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# Oxidative aryl coupling reactions: a biomimetic approach to configurationally unstable or axially chiral biaryl natural products and related bioactive compounds[1]

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**Abstract**—Phenolic and non-phenolic oxidative aryl coupling reactions were successfully used in the efficient synthesis of diverse natural products and related compounds in the fields of biphenyls, biscarbazoles and bisnaphthylisoquinolines. For sterically more hindered biaryls, which consequently show the phenomenon of axial chirality, the products were prepared in an atropisomerically pure form. Their absolute axial configurations were assigned mainly by experimental and computational CD investigations. © 2000 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Nature provides a vast number of (frequently axially chiral) biaryl natural products with great structural divergence. For most of them, a biosynthetic origin of the biaryl axis by oxidative phenolic coupling is most probable or has even been proven.[2–5] Following this biosynthetic precedent, a great number of biaryls have been prepared biomimetically, utilizing a broad variety of oxidizing agents,[3,4,6–8] which usually have to be optimized specifically for each particular case. As a necessary precondition for these coupling reactions, the aromatic portions have to be electron rich (ideally phenolic). But even if this is fulfilled, additional problems can arise from the presence of more than one reactive site in the phenolic precursor, so that, depending on the steric and electronic situation, the formation of different regioisomers must be taken into account, besides polymers, overoxidized products, or diaryl ethers.[3,4,7] For this reason, it is not always predictable which of the possible products will be formed predominantly, so that the choice—and thorough optimization—of the oxidizing reagent becomes an important precondition for successful transformations. Numerous investigations on oxidative coupling reagents and their use in biomimetic natural product biaryl syntheses have been part of reviews,[3,4,6–8] so that in this paper, we want to focus on recent achievements in our laboratory, here exemplarily on the synthesis of bioactive biphenyls like mastigophorene A (*P*-**1**)[9], dimeric carbazole alkaloids like bismurrayaquinone-A (**2**) and murrastifoline-F (**3**), and several natural and non-natural dimeric naphthylisoquinolines, e.g. michellamine A (*P*,*P*-**4**) (Fig. 1). Bismurrayaquinone-A (**2**) is a constitutionally symmetric dimer of a monomeric carbazole alkaloid, while murrastifoline-F (**3**) is an unsymmetric dimeric carbazole, both of them axially chiral and thus potentially occurring as atropo-enantiomers. By contrast, mastigophorenes like *P*-**1**, which are likewise constitutionally symmetric, have two (homochiral) stereogenic centers and can exist as—thus $C_2$-symmetric—atropo-*diastereomers*. Michellamine A (*P*,*P*-**4**) is a likewise $C_2$-symmetric molecule possessing four stereogenic centers and even three biaryl axes: the two outer ones are homochiral, but the one created during the oxidative dimerization[10] is configurationally unstable. These constitutional and stereochemical aspects as well as the in some cases most promising bioactivities make such bi- or quarteraryl natural products most attractive synthetic target molecules. Some background information on the respective classes of substances will be given in the corresponding chapters.

## 2. Results and discussion

### 2.1. Mastigophorenes A and B by phenolic oxidative coupling of herbertenediol

The mastigophorenes (**1**) were isolated from the liverwort *Mastigophora diclados* (Hepaticae) and are remarkable for their neurotrophic activities.[11] For their biosynthetic origin, a dimerization of the sesquiterpene (−)-herbertenediol (**9**, Scheme 2) was proposed.[11] In the course of a partial synthesis of the structurally closely related, but sterically less congested and thus configurationally unstable bissesquiterpene aquaticenol, an oxidative coupling of monomeric units

*Keywords*: oxidative biaryl coupling; biphenyls; biscarbazoles; dimeric naphthylisoquinolines.

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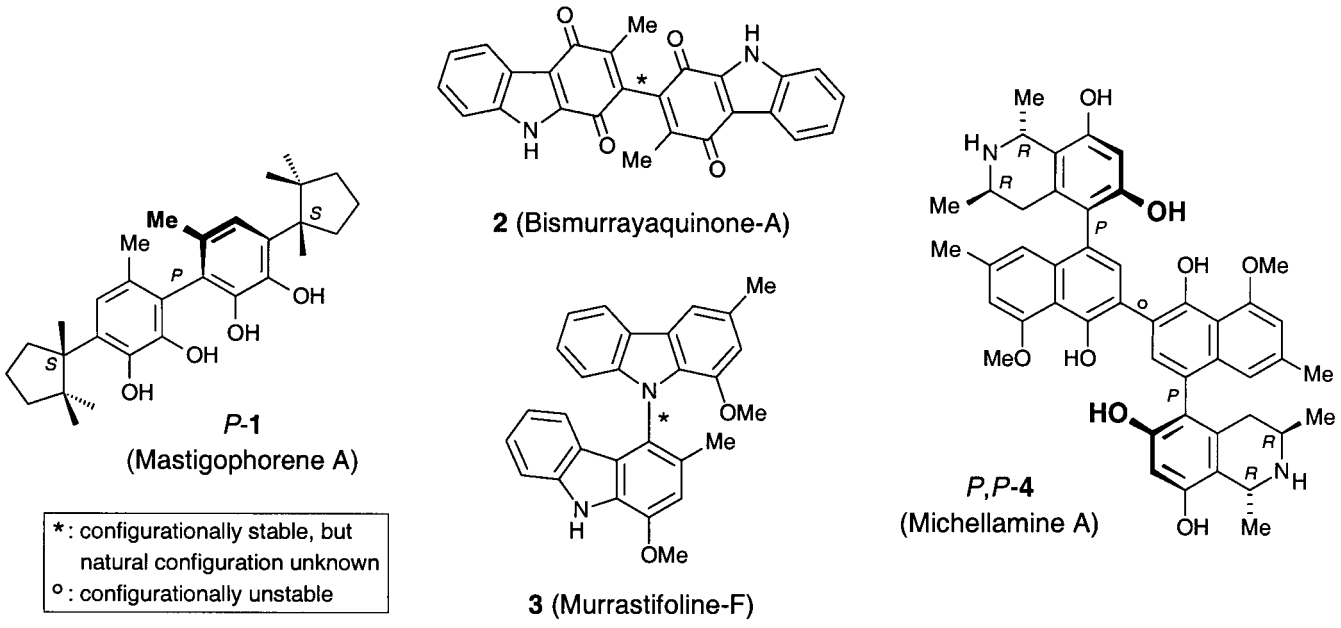
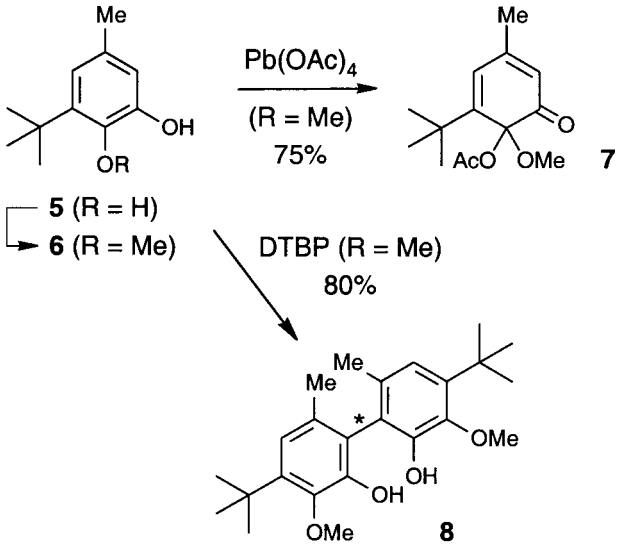



**Figure 1.** Naturally occurring biaryls as synthetic target molecules.

had already been achieved using DDQ.[12] Our dimerization reactions on herbertenediol (**9**) were based on previous mechanistic investigations on phenol and 3,5-dimethylphenol as model systems, which had shown di-*tert*-butyl peroxide (DTBP) or di-*tert*-butyl peroxyoxalate to be efficient reagents to provide predominantly the corresponding *ortho*–*ortho'*-coupled biaryls.[13] Since such a structural feature is also present in the mastigophorenes, peroxo reagents of that type seemed worth being tried for the synthesis of these natural products, too. For the evaluation of coupling agents and conditions for the biomimetic mastigophorene synthesis, the simplified analog **5**, in which the chiral cyclopentyl residue is replaced by the likewise lipophilic *tert*-butyl group, was chosen as the monomeric model phenol (Scheme 1).[14] Several coupling attempts directly on **5**, using DTBP, $Pb(OAc)_4$, $Ag_2O$, or $FeCl_3$ gave only complex product mixtures, so that the less reactive—and chemically more robust—methyl ether **6** was prepared for further trials. Upon treatment of this now monophenolic precursor **6** with $Pb(OAc)_4$ as the oxidizing reagent, the dienone **7** (*ortho*-quinole acetate) was obtained as the only product in 75%, hinting at intermediate cationic species.[4,15] A coupling to the desired dimer **8**—of course here in a racemic form—succeeded in 80% with DTBP,[14] whereas a reaction with $VO(acac)_2$ in the presence of oxygen led only to decomposition (Scheme 1).

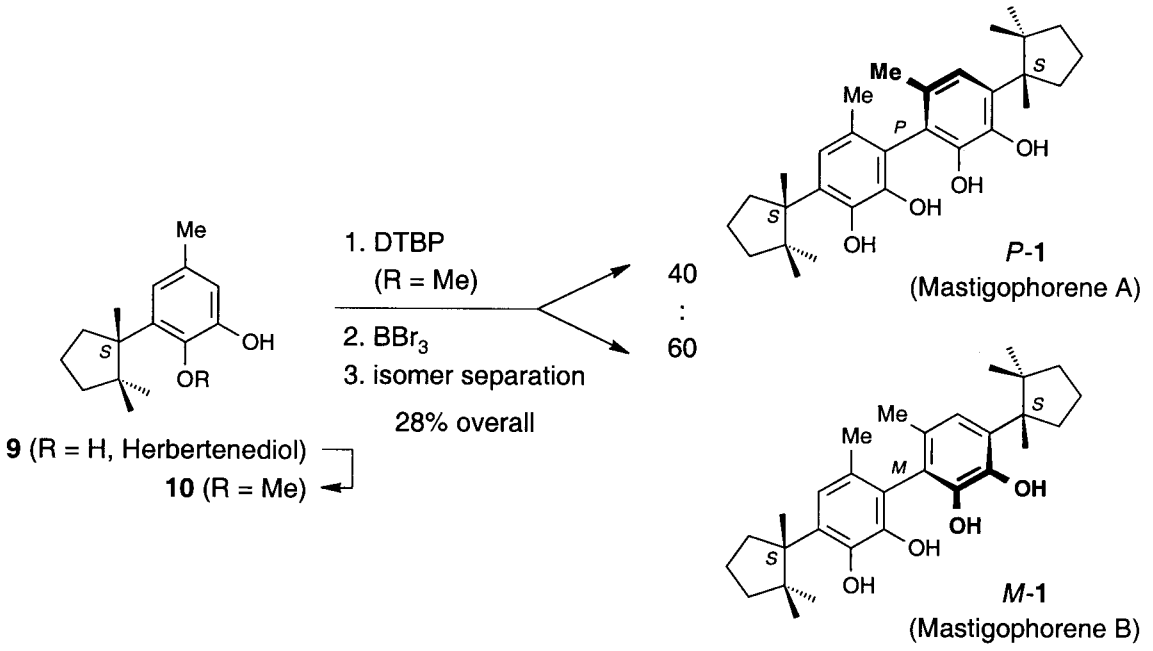



**Scheme 1.** Dimerization of **6** as a simplified herbertenediol monomethyl ether analog.

These reaction conditions, as pre-optimized for the easily available simplified analog **6**, were then applied to the monomethyl ether **10** of the authentic monomer herbertenediol (**9**) (Scheme 2), prepared both by partial synthesis from a related natural product available through isolation and by total synthesis.[16,17] In this case, due to the presence of stereogenic centers in the monomers, the reaction leads to diastereomeric products, giving, however, only very low asymmetric inductions with a diastereomeric ratio of 60:40 in favor of mastigophorene B (*M*-**1**).[16] The isomers were easily separated by preparative TLC after *O*-demethylation to yield the atropisomerically pure mastigophorenes A (*P*-**1**) and B (*M*-**1**) in a moderate 28% yield, along with 42% of herbertenediol (**9**). In an attempt to increase the asymmetric induction by the use of sterically more demanding alkyl ethers, the chemical coupling yield dropped dramatically, as also did the diastereomeric excess. The absolute configurations of the products were established by comparison of their $^1H$ NMR data with those published for the isolated compounds, which had been assigned stereochemically by means of circular dichroism (CD) spectroscopy applying the exciton chirality method.[11]

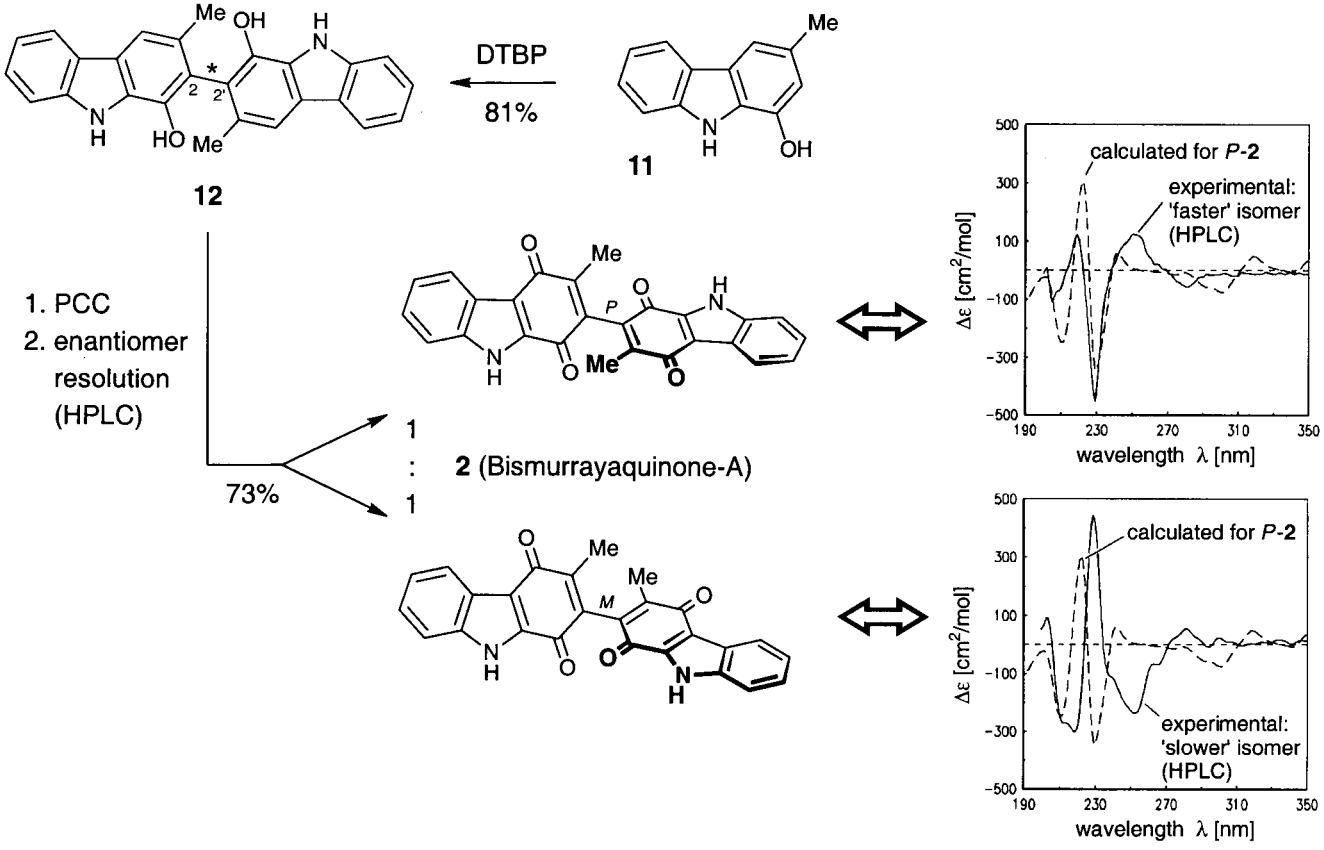
### 2.2. Dimeric biaryl carbazole alkaloids

Although 14 representatives of the class of—*C*,*C*- or *C*,*N*-coupled—dimeric biaryl carbazole alkaloids have been isolated so far from plant material of the genus

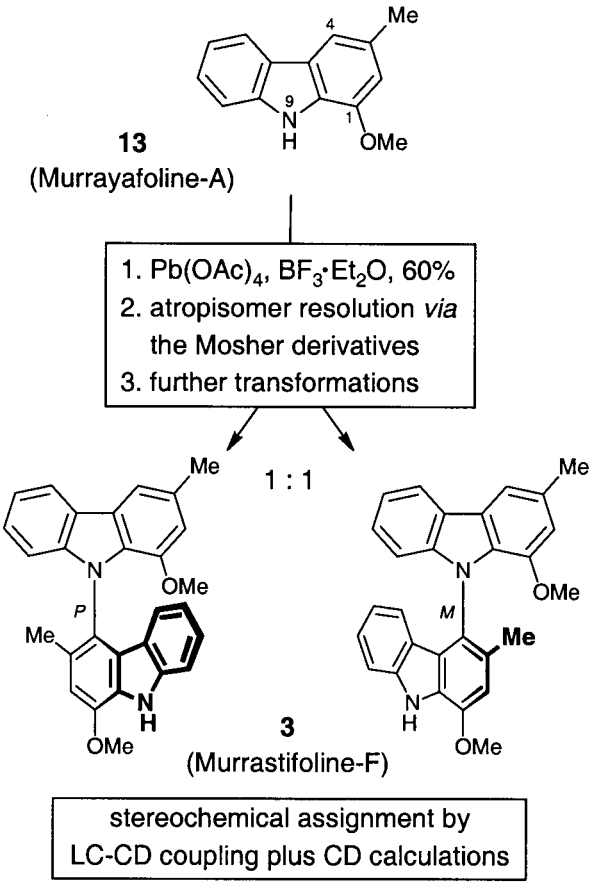



**Scheme 2.** Biomimetic synthesis of atropo-diastereomeric mastigophorenes.

*Murraya*,[2,18–20] only very few synthetic, pharmacologic, or biosynthetic investigations have been reported.[2] Due to the large size and high number of *ortho*-substituents next to the biaryl axis, most of these biaryl compounds should display the phenomenon of atropisomerism. Still, none of the reports on the isolation and structural elucidation has taken into account the aspect of axial chirality and the structures of such biscarbazole alkaloids have been drawn as if they were flat at the axis. Thus, not even $\alpha_D$ values have been given, leaving open whether they have been measured at all, even in most recent reports.[19] Because of the difficult availability of the plants and thus of the natural




**Scheme 3.** Phenolic oxidative coupling as the decisive step in the synthesis of bismurrayaquinone-A (**2**), and stereochemical assignment by quantum chemical CD calculations.




**Scheme 4.** First total synthesis and stereoanalysis of murrastifoline-F (**3**).

biscarbazoles, a synthetic access was required for more detailed stereoanalytical investigations on these biaryls. First oxidative coupling reactions on—albeit unnatural—carbazoles were achieved by Moody et al. with dibenzoyl peroxide, leading to the corresponding 4,4′-dimers.[21]

**2.2.1. Bismurrayaquinone-A: by a phenolic coupling reaction.** Bismurrayaquinone-A (**2**), a dimeric carbazole-quinone from *Murraya koenigii*,[20] was synthesized from 1-hydroxy-3-methylcarbazole (**11**), which is a natural product itself. This phenolic monomer **11** was prepared from aniline and 3-methylcyclohexanone,[22,23] and was then smoothly dimerized with DTBP in 81% yield to give biscarbazole **12** as the only product (Scheme 3).[23–25] The first synthesis of a natural biscarbazole was completed by PCC oxidation to give the desired quinone **2**.

The configurational stability of such biscarbazoles was proven for the first time at the level of the coupling product **12** and was confirmed for bismurrayaquinone-A (**2**) by the successful HPLC resolution of the atropo-enantiomers on a chiral phase for both types of molecules.[23,24] Exemplarily for the alkaloid **2**, even the absolute configuration was assigned to the pure isomers by means of CD spectroscopy involving quantum chemical CD calculations by methods established and further improved in our group.[24,26] For **12**, the separation of the atropisomers was also achieved after derivatization with a chiral reagent, followed by elimination of the auxiliary to give, again, pure atropo-enantiomers, now on a preparative scale.[25]

The biscarbazole **12** and its monomer **11** were found to exhibit moderate antimalarial activity in vitro against *Plasmodium falciparum*.[27]

The total synthesis of another biscarbazole alkaloid, bis-2-hydroxy-3-methylcarbazole, was achieved by oxidative phenolic coupling with *p*-chloranil as the oxidizing agent.[28]

**2.2.2. First total synthesis of an *N,C*-coupled biarylic biscarbazole alkaloid, murrastifoline-F, by non-phenolic oxidative coupling.** During the synthesis of 1-hydroxy-3-methylcarbazole (**11**), the isolation of pure material can sometime cause problems and reduce the yield and this is—even more so—the case for the dimer **12**. Therefore, we switched over to non-phenolic coupling reactions using a naturally O-protected *Murraya* alkaloid, murrayafoline-A (**13**), as the starting material. This carbazole was synthesized from indole-3-carbaldehyde and proved to be much easier to handle.[29] Oxidative dimerizations using $PhI(CF_3CO_2)_2$ [bis(trifluoroacetoxy)iodobenzene, BTIB] and $VOF_3$ failed completely, it was not even possible to recover the starting material due to complete decomposition. Only with $Pb(OAc)_4$ in the presence of $BF_3$ etherate, a coupling product was found—not with the expected *C,C*-bond formation, though, but through coupling between the endocyclic (pyrrolic) nitrogen and C-4 of a second carbazole molecule to give the natural product murrastifoline-F (**3**), another alkaloid from *Murraya koenigii*,[20] as the main product in as much as 60% yield (Scheme 4).[30] This constitutes the first synthesis of a *N,C*-coupled biarylic biscarbazole alkaloid. Nothing is known as yet about the stereochemistry of murrastifoline-F (**3**), it has not even been reported whether the natural product is optically active or not, no $\alpha_D$ has been given. The availability of this unprecedented constitutionally unsymmetric hetero-biaryl now through our total synthesis allowed us to investigate the molecule for the first time with respect to its potential rotational isomerism.

In contrast to its publication as a 'flat' structure, murrastifoline-F (**3**) is a stereochemically interesting compound, which can exist in the form of configurationally stable atropisomers. This was demonstrated by *O*-demethylation and subsequent preparative TLC resolution of the corresponding *O*-Mosher derivatives of the synthetic atropisomers and further purification by HPLC on a chiral phase. The absolute configuration of the two atropo-enantiomers was assigned after conversion back to the natural product, again by quantum chemical CD calculations and comparison with the experimental spectra thus obtained for the first time.[30] The applicability of quantum chemical CD calculations to this totally unprecedented structural type of an axially chiral hetero-biaryl exemplifies, once again, the efficiency of this method, without the necessity of having to rely on empirical rules or needing the availability of structural similar reference compounds.

### 2.3. Dimeric naphthylisoquinoline alkaloids and related compounds

**2.3.1. The michellamines.** Naphthylisoquinoline alkaloids constitute a rapidly growing class of pharmacologically important acetogenic[31] natural products, in which a broad

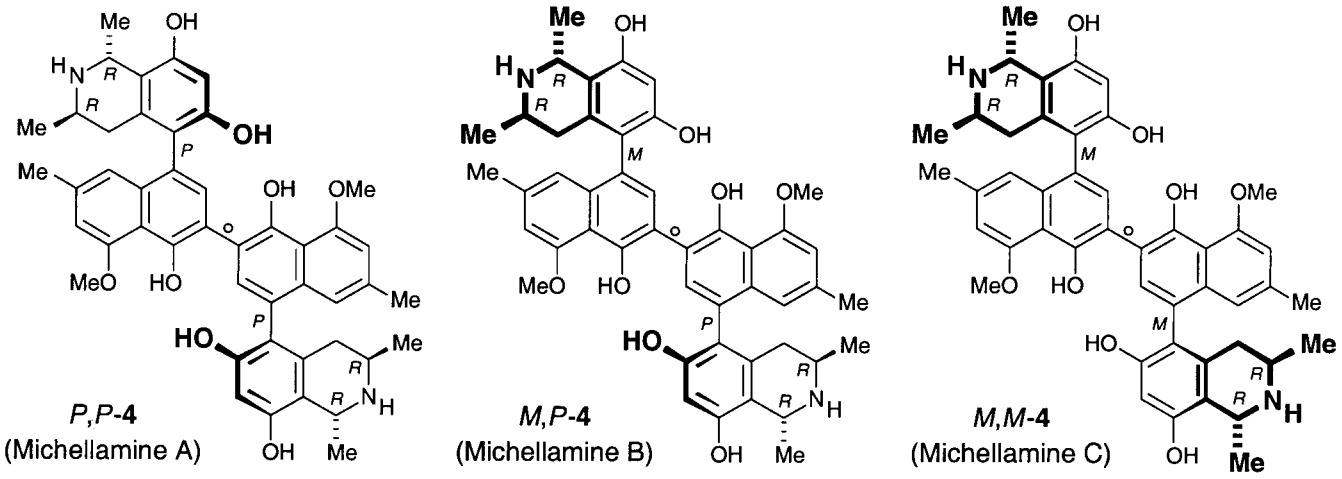
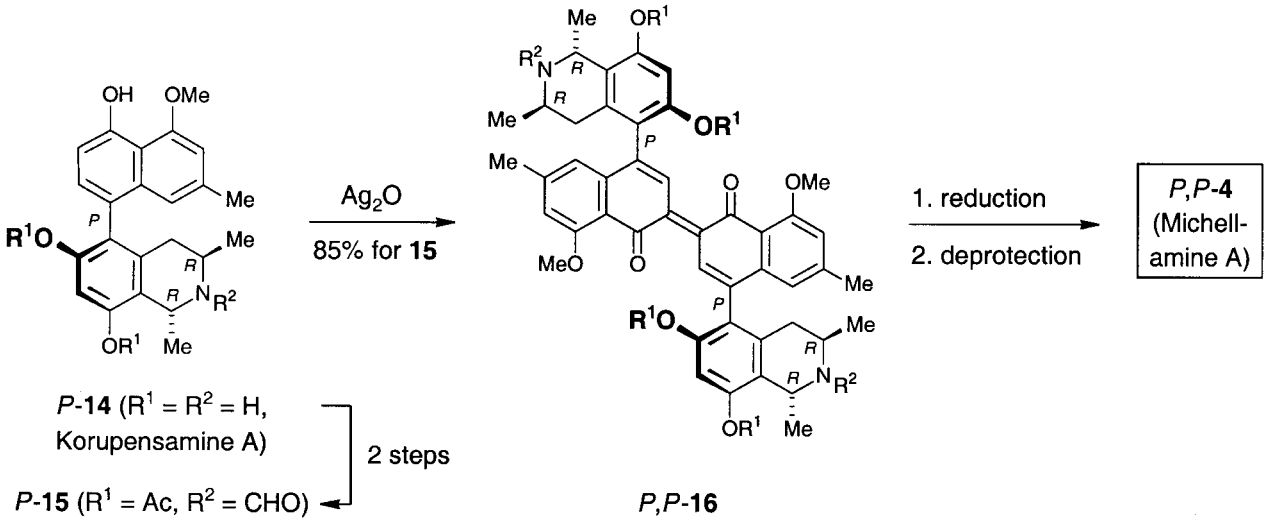



**Figure 2.** Michellamines A (*P*,*P*-**4**), B (*M*,*P*-**4**), and C (*M*,*M*-**4**).

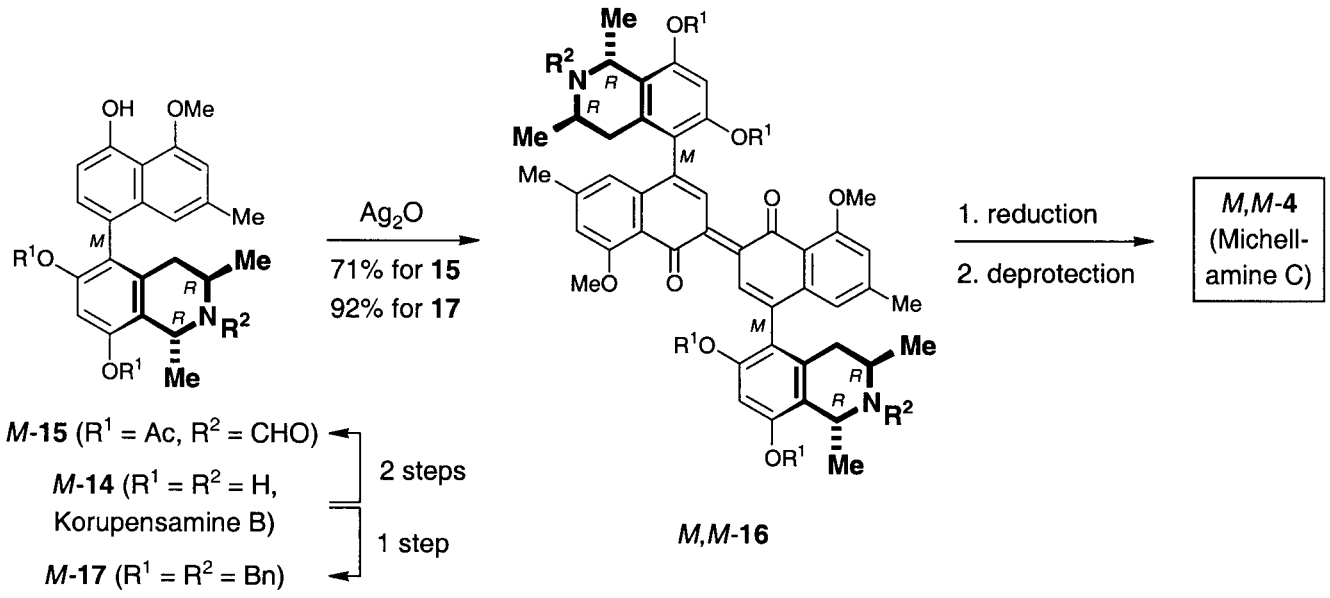
diversity is attained by a nearly combinatorial variation of only few different structural features.[32,2] Among the by now ca. 80 representatives of this class of—mostly axially chiral—natural products, the michellamines from *Ancistrocladus korupensis* (Ancistrocladaceae)[33] are the only dimeric naphthylisoquinoline alkaloids and thus constitute naturally occurring quarteraryl compounds. The promising antiviral activities of michellamines A, B, and C (**4**) (Fig. 2) against HIV-1 and HIV-2 [33] have triggered numerous efforts to synthesize these—at first sight complex—molecules and related compounds.[34–39]

For the total synthesis of michellamines, two principal strategies have been pursued: the construction of a binaphthalene containing the central biaryl bond and its subsequent coupling with the two isoquinoline parts on the one hand,[40] and the dimerization of the monomeric halves,[41–43] viz. the korupensamines A (*P*-**14**) and B (*M*-**14**), on the other. Whereas the first strategy materialized by reductive and 'redox-neutral' coupling reactions, the second one was based on a biomimetic oxidative dimerization strategy. For the realization of the latter, a whole series of—more or less atroposelective—synthetic pathways to the korupensamines were elaborated,[44–48,36–38] not all of them, however, leading to the authentic alkaloids.[37,38,46,47] The first synthesis, as achieved in our group, profited by an—albeit weak—asymmetric induction by the already existing stereocenters in the isoquinoline part,[44] while our later, much more effective approach succeeded by the lactone methodology.[45,49]

First attempts to obtain michellamines directly, by an oxidative phenolic coupling of authentic, unprotected korupensamines (**14**), e.g. of korupensamine A (*P*-**14**), using $Ag_2O$, $FeCl_3$, $K_3[Fe(CN)_6]$, or DTBP, led to complex product mixtures, exclusively, so that a protective group strategy had to be developed. *N*-formylation and specific *O*-acetylation in the isoquinoline part of **14** to give the korupensamine derivative *P*-**15** permitted an efficient oxidative coupling with $Ag_2O$, giving the—hence overreacted—diphenoquinone *P*,*P*-**16** (Scheme 5) in 85%.[41] Other oxidants led to complete decomposition {e.g. $K_3[Fe(CN)_6]$, $FeCl_3$} or did not effect any reaction (e.g. DTBP). Subsequent reduction of *P*,*P*-**16** and deprotection gave michellamine A (*P*,*P*-**4**). The diphenoquinone formation is typical of the phenolic oxidative dimerization of




**Scheme 5.** Total synthesis of michellamine A (*P*,*P*-**4**) by oxidative coupling involving a protective group strategy.

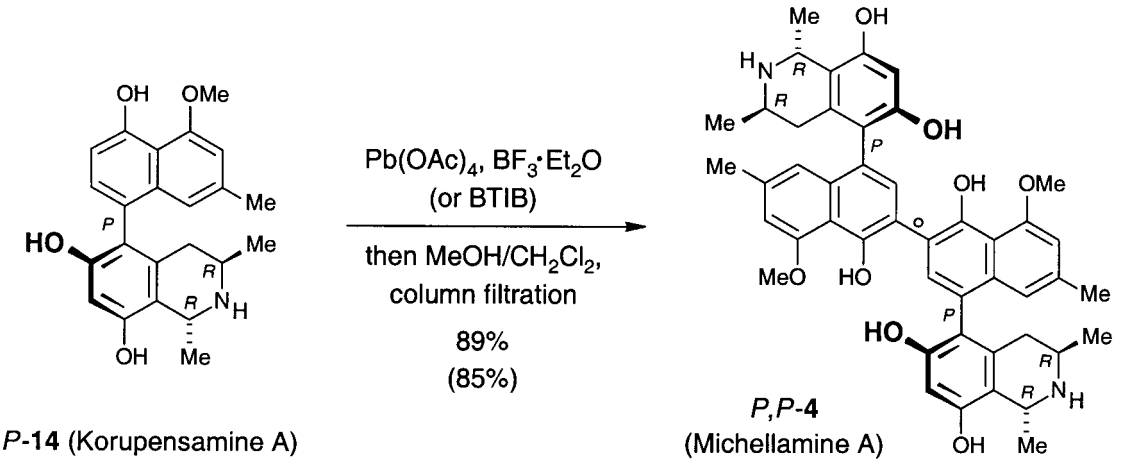



**Scheme 6.** Total synthesis of michellamine C (*M*,*M*-**4**) using different protective groups.

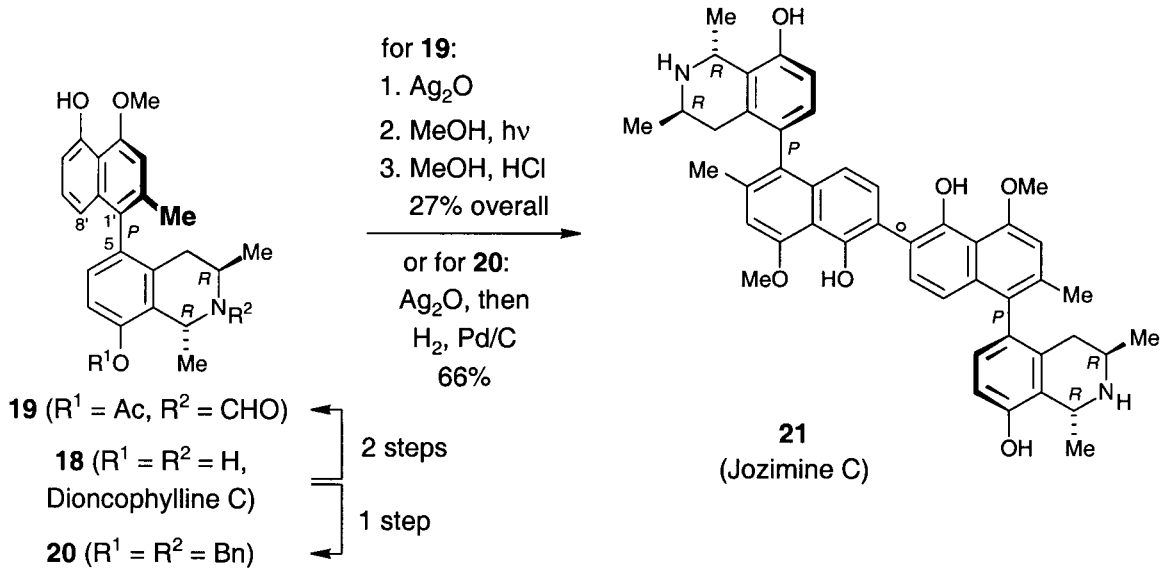
sterically not hindered aromatics;[50] because of the facile reduction of this (usually deeply violet colored) ene-dione system with various reductants ($NaBH_4$, $H_2$-Pd/C, etc.), sometimes even just during workup in methanol (as the reducing agent!) in the presence of incandescent light, this additional dehydrogenation does not constitute any restriction to the applicability of the method. That this secondary and preparatively reversible over-oxidation is entirely independent of the coupling step itself can be seen by the fact that sterically highly hindered biaryls (see Schemes 1–3) likewise give high coupling yields, now without any ene-dione formation.

By the same reaction sequence, korupensamine B (*M*-**14**) gave *M*-**15** and eventually michellamine C (*M*,*M*-**4**) in 71% coupling yield (Scheme 6), while a 1:1 mixture of the two protected korupensamines **15** led to the statistically expected 1:2:1 ratio of michellamines A (*P*,*P*-**4**), B (*M*,*P*-**4**), and C (*M*,*M*-**4**).[41] A shorter and more effective approach to michellamine C (*M*,*M*-**4**) was found using benzyl protective groups for both the endocyclic nitrogen and the phenolic groups. The coupling yield for *M*-**17** increased to 92% and by hydrogenolysis, reduction of the diphenoquinone *M*,*M*-**16** and deprotection were achieved simultaneously, thus shortening the overall sequence down to three steps.

A further improvement and shortening of the reaction sequence was imaginable only by performing the coupling directly, without any protective groups. This was first achieved by using the authentic korupensamine-dimerizing enzyme isolated from *Ancistrocladus korupensis* in our group, albeit with low turn-over rates.[43] Very recently, we have succeeded in chemically dimerizing free korupensamines A (*P*-**14**) and B (*M*-**14**) even on a preparative scale. As exemplified in Scheme 7 for the dimerization of korupensamine A (*P*-**14**), treatment of the alkaloid with $Pb(OAc)_4$ in the presence of $BF_3$ etherate led to the respective diphenoquinones (corresponding to **16** in Scheme 5 and 6, but with $R^1$=$R^2$=H), which were reduced in situ,

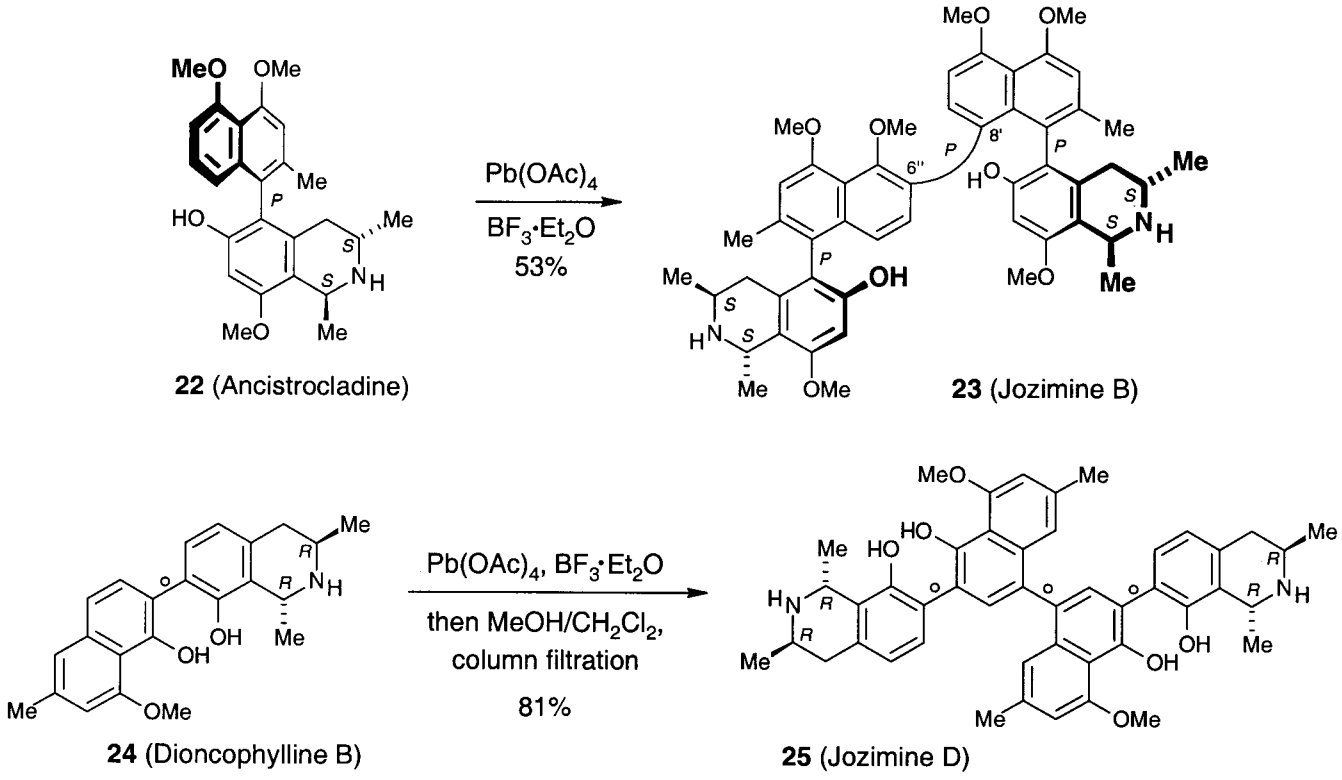



**Scheme 7.** Exemplarily for korupensamine A (*P*-**14**): 'one-step' dimerization of authentic, unprotected korupensamines to give the corresponding michellamines.

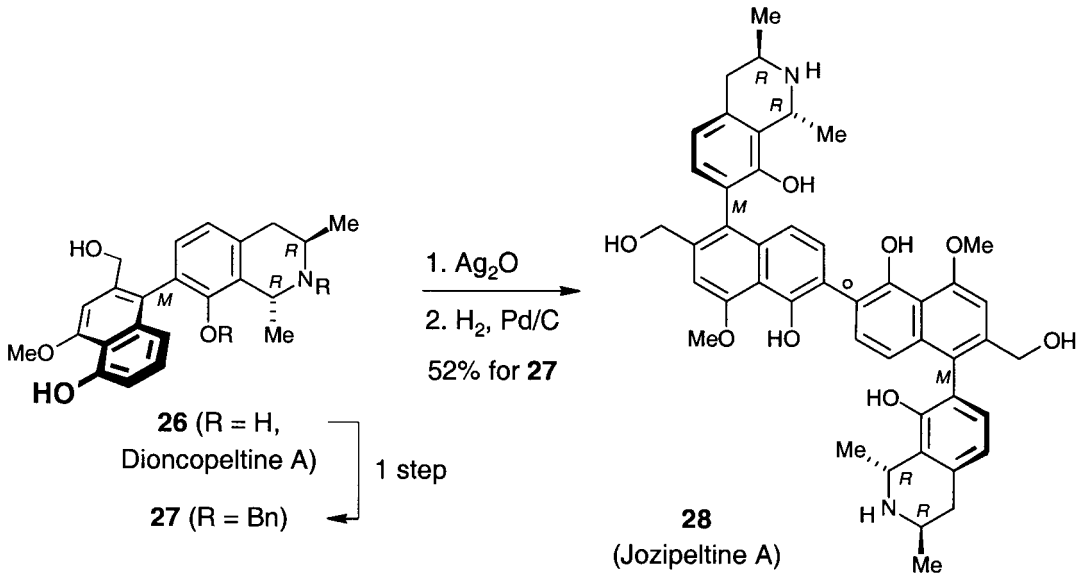



**Scheme 8.** Synthesis of the unnatural dimer jozimine C (**21**) from the alkaloid dioncophylline C (**18**).

just while passing through a short silica gel column with a $MeOH/CH_2Cl_2$ eluent, to give the respective michellamine (here *P*,*P*-**4**) in an essentially one-step synthesis, in 89% yield (Scheme 7).[42] In the same way, free, unprotected korupensamine B (*M*-**14**) provided michellamine C (*M*,*M*-**4**), and a 1:1 mixture of korupensamines A and B generated a 1:2:1 mixture of michellamines A (*P*,*P*-**4**), B (*M*,*P*-**4**), and C (*M*,*M*-**4**) (not shown in Scheme 7). Although to get a statistical 1:2:1 mixture looks unfavorable at first sight, this constitutes the presently most effective michellamine B synthesis from korupensamines, due to the fact that no protective groups are required, combined with the high coupling yields—more convenient than a 'stereospecific' michellamine synthesis[37] by separate bromination and boronation of previously resolved korupensamine A and B derivatives, followed by a reductive cross-coupling. The work described here underlines the high value of biomimetic biaryl coupling techniques. Similar results were obtained using $PhI(CF_3CO_2)_2$ (BTIB)[51] as the oxidizing agent, giving an 85% overall yield.[42]




**Scheme 9.** Direct oxidative coupling of naphthylisoquinoline alkaloids with $Pb(OAc)_4$.




**Scheme 10.** Synthesis of jozipeltine A (**28**) by $Ag_2O$ coupling.

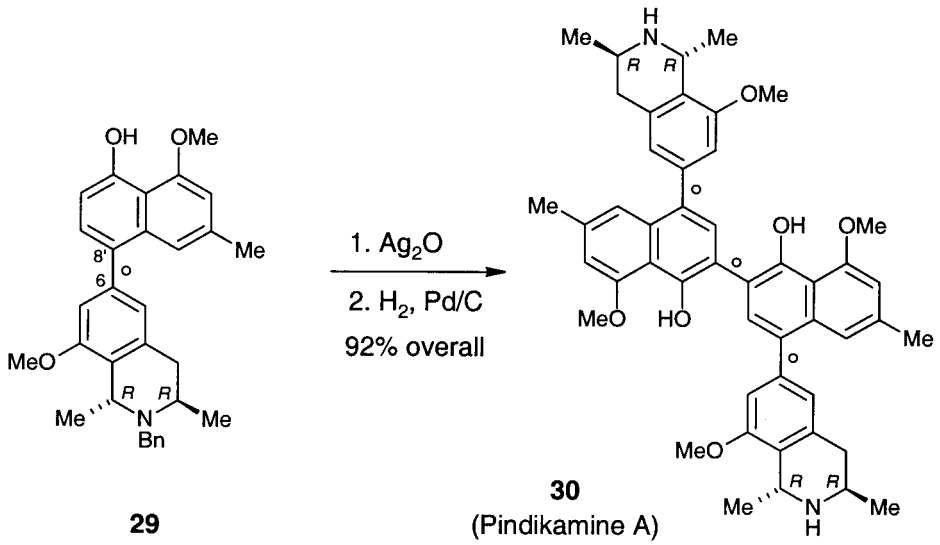
**2.3.2. Unnatural dimers of natural and artificial monomeric naphthylisoquinolines: jozimines B, C, and D, as well as jozipeltine A and pindikamine A.** Given the interesting pharmacological profile of the michellamines—high antiviral activity albeit with a certain toxicity—it seemed most promising to synthesize further, now non-natural dimeric naphthylisoquinolines by likewise coupling other alkaloids, available by total synthesis or by isolation from plant material. First attempts to dimerize protected dioncophylline A under similar reaction conditions as for the oxidative coupling to protected michellamines led to complex reaction mixtures, so that bis-dioncophylline A ('jozimine A') was finally synthesized by a (reductive) Klar-Wittig coupling and is therefore not subject of this article.[52]

Jozimine C (**21**), an (as yet) unnatural dimer of dioncophylline C (**18**), however, was first prepared via a pathway analogous to the initial protective group strategy for the synthesis of michellamines (cf. Schemes 5 and 6).[53] After *N*-formylation and *O*-acetylation of **18**, again specifically leaving the hydroxy group on the naphthalene part unreacted, oxidative coupling of **19** with $Ag_2O$ (here in 40% yield),[54] subsequent reduction of the intermediate diphenoquinone, and final removal of the protective groups yielded jozimine C (**21**) (Scheme 8). Also in this case, the shorter variant via the dibenzyl protected derivative (here **20**) gave better results: Coupling and now in situ reduction of the intermediate diphenoquinone along with simultaneous deprotection proceeded in an overall yield of 66%.[55]

A direct oxidative coupling of free, unprotected naphthylisoquinoline alkaloids succeeded for the syntheses of jozimines B (**23**) and D (**25**), which were prepared from ancistrocladine (**22**) and dioncophylline B (**24**), respectively, using $Pb(OAc)_4$ as the agent (Scheme 9). The oxidative dimerization of ancistrocladine (**22**) constitutes an instructive 'competition experiment' between a phenolic oxidative coupling in the isoquinoline part (which was not found to react, not even in traces) and a non-phenolic oxidative coupling in the *O*-methyl 'protected', but bicyclic naphthalene part, of which the latter occurs in a high chemo-, regio-, and stereoselectivity. The absolute configuration at the new central biaryl axis of **23** was established as *P*, exclusively, by specific NOE interactions between the two halves of the molecule and by quantum chemical CD calculations.[56] Because of the high steric hindrance (efficiently overcome in the coupling reaction!) and the presence of phenol ethers, no overoxidation to an intermediate diphenoquinone was observed in the dimerization of **22** and the reaction mixture thus remained essentially colorless. Jozimine B (**23**) is the first constitutionally unsymmetric synthetic dimer of a natural naphthylisoquinoline and is, moreover, a further example for the very small but interesting class of configurationally stable and stereochemically attributed 1,8-diarylnaphthalenes.[57]

Jozimine D (**25**), by contrast, is formed through a *phenolic* oxidative coupling, again in the naphthalene part exclusively; no coupling was found to occur in the monocyclic aromatic part of the isoquinoline. The intermediate diphenoquinone, again observed in this conversion, was reduced to **25** during workup in $MeOH/CH_2Cl_2$ in an overall yield from **24** to **25** of 81%.[42] Jozimine D (**25**) is the first unnatural dimer of a natural naphthylisoquinoline with a central biaryl axis linking two *peri* positions and simultaneously, the first one with three configurationally unstable biaryl axes.

Another interesting dimer of a naphthylisoquinoline alkaloid is jozipeltine A (**28**).[58] It is the as yet only such synthetic dimer that has the same high number of free OH groups (three per monomeric half) as michellamines and was thus considered as a rewarding synthetic target molecule. It was prepared by an oxidative dimerization of the benzyl protected derivative **27** of dioncopeltine A (**26**) (52% yield)[54] with $Ag_2O$ (Scheme 10) as previously achieved for the synthesis of (protected) michellamines (cf. Scheme 6). The intermediate diphenoquinone was




**Scheme 11.** Pindikamine A (**30**), a completely unnatural dimeric naphthylisoquinoline with three configurationally unstable axes.

reduced by hydrogenation in the presence of Pd/C, with simultaneous cleavage of the benzyl protective groups.

In the search of structurally and stereochemically simplified, but likewise bioactive analogs of michellamines, pindikamine A (**30**) was synthesized (Scheme 11);[59] it is a completely synthetic quateraryl, consisting of unnatural, 6,8′-coupled monomeric naphthylisoquinoline halves, and has three freely rotating biaryl axes. Its synthesis from an *N*-benzyl protected monomeric precursor followed the improved preparation of michellamine C (cf. Scheme 6), by treatment with $Ag_2O$, here followed by hydrogenolytic deprotection with simultaneous reduction of the—again overoxidized—diphenoquinone intermediate. The excellent coupling yield of 94% and still very good overall yield of 92% to give pindikamine A (**30**) demonstrates the high synthetic value of oxidative phenolic coupling reactions—once the correct protective group strategy has been elaborated and the appropriate oxidant has been found and optimized.

**2.3.3. Bioactivities of the unnatural dimeric naphthylisoquinolines prepared.** The syntheses of all these interesting quateraryls through phenolic or non-phenolic oxidative dimerization gave valuable insight into structure–activity relationships for the anti-HIV—and antimalarial—activities of this class of compounds. Indeed, while most of these dimers were too toxic to exhibit a noticeable anticytopathic activity on HIV-infected human cell lines, jozimine C (**21**) was detected to be the first unnatural dimer of a natural naphthylisoquinoline whose anti-HIV activity is virtually identical to that of michellamines.[42,53,60] Entirely unexpected was the discovery that some of these dimers display significantly increased antimalarial activities as compared to their monomeric precursors, examples being jozimines A, B (**23**), D (**25**), and pindikamine A (**30**).[42,56,59,60] The fact that other dimers, like jozimine C (**21**) and jozipeltine A (**28**) were less active than the corresponding monomers,[53,58,60] must have to do with the apparently too high number of free OH groups for the dimers. This gives useful further information on structural requirements to be fulfilled for high antimalarial activities.

## 3. Conclusion

The oxidative coupling of phenolic and non-phenolic aromatics represents a powerful tool for the biomimetic synthesis of biaryl natural products and their structural analogs. Applied to the dimerization of most different monomeric units like phenols, carbazoles, and naphthylisoquinolines, the coupling reactions usually lead to essentially one single biaryl product in good to excellent yields, possible side products being detectable only in traces (if at all). This, however, requires to optimize the reaction conditions very carefully in each single case, by testing a broad variety of oxidizing reagents and further reaction conditions, in order to avoid complex product mixtures or even the entire decomposition of the starting material. For target molecules with a low steric hindrance at the newly generated biaryl axis, an overoxidation to deeply colored ene-diones can occur, but does by no means constitute a disadvantage—rather do these (rigid) compounds sometimes constitute useful, nicely isolable intermediates for further purification, characterization, and they can be reduced without any additional synthetic effort, just in methanol during workup in the presence of incandescent light. For the systems presented in this paper, DTBP, $Pb(OAc)_4$, $Ag_2O$, and $PhI(CF_3CO_2)_2$ turned out to be most effective reagents in phenolic and non-phenolic aryl coupling reactions.

## 4. Experimental

All reactions were carried out with dried solvents and glassware and under inert atmosphere unless otherwise stated. IR spectra were recorded on a Perkin–Elmer 1420 infrared spectrophotometer and reported in wave numbers ($cm^{-1}$).

**Table 1.** Oxidative coupling with DTBP

| Compound | Solvent [ml/mmol] | Equiv. of DTBP[a] | Time[a] [h] | Yield [%] | Product | Ref. |
|---|---|---|---|---|---|---|
| **6** | 10 | 2.0 | 4 | 80 | **8** | 14 |
| **10** | 10 | 1.12+0.28 +0.28+0.28 | 5+5 +5+5 | 28[b] | **1** | 16 |
| **11** | 30 | 1.0+0.43 | 16+6 | 81 | **12** | 24 |

[a] Further additions of oxidizing agent and the respective reaction times are marked by '+'.
[b] Overall yield after demethylation with $BBr_3$ and separation of atropo-diastereomers.

The $^1$H NMR spectra were recorded on a Bruker AC 200 (200 MHz). The chemical shifts are given in parts per million (ppm) with the deuterated solvent as internal reference. The coupling constants *J* are given in Hertz. Mass spectra were recorded on a Finnigan MTA 8200 spectrometer at 70 eV in the EI mode, the relative intensities are given in brackets. Elemental analysis: Microanalytical Laboratory of the University of Würzburg, LECO CHNS-932. Column chromatography was performed on silica gel 63–200 μm (Merck). HPLC: combination of a Waters 600E pump, a Nova-Pak $C_{18}$ column (Waters, 200×25 mm, 6 μm, integrated guard pak), and a Waters 996 photodiode array detector. Solvent: $H_2O$–$CF_3COOH$ buffer (pH=2.5)/MeOH (52:48), isocratic. The oxidizing agents are commercially available. Spectroscopic data can be obtained from the references cited.

### 4.1. General procedure for the coupling with DTBP

To a solution of the starting material in chlorobenzene, di-*tert*-butyl peroxide was added. The mixture was heated under reflux for the time indicated in Table 1. Upon removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel.

**4.1.1. Bismurrayaquinone-A (2).**[24] To a solution of 178 mg (815 μmol) PCC in 25 ml $CH_2Cl_2$, a solution of 64.0 mg (163 μmol) **12** in 5 ml $CH_2Cl_2$ was added. After 0.5 min, 150 ml $Et_2O$ were added and the supernatant liquid was decanted from the black gum, which was washed twice with 20 ml $Et_2O$. Passing the combined organic layers through a short column of silica gel and removal of the solvent yielded 50.1 mg (73%) of **2** as an orange-colored powder.

### 4.2. General procedure for the oxidation with $Pb(OAc)_4$

To a solution of the starting material in the solvent and at the temp. indicated in Table 2, $Pb(OAc)_4$ and an additive were added. After stirring for the time shown in Table 2, water (in case of **6**, a saturated aqueous solution of $NaHCO_3$) was added and the phases were separated. For the conversion of compounds **6**, **13**, and **22**, extraction of the aqueous layer with several portions of $CH_2Cl_2$, drying of the combined organic layers over $MgSO_4$, and removal of the solvent yielded a crude product, which was further purified by column chromatography. For the coupling of the naphthylisoquinolines **14** and **24**, extraction of the organic phase with $H_2O$/MeOH (8:2), evaporation of the solvent of the combined aqueous layers under reduced pressure and finally lyophilization gave a residue, which was dissolved in $CH_2Cl_2$/MeOH (8:2) and passed through a short silica gel column using the same solvent as the eluent. Purification of the crude product obtained after removal of the solvent succeeded by HPLC.

**4.2.1. 6-Acetyloxy-5-tert-butyl-6-methoxy-3-methylcyclohexa-2,4-dien-1-one (7).** Colorless oil; IR (KBr): $\tilde{\nu}$ 3020 (Ar–H), 2930, 2880, 2840, 2800 (C–H), 1720, 1660 (C=O); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=1.23 (s, 9H, $C(CH_3)_3$), 2.07 (d, *J*=1.5 Hz, 3H, Ar–$CH_3$), 2.12 (s, 3H, $CH_3COO$), 3.34 (s, 3H, $OCH_3$), 5.89–5.91 (m, 1H, 2-H), 6.17 (d, *J*=1.5 Hz, 1H, 4-H); MS: *m/z* (%)=252 (0.1) [$M^+$], 194 (15) [$M^+-CH_2CO_2$], 179 (28) [194−$CH_3$], 154 (100) [194−$C_4H_8$]; Anal. calcd for $C_{14}H_{20}O_4$ (252.3): C, 66.65; H, 7.99. Found: C, 66.40; H, 7.87.

### 4.3. General procedure for the oxidative coupling with $Ag_2O$

A mixture of the protected naphthylisoquinoline in $CHCl_3$ containing 0.2% $NEt_3$ and 20 equiv. of $Ag_2O$ was stirred at rt in the dark in an air atmosphere for the time indicated in Table 3. For the conversion of **15**, **17**, **19**, **20**, and **27**, the solvent was removed and the residue purified by column chromatography on silica gel with $CH_2Cl_2$/MeOH (20:1) (for **15**, **19**, **20**, and **27**) or simply filtered after addition of $CH_2Cl_2$ (for **17**). The reaction mixture of the coupling of **29** was directly filtered through silica gel and the solvent was

**Table 2.** Oxidation with $Pb(OAc)_4$

| Compound | Solvent | Temp. [°C] | Equiv. of $Pb(OAc)_4$ | Additive [ml/mmol] | Time [min] | Yield [%] | Product | Ref. |
|---|---|---|---|---|---|---|---|---|
| **6** | $CH_2Cl_2$ | −78, −78→rt | 1.00 | Pyridine, 0.2 | 60 | 75 | **7** | – |
| **13** | $CH_3CN$ | rt | 0.55 | $BF_3{\cdot}Et_2O$, 1.7 | 210 | 60 | **3** | 30 |
| *P*-**14** | $CH_2Cl_2$ | 0 | 1.07[a] | $BF_3{\cdot}Et_2O$, 2.2[b] | 5 | 89 | *P*,*P*-**4** | 42 |
| *M*-**14** | $CH_2Cl_2$ | 0 | 1.07[a] | $BF_3{\cdot}Et_2O$, 2.2[b] | 5 | 89 | *M*,*M*-**4** | 42 |
| **22** | $CH_2Cl_2$ | rt | 1.96[a] | $BF_3{\cdot}Et_2O$, 0.7[b] | 5 | 53 | **23** | 56 |
| **24** | $CH_2Cl_2$ | 0 | 1.20[a] | $BF_3{\cdot}Et_2O$, 1.7[b] | 5 | 81 | **25** | 42 |

[a] Addition of $Pb(OAc)_4$ dissolved in $CH_2Cl_2$ over a period of 5 min to the solution of $BF_3$ and starting material in $CH_2Cl_2$ at 0°C.
[b] The solution of $BF_3$ and starting material in $CH_2Cl_2$ was stirred for 1 min prior to the addition of $Pb(OAc)_4$.

**Table 3.** Oxidative coupling with $Ag_2O$

| Compound | Solvent [ml/10 μmol] | Time [h] | Coupling yield [%] | Reduction/deprotection[a] | Yield[b] [%] | Product | Ref. |
|---|---|---|---|---|---|---|---|
| *P*-**15** | 6 | 120 | 85 | **A/B** | 67 | P,*P*-**4** | 41 |
| *M*-**15** | 6 | 120 | 71 | **A/B** | 67 | *M*,*M*-**4** | 41 |
| *M*-**17** | 1 | 2 | 92 | **C** | 94 | *M*,*M*-**4** | 41 |
| **19** | 0.4 | 39[c] | 40 | **B** | 67 | **21** | 53 |
| **20** | 1 | 6 | – | **C** | 66[d] | **21** | 55 |
| **27** | 1 | 4[e] | – | **C** | 52[d] | **28** | 58 |
| **29** | 1 | 6 | 94 | **C** | 98 | **30** | 59 |

[a] Procedures **A**–**C** are described below.
[b] Yield only for the reduction/deprotection procedure.
[c] This reaction was run at 4°C with 11 equiv. of $Ag_2O$.
[d] Overall yield.
[e] Reaction can be accelerated at 40°C.

evaporated. All products were crystallized from $CH_2Cl_2$/petroleum ether.

### 4.4. Procedures for the reduction and deprotection of diphenoquinones obtained by oxidative coupling[41,59]

**4.4.1. Method A.** The diphenoquinone (1.0 equiv.) was treated with 5.0 equiv. of $NaBH_4$ in 2-propanol for 10 min at 20°C. After evaporation of the solvent, the residue was dissolved in $Et_2O$ and was extracted against water. The combined organic phases were dried ($Na_2SO_4$) and the solvent was removed in vacuo. A solution of the resulting oil in MeOH was treated with several 1 ml portions of cold saturated methanolic HCl over a period of 24 h while gently refluxing. Evaporation of the solvent yielded the crude product.

**4.4.2. Method B.** The diphenoquinone was dissolved in MeOH and the solution was irradiated (visible light, Osram Power Star HQI/D discharge lamp) for 15 min. After partial evaporation of the solvent, the solution was treated with several 1 ml portions of cold saturated methanolic HCl over a period of 24 h while gently refluxing. Evaporation of the solvent yielded crude product.

**4.4.3. Method C.** Benzyl protected diphenoquinones were hydrogenated in $CH_2Cl_2$/MeOH (1:1) or pure MeOH (for **27**) in the presence of Pd/C (10%). After stirring for 6–17 h at normal pressure, the catalyst was filtered off and washed with MeOH. Removal of the solvent yielded crude product.

### 4.5. General procedure for dimerization reactions using BTIB

To a cooled solution (0°C) of korupensamines A (*P*-**14**) or B (*M*-**14**) in $CH_2Cl_2$ and $BF_3$ etherate (2.0 ml/mmol), 1.25 equiv. BTIB were added over a periode of 5 min. After stirring for further 5 min, water was added and the phases were separated. The organic phase was extracted with $H_2O$/MeOH (8:2) and the solvent of the combined aqueous layers was evaporated under reduced pressure and by lyophilization. The residue was dissolved in $CH_2Cl_2$/MeOH (8:2) and passed through a short silica gel column using the same solvent. Purification of the crude product obtained after removal of the solvent was achieved by HPLC and yielded michellamines A (*P*,*P*-**4**) and C (*M*,*M*-**4**), respectively, in 85% yield.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