17.9, 19.3, 29.3, 33.0, 43.8, 46.9, 53.4, 55.5, 105.7, 108.8, 118.0, 119.9, 124.5, 126.2, 130.9, 131.3, 136.2, 150.9, 156.9, 157.3 ppm.

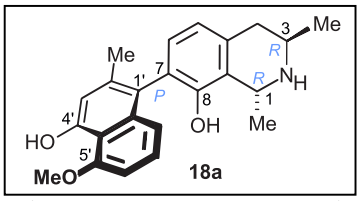
HRMS (ESI, positive) calcd. for $C_{24}H_{28}NO_3$ $[M + H]^+$ 378.2064; found 378.2054.

4'-*O*-Demethyldioncophylline A (18a) and 5'-*O*-demethyldioncophylline A (63a):

All reactions were performed under an N_2 atmosphere.

To a solution of dioncophylline A (**4a**) (40.0 mg, 1.0 equiv., 106 µmol) in 5 mL abs. CH_2Cl_2, iodotrimethylsilane (176 mg, 122 µL, 8 equiv., 880 µmol) was added. This mixture was stirred at room temperature for 12 h. Cautious addition of water stopped the reaction. The solvent was removed under reduced pressure. The crude product was filtered over a short pad of Celite to yield **18a** and **63a** (38.5 mg, 106 µmol, quant.) as a 1:1 mixture. The regioisomers were separated on a Symmetry-RP18 HPLC column

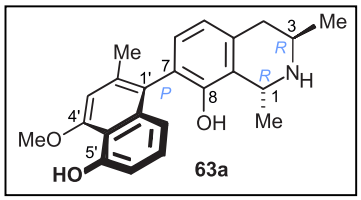
using a gradient system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeCN + 0.05% TFA): 10 mL min^{-1}; 0 min 30% B, 23 min 45% B, 24 min 30% B, 25 min 30% B. The faster eluting peak was identified as 5'-*O*-demethyldioncophylline A (**63a**) the later one as 4'-*O*-demethyldioncophylline A (**18a**).



^{1}H NMR (MeOD, 400 MHz): δ = 1.53 (d, J = 6.4 Hz, 3H, CH_3), 1.69 (d, J = 6.3 Hz, 3H, CH_3), 2.10 (s, 3H, CH_3) 2.93 (dd, J = 17.6 Hz, 11.5 Hz, 1H, CH_2), 3.23 (dd, J = 18.0 Hz, 4.9 Hz, 1H, CH_2), 3.91 (m, 1H, CH), 4.09 (s, 3H, OCH_3), 4.85 (q, J = 6.8 Hz, 1H, CH), 6.81 (s, 1H, Ar-H), 6.86 (m, 3H, Ar-H), 6.93 (d, J = 7.6 Hz, 1H, Ar-H), 7.16 (dd, J = 8.3 Hz, 8.0 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 17.9, 19.3, 20.5, 34.5, 45.2, 56.8, 104.6, 113.7, 120.2, 121.2, 122.0, 124.3, 125.9, 127.1, 132.3, 132.8, 137.8, 138.7, 152.4, 157.9 ppm.

HRMS (ESI, positive) calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907; found 364.1900.



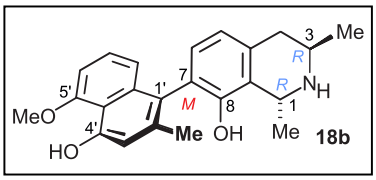
^{1}H NMR (MeOD, 400 MHz): δ = 1.53 (d, J = 6.2 Hz, 3H, CH_3), 1.70 (d, J = 6.5 Hz, 3H, CH_3), 2.16 (s, 3H, CH_3) 2.94 (dd, J = 18.7 Hz, 12.2 Hz, 1H, CH_2), 3.23 (dd, J = 17.1 Hz, 4.6 Hz, 1H, CH_2), 3.90 (m, 1H, CH), 4.12 (s, 3H, OCH_3), 4.86 (q, J = 5.7 Hz, 1H, CH), 6.69 (d, J = 8.4 Hz, 1H, Ar-H), 6.72 (d, J = 7.2 Hz, 1H, Ar-H), 6.86 (d, J = 7.6 Hz, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 6.93 (d, J = 7.8 Hz, 1H, Ar-H), 7.13 (dd, J = 8.3 Hz, 7.7 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 18.2, 19.5, 20.9, 34.7, 45.4, 56.9, 108.2, 110.7, 115.3, 117.7, 121.5, 122.3, 125.9, 127.0, 128.7, 132.6, 132.7, 137.3, 138.1, 152.5, 156.3, 157.7 ppm.

HRMS (ESI, positive) calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907; found 364.1900.

4'-*O*-Demethyl-7-*epi*-dioncophylline A (18b):

All reactions were performed under an N_2 atmosphere.



A degassed solution of 4'-*O*-demethyldioncophylline A (**18a**) (10.0 mg, 1.0 equiv., 27.5 µmol) in 0.5 mL tetralin was heated to 165 °C for 4 h. The solvent tetralin was removed by eluting with *n*-hexane over a column of deactivated silica gel. The atropo-diastereomeric mixture of **18a**/**18b** was obtained by flushing the column with CH_2Cl_2/MeOH (9:1). The two atropo-diastereomers were resolved by preparative HPLC on a Symmetry-RP18 HPLC column using a gradient system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeCN+ 0.05% TFA): 10 mL min^{-1}; 0 min 30% B, 35 min 60% B, 36 min 95% B, 41 min 95% B, 42 min 30% B, 45 min 30% B. The faster eluting peak at 18.5 min was identified as 4'-*O*-demethyl-7-*epi*-dioncophylline A (**18b**) the later-eluting one at 19.3 min as 4'-*O*-demethyldioncophylline A (**18a**).

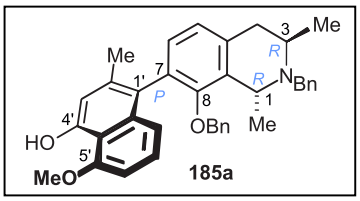
^{1}H NMR (MeOD, 400 MHz): δ = 1.53 (d, J = 6.4 Hz, 3H, CH_3), 1.71 (d, J = 6.9 Hz, 3H, CH_3), 2.09 (s, 3H, CH_3) 2.92 (dd, J = 17.6 Hz, 11.7 Hz, 1H, CH_2), 3.263 (m, 1H, CH_2), 3.93 (m, 1H, CH), 4.09 (s, 3H, OCH_3), 4.86 (m, 1H, CH), 6.81 (s, 1H, Ar-H), 6.85 (d, J = 8.9 Hz, 1H, Ar-H), 6.91 (m, 3H, Ar-H), 7.20 (dd, J = 8.5 Hz, 7.5 Hz, 1H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 18.8, 20.1,21.5, 31.5, 35.3, 45.9, 55.5, 57.6, 57.7, 107.8, 111.0, 120.2, 122.1, 126.7, 128.4, 133.1, 133.4, 138.3, 153.1, 159.1, 159.5 ppm.

HRMS (ESI, positive) calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907; found 364.1893.

Attempted Synthesis of Jozimine A_2 and its Atropisomers

4'-*O*-Demethyl-8-*O*,*N*-dibenzyldioncophylline A (185a):



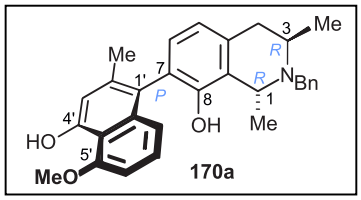
A mixture of 4'-*O*-demethyldioncophylline A (**18a**) (6.80 mg, 1.0 equiv., 18.7 µmol), Cs_2CO_3 (12.2 mg, 2.0 equiv., 37.4 µmol), and benzyl bromide (3.20 mg, 1.0 equiv., 18.7 µmol) in 5 mL acetone was stirred for 3 h at room temperature. Then, after heating to reflux, another equivalent benzyl bromide (3.20 mg, 1.0 equiv., 18.7 µmol) was added gradually (in steps of 0.25 equiv. while always checking the reaction progress by HPLC). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 10:1) and on a Chromolith Performance RP-18 HPLC column using a gradient system consisting of the solvents A (H_2O + 0.05% TFA) and B (MeCN+ 0.05% TFA): 8 mL min^{-1}; 0 min 44% B, 6 min 56% B, 8 min 97% 9 min 97% B, 9.5 min 44% B, 11 min 44% B, to yield (7.93 mg, 15.0 µmol, 80%) of **185a**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.63 (d, J = 6.2 Hz, 3H, CH_3), 1.77(d, J = 6.5 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3) 3.11 (dd, J = 18.8 Hz, 12.0 Hz, 1H, CH_2), 3.03 (dd, J = 17.7 Hz, 5.1 Hz, 1H, CH_2), 3.74 (m, 2H, NCH_2Ph, OCH_2Ph), 3.97 (d, J = 10.3 Hz, 1H, OCH_2Ph), 4.09 (s, 3H, OCH_3) 4.37 (m, 1H, CH), 4.61 (q, J = 6.3 Hz, 1H, CH), 4.72 (d, J = 12.6 Hz, 1H, NCH_2Ph), 6.42 (m, 2H, Ar-H), 6.79 (d, J = 8.0 Hz, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 7.05-7.19 (m, 6H, Ar-H), 7.30-7.51 (m, 7H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 17.2, 19.3, 20.6, 22.6, 29.8, 30.8, 31.1, 49.9, 50.0, 53.6, 56.4, 103.4, 113.1, 113.9, 114.4, 117.2, 119.4, 120.1, 123.9, 124.5, 125.3, 126.2, 127.1, 127.4, 127.5, 128.0, 128.3, 128.6, 129.1, 129.6, 130.0, 130.2, 131.2, 131.4, 133.6, 135.7, 136.2, 137.6, 154.4, 154.5, 156.7, 160.7, 161.1 ppm.

HRMS (ESI, positive) calcd. for $C_{37}H_{38}NO_3$ $[M + H]^+$ 544.2846; found 544.2885.

4'-*O*-Demethyl-*N*-benzyldioncophylline A (170a):



To a solution of 4'-*O*-Demethyldioncophylline A (**18a**) (7.70 mg, 1.0 equiv., 21.2 µmol) in 3 mL acetone, Cs_2CO_3 (27.6 mg, 4.0 equiv., 84.7 µmol) and benzyl bromide (3.62 mg, 1.0 equiv., 21.2 µmol) were added at room temperature and the mixture was stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 5:1) to yield **170a** (8.90 mg, 16.4 µmol, 78%) as a yellow oil.

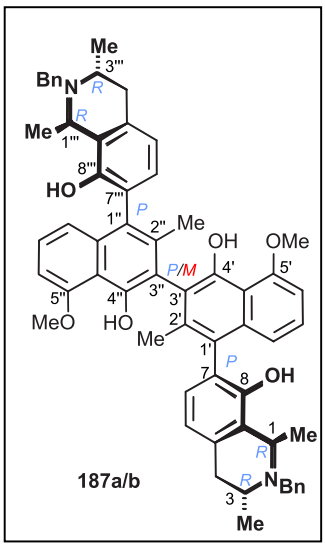
^{1}H NMR (MeOD, 400 MHz): δ = 1.41 (d, J = 6.4 Hz, 3H, CH_3), 1.46 (d, J = 6.5 Hz, 3H, CH_3), 2.10 (s, 3H, CH_3) 2.88 (m, 2H, CH_2), 4.09 (s, 3H, OCH_3) 4.27 (m, 1H, CH), 6.79-7.00 (m, 4H, Ar-H), 7.21-7.41 (m, 6H, Ar-H) ppm.

^{13}C NMR (MeOD, 100 MHz): δ = 20.6, 30.5, 30.9, 33.2, 56.8, 104.7, 113.7, 120.7, 121.4, 127, 128.7, 128.9, 129.1, 129.6, 130.3, 130.9, 137.9, 138.8, 153.1, 156, 158 ppm.

HRMS (ESI, positive) calcd. for $C_{30}H_{32}NO_3$ $[M + H]^+$ 454.2382; found 454.2367.

N,N'''-Dibenzyljozimine A_2 and 3'-*epi*-N,N'''-dibenzyljozimine A_2 (187a/b):

All reactions were performed under an N_2 atmosphere.



To a solution of 4'-*O*-Demethyl-*N*-benzyldioncophylline A (**170a**) (2.5 mg, 1.0 equiv., 5.50 µmol) in 2 mL abs. CH_2Cl_2 a solution of $Pb(OAc)_4$ in dry CH_2Cl_2 (1.25 mg, 0.5 equiv., 2.75 µmol) was added dropwise at 0 °C. After stirring for 15 min at 0 °C, $Na_2S_2O_3$ was added to stop the reaction. The mixture was concentrated in vacuo. The crude product was purified by column chromatography on deactivated silica (SiO_2, *n*-hexane/EtOAc, 1:1) to yield *N*,*N*'''-dibenzyljozimine A_2 (**187a**) and 3'-*epi*-*N*,*N*'''-dibenzyldibenzyljozimine A_2 (**187b**) (1.23 mg, 2.74 µmol, 50%) as a diastereomeric mixture. At this stage the atropo-diastereomers were not resolvable.

HRMS (ESI, positive) calcd. for $C_{60}H_{61}N_2O_6$ $[M + H]^+$ 905.4524, found 905.4510.

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