Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products

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1. Introduction

Intellectual curiosity has always been one of the major driving forces leading to new advances in chemistry. At the onset of the 20th century, the fact that biaryls could be optically active even if lacking asymmetrically substituted carbon atoms arose interest, hinting at a novel type of stereomerism. It took quite a while (and some bizarre explanations)[1] until in 1922 Christie and Kenner[2] first correctly recognized that the phenomenon was the consequence of a hindered rotation about the aryl−aryl single bond—hence termed atropisomerism by Kuhn. Still, no particular attention was initially paid to this class of stereoisomers until enantiomerically pure biaryls, such as BINAP (**1**),[3] were found to be excellent ligands in asymmetric catalysis and until the chiral biaryl unit was recognized as the decisive structural element of many natural products (Figure 1).[4,5]

With the modern screening techniques and the bioassay-guided search for novel compounds, the number of isolated axially chiral natural biaryls is steadily increasing.[4] This class of secondary metabolites is characterized by a broad structural diversity, reaching from relatively simple molecules like the C_2-symmetric biphenyl **2**, which solely contains the element of axial chirality,[6] to more complex compounds, like, e.g., the dimeric naphthylisoquinoline alkaloids michellamine A [(*P*,*P*)-**3**] and its axial epimer (i.e., its atropodiastereomer), michellamine B [(*P*,*M*)-**3**],[7,8] which possess even three biaryl axes, of which the two outer ones are stereogenic, while

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Tobias Gulder was born in Regensburg, Germany, in 1978. From 1998 to 2004, he conducted his undergraduate studies in chemistry at the University of Würzburg, followed by his Ph.D. in analytical and synthetic natural product chemistry (with Prof. G. Bringmann), for which he reveived the prize of the Faculty of Chemistry and Pharmacy of the University of Würzburg in 2008 and the DECHEMA Ph.D. award in 2009. For his postdoctoral work, he joined the B. S. Moore group at the Scripps Institution of Oceanography (UC San Diego, U.S.A.), where he worked on the elucidation and utilization of biosynthetic pathways, funded by the DAAD. In July 2010, he returned to Germany, supported by a DAAD reintegration fellowship, and joined the Kekulé Institute of Organic Chemistry in Bonn, where he will be starting an independent research program at the end of the year.

rotation is not hampered at the central one.[9,10] In the famous glycopeptide vancomycin (**4**),[11] the chiral biaryl unit is embedded into a sophisticated framework that comprises numerous stereogenic centers and two planar-chiral elements, which all together create the rigid 3D structure of the molecule.[12−14]

The optical purity of biaryls occurring in nature can vary largely. Although many compounds are produced in an atropisomerically pure form by nature as, e.g., **4**,[14] some biaryls, like **2**, have been isolated as racemates[6] and others

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are scalemic, i.e., enantiomerically enriched.[15] In a similar way, if equipped with additional stereogenic centers, quite a number of biaryls may occur as atropodiastereomeric mixtures like the aforementioned michellamines **3**, of which the (*P*,*P*)- and (*P*,*M*)-configured isomers are of natural origin.[8−10] During the past two decades, increasing interest has been given to a number of axially chiral biaryls because of their promising pharmacological profiles. As an example, **3**, in particular the atropodiastereomer (*P*,*M*)-**3**, was found to exhibit significant anti-HIV activity in vitro.[8,16] Nevertheless, the certainly most prominent axially chiral biaryl today is the heptapeptide-derived complex antibiotic vancomycin (**4**), which is in clinical use as a medical drug of last resort,[12] although, meanwhile, resistance toward even this drug has been reported.[12,17]

Both the unique structures and the promising biological activities make axially chiral natural biaryls highly rewarding, but also challenging, targets for total synthesis. This article, covering the literature up to the beginning of 2010, provides a comprehensive review on the atroposelective total synthesis of axially chiral biaryl natural products, from simple and easily available precursors to the desired final target molecules.[18] Major emphasis is given to the stereochemical key step, in which the absolute configuration at the biaryl axis is established. Syntheses of merely racemic natural biaryls or just enantiomeric resolutions, e.g., by chromatography on a chiral phase or through separation of diastereomeric derivatives, are not treated.

This review is divided into three major parts: section 2 gives some general information, including an overview on the manifold structural facets within the broad class of axially chiral natural biaryls (section 2.1), the preconditions necessary for the occurrence of axial chirality (section 2.2), and the different basic concepts successfully applied in the atroposelective construction of the biaryl axis (section 2.3). The total synthesis of nonbridged and bridged biarylic natural products is described in sections 3 and 4.

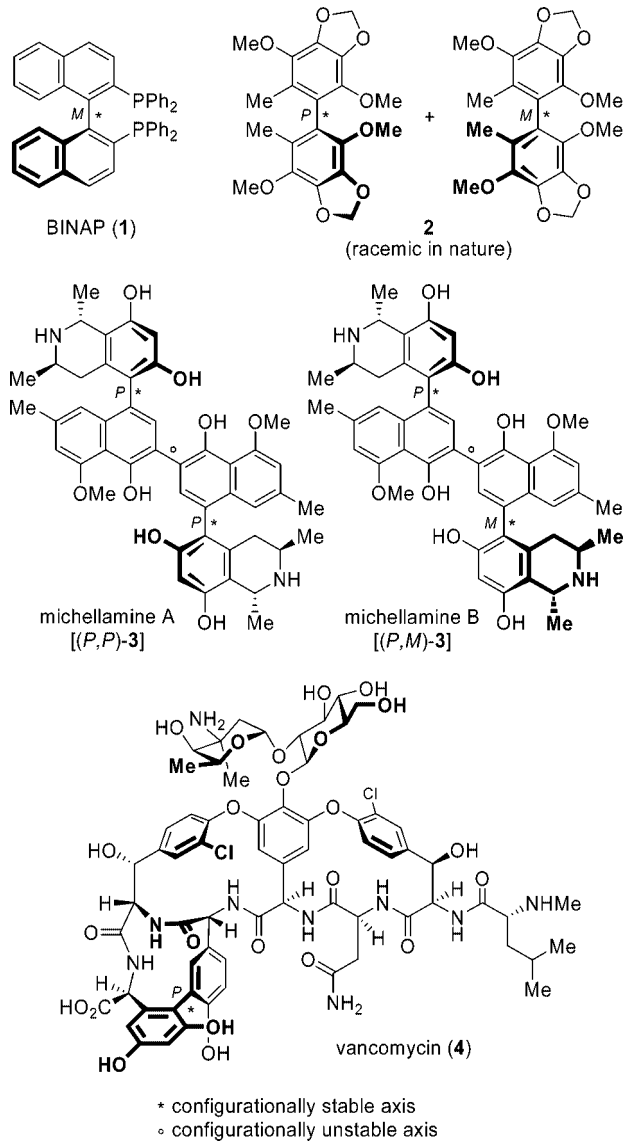


Figure 1.

2. General Remarks

2.1. Classification of Configurationally Stable Axially Chiral Biaryl Natural Products

Although a large number (certainly more than 1000) of biaryls equipped with a configurationally stable axis have so far been isolated from nature, and despite their other remarkable bioactivities,[4,5] only a small portion of these chiral compounds has as yet been prepared by atroposelective total synthesis. This section will thus give a short overview on axially chiral natural products, with their overwhelming structural diversity and their, in part, high complexity, evidencing the challenges associated with their total synthesis. The following categorization has been done according to the basic structures of the target molecules and the number of representatives known for that particular type, despite the existence of many borderline cases.[4] In all of the subgroups thus defined, the corresponding derivatives with related, but quinoid or partially reduced, rings have been included, although these are, strictly speaking, not aromatic.

A first-line classification into nonbridged and bridged biaryls is obvious for structural reasons; moreover, the existence or nonexistence of a bridge has a profound influence on the configurational stability of the biaryl (see section 2.2) and, in addition, on the method to be applied for the asymmetric induction at the axis (see section 2.3).

Natural products with a nonbridged axially chiral biaryl system can be categorized into four major structural subclasses: isocyclic biaryls, biaryls with fused heterocycles, genuine heterobiaryls, and multiply coupled biaryls, some representatives of which are shown in Figure 2. The first group, characterized by a relatively simple isocyclic, i.e., all-carbon biaryl system, consists of four subcategories: biphenyls, binaphthalenes, biphenanthrenes, and bianthracenes, and cross-coupled combinations thereof. Well-known examples of the first two subgroups are the nerve-growth stimulating biphenyl mastigophorene A [(*P*)-**5**][19] and the binaphthalene gossypol [(*M*)-**6**],[20] which shows antispermatogenic,[21] antitumor,[22] and antimalarial[23] activities, depending on the axial configuration. Both compounds are C_2-symmetric, but in addition to a chiral biaryl axis, (*P*)-**5** contains two stereocenters as further elements of chirality. The polyketide-derived, constitutionally unsymmetric, since 9,2′-coupled, dimeric[24] preanthraquinone phlegmacin B_1 [(*M*)-**7**][25] has been categorized here to belong to the class of bianthracenes.[26] All other biaryls composed of two different nonheterocyclic aromatic moieties have been classified as "mixed" isocyclic biaryls. A typical representative of this class is the antimalarial[27,28] and antitumoral[29] phenylanthraquinone (+)-knipholone [(*P*)-**8**].[30]

Another major class of biaryls possesses fused heterocycles, with the heteroatom(s) outside an isocyclic biaryl core, among them oxygen- or nitrogen-containing ring systems. An example of the first group is the bioxanthracene (−)-ES-242-4 (**10**) produced by *Verticillum* species.[31] As for many naturally occurring biaryls, its absolute configuration at the axis was not assigned during structural elucidation, and the configuration at the stereocenters has only been established by its total synthesis.[32] Biflavonoids[4,33] and bicoumarins[34] bearing α- and γ-pyranone motifs belong to this class, too, but they are treated separately, because of their large natural abundance. An example of the latter group is (+)-kotanin [(*P*)-**9**].[35,36] Besides these oxygen-heterocyclic metabolites, the *N*-containing biaryls, mostly dimeric or cross-coupled alkaloids, deserve special interest both for their structures and their bioactivities, like the dicationic bis-β-carboline alkaloid blumeanine [(*M*)-**12**],[37] which is characterized by a sophisticated molecular framework, with the biaryl unit as a central structural element. Within this subclass of biaryls, the naphthylisoquinoline alkaloids constitute a subgroup of increasing importance.[10,38−40] These plant secondary metabolites have been isolated from paleotropical lianas of the Dioncophyllaceae and Ancistrocladaceae families.[10] They have received particular attention because of their large structural diversity, the unprecedented biosynthetic origin of isoquinoline alkaloids from acetate/malonate units (instead of aromatic amino acids),[41] and the promising antiinfective activities.[10,42,43] Two of the dimeric members of this subclass, the highly anti-HIV active michellamines A and B, (*P*,*P*)-**3** and (*P*,*M*)-**3**, have already been mentioned in the Introduction (see Figure 1).[9,10] Another typical representative is dioncophylline C [(*P*)-**11**],[44−46] which exhibits highly promising in vitro and in vivo antimalarial properties.[42,47]

In contrast to the large number of heterocyclic biaryls with a central isocyclic biaryl core, truly axially chiral hetaryl−aryl-coupled or even hetaryl−hetaryl-coupled ones are rare in nature. The probably most famous representative of this class

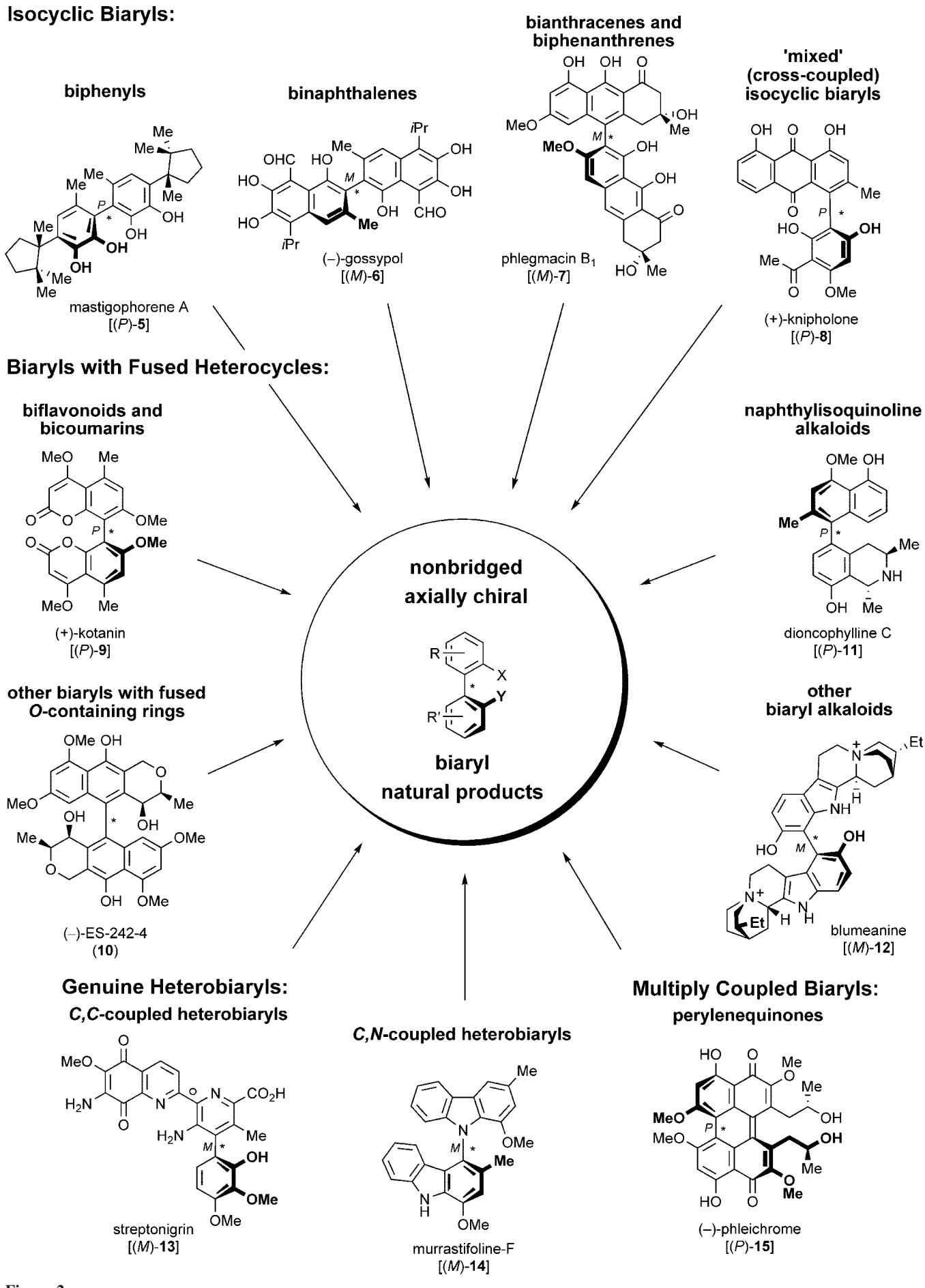

Isocyclic Biaryls:
biphenyls
mastigophorene A
[(P)-5]
binaphthalenes
(–)-gossypol
[(M)-6]
bianthracenes and biphenanthrenes
phlegmacin B1
[(M)-7]
'mixed' (cross-coupled) isocyclic biaryls
(+)-knipholone
[(P)-8]
Biaryls with Fused Heterocycles:
biflavonoids and bicoumarins
(+)-kotanin
[(P)-9]
naphthylisoquinoline alkaloids
dioncophylline C
[(P)-11]
nonbridged axially chiral
biaryl natural products
other biaryls with fused O-containing rings
(–)-ES-242-4
(10)
other biaryl alkaloids
blumeanine
[(M)-12]
Genuine Heterobiaryls:
C,C-coupled heterobiaryls
streptonigrin
[(M)-13]
C,N-coupled heterobiaryls
murrastifoline-F
[(M)-14]
Multiply Coupled Biaryls:
perylenequinones
(–)-phleichrome
[(P)-15]

Figure 2.

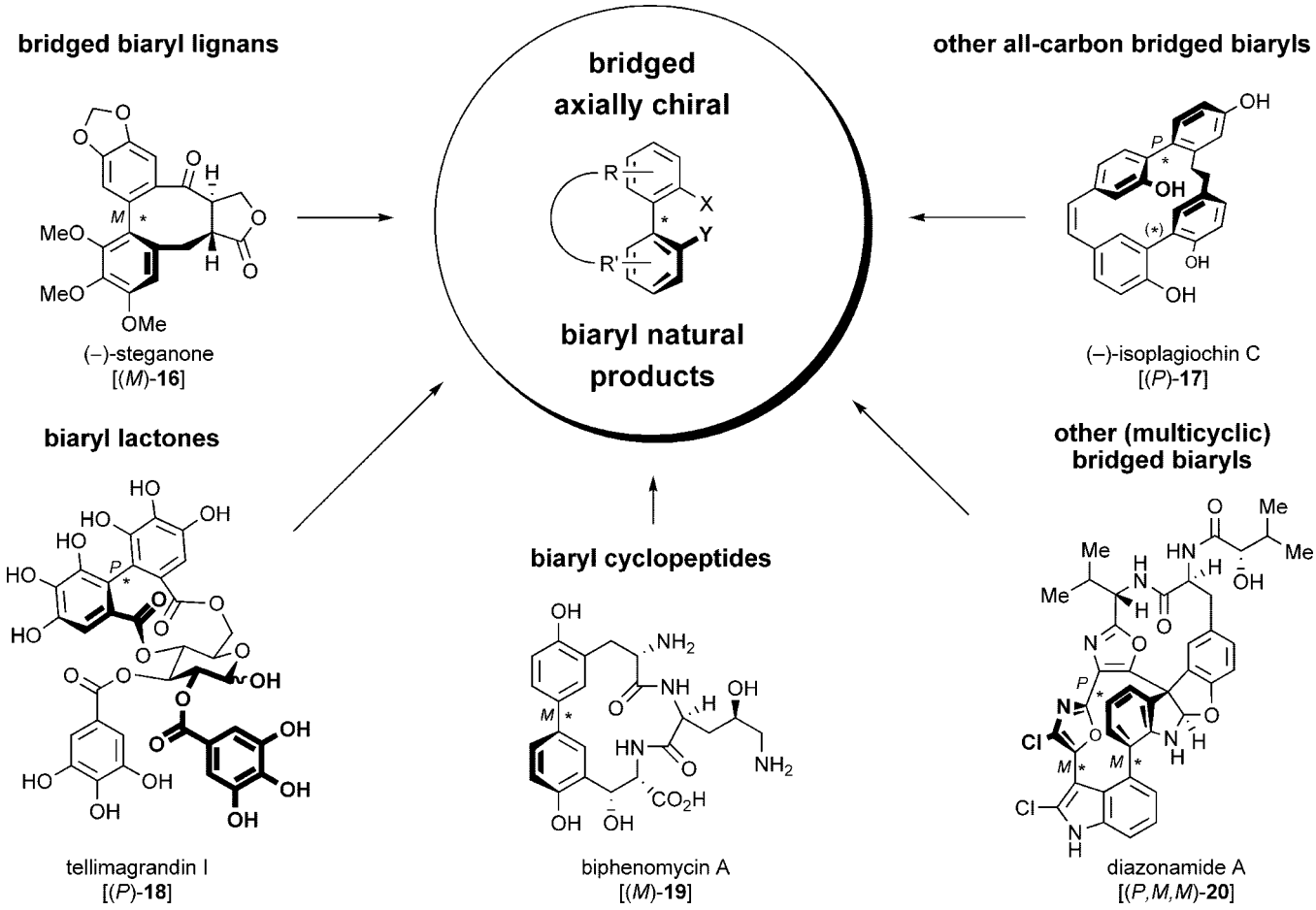


Figure 3.

is the antitumor-active[48] natural product streptonigrin [(*M*)-**13**].[49,50] Naturally occurring *C*,*N*-coupled biaryls like the biscarbazole murrastifoline-F [(*M*)-**14**][51] have been stereochemically investigated in only a few cases.[52,53] More recently, the first *N*,*C*-coupled naphthylisoquinoline alkaloids have been discovered[54,39] and synthesized.[53]

There is at least one more important type of biaryl that is not covered by the aforementioned categories, viz. the perylene-[55,4] and phenanthroperylene-type[56] biaryls, here summarized within the category "multiply coupled biaryls". This subgroup is characterized by a second or (formally) even third aryl−aryl linkage, which flattens the inner molecular core, but still lets axial chirality persist. Most of these colored mold pigments like (−)-phleichrome [(*P*)-**15**][57] are photochemically active, and their application in the photodynamic therapy (PDT), to treat cancer, is an attractive concept.[58,59]

The second major class of biaryls is characterized by the existence of a large-ring bridge additionally connecting the two aromatic portions (Figure 3). According to the structure of the bridge, these compounds can be divided into five subclasses: bridged biaryl lignans, other all-carbon bridged biaryls, biaryl lactones, biaryl cyclopeptides, and other multicyclic bridged biaryls.

Because of their high natural abundance, bridged biaryl lignans are treated as a separate class; they are characterized by a dibenzocyclooctadiene moiety and a relatively simple structure as compared to those of most of the other bridged biaryls. In addition, they possess interesting pharmacological profiles. As an example, (−)-steganone [(*M*)-**16**][60] exhibits antihepatotoxic and microtubulin-aggregation inhibiting activities.[5,60−62] Other biaryls devoid of a heteroatom in the bridge, like the cyclic bisbibenzyl (−)-isoplagiochin C [(*P*)-**17**],[63] whose absolute stereostructure has been established in the authors' group,[64,65] comprise the class of other all-carbon bridged biaryls. The ellagitannins,[66] here tellimagrandin I [(*P*)-**18**],[67] which possess one or more axially chiral dibenzoic acid units around a central glucose core, are typical representatives of the class of large-ring bridged biaryl lactones. Biarylic cyclopeptides, among them the well-known antibiotic vancomycin (**4**, see Introduction, Figure 1), are characterized by a framework composed of proteinogenic and nonproteinogenic amino acids. Besides this compound and an appreciable number of related structural analogues, only a small number of further biaryl cyclopeptides are known, such as, e.g., biphenomycin A [(*M*)-**19**].[68] Finally, the structures of some bridged biaryls do not fit into any of the mentioned classes, so that they are categorized as "other multicyclic bridged biaryls". One example is diazonamide A [(*P*,*M*,*M*)-**20**],[69] which possesses an unprecedented molecular architecture and exhibits a nanomolar in vitro activity against a variety of human cancer cell lines.[69−71] It should be noted that the originally proposed constitution was revised in 2001[72,73] and the new structure was confirmed by total synthesis in 2002−2004.[71,74−76]

The above short overview demonstrates the broad structural variety and the rewarding pharmacological profiles found for axially chiral natural biaryls, which make them highly attractive target molecules for atroposelective total syntheses, even though the pronounced complexity often prevents an easy preparative access. This is probably the main reason why some of the subclasses are still "synthetically untouched".

2.2. Axial Chirality in Naturally Occurring Biaryls

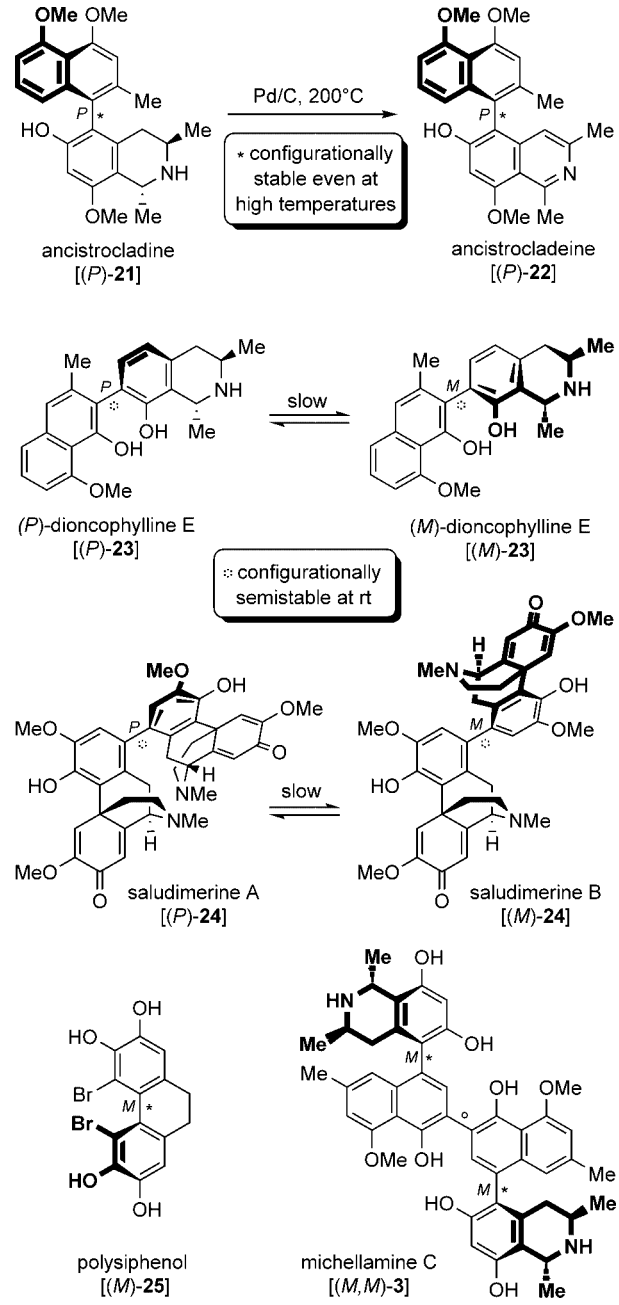
All biaryls covered in this review are characterized by a rotationally hindered axis, giving rise to the phenomenon of atropisomerism. In some respect, this axial chirality differs from the "normal", ubiquitously found isomerism due to the presence of stereogenic centers, so that it appears useful to briefly present the preconditions required for the occurrence of axial chirality and for the configurational stability of biaryls. More detailed information can be found in the literature.[4,77−81]

The configuration of a stereogenic carbon atom can only be inverted by breaking a bond. For the interconversion of atropisomeric biaryls, by contrast, in principle no bond cleavage is required since atropisomerism, as a form of *conformational* isomerism, is caused by the hindered rotation about an aryl−aryl single bond. The macroscopic appearance of a particular atropisomer either can be due to kinetic reasons, i.e., if the rotation about the axis is hindered by sufficiently large substituents, or can be controlled thermodynamically if a—diastereomeric—orientation at a relatively nonhindered axis is energetically preferred, e.g., as a consequence of conformational constraints caused by the presence of a bridge.

The configurational stability of a kinetically hindered biaryl axis is mainly determined by two factors, viz. the height of the rotational barrier, which is given by the structure of the biaryl (see below), and the thermal energy available to overcome it. This implies that, for a particular—definite—barrier given, no axial configuration can, at least in theory, be "indefinitely" stable, although the atropisomerization process can be (unmeasurably) slow, depending on the respective temperature. The naphthylisoquinoline alkaloid ancistrocladine [(*P*)-**21**],[82,83] for example, possesses a very high rotational barrier (Scheme 1). It thus can be dehydrogenated at 200 °C to give ancistrocladeine [(*P*)-**22**] without loss of chiral information at the axis; heating to higher temperatures leads to decomposition of the molecule.[84] Dioncophylline E (**23**), by contrast, is a configurationally semistable biaryl at the verge of atropisomerism;[85] its atropodiastereomers, (*M*)-**23** and (*P*)-**23**, can be resolved by chromatography, but interconversion takes place at room temperature, leading back to the original diastereomeric mixture within a few hours. Even though the axially chiral biaryls treated within this article normally possess sufficient configurational stabilities ($t_{1/2,M \rightleftharpoons P} \gg 1$ day at room temperature), one always has to take care that no unwanted atropisomerization at the axis takes place, e.g., in the course of a total synthesis, in particular when applying harsh reaction conditions (basic, acidic, high temperature, light), or during isolation. An example of the latter case is michellamine C [(*M*,*M*)-**3**], which was originally isolated together with its truly natural diastereomers, michellamines A [(*P*,*P*)-**3**] and B [(*P*,*M*)-**3**] (see Figure 1), but then (*M*,*M*)-**3** turned out to be an artifact formed during a too-harsh isolation procedure.[9,10]

Following some rules of thumb, the configurational stability of a biaryl can already be estimated from its structure, in particular from the number of substituents next to the axis and their sizes, and from the existence and length of a bridge. For unbridged biaryls with four *ortho*-substituents, as, e.g., in (*P*)-**21**,[84] configurational stability can be expected. This is also true for most of the 3-fold *ortho*-substituted biaryls [compare the two "outer" axes of the dimeric naphthylisoquinoline alkaloid (*M*,*M*)-**3**],[9,10] although slow rotation about the axis may occur if the three *ortho*-substituents are small, as in the

Scheme 1



naphthylisoquinoline dioncophylline E (**23**).[85] Nonbridged biaryls with two or fewer substituents next to the axis normally do not give rise to stable atropisomers [cp. the central axis of (*M*,*M*)-**3**], but again, exceptions involving semistable rotational isomers are possible as, e.g., for saludimerins A and B [(*M*)- and (*P*)-**24**].[86]

The situation changes if the two aromatic portions of a biaryl are linked by a bridge. Small bridges, e.g., leading to five-[87] or six-membered rings, lower the rotational barrier considerably, so that stable axial isomers will result only with very large substituents next to the axis, as in polysiphenol [(*M*)-**25**].[88] Larger rings, by contrast, can induce stable axial chirality even in biaryls with low steric hindrance, due to conformational restraints caused by the bridge. In combination with stereogenic units in the bridge, a thermodynamically driven formation of only one atropisomer can be observed in natural biaryls with just one or two substituents next to the axis, as, e.g., in diazonamide A [(*P*,*M*,*M*)-**20**]

(Figure 3, section 2.1), and even for compounds lacking any *ortho*-substituent next to the axis like biphenomycin A [(*M*)-**19**] (Figure 3, section 2.1).

2.3. Atroposelective Biaryl Coupling Reactions in Natural Product Total Synthesis

The rapidly increasing interest in axially chiral biaryls has led to the development of a broad variety of highly successful methods for their atroposelective construction,[18,77,79−81,89,90] of which, however, only few have so far been applied to the total synthesis of natural products. Because these methods will play a role throughout the following two sections, their basic principles will be described here. There are four conceptionally different strategies (Scheme 2):

- atropodiastereoselective biaryl coupling reactions of chirally modified arenes, either with internal asymmetric induction (stereogenic element remains in the target molecule) or by applying an artificial chiral bridge;
- dynamic kinetic resolutions of configurationally labile (e.g., lactone-bridged) biaryls;
- and, more recently, direct, atropoenantioselective biaryl couplings.

The first method, the atropodiastereoselective biaryl coupling with internal asymmetric induction, is well suited if the target biaryl itself bears additional stereogenic centers in the proximity of the axis. This concept has mainly been applied to the total synthesis of bridged natural biaryls. The optimum protocols for the construction of the aryl−aryl single bond, here generalized as **28** → (*P*)-**29**, depend on the actual system, and both oxidative procedures and Suzuki-type couplings have been successful.

Atropodiastereoselective biaryl couplings that use an artificial chiral auxiliary have been performed either inter- or intramolecularly, usually with internal asymmetric induction. An efficient access to biaryl 2,2′-diols of type (*P*)-**35** was developed by the Lipshutz group.[91] Starting from the *ortho*-bromophenols **30** and **31**, stepwise etherification with a C_2-symmetric diol, usually with 1,4-di-*O*-benzyl-L-threitol [(*S*,*S*)-**32**], under Mitsunobu conditions (i.e., with configurational inversion on the chiral auxiliary) delivers the tethered diethers (*R*,*R*)-**33**, which can be coupled intramolecularly via higher-order cuprates to give bridged biaryls like (*P*,*R*,*R*)-**34** in good yields and with an excellent chirality transfer. Cleavage of the artificial bridge delivers the desired axially chiral biaryl diols (*P*)-**35**.

Two important closely related intermolecular coupling procedures using chiral *ortho*-oxazoline moieties as the stereochemically controlling units were established by Meyers and co-workers.[92−94] The required chiral *ortho*-bromo and *ortho*-methoxy oxazolinyl arenes of type (*S*)-**38** are conveniently prepared from the corresponding aryl carboxylic acids **36** and a chiral amino alcohol, usually L-valinol [(*S*)-**37**]. Treatment of (*S*)-**38a** with an *ortho*-methoxy substituted aryl Grignard reagent **39** effects a regioselective nucleophilic displacement of the methoxy function in (*S*)-**38a** to give unsymmetric biaryls of type (*P*,*S*)-**40** in good chemical and optical yields. The *ortho*-methoxy group in **39** is pivotal for the formation of a well-defined transition state and, thus, for a high asymmetric induction. C_2-symmetric biaryls like (*P*,*S*,*S*)-**42** can be prepared in high diastereomeric purities by Ullmann coupling of (*S*)-**38b**. The chiral oxazoline moieties of (*P*,*S*)-**40** and (*P*,*S*,*S*)-**42** can be converted in a few steps into *ortho*-methyl groups to give C_1-symmetric *ortho*-methoxy,*ortho*′-methyl biaryls like (*P*)-**41** and C_2-symmetric *ortho*,*ortho*′-dimethyl substituted ones like (*P*)-**43**. Such substitution patterns are found in many natural products.[4]

All these three auxiliary-based atropodiastereoselective coupling strategies permit access to axially chiral biaryls in reliably good to high chemical and optical yields. Restrictions are the required functionality patterns and the additional steps necessary to attach and remove the chiral auxiliary. Other, less commonly used asymmetric biaryl coupling strategies likewise using chiral auxiliaries will be described when presenting their application in the synthesis of natural biaryls.

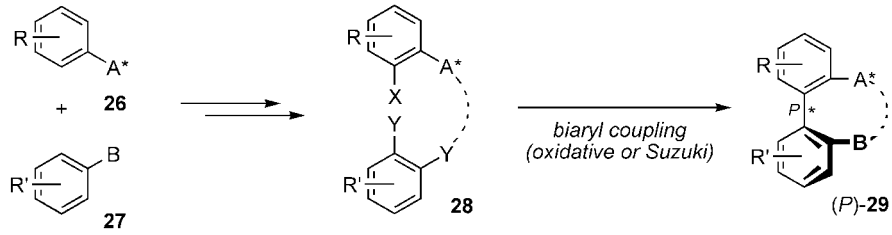
The third major strategy for the atroposelective total synthesis of natural biaryls was developed in the authors' lab.[95−98] Linkage of an *ortho*-bromo carboxylic acid and a phenol delivers the esters **44**, which can be coupled intramolecularly in high yields under palladium catalysis. Because of the short length of the bridge, the biaryl lactones of type **45** thus obtained exist as mixtures of their rapidly interconverting atropisomers, (*M*)-**45** and (*P*)-**45**.[99]

They serve as the substrate for the following dynamic kinetic resolution, which can be achieved within an atropisomer-selective cleavage of the lactone bridge by using a wide variety of chiral *H*-,[98,100−103] *N*-,[104] and *O*-nucleophiles.[105] One of the two atropisomers, e.g., only (*M*)-**45**, is attacked and transformed into a ring-opened, and thus configurationally stable, biaryl, while the remaining one, here (*P*)-**45**, steadily resupplies the consumed (*M*)-**45** via the equilibrium (*M*)-**45** ⇆ (*P*)-**45**. In this way, virtually complete conversion of **45** into a single axially chiral biaryl is achieved. Most successful are atropoenantioselective reductions using BH_3·THF (tetrahydrofuran) in the presence of the oxazaborolidine (*R*)-**46**,[106] delivering the (*P*)-configured biaryl diols (*P*)-**47** in high yield and with excellent stereocontrol.[98,100−103] Most of these reactions were performed with stoichiometric quantities of **46**, but excellent results have also been achieved when using catalytic amounts of **46**.[101] As in the Meyers methodology, the resulting *ortho*-hydroxymethylene function can be further transformed, e.g., by deoxygenation to give a methyl group,[45,107] and the phenolic hydroxy substituent can be removed reductively,[45] or may be substituted, e.g., by a phosphine function.[108] This "lactone concept", which allows easy access to biaryls with a broad substitution pattern, provides several further advantages. The introduction of the chiral information at the axis (here: **45** → **47**) occurs independently from the coupling step (**44** → **45**) and under mild conditions; an unwanted atropisomeric byproduct can be recycled by recyclization back to the lactone **45** (in the case of the diol **47**, by oxidation), and the atropisomer of (*P*)-**47**, (*M*)-**47**, can be prepared from the same precursor **45** just by using the other enantiomer of the ring-cleaving reagent, here (*S*)-**46** instead of (*R*)-**46**. An extension of this strategy to the dynamic kinetic resolution of biaryl hydroxy aldehydes[109] (which are formally ring-opened but actually in an equilibrium with their cyclic—and thus configurationally unstable—lactol isomers) and to the nondynamic kinetic resolution of configurationally stable seven-membered biaryl lactones[110−112] has also been successful. These benefits have rendered the lactone method one of the most widely used strategies for the atroposelective preparation of axially chiral biaryls with many applications in the field of natural and unnatural target molecules.

The ideal pathway to stereochemically homochiral biaryls—and thus, one of the final goals of atroposelective synthesis—would of course result from atropoenantioselective

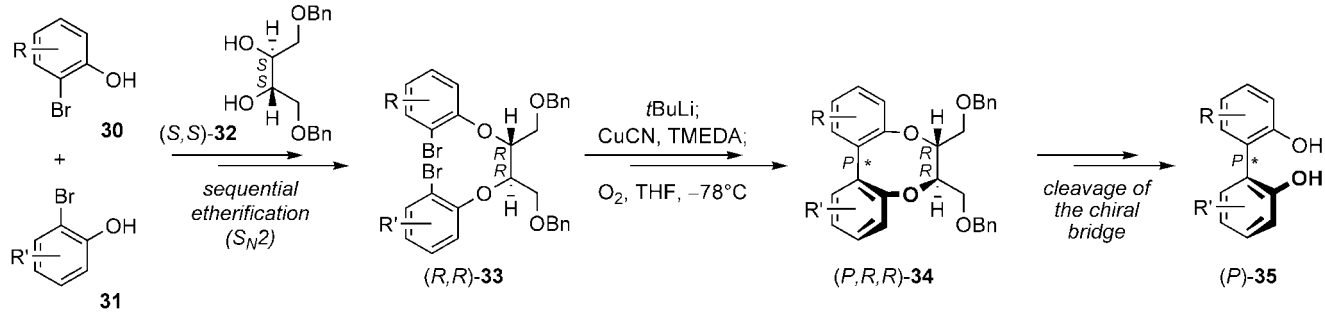
Scheme 2

Atropodiastereoselective Biaryl Couplings With an Intrinsic Chiral Auxiliary: (diverse authors)

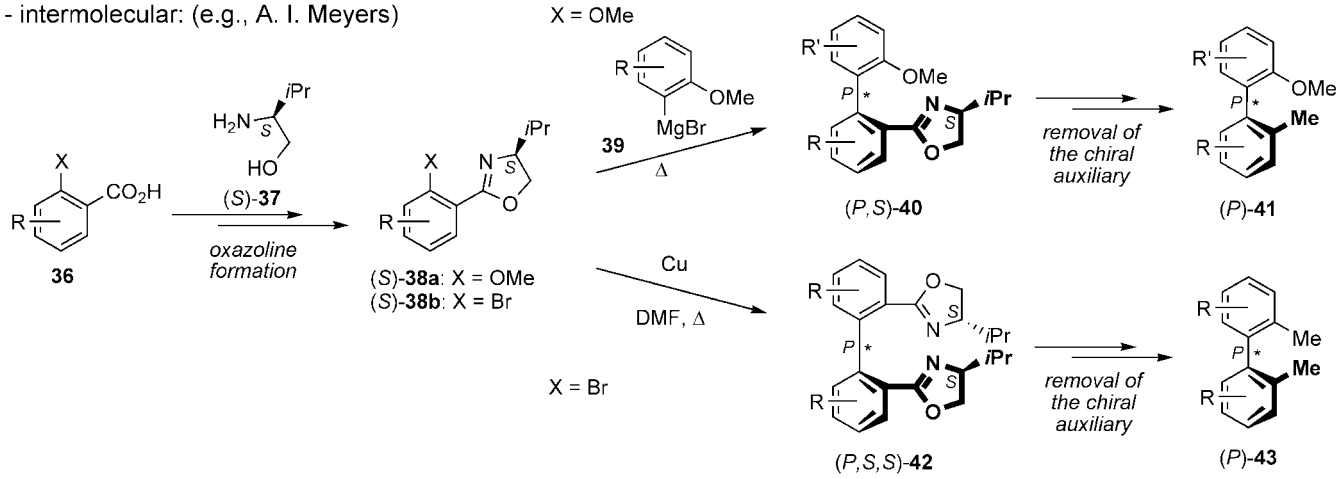


Atropodiastereoselective Biaryl Couplings Using an Artificial Chiral Auxiliary:

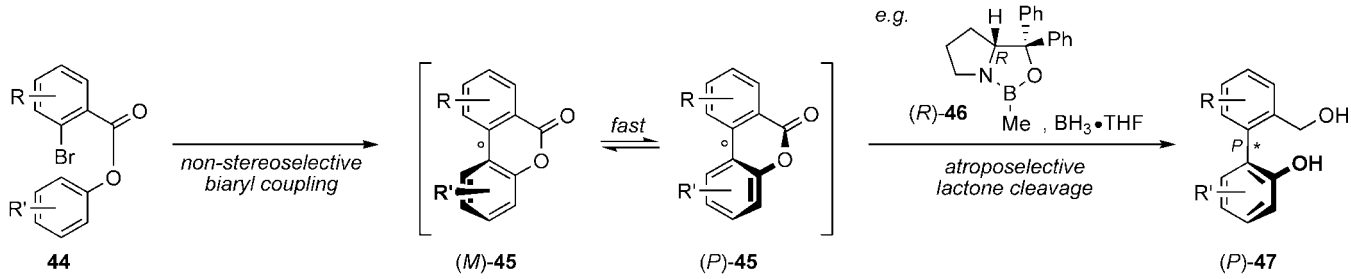
- intramolecular: (e.g., B. H. Lipshutz)



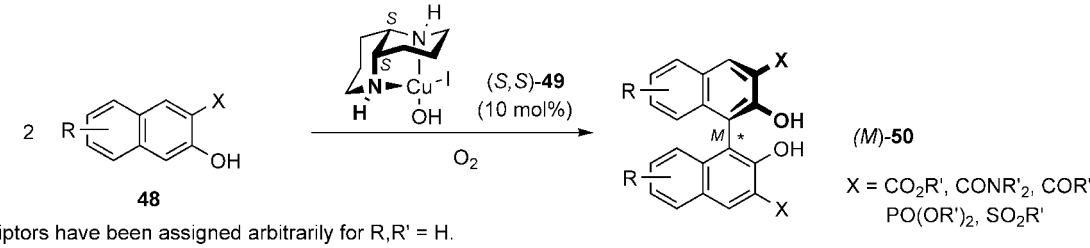
- intermolecular: (e.g., A. I. Meyers)



Dynamic Kinetic Resolution of Configurationally Labile Biaryls: (e.g., lactones, G. Bringmann)



Atropoenantioselective (Oxidative) Homocouplings: (e.g., M. C. Kozlowski)



Note: All stereodescriptors have been assigned arbitrarily for R,R' = H.

coupling reactions in the presence of a chiral catalyst.[18,79,81,90] Convincing examples that provide the target biaryls in excellent optical purities are still rare, but significant advances have recently been made in the field of atropoenantioselective oxidative homocouplings. As an example, Kozlowski and co-workers developed an efficient access to highly enantiopure 3,3′-disubstituted 2,2′-binaphthols of type (*M*)-**50** from the corresponding 2-naphthols **48** with molecular oxygen as the stoichiometric oxidant in the presence of catalytic amounts of the chiral (diaza-*cis*-decalin)copper(II) complex (*S*,*S*)-**49**.[18,113] Other atropoenantioselective procedures will be discussed in the context of the respective application.

3. Nonbridged Natural Biaryls

3.1. Isocyclic Biaryls

3.1.1. Simple Biphenyls: Mastigophorenes A and B

Biphenyls constitute the simplest class of naturally occurring biaryls. Their structural variety ranges from constitutionally symmetric derivatives with few substituents to cross-coupled biaryl systems often further equipped with a complex substitution pattern. Because of the small size of the phenyl ring, however, many of these compounds have a low atropisomerization barrier. Consequently, there are only a small number of axially chiral biphenyls, and even fewer have so far been synthesized atroposelectively.

One example of a constitutionally symmetric biphenyl is the "dimeric"[24] sesquiterpene mastigophorene A [(*P*)-**5**] (Figure 4), which was isolated from the liverwort *Mastigophora diclados*,[19,114] along with its atropodiastereomer, mastigophorene B [(*M*)-**5**]. Both biaryls are attractive target molecules, due to their promising nerve-growth stimulating activities, which might be of relevance to develop new agents against neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.[115] Biosynthetically, (*P*)-**5** and (*M*)-**5** are likely to be formed by one-electron oxidative phenolic coupling of the monomeric precursor (−)-herbertenediol [(*S*)-**51**],[116] also occurring in the same liverwort.

Several syntheses of mastigophorenes A [(*P*)-**5**] and B [(*M*)-**5**] followed the proposed biosynthetic pathway.[19] The biomimetic phenol-oxidative coupling of (*S*)-**51** or its mono-*O*-methylated derivative, however, led to low asymmetric

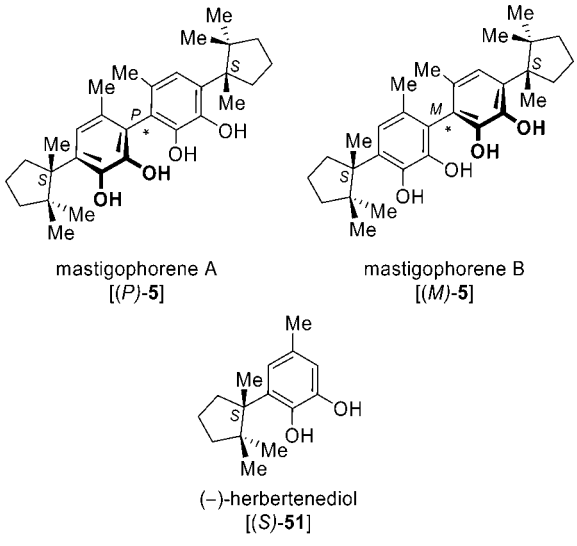
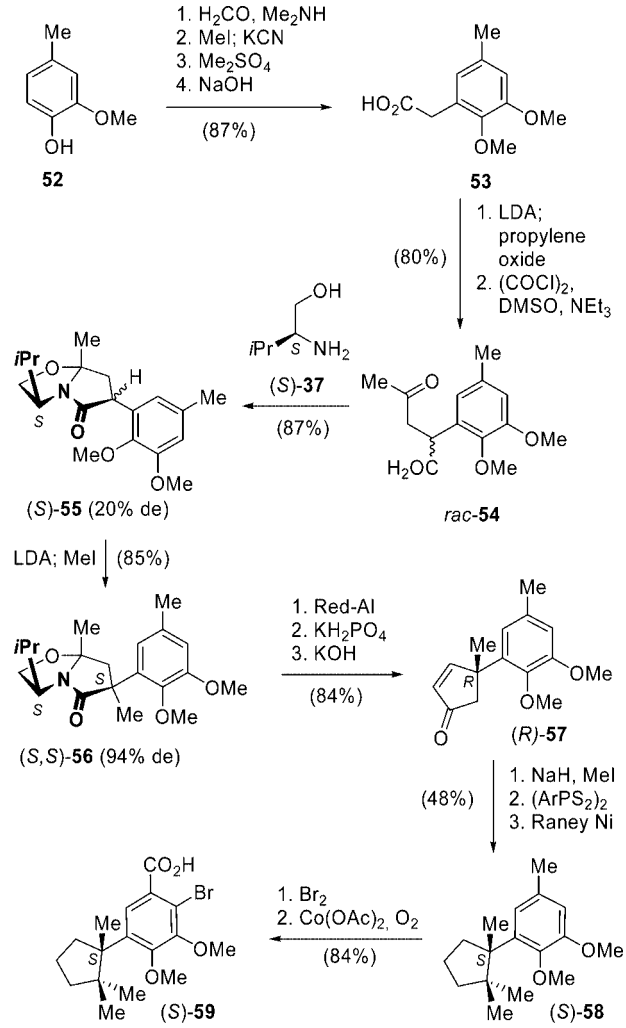


Figure 4.

Scheme 3

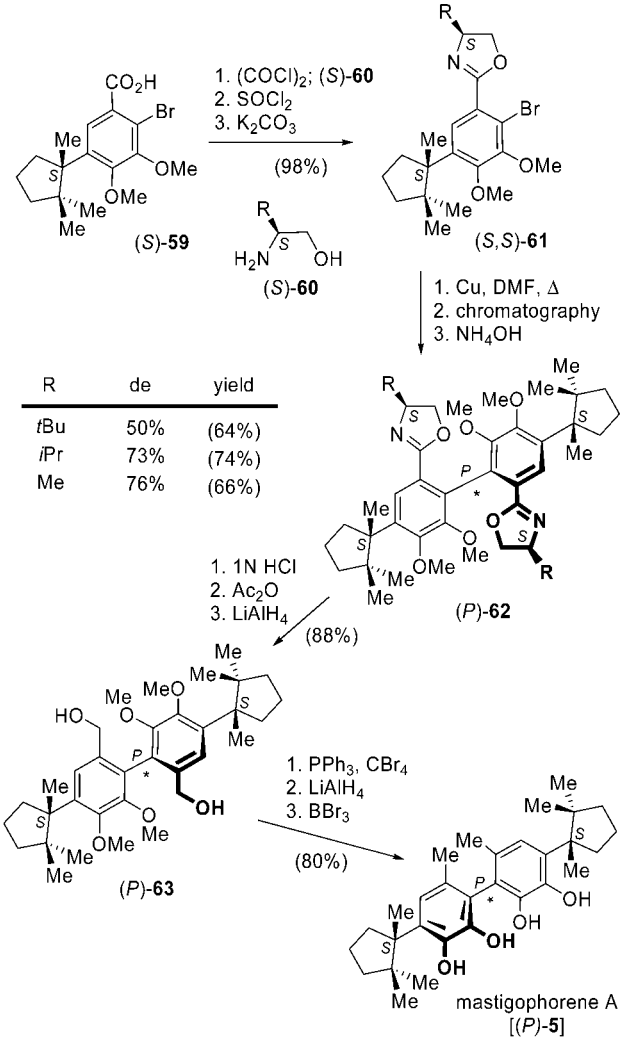


Semicolons between reagents in Schemes indicate that the transformation consists of several consecutive steps done in a single operation. Thus, e.g., "LDA; propylene oxide" means: deprotonation followed by electrophilc trapping.

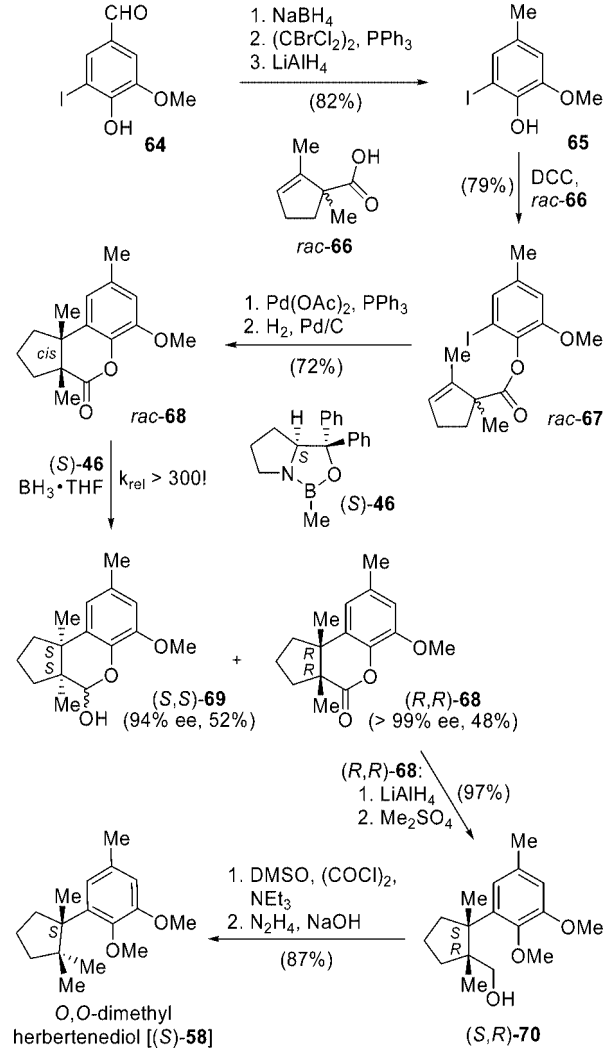
inductions, with diastereomeric ratios of (*P*)-**5**/(*M*)-**5** = 40:60[117] and 36:64,[118] respectively, which is, remarkably, almost identical to that of the natural mixture of 37:63.[19]

A short time after the atropoenantioselective synthesis of simplified model mastigophorenes (with the chiral cyclopentyl residue replaced by a *tert*-butyl group),[119] the first atroposelective synthesis of the authentic natural products, (*P*)-**5** and (*M*)-**5**, was reported by Degnan and Meyers,[120] who applied their diastereoselective, *ortho*-oxazoline-mediated Ullmann reaction in the stereochemically decisive coupling step. The enantiopure monomeric precursor (*S*)-**59** was prepared by "deracemizing alkylation" (Scheme 3). For this purpose, the racemic ketoacid *rac*-**54**, available from phenol **52** in six steps (70% yield) via the carboxylic acid **53**, was condensed with (*S*)-valinol [(*S*)-**37**] to give the chiral bicyclic lactam (*S*)-**55** as a diastereomeric mixture (20% diastereomeric excess (de)). This low stereoselectivity was, however, without relevance since deprotonation of both epimers led to the same enolate, which was *C*-methylated diastereoselectively, from the less-hindered "*endo*" face, affording (*S*,*S*)-**56** in 94% de. Reduction of the lactam (*S*,*S*)-**56** followed by aldol condensation delivered the cyclopentenone (*R*)-**57**, which was dimethylated in the α-position next to the carbonyl group and deoxygenated to give the herbertene-

Scheme 4



Scheme 5

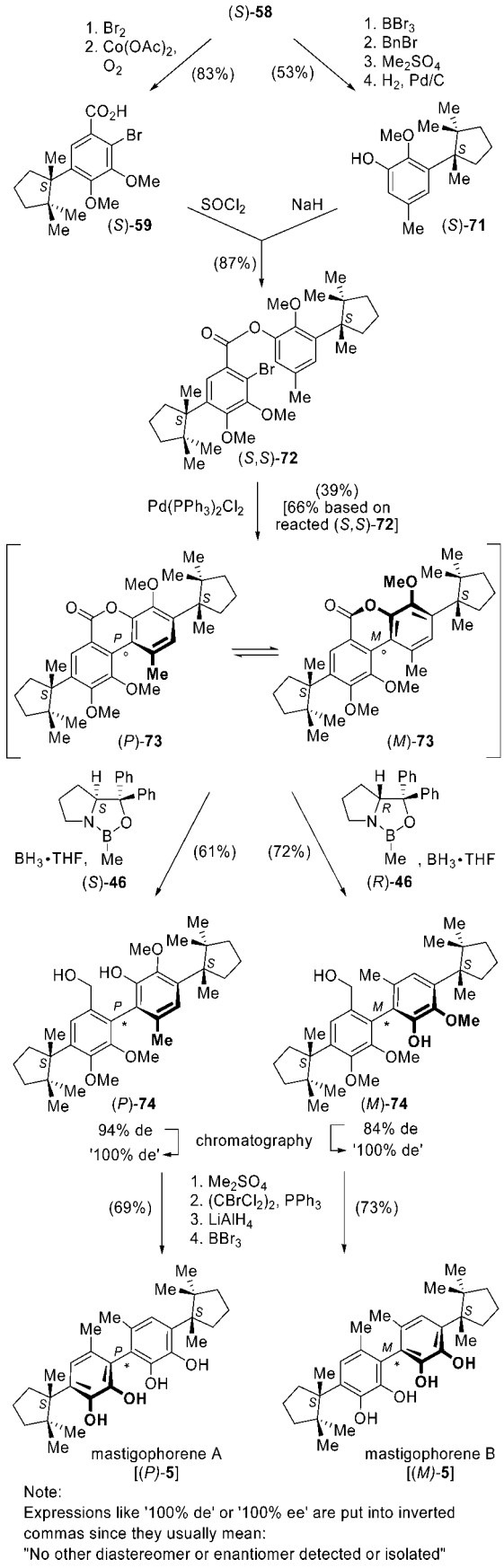


diol derivative (*S*)-**58**. The enantiopure bromo-activated benzoic acid (*S*)-**59** was obtained in 84% yield, by bromination of the benzene ring and oxidation of the aromatic methyl function.

The chiral information required for the asymmetric Ullmann coupling (Scheme 4) was introduced in four steps by condensation of (*S*)-**59** with an (*S*)-configured amino alcohol, e.g., with (*S*)-alaninol [(*S*)-**60**, 98% yield]. The resulting chiral *ortho*-oxazolinyl arenes (*S*,*S*)-**61** (R = *t*Bu, *i*Pr, Me) were treated with elemental copper to give the desired (*P*)-configured biaryls (*P*)-**62** in good yields (64−74%). The diastereomeric ratio (*P*)-**62**/(*M*)-**62** showed an unexpected influence of the substituents R at the oxazoline portion. In contrast to other asymmetric Ullmann couplings,[94,121] the best diastereomeric excess of 76% was realized with the (*S*)-alaninol derivative of (*S*,*S*)-**61**, i.e., with R = Me, whereas the chiral induction decreased with bulkier directing groups, e.g., for R = *t*Bu (50% de). Expectedly, the (*M*)-atropisomer was accessed with comparable yields and diastereoselectivities when using the (*R*)-configured oxazoline precursors. All attempts to resolve the atropodiastereomeric mixture (*P*)-**62**/(*M*)-**62** failed, but, fortunately, only the major isomer (*P*)-**62** formed a stable copper(I) complex, whereas (*M*)-**62** did not. This fortunate circumstance in combination with the substantially different chromatographic behavior of complexed (*P*)-**62** vs uncomplexed (*M*)-**62** now permitted a facile resolution by column chromatography. Decomplexation of pure (*P*)-**62** with NH_4OH finally released the diastereomerically homogeneous product (*P*)-**62**. Acidic cleavage of the chiral oxazoline moieties and reduction delivered the diol (*P*)-**63**, which was side-chain deoxygenated and *O*-demethylated to give the natural product mastigophorene A [(*P*)-**5**] in 27 steps with an overall 6% yield.

Nearly in parallel, the second atroposelective total synthesis of (*P*)-**5** and (*M*)-**5** was achieved by the authors' group,[122] by using the lactone method.[95−98] In this case, the required monomeric precursor, *O*,*O*-dimethyl herbertenediol [(*S*)-**58**], was prepared from iodoarene **64** (Scheme 5). After transformation of the aldehyde function into a methyl group, esterification of **65** with *rac*-**66** delivered *rac*-**67**, which was subjected to a palladium-catalyzed coupling reaction. Hydrogenation of the double bond in the five-membered ring resulted in the *cis*-configured—yet racemic—lactone *rac*-**68**. Kinetic resolution of *rac*-**68** by an enantiomer-differentiating reduction with borane in the presence of 60 mol % of (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-[1,3,2]oxazaborole [(*S*)-CBS catalyst][106] (*S*)-**46** delivered, besides the lactol (*S*,*S*)-**69**, the unreacted lactone (*R*,*R*)-**68** in excellent 48% chemical yield (i.e., 96% based on the maximum possible yield for that enantiomer) and >99% enantiomeric excess (ee) ($k_{rel} > 300$). Reductive ring-opening of (*R*,*R*)-**68** and *O*-methylation of the phenolic hydroxy group afforded (*S*,*R*)-**70** (97% yield). This benzylic alcohol (*S*,*R*)-**70** was converted into the herbertenediol derivative (*S*)-**58** in a two-step oxidation−deoxygenation sequence.

Scheme 6

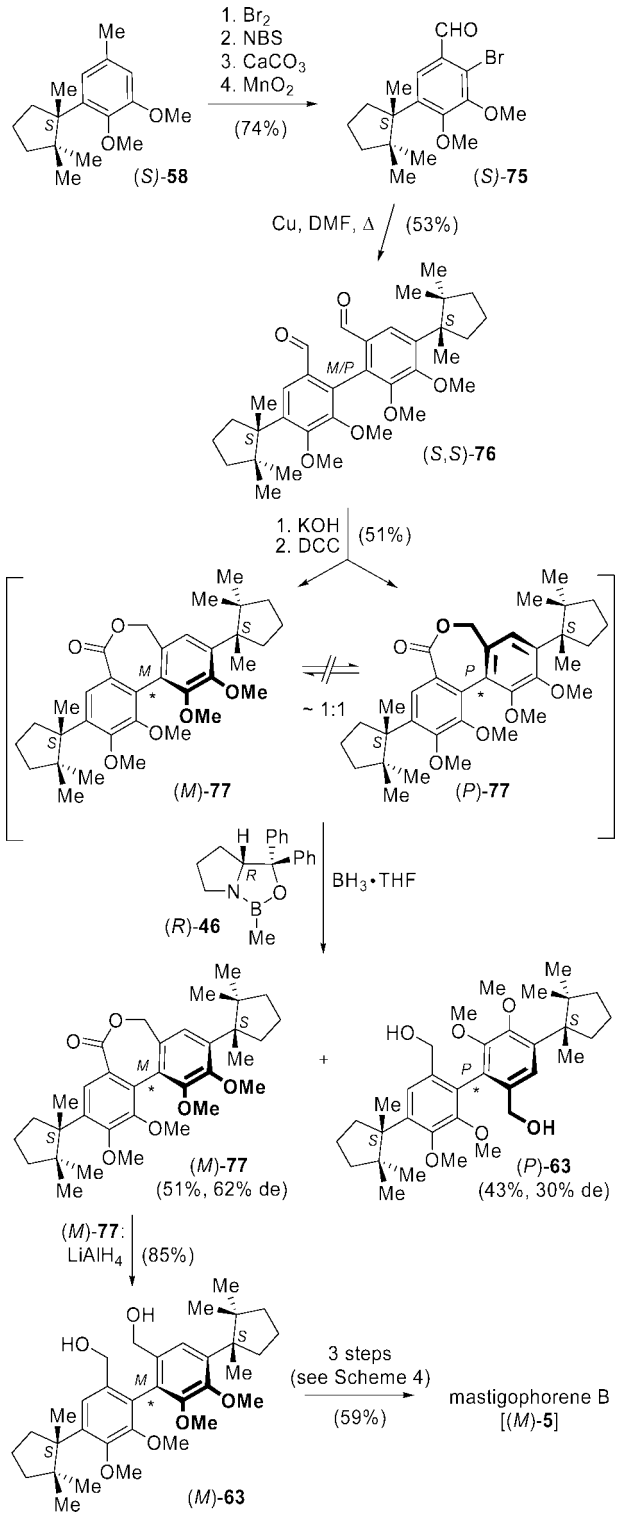


The coupling precursor (*S*,*S*)-**72** was prepared from two molecules of (*S*)-**58** (Scheme 6). Bromination of the aromatic ring and oxidation of the aromatic methyl group of (*S*)-**58** delivered the bromobenzoic acid (*S*)-**59** in 83% yield. The phenolic compound (*S*)-**71** was obtained by 2-fold *O*-demethylation of (*S*)-**58**, followed by regioselective benzylation at the less-hindered phenol group, *O*-methylation at the remaining hydroxy function, and hydrogenolytic *O*-debenzylation. The two building blocks (*S*)-**59** and (*S*)-**71** were linked by esterification to give (*S*,*S*)-**72**, which was submitted to an intramolecular Pd^0-mediated biaryl coupling delivering the configurationally unstable biaryl lactone (*P*)-**73** ⇆ (*M*)-**73** in 39% yield, along with 41% of recovered starting material (*S*,*S*)-**72**. The reductive ring cleavage of **73** proceeded highly atropodiastereoselectively, with dynamic kinetic resolution. Thus, application of an overstoichiometric amount of borane activated by (*S*)-**46**[106] afforded the now configurationally stable, ring-opened biaryl (*P*)-**74** in excellent 94% de, while the analogous reaction of **73** with the other oxazaborolidine enantiomer, (*R*)-**46**, diastereo-divergently yielded (*M*)-**74**, yet with lower asymmetric induction (84% de). In both cases, stereochemically pure material was obtained by column chromatography. The final natural target molecules, the mastigophorenes A [(*P*)-**5**] and B [(*M*)-**5**], were available in four further steps from (*P*)-**74** and (*M*)-**74**, respectively, by *O*-methylation, reductive removal of the benzylic hydroxy function, and deprotection of the phenol groups. In summary, this synthetic pathway not only gave access to axially chiral biaryls in high optical yields but also provided both atropodiastereomers of **5** via the same "late" precursor, viz. the configurationally unstable lactone **73**, just by using enantiomeric reagent combinations, here the CBS reagent (*S*)-**46** or (*R*)-**46**, for the cleavage of the bridge.

The lactone method is not restricted to the dynamic kinetic resolution of biaryls that are configurationally labile due to the presence of a bridge forming a six-membered ring but can also be applied to seven-membered biaryl lactones, which are configurationally more stable at the axis, thus just permitting a normal, nondynamic kinetic resolution.[95] This approach was likewise used for the synthesis of (*P*)-**5** and (*M*)-**5** (Scheme 7).[123] Starting from *O*,*O*-dimethyl herbertenediol [(*S*)-**58**] (see Scheme 5), the bromoaldehyde (*S*)-**75** was prepared in four steps. Ullmann coupling of (*S*)-**75** delivered the biaryl (*S*,*S*)-**76** as an atropodiastereomeric mixture, without any asymmetric induction at the axis. Disproportionation of the aldehyde functions by Cannizzaro reaction and subsequent intramolecular esterification yielded lactone **77** as an almost 1:1 mixture of atropodiastereomers. In the atropodiastereomer-differentiating reduction of **77** with borane and the CBS catalyst[106] (*R*)-**46**, the diol (*P*)-**63** was obtained with a low 30% de, while the recovered, unreacted lactone (*M*)-**77** possessed a better diastereomeric excess of 62%. Ring-opening of (*M*)-**77** with $LiAlH_4$ and further conversion of (*M*)-**63** as described in Scheme 4 completed the synthesis of mastigophorene B [(*M*)-**5**].

The nondynamic kinetic resolution of lactone (*M*)-**77** is particularly well suited for constitutionally symmetric biaryls, because it avoids the need of preparing two different aryl compounds (compare Scheme 6); it thus provides the as-yet shortest atroposelective approach to the dimeric[24] sesquiterpene mastigophorene B [(*M*)-**5**] (23 steps overall). But compared to the two syntheses described before, it suffers from a lower atroposelectivity in the introduction of the chiral information at the biaryl axis.

Scheme 7



3.1.2. Binaphthalenes and Binaphthoquinones

In 1886, Longmore[124] isolated the binaphthalene pigment gossypol (**6**, Figure 5) from the seeds of the cotton plant *Gossypium hirsutum*.[125] This C_2-symmetric molecule contains a rotationally hindered axis as the only element of chirality. Its absolute configuration was established by Snatzke's and Huang's groups in 1988,[126] by circular dichroism investigations with application of the exciton chirality theory.[127] Biosynthetically, gossypol (**6**) is built up by phenol-oxidative dimerization of its "monomeric" portion, hemigossypol (**78**).[128] The enantiomeric ratios of naturally occurring **78**

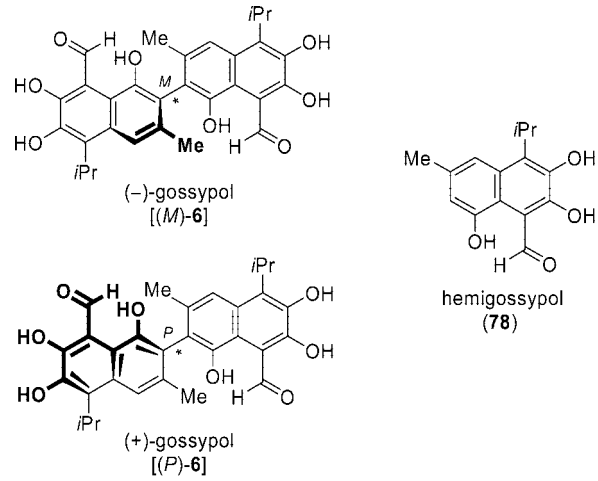


Figure 5.

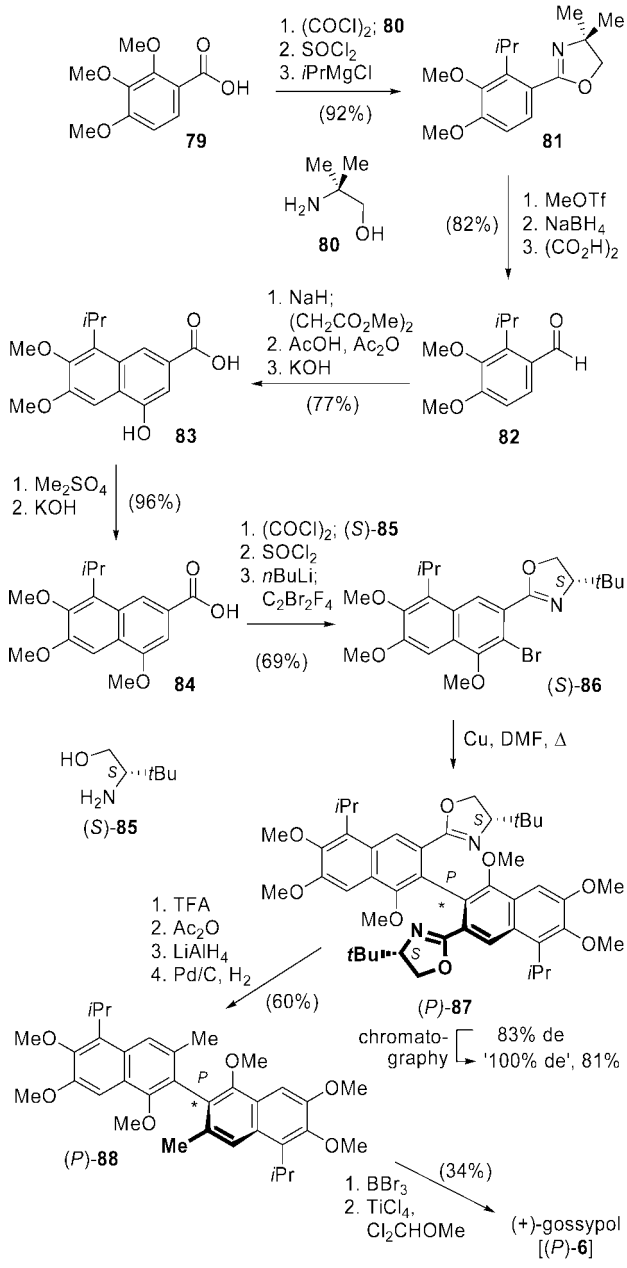
range from 30% ee in favor of (*M*)-**6** up to 90% ee for (*P*)-**6** in different *Gossypium* and *Thespesia* species.[129] Gossypol (**6**), in particular its levorotatory enantiomer, (*M*)-**6**, exhibits antispermatogenic[21,130] and anticancer[22,131] activities and selectively inhibits HIV-1 replication.[132]

After several total syntheses of **6** in a racemic form,[125,133] all following the biomimetic oxidative dimerization pathway, Meyers and Willemsen[134,135] reported the first atroposelective synthesis of (*P*)-**6** in 1997 using their well-established asymmetric Ullmann reaction of chiral oxazoline-activated arenes.[94,121]

Starting from commercially available 2,3,4-trimethoxybenzoic acid (**79**), the carboxyl group was converted into an (achiral) oxazoline moiety, thus permitting the nucleophilic substitution of the *ortho*-methoxy group by an isopropyl function to give **81** (Scheme 8).[134] Reductive cleavage of the oxazoline ring delivered aldehyde **82**, which was subjected to a Stobbe condensation, followed by acidic cyclization and saponification of the methyl ester to yield the naphthoic acid **83**. After *O*-methylation, the now chiral oxazoline substituent was introduced by treatment of the acid chloride of **84** with (*S*)-*tert*-leucinol [(*S*)-**85**]. Bromination next to the five-membered ring afforded the monomeric coupling precursor (*S*)-**86** in 39% overall yield over 14 steps. The stereochemical key step, the atropodiastereoselective Ullmann coupling of bromo oxazoline (*S*)-**86**, was accomplished in refluxing dimethylformamide (DMF), giving (*P*)-**87** in 83% de (100% de and 81% yield after chromatographic separation). Conversion of the two oxazoline moieties into methyl groups was achieved by acid-mediated cleavage and subsequent reduction. The resulting apogossypol hexamethylether [(*P*)-**88**] was *O*-demethylated to give, after formylation of the two naphthalene nuclei using α,α-dichloromethyl methyl ether and $TiCl_4$, the natural product (+)-gossypol [(*P*)-**6**], albeit in only 34% yield over the last two steps.

To avoid the two final low-yielding transformations from (*P*)-**88** to (*P*)-**6**, Meyers and Willemsen[134,135] investigated a second approach, in which a methoxymethyl group, a precursor for the latter formyl group, was installed at an earlier stage. For this purpose, oxazoline **81** was deprotonated with α-ethoxyvinyllithium (**89**) in the presence of hexamethylphosphoramide (HMPA), trapped with DMF, reduced, and *O*-methylated to give benzylic ether **90** (Scheme 9). Transformation of **90** into the chiral (*S*)-oxazolinyl naphthalene (*S*)-**91** was achieved in 32% yield, using the

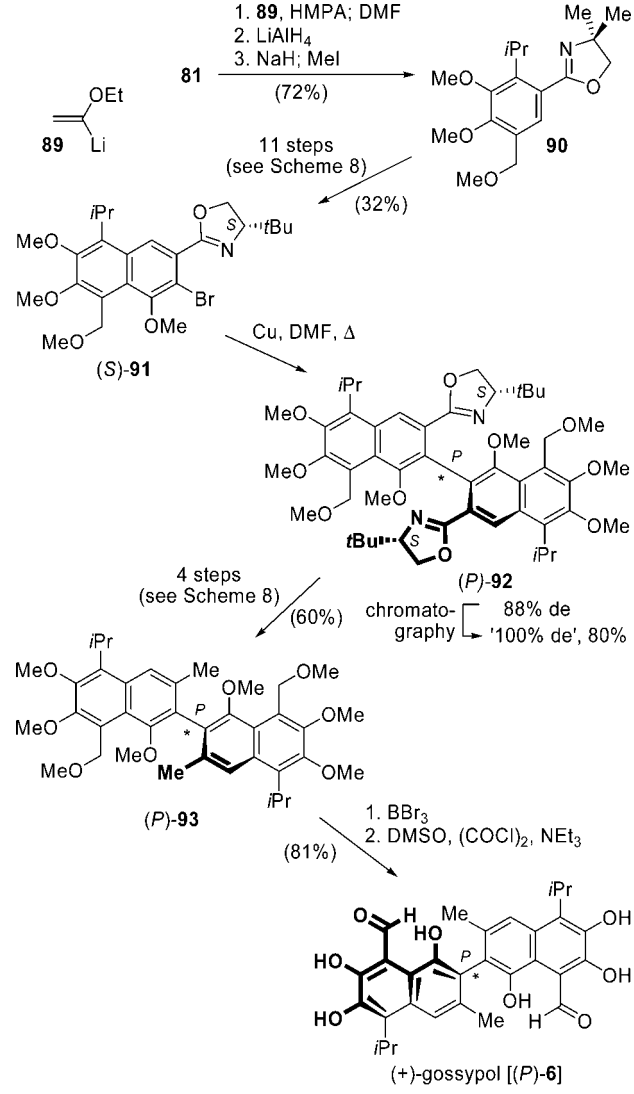
Scheme 8



procedure described in Scheme 8. The decisive Ullmann coupling step provided biaryl (*P*)-**92** again in good chemical (80%) and optical yields (88% de, raised to 100% de by column chromatography). Cleavage of the chiral building block under acidic conditions and deoxygenation of the resulting benzylic diol as in the first synthesis (see Scheme 8) gave the dimeric naphthalene (*P*)-**93**, which was *O*-demethylated at all eight ether functions. Swern oxidation of the benzylic alcohol functions delivered (+)-gossypol [(*P*)-**6**] in a substantially improved yield of 81% over the last two steps. Compared to the first approach, this route, although being slightly longer (24 vs 21 steps), gives a better overall yield (8% vs 6%).

Two more representatives of the class of dimeric isocyclic biaryls were prepared atropoenantioselectively, the acetogenic binaphthoquinone (−)-isodiospyrin [(*M*)-**94**][136−140] and its "8′-hydroxy"[141] derivative (*M*)-**95** (Figure 6).[136,138,142] Both are pigments of the genera *Diospyros*[136,137] and *Euclea*,[138,139] biosynthetically derived from the acetogenic naphthoquinone

Scheme 9



7-methyljuglone (**96**).[143] Whereas **94** only occurs as the (*M*)-atropisomer,[143] **95** was also isolated in a racemic form.[138] The constitutions of **94** and **95** were confirmed by Laatsch[144] in the course of a nonenantioselective total synthesis, while their absolute configurations were established in 1997 by Sargent's group within the first atropisomer-selective preparation of unnatural (*P*)-**94** and natural (*P*)-**95**,[145,146] using Meyers' diastereoselective cross-coupling of a Grignard reagent with a chirally modified naphthalene.

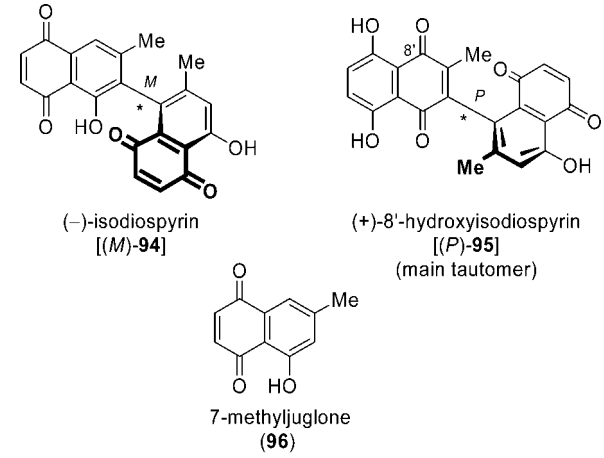
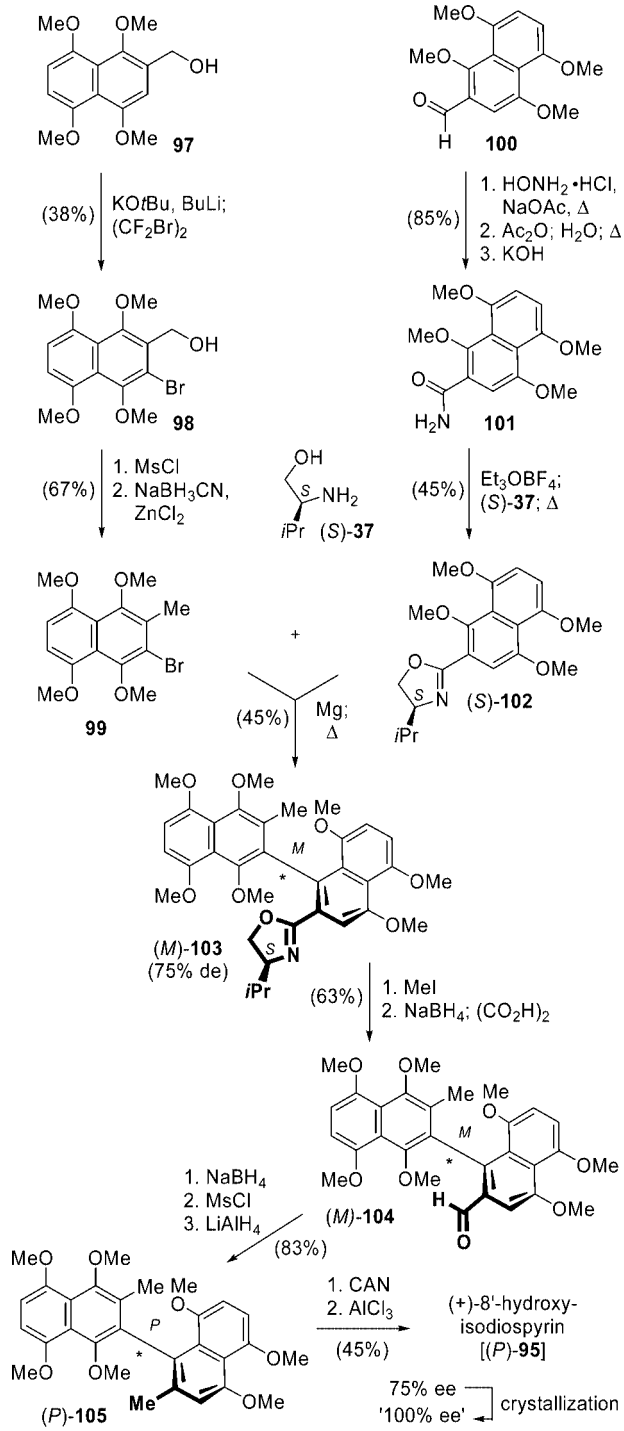
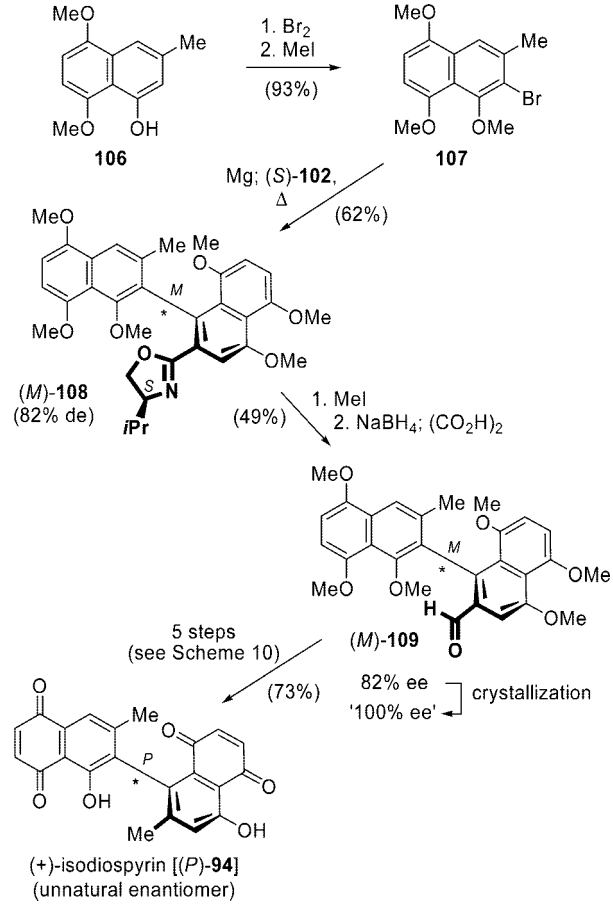


Figure 6.

Scheme 10



Scheme 11



The atroposelective synthesis of 8′-hydroxyisodiospyrin[141] [(*P*)-**95**][145,146] (Scheme 10) started with the known[147] aldehyde **100**, which was converted into the (*S*)-valinol derived oxazoline (*S*)-**102** in four steps under standard conditions via amide **101**. The Grignard reagent prepared from **99**, which in turn had been obtained from the benzylic alcohol **97**,[148] was reacted with (*S*)-**102**, leading to the biaryl (*M*)-**103** with nucleophilic aromatic substitution of the methoxy group ortho to the oxazoline moiety. The asymmetric coupling step proceeded in low chemical yield (45%), but with acceptable 75% de. All attempts to resolve the atropisomers of **103**, however, failed at this stage of the reaction sequence. Cleavage of the oxazoline ring of (*M*)-**103** by *N*-methylation followed by reduction furnished the aldehyde (*M*)-**104**. Further reduction and deoxygenation afforded binaphthalene (*P*)-**105**, which was oxidized to the corresponding biquinone with ceric ammonium nitrate (CAN). Deprotection of all phenolic hydroxy groups gave the natural product (+)-8′-hydroxyisospyrin [(*P*)-**95**], whose enantiomeric excess was enhanced from 75% to nearly 100% by crystallization. In summary, (*P*)-**95** was obtained in an overall yield of ca. 1% over 15 steps.

Following a similar protocol, (+)-isodiospyrin [(*P*)-**94**] was prepared in an enantiomerically pure form (Scheme 11).[146] The naphthalene **107**, as obtained by bromination and *O*-methylation of the naphthol **106**, and the (*S*)-oxazolinyl naphthalene (*S*)-**102** (see Scheme 10) were coupled in the presence of magnesium to deliver the binaphthalene (*M*)-**108** in 62% yield and 82% de. Reductive cleavage of the oxazoline ring of (*M*)-**108** gave aldehyde (*M*)-**109**, which was crystallized to provide enantiopure material. For the completion of the synthesis of isodiospyrin, the same route was followed as for the preparation of (*P*)-**95** (see Scheme 10). By this approach, however, only the unnatural (+)-enantiomer (*P*)-**94** was accessible in 14 steps and 7% overall yield.

3.1.3. Cross-Coupled Biaryls: Phenylanthraquinones

Among the more than 100 isolated anthraquinone natural products that possess a biaryl axis,[4] constitutionally unsymmetric phenylanthraquinones[30] like (+)-knipholone [(*P*)-**8**] and (+)-knipholone anthrone [(*P*)-**110**] (Figure 7) and their derivatives[149,150] are of special interest. The biosynthetic pathway leading to these metabolites includes a presumably enzyme-controlled, highly chemo-, regio-, and stereoselective

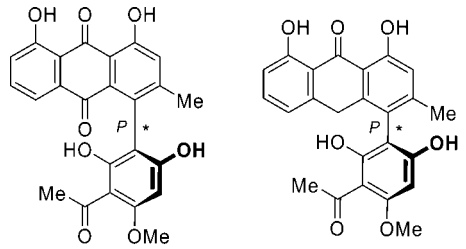
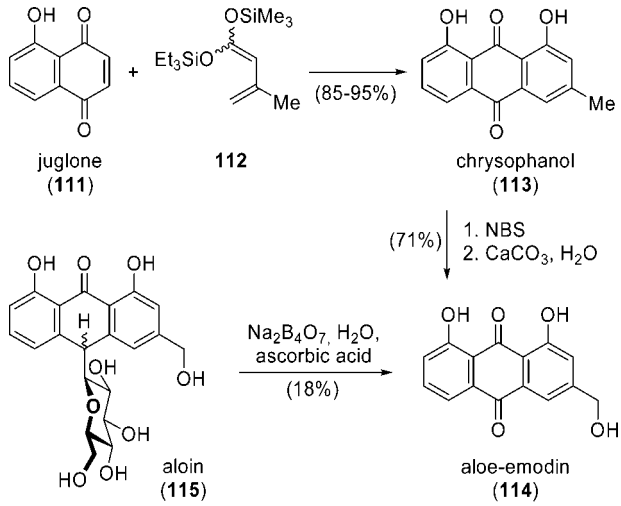


Figure 7.

Scheme 12

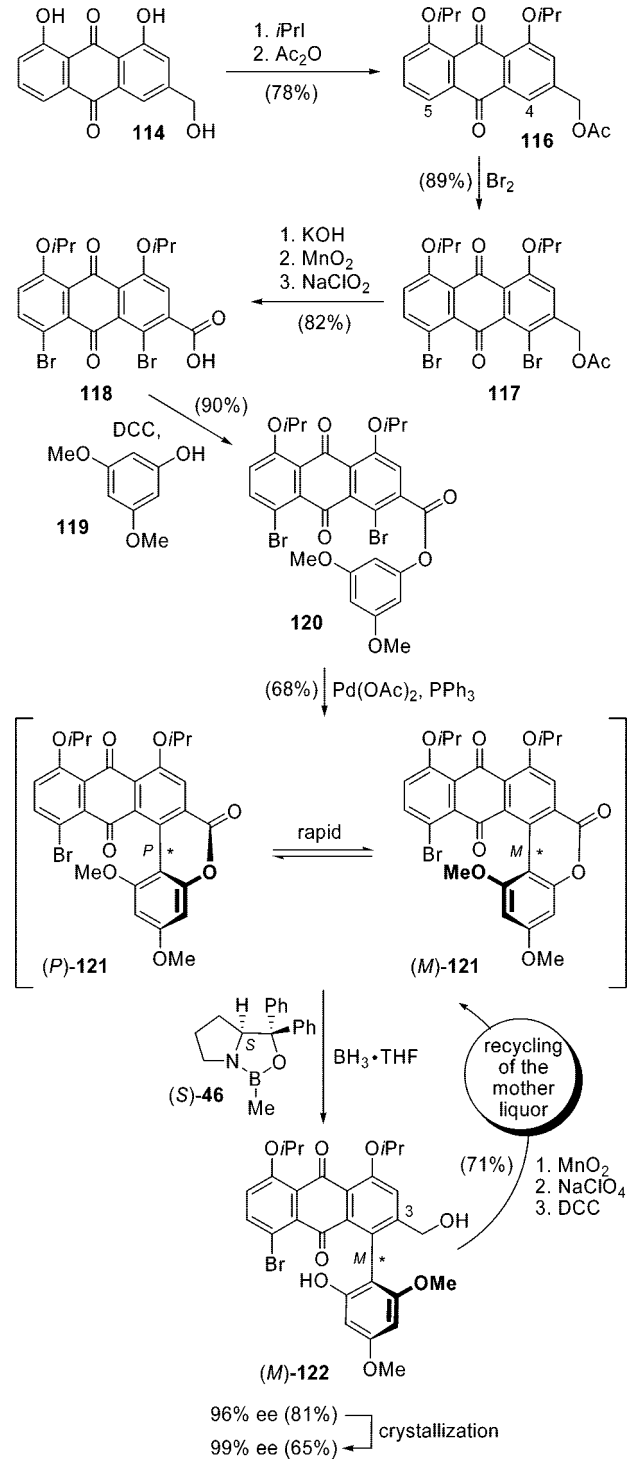


mixed biaryl coupling step[151] and not a—more or less spontaneous, possibly nonenzymatic—"dimerization" as for some biscarbazoles or dimeric anthraquinones (see section 3.2.5).[152] This assumption is supported, i.e., by the optical activity of (*P*)-**8**, although, on the other hand, many of these plant-derived compounds are not fully enantiopure in nature. Some of these mixed biaryls possess significant antimalarial[27] and antitumoral[29] activities, antioxidant properties,[153] and inhibitory effects on leukotriene formation,[154] which makes them interesting candidates in the search for new medical drugs.

The only reported atropoenantioselective total syntheses of (+)-knipholone [(*P*)-**8**], (+)-knipholone anthrone [(*P*)-**110**], and closely related phenylanthraquinones have so far been elaborated in the authors' group, by using the lactone method.[28,30,150,155,156] This approach is ideally suited for the convergent preparation of constitutionally unsymmetric biaryls like (*P*)-**8** and (*P*)-**110**. The precursor to the "northern" part of (+)-knipholone [(*P*)-**8**] (Scheme 12), aloe-emodin (**114**), is readily accessed from the commercially available natural product chrysophanol (**113**) by benzylic bromination and hydrolysis.[28] Compound **113** can also be isolated in large quantities from natural sources or it can be synthetically prepared by Diels–Alder reaction of juglone (**111**) with the diene **112**.[157] Alternatively, aloe-emodin (**114**) can be synthesized from the (likewise purchasable, albeit quite expensive) natural *C*-glyoside aloin (**115**).[158]

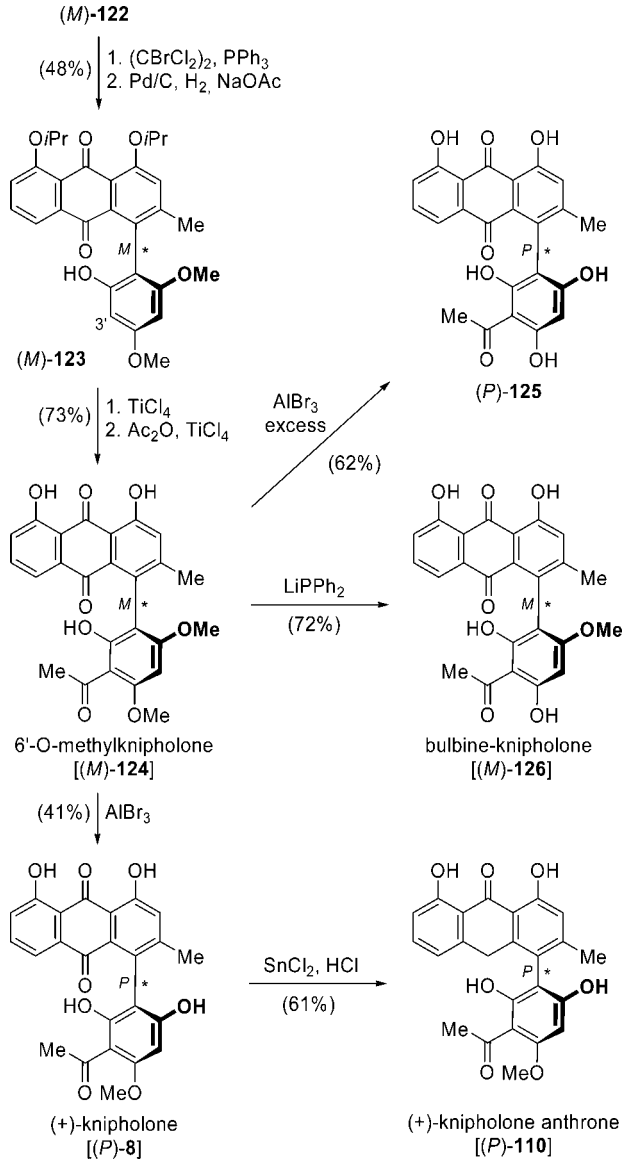
The synthesis of the intermediate (*M*)-**122** started with aloe-emodin (**114**, Scheme 13).[28] Isopropylation of the phenolic hydroxy groups and acetylation of the benzylic hydroxy function furnished **116** in 78% yield. The envisaged exclusive monobromination of **116** in the 4-position proved to be difficult, but dibromination in both the 4- and 5-

Scheme 13



positions, by using an excess of bromine, occurred smoothly and delivered **117** in 89% yield. The unwanted additional bromine substituent at C5 did not interfere with any of the subsequent synthetic transformations and was easily eliminated at a later stage, together with another reductive hydrodebromination, which was required anyhow (see Scheme 14). Saponification and stepwise oxidation of **117** afforded acid **118** (82% yield), which was esterified with dimethoxyphenol (**119**) to give **120** (90% yield). Intramolecular palladium-catalyzed coupling delivered the lactone **121** as a mixture of its interconverting atropoenantiomers, (*P*)-**121** and (*M*)-**121**, thus permitting a dynamic kinetic resolution. Atropoenantioselective reductive ring-opening with BH_3•

Scheme 14



THF in the presence of 3.0 equiv of the CBS reagent[106] (*S*)-**46** gave the (*M*)-configured diol **122** in high enantiomeric purity (96% ee) and chemical yield (81%).

In agreement with the finally attained natural product, (+)-knipholone (**8**), which had—wrongly—been assigned as (*M*)-configured,[159] this diol **122** was initially attributed the (*P*)-configuration.[28,155] This, however, would have meant that **121** would be the only lactone that would open such that (*S*)-**46** gives the product with the phenolic OH group above the plane. This inconsistency has meanwhile triggered a reinvestigation—and revision—of the stereostructure of (+)-knipholone (**8**), showing it to be (*P*)-configured.[156] Thus, the previously assumed gap has been closed. The stereochemical outcome of all such ring-cleaving reactions within the lactone concept is indeed reliably predictable, and the method can thus even be used for the elucidation of absolute axial configurations of natural biaryl products. Consequently, the diol **122** obtained by reduction using (*S*)-**46** had the desired (*M*)-configuration. It was further transformed into enantiomerically pure material (99% ee, 65% yield) by crystallization. The optically less pure diol recovered from the mother liquor of **122** can be recycled by reoxidation and cyclization to give back the configurationally unstable lactone **121** in good 71% yield, thus permitting conversion of almost all of the starting material into the desired (*M*)-atropoenantiomer.

The hydroxymethylene substituent at C3 of (*M*)-**122** was transformed into a methyl group by hydroxy/bromine exchange and hydrodebromination (Scheme 14).[28,155] Using hydrogenolytic conditions for the latter reaction, the unwanted additional bromine substituent at C5 was removed, too, without any extra step, giving (*M*)-**123** in 48% yield. Deprotection of the hydroxy functions of the anthraquinone moiety and acetylation at C3′ by Fries rearrangement afforded the plant metabolite 6′-*O*-methylknipholone [(*M*)-**124**] in 73% yield, which was converted into several *O*-demethylated derivatives—all of them natural products—by utilizing different ether cleavage conditions. The fully *O*-demethylated derivative (*P*)-**125** was obtained when using an excess of $AlBr_3$ (62% yield), while selective *O*-demethylation with $LiPPh_2$ and $AlBr_3$ afforded bulbine−knipholone [(*M*)-**126**] (72%) and (+)-knipholone [(*P*)-**8**] (41%), respectively. Reduction of (*P*)-**8** with $SnCl_2$ gave (+)-knipholone anthrone [(*P*)-**110**] in 61% yield.

By this first, and still only, synthetic approach to chiral phenylanthraquinones, five knipholone-type natural products were synthesized from a single and—on the time-average—achiral precursor, **121**, with a highly efficient dynamic kinetic resolution of a configurationally labile lactone as the stereochemical key step.

3.2. Biaryls with Annellated Heterocycles

3.2.1. Bicoumarins

Naturally occurring bicoumarins (Figure 8) as produced by fungi, in particular by *Aspergillus* species,[4] are biosynthetically built up by oxidative homocoupling of the polyketidic coumarins siderin (**127**), umbelliferone (**128**), or esculetin (**129**). Although no cross-coupling products between these monomeric basic units have so far been observed,[4] this "dimerization"[24] gives rise to both constitutionally symmetric and unsymmetric products. As an example, the symmetric 6,6′-coupled isokotanin A [(*M*)-**130**] is found in the sclerotia of *Aspergillus alliaceus*, where it acts as an antifeedant for protection against predators.[160] The 8,8′-connected (+)-kotanin [(*P*)-**9**] was first isolated in 1971 from *Aspergillus clavatus* by Büchi et al.,[161] who also developed the first

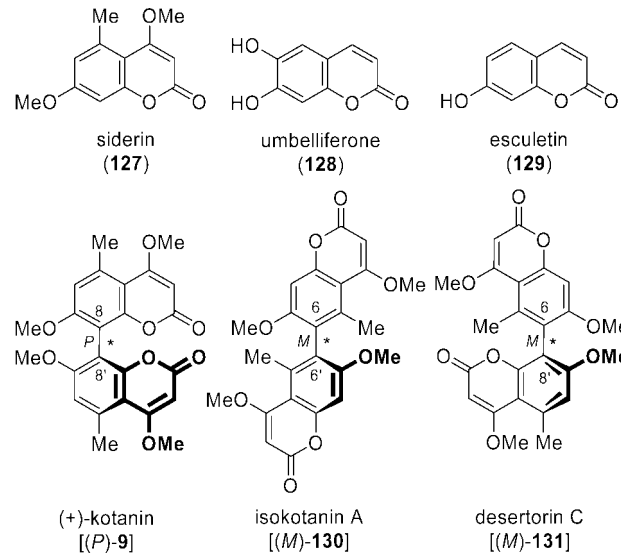
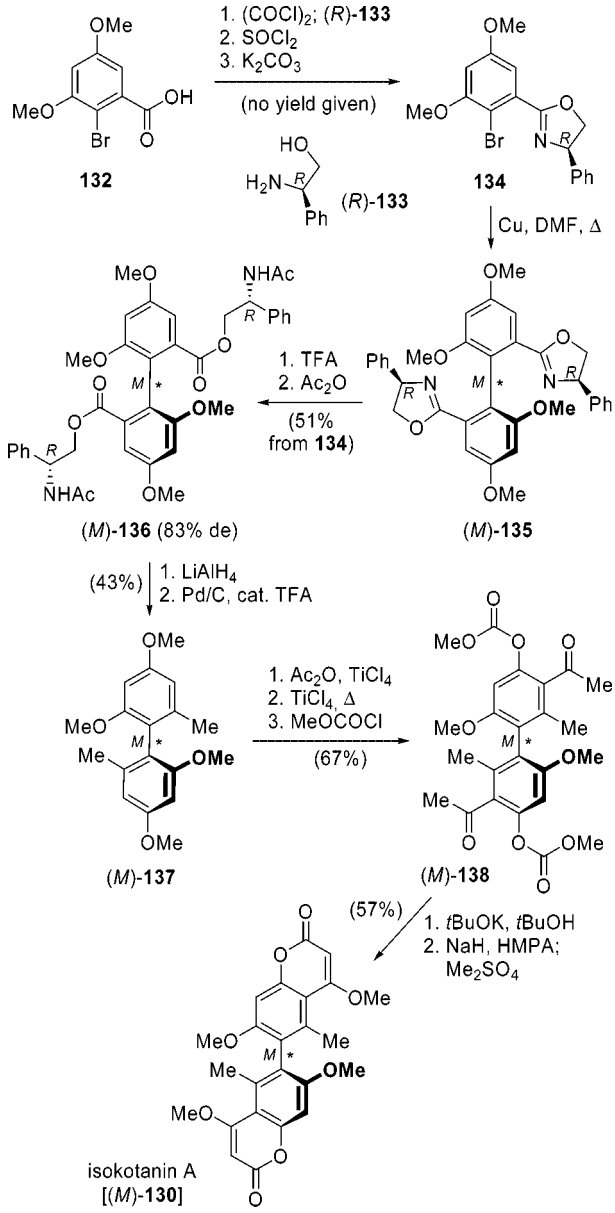


Figure 8.

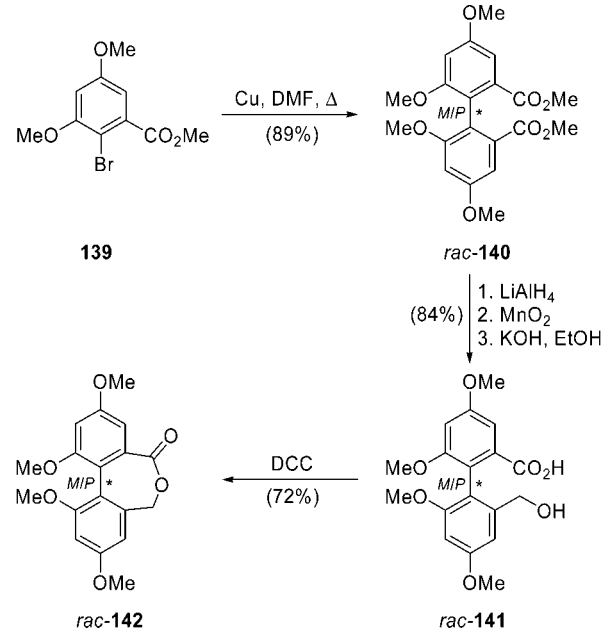
Scheme 15



synthesis of racemic **9**.[35] The regio- and stereoselective biosynthesis of (*P*)-**9** by phenol oxidative biaryl coupling has recently been elucidated in *A. niger*.[162] An example of an unsymmetrically 6,8′-coupled bicoumarin is desertorin C [(*M*)-**131**] from *Emericella desertorum*.[4] All bicoumarins that have so far been synthesized in enantiopure form, viz. **9**, **130**, and **131**, are siderin-derived metabolites.

The first synthesis of both atropisomers of isokotanin A [(*M*)-**130**] was reported by Lin and Zhong, who also assigned the absolute configuration of the natural product.[163] The oxazoline **134** (Scheme 15), accessible from the acid **132** and readily available enantiopure (*R*)-phenylglycinol [(*R*)-**133**],[121] was coupled under Ullmann conditions to give the biaryl (*M*)-**135**. After acid-catalyzed hydrolysis of the oxazoline moieties and acetylation, the de of the product was determined to be 83% at the stage of the diester (*M*)-**136**. Further reduction of (*M*)-**136** led to (*M*)-**137** (43%), which was regioselectively *C*-acetylated by Friedel−Crafts reaction, followed by an *O*-demethylation in the chelated positions and a methoxy-carbonylation to give the diketone (*M*)-**138** in 67% yield. Conversion of (*M*)-**138** into natural isokotanin

Scheme 16

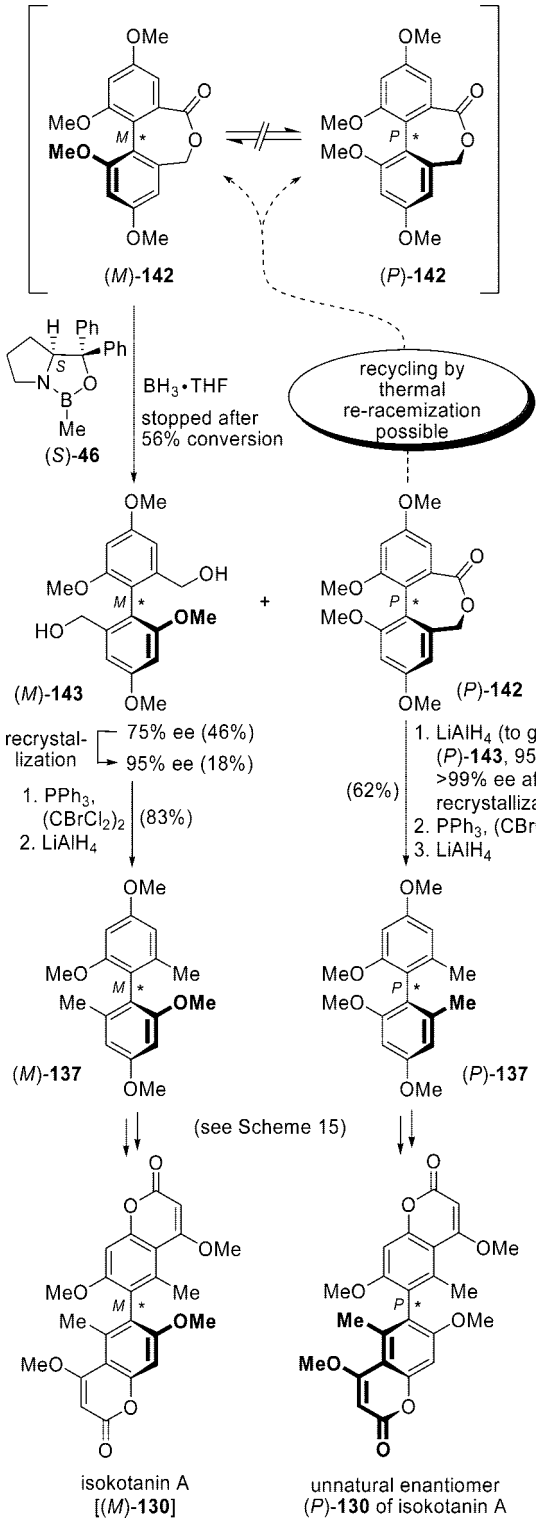


A [(*M*)-**130**] was achieved by cyclization under basic conditions and *O*-methylation (57% yield). In summary, isokotanin A [(*M*)-**130**] was prepared in 10 steps from the oxazoline **134**, with an overall yield of 8.5% using (*R*)-**133** as the chiral auxiliary. Starting from (*S*)-phenylglycinol [(*S*)-**133**], the unnatural enantiomer (*P*)-**130** was synthesized in the same manner and with comparable yields.[163]

A different strategy for the atropoenantiodivergent synthesis of either enantiomer of isokotanin A, (*M*)-**130** or, optionally, (*P*)-**130**, via axially chiral central biphenyl building blocks of type **137** (see Scheme 15), was developed in the authors' group based on the kinetic resolution of a lactone-bridged biarylic precursor.[112] The key intermediate, the racemic lactone *rac*-**142** (Scheme 16), was prepared from the bromo ester **139**[164] in five steps and 54% overall yield. Nonstereoselective Ullmann coupling of **139** afforded *rac*-**140**, which was reduced to the respective diol, oxidized to the dialdehyde, and subjected to a Cannizzaro disproportionation to give *rac*-**141**. Final cyclization under modified Steglich conditions[110,111] delivered the racemic lactone *rac*-**142**.

In contrast to the helicene-like, distorted, six-membered lactones like **121** (see Scheme 13), the three-atom bridge in the seven-membered lactone *rac*-**142** results in a "relaxed", strain-free biaryl[165] with a "normal" atropisomerization barrier (i.e., like for open-chain biaryls), sufficiently high to prevent interconversion at room temperature. This sets the basis for a normal, i.e., nondynamic, kinetic resolution of **142** by atropoenantioselective reduction with $BH_3 \cdot THF$ in the presence of the CBS reagent[106] (*S*)-**46** (Scheme 17). By stopping the reaction at 56% conversion, the alcohol (*M*)-**143** was obtained in 46% yield and 75% ee (95% ee after recrystallization), along with the unreacted lactone (*P*)-**142** (43% yield, 95% ee), which may be thermally racemized and used for a renewed ring-opening. This, in principle, permits successive conversion of virtually all of the starting material into the desired alcohol (*M*)-**143**. Alternatively, (*P*)-**143** can be used for the preparation of unnatural (*P*)-configured isokotanin [(*P*)-**130**], which, because of the high enantiopurity of (*P*)-**142**, seemed rewarding, too. Reduction of (*P*)-**142** delivered (*P*)-**143** in >99% ee after recrystalli-

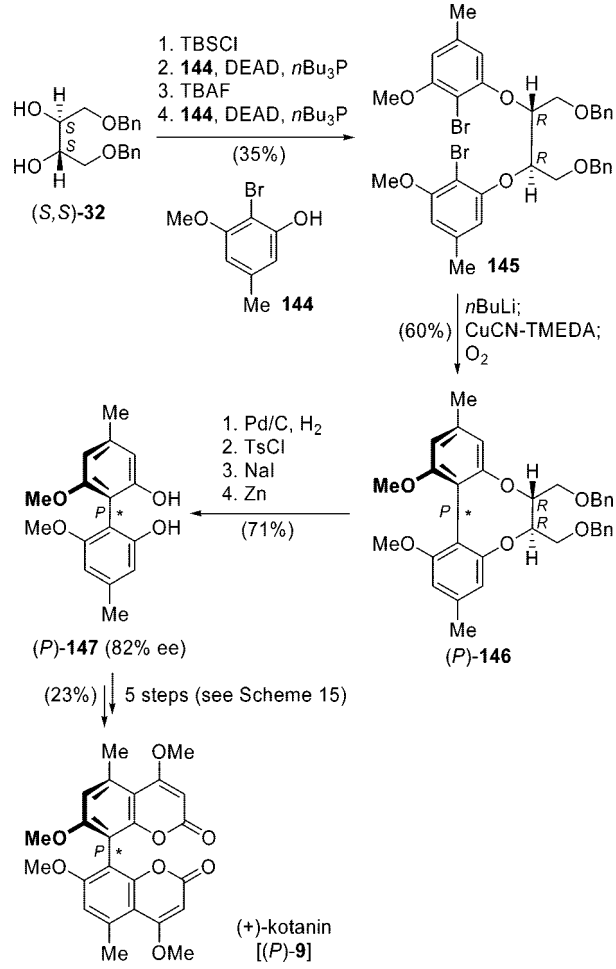
Scheme 17



zation. The two alcohols (*M*)-**143** and (*P*)-**143** were subjected to hydroxyl−bromine exchange and reduced to give (*M*)-**137** and (*P*)-**137** in >80% yield each. The final synthetic steps toward natural isokotanin A [(*M*)-**130**] and its atropoenantiomer, (*P*)-**130**, were accomplished by following Lin's procedure (see Scheme 15).

Lin and Zhong also succeeded in the first and so far only atroposelective synthesis of (+)-kotanin [(*P*)-**9**][166] by applying Lipshutz's intramolecular oxidative coupling of cyanocuprates.[91] The bridged coupling precursor **145** was prepared from the chiral tether 1,4-di-*O*-benzyl-L-threitol[167]

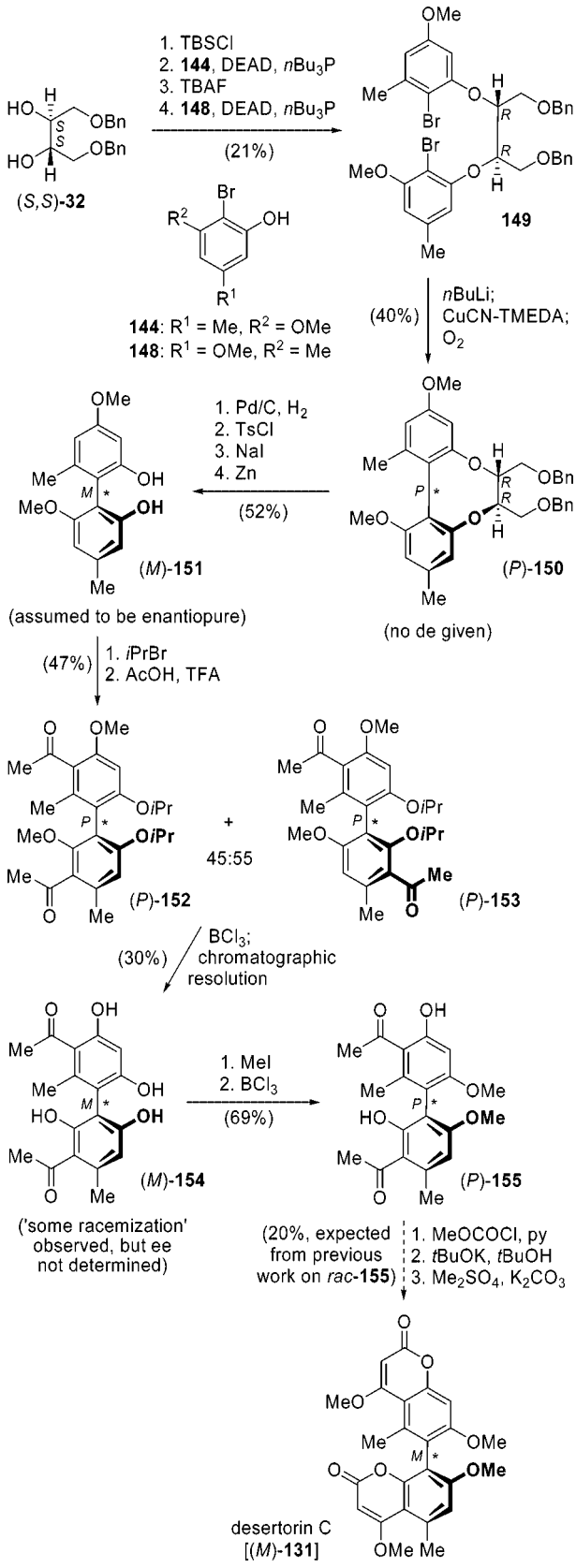
Scheme 18



[(*S*,*S*)-**32**] by stepwise attachment of 2 equiv of the bromophenol **144**[168] under Mitsunobu conditions, with inversion at both stereocenters (Scheme 18, 35% overall yield). Intramolecular cyanocuprate-mediated coupling reaction of **145**, by lithiation with *n*BuLi and transmetalation with CuCN−TMEDA to give the cuprate, followed by exposure of the reaction mixture to dry oxygen, delivered (*P*)-**146** in 60% yield. Twofold *O*-debenzylation, *O*-tosylation, tosyloxy−iodine exchange, and reduction with zinc powder afforded the biphenol (*P*)-**147** in 64% overall yield and 82% ee, from which enantiopure material of (*P*)-**147** was obtained by recrystallization. Conversion of (*P*)-**147** into natural (+)-kotanin [(*P*)-**9**] was accomplished in analogy to the synthesis of isokotanin A [(*M*)-**130**] described in Scheme 15. The formation of the natural product succeeded in 14 steps with an overall yield of ~3%.

Again by application of the Lipshutz method, both atropoenantiomers of the 6,8′-coupled bicoumarin desertorin C [(*M*)-**131**] were prepared by Sargent's group[169] as part of a formal total synthesis.[170] The required constitutionally unsymmetric and chirally modified coupling precursor **149** (Scheme 19) was accessed from (*S*,*S*)-**32** by stepwise attachment of the two different bromophenols **144** and **148**[171] under Mitsunobu conditions (21% yield). Asymmetric Ullmann coupling delivered the threitol-bridged biaryl (*P*)-**150** in 40% yield, which was converted into the diol (*M*)-**151** according to the procedures shown in the preceding Scheme 18 (52% yield).[166] This biaryl was assumed to be enantiopure because it was not resolved on different chiral phases. Moreover, no ^{1}H NMR signal doubling was observed for

Scheme 19



the respective Mosher diester derivative. *O*-Isopropylation of the two phenolic OH groups of (*M*)-**151** provided the basis for a 2-fold *C*-acetylation at the positions between the methyl and the methoxy groups. The latter reaction, however, failed to proceed regioselectively, giving an inseparable 45:55 mixture of the diketones (*P*)-**152** and (*P*)-**153**. In situ O-dealkylation with BCl_3 delivered the required tetrol (*M*)-**154** (albeit in only 30% yield), which was now separable from the undesired regioisomeric byproduct. At this stage, "some racemization" was observed but not quantified. Exhaustive *O*-methylation followed by selective *O*-demethylation of the positions next to the acetyl groups provided the diol (*P*)-**155**, an intermediate of Sargent's former synthesis of racemic desertorin C (**131**).[169] In view of these findings, (*P*)-**155** might analogously be converted into natural desertorin C [(*M*)-**131**] in three further steps (yet with the uncertainty of a possible further loss in enantiomeric purity). On the basis of this assumption, an atroposelective synthesis of (*M*)-**131** from (*S*,*S*)-**32** would require a total of 17 steps with an overall yield of <1%.

In conclusion, only few atroposelective syntheses have so far been reported for natural bicoumarins, and all target molecules were symmetric or unsymmetric "dimers"[24] of siderin (**127**). The lactone method, as developed by the authors' group, provides the possibility of preparing either atropoenantiomer of isokotanin (**130**) by just a single kinetic resolution experiment.[112] The methods elaborated in Lin's group, using Meyers' oxazoline approach[163] or the Lipshutz method,[166] deliver good optical and chemical yields, whereas Sargent's synthesis[170] suffers from low overall yields and poor selectivities.

3.2.2. Biflavonoids

"Dimeric"[24] flavones are widely spread in the plant kingdom.[4] Many of these so-called biflavonoids are most likely configurationally stable and, thus, axially chiral, even if they are devoid of additional stereocenters. Nevertheless, the determination of the absolute axial configuration of most of these compounds remains an as yet open problem, which is frequently even unrecognized. From a pharmacological point of view, biflavonoids have not been intensively explored either, but spasmolytic,[172] antiarthritic,[173] and antiviral[174] activities, reduction of histamine expression,[175] phospholipase[176] and phosphodiesterase inhibition,[177] and antimalarial[4] activities were reported[4,178] but never discussed in relation to their absolute axial configuration. In many cases, the dimers exhibited more pronounced bioactivities than the monomers.[4] There are only a few reports on the total synthesis of optically pure biflavonoids,[33] mainly using the resolution of racemic material by conversion into separable diastereomers (e.g., via camphorsulfonates[179] or prolylates[180]). In 1997, Lin and Zhong succeeded in the atropoenantioselective synthesis of the tetramethoxy derivative (*M*)-**156** of cupressoflavone (Figure 9),[181] using the intramolecular oxidative coupling technique elaborated by Lipshutz. 1,4-Di-*O*-benzyl-D-threitol [(*R*,*R*)-**32**] was reacted with 2 equiv of the iodophenol **157** to afford the diether (*S*,*S*)-**158** (22% yield), which was subjected to a cyanocuprate-mediated intramolecular biaryl coupling, giving (*M*)-**159** in 75% yield (Scheme 20).[181] Removal of the artificial chiral

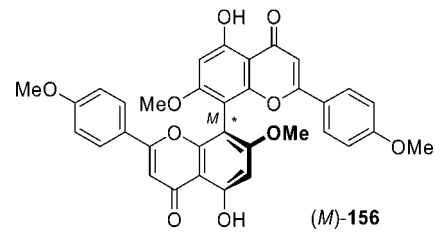
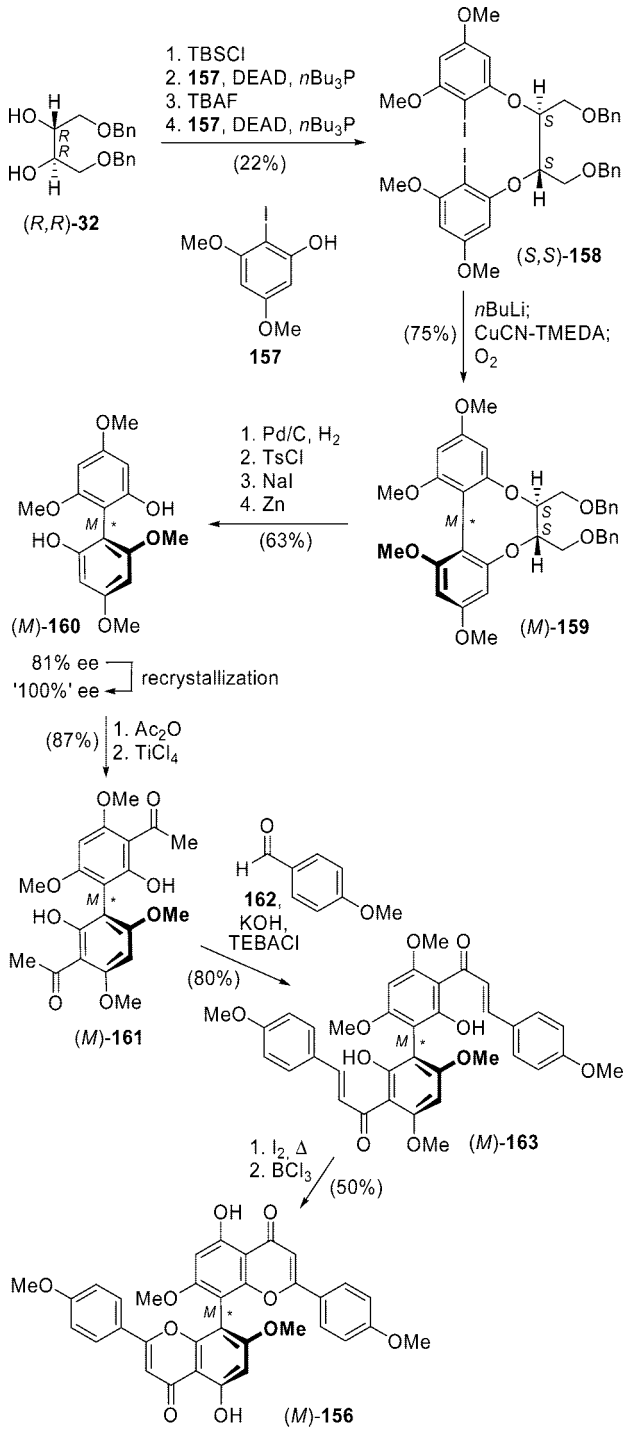


Figure 9.

Scheme 20



bridge (see also Schemes 18 and 19, 4 steps, 63% yield) led to the biphenol (*M*)-**160** in 81% ee, which was converted into stereochemically homogeneous material by a recrystallization step. The product (*M*)-**160** was *O*-acetylated and subjected to a Fries rearrangement to afford the diketone (*M*)-**161**, which was condensed with *p*-anisaldehyde (**162**), delivering the bichalcone (*M*)-**163** in 80% yield. Subsequent ring closure upon heating with iodine and selective *O*-demethylation gave the target molecule, the natural biflavone (*M*)-**156**, in 50% yield. This, so far only, synthetic access to simple biflavones should, in principle, also be applicable to the atropoenantioselective preparation of many other natural products of this type.

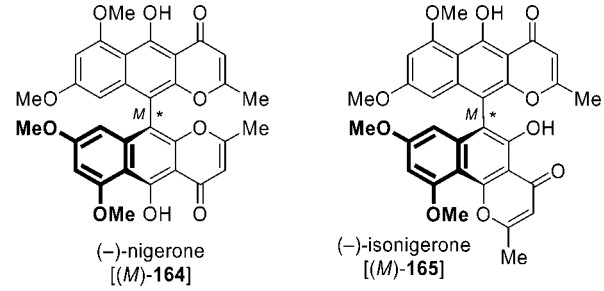


Figure 10.

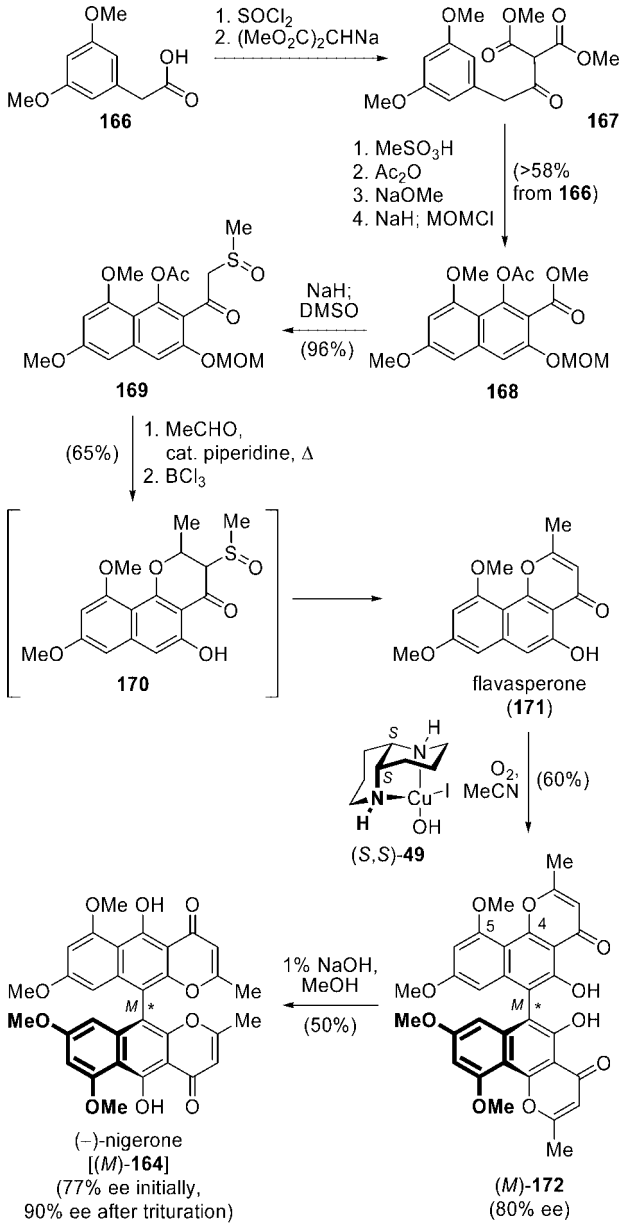
3.2.3. Binaphthopyrones

Binaphthopyrones constitute a small class of metabolites mainly occurring in fungi. Two prominent examples of these natural products are the naphtho-γ-pyrones nigerone (**164**) and isonigerone (**165**, Figure 10).[182] They are toxic compounds isolated from *Aspergillus niger*, the most common fungal contaminant of stored groceries.[183] These yellow pigments furthermore display antitumoral[184] and antibacterial[185] activity.

The first and as yet only total synthetic access to a bisnaphthopyrone, (−)-nigerone [(*M*)-**164**], was developed by Kozlowski and co-workers in 2007, by applying a Cu(II)-mediated atropoenantioselective oxidative biaryl coupling reaction as the key step (Scheme 21).[18,186] Initial studies on suitable coupling precursors for the construction of the biaryl bond in **164** revealed that the use of sterically constrained 2-naphthols like the natural product flavasperone (**171**),[187] also a potential monomeric biosynthetic precursor to **164**, is critical to achieve good asymmetric inductions. The preparation of **171** started with the phenylacetic acid **166**, the acid chloride of which was reacted with sodium dimethyl malonate to give **167**. Cyclization of **167** followed by *O*-acetylation, aromatization, and introduction of an *O*-methoxymethyl (*O*-MOM) group furnished naphthalene **168**. Reaction with the anion of dimethylsulfoxide gave the ketosulfoxide **169**, which was transformed, in one pot, into flavasperone (**171**) by aldol condensation, in situ deacetylation, cyclization to the presumable intermediate **170**, and elimination of sulfinic acid, followed by removal of the *O*-MOM protective group.

With the required coupling precursor **171** in hand, the atroposelective biaryl coupling step using the (diaza-*cis*-decalin)copper(II) complex (*S*,*S*)-**49** as a catalyst was explored.[186] Interestingly, initial attempts using 10 mol % of (*S*,*S*)-**49** in the coupling reaction resulted in low turnover rates, yielding only 36% of the biaryl (*M*)-**172** after 7 days at 40−45 °C, albeit with good asymmetric inductions (80% ee). The slow reaction rate was apparently caused by the excellent chelation of the copper catalyst (*S*,*S*)-**49** to the planar ring system of **171**. In fact, raising the amount of (*S*,*S*)-**49** to stoichiometric quantities largely improved the chemical yield (60%), with complete conservation of the good asymmetric induction. Nevertheless, the yield was still moderate, now probably a consequence of an unwanted iodination at C1 caused by the large amounts of the iodide-containing reagent (*S*,*S*)-**49**. This side reaction can be successfully suppressed by replacing the iodide in (*S*,*S*)-**49** by chloride or tetrafluoroborate, thus permitting improved yields, but at the expense of a reduced optical purity of the product (*M*)-**172** (60−72% ee). The final switch of the γ-pyrone moiety in (*M*)-**172** to the required α-pyrone ring in (*M*)-**164** was achieved in 50% yield with 1% NaOH in

Scheme 21



methanol,[188] involving a pyrone opening−closing sequence triggered by Michael addition/elimination reactions. According to AM1 calculations, the driving force for this rearrangement is the reduction of steric repulsion, which is much higher in (*M*)-**172** due to the coplanar arrangement of the substituents at C4 and C5, in contrast to the relaxed conformation in (*M*)-**164**. The optical purity of (−)-nigerone [(*M*)-**164**] was only slightly decreased during the isomerization process (<3% loss of ee). Trituration of the final product from ethyl acetate/hexanes yielded (*M*)-**164** in 90% ee.[186]

By following the same synthetic route, but using the enantiomeric catalyst (*R*,*R*)-**49**, the other atropoenantiomer of the natural product, (*P*)-**164**, was obtained.[186] The late introduction of the biaryl axis thus provided an elegant and rational way to produce both atropoenantiomeric forms of nigerone (**164**) from the same "late" achiral precursor, **171**.

3.2.4. Naphthylisoquinoline Alkaloids

The naphthylisoquinoline alkaloids, isolated from the rare tropical lianas of the Dioncophyllaceae and Ancistrocladaceae families, are a rapidly growing class of secondary metabolites (for selected representatives of the main coupling types, see Figure 11).[4,10] Biosynthetically, they are built up by phenoloxidative coupling of a naphthalene and an isoquinoline portion, which are—unprecedented for isoquinoline alkaloids—both formed via an acetate−malonate pathway.[10,41] The existence of several possible coupling sites, both in the naphthalene portion **173** (C1′, C3′, C6′, C8′) and in the isoquinoline moiety **174** [C5, C7, and, as found more recently, N2 in the isoquinoline part like in (*M*)-**176** and (*M*/*P*)-**177**],[10,39,54] leads to a maximum of 12 possible coupling types and, thus, to a group of natural products with a high degree of structural diversity. Some examples of these alkaloids are the 5,1′-linked ancistrocladine [(*P*)-**21**] and the 7,1′-coupled ancistrocladisine [(*P*)-**178**], both from *Ancistrocladus heyneanus*,[83,189] as well as the 5,8′-connected korupensamine A [(*P*)-**182**] from *Ancistrocladus korupensis*.[190] The dimer of the latter compound is the pharmacologically likewise interesting quateraryl michellamine A [(*P*,*P*)-**3**],[8] belonging to the group of highly anti-HIV active dimeric naphthylisoquinoline alkaloids.[8,9,191] Because of their intriguing structural properties (being equipped with stereogenic centers in the isoquinoline part and with a—usually—chiral biaryl axis) and their interesting bioactivities (ranging from antimalarial properties in vitro and in vivo[10,38,42,43] to fungicidal and insect growth retarding and antifeedant effects[192]), both mono- and dimeric alkaloids of this type constitute challenging and rewarding synthetic targets.

The total synthesis of naphthylisoquinoline alkaloids requires not only the stereoselective construction of the asymmetric centers in the isoquinoline moiety but, in particular, the atroposelective formation of the chiral biaryl axis. It was initially for this specific goal that the "lactone method" (see section 2.3) was developed by the authors' group, paving the way for the directed preparation of numerous representatives of this class of natural products. Its applicability was demonstrated by the first total syntheses of naphthylisoquinoline alkaloids, among them ancistrocladine [(*P*)-**21**], ancistrocladisine [(*P*)-**178**], and dioncophylline A.[193−195] With the upcoming knowledge about the significant bioactivities found for some naphthylisoquinolines alkaloids, this class of natural products then came into the focus of several other groups, like those of Sargent and co-workers[196,197] and Rizacassa and Sargent,[198] who used intermolecular coupling techniques as elaborated by Meyers et al. (see section 2.3) and, later, the groups of Hoye,[199] Rao,[200] Dawson,[201] Uemura,[202−206] and Lipshutz.[207] Since this work through 1997 has already been comprehensively covered in previous review articles[4,10] and in a concise report in 1998 by Rizzacasa,[208] it will not be presented here in detail, except for the two early total syntheses of ancistrocladisine [(*P*)-**178**] and ancistrocladine [(*P*)-**21**], including a representative approach to the chiral isoquinoline portions.

The tetrahydroisoquinoline moiety, with its characteristic 6,8-dioxy substitution pattern and the two stereocenters next to the nitrogen atom, is an important building block for this class of natural products.[193,209,210] A general approach to *trans*-configured tetrahydroisoquinolines is shown in Scheme 22. The synthesis started from the aryl propanone **183**, which was reductively aminated with (*S*)-phenylethylamine (**184**), by stereoselective hydrogenation of the intermediate imine

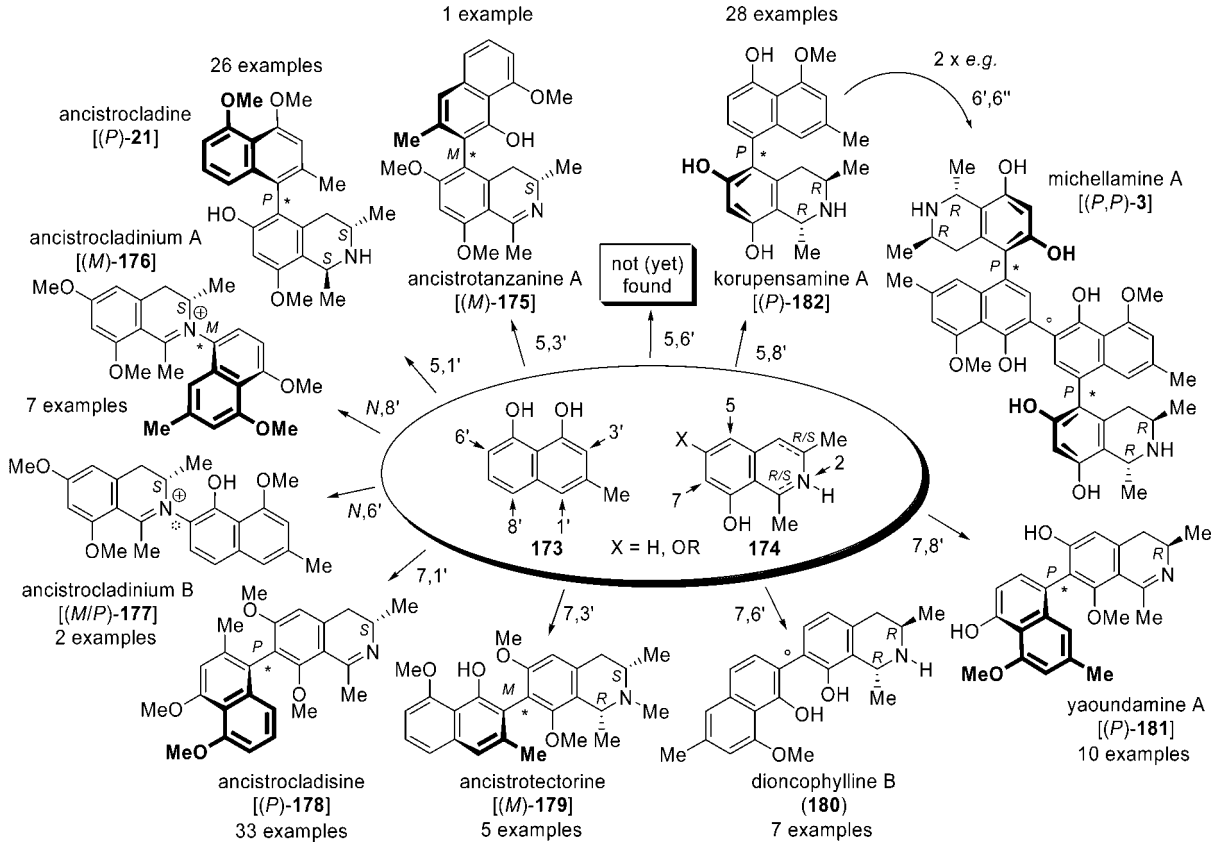
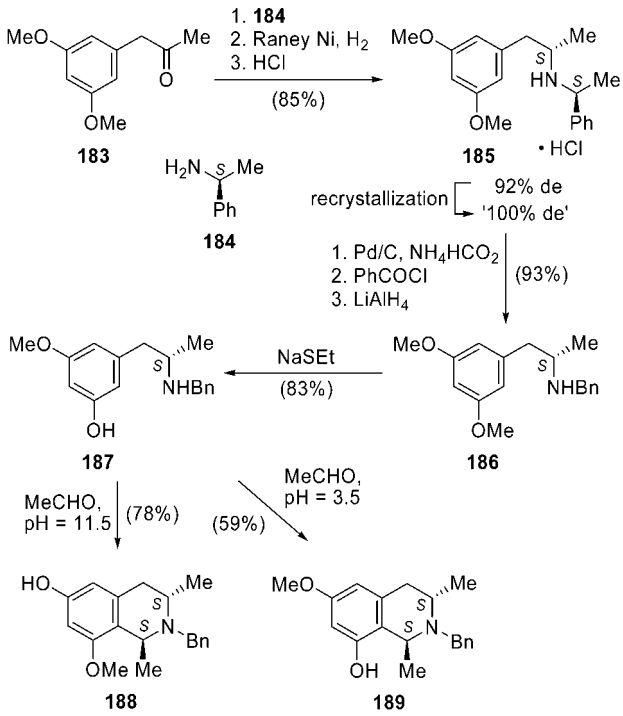


Figure 11.

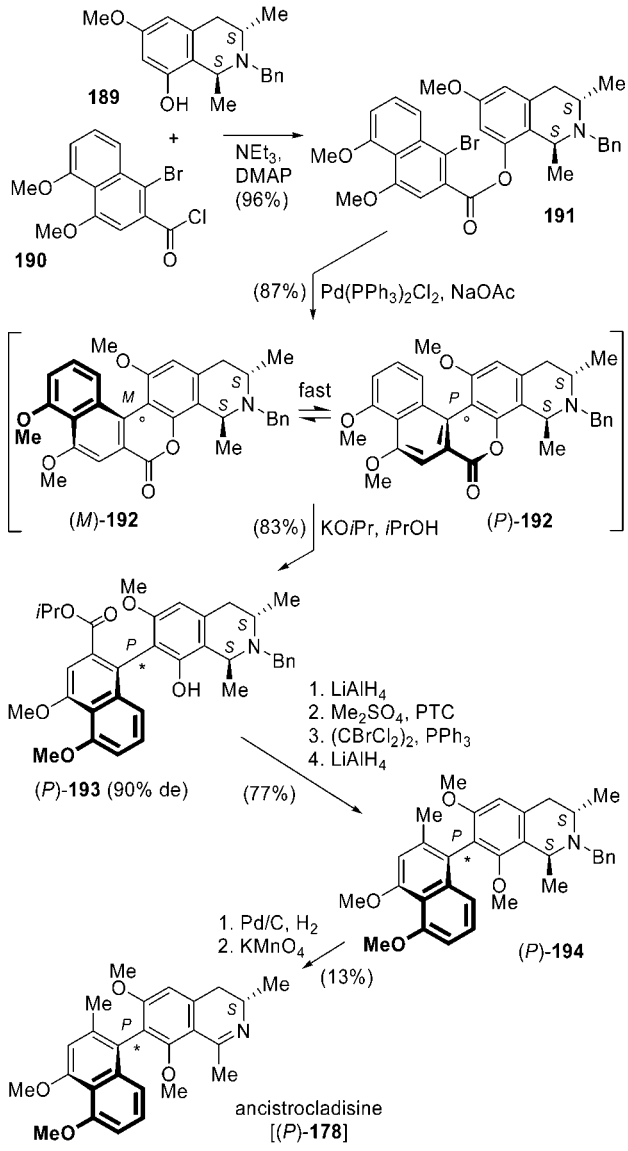
Scheme 22



over Raney-Ni, to establish the homobenzylic stereocenter (92% de, raised to 100% de by recrystallization) to give the secondary amine **185**. The chiral *N*-phenylethyl substituent was replaced by a nonbranched *N*-benzyl protective group through hydrogenolytic cleavage, *N*-benzoylation, and amide reduction to give **186**. Mono-*O*-demethylation with NaSEt afforded the phenol **187** (83% yield), which underwent a highly diastereoselective Pictet-Spengler ring closure reaction with acetaldehyde to deliver *trans*-configured isoquinolines, exclusively. The regioselectivity was controlled by the choice of the pH value. Whereas the 6-hydroxy-8-methoxy tetrahydroisoquinoline **188** was formed as the major product under mild basic conditions (pH = 11.5, 78%), the 6-methoxy-8-hydroxy regioisomer **189** was obtained predominantly under slightly acidic conditions (pH = 3.5, 59%).

Ancistrocladisine [(*P*)-**178**, Scheme 23] was one of the first naphthylisoquinoline alkaloids synthesized with complete regio- and stereocontrol, despite the high steric hindrance next to the axis (four *ortho*-substituents) and the presence of two identical *ortho*-functionalities in the dihydroisoquinoline part—a difficult problem to any intermolecular coupling method,[211] but easily overcome by using the lactone method[195] (see section 2.3). Prefixation of the two aromatic "halves", **189** and the known[210,212] 1-bromonaphthoic acid chloride **190**, gave the ester **191**, which was subjected to a Pd-catalyzed intramolecular biaryl coupling. The lactone **192**, thus obtained in good 87% yield, exists as a mixture of its two atropodiastereomeric forms, (*M*)-**192** and (*P*)-**192**, which rapidly interconvert at room temperature, as obvious from its ^{1}H NMR spectra, which shows only a single set of signals. Atropodiastereoselective cleavage of the lactone bridge succeeded with chiral or—due to the presence of stereogenic centers in **192**—even achiral *O*-nucleophiles delivering the respective configurationally stable, ring-opened biaryl ester such as (*P*)-**193** in 83% yield and good 90% de, even when using potassium isopropylate as a simple and cheap achiral reagent. As evident from mechanistic and quantum chemical investigations on related model lactones,[111] the high atropodiastereoselectivity observed in this step is a consequence of a kinetically controlled preferred attack of the isopropylate anion on the (*M*)-helically distorted isomer of **192**, exclusively. Reduction of the ester

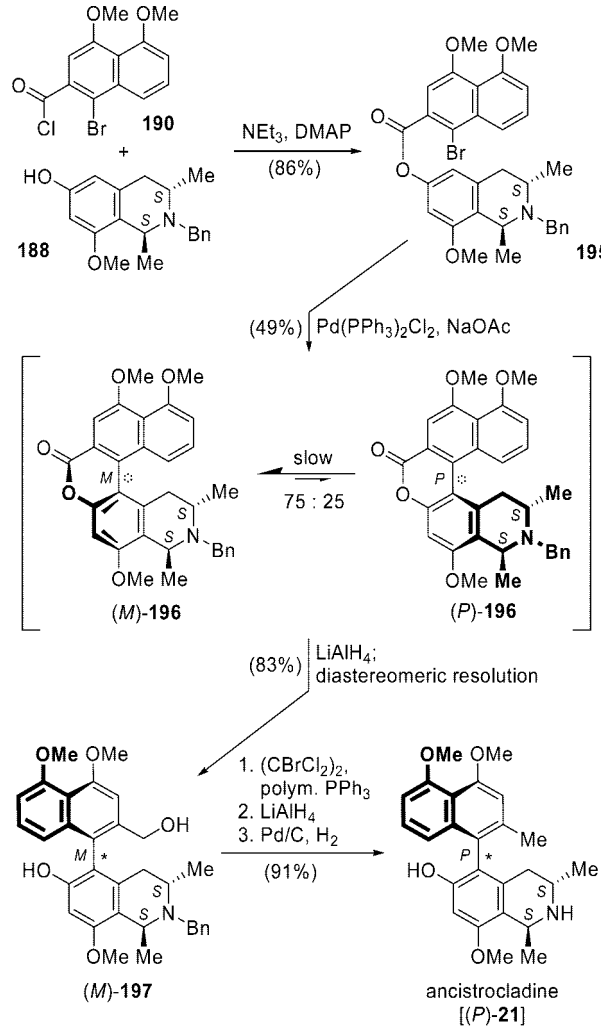
Scheme 23



function of (*P*)-**193**, *O*-methylation of the free phenolic hydroxy group, and a two-step deoxygenation of the hydroxymethylene unit delivered the methyl compound (*P*)-**194**, which, after *N*-debenzylation, was oxidized against a stereoelectronically unfavorable 1,3-*trans* array, to give the natural alkaloid ancistrocladisine [(*P*)-**178**] in nine steps and 7% overall yield from **189** and **190**.

Whereas the stereoselective construction of the biaryl system in (*P*)-**178** relied on the—kinetically controlled—atroposelective ring cleavage of the lactone **192**, the atropisomeric ratio at the axis of the related alkaloid ancistrocladine [(*P*)-**21**] was based on a thermodynamically controlled equilibration at the level of a configurationally semistable biaryl lactone. As compared to (*P*)-**178**, the target molecule (*P*)-**21** possesses an even higher rotational barrier. Still, Pd^{II}-catalyzed biaryl coupling of the ester **195**, prepared from **188** (see Scheme 22) and **190**, smoothly gave the lactone **196** in 49% yield (Scheme 24).[210] In this case, because of the even higher steric hindrance at the biaryl axis, the two helically distorted atropodiastereomers, (*M*)-**196** and (*P*)-**196**, are distinguishable by NMR at room temperature, because they interconvert more slowly ($t_{1/2} \approx 1$ min at 299 K), with the desired ancistrocladine-like stereo-orientation prevailing (diastereomeric ratio (dr) = 75:25); this equilibrium can be

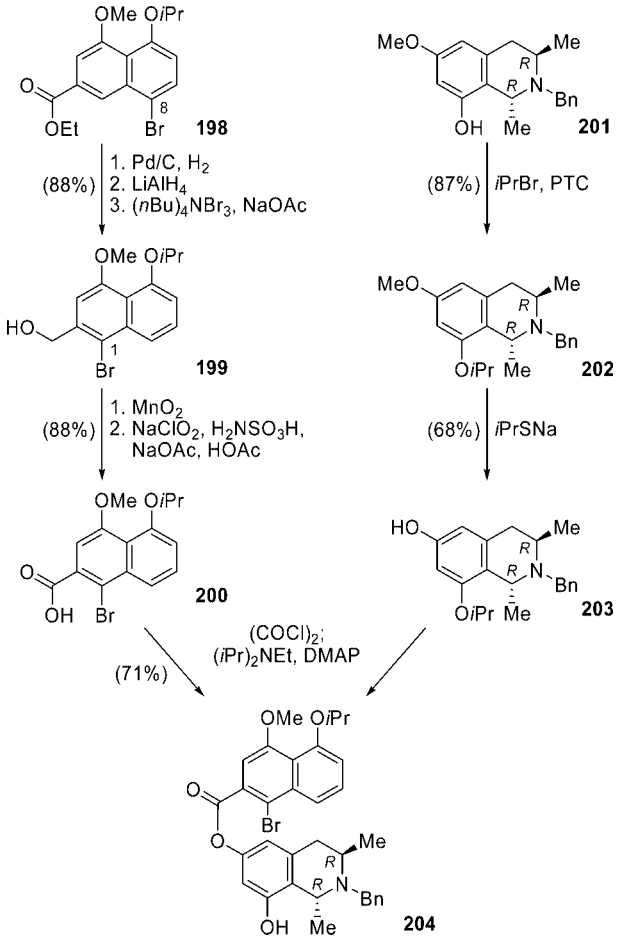
Scheme 24



completely shifted toward the desired (*M*)-atropisomer (dr = 100:0) by attaching an *N*-trifluoroacetic acid (TFA) substituent to the nitrogen atom. The thermodynamically controlled diastereomeric ratio (e.g., of 75:25 in the case of *N*-benzyl) was conserved by rapid reduction with $LiAlH_4$ to give the configurationally stable alcohol (*M*)-**197** in 83% yield after chromatographic purification. Final deoxygenation of the hydroxymethyl group and *N*-debenzylation delivered ancistrocladine [(*P*)-**21**] (six steps, 18% yield from **188**/**190**). Later attempts by other groups using intermolecular coupling methods only gave modified unnatural analogues or even failed to form the required biaryl axis entirely,[211,197] again showing the specific advantage of the lactone method, in particular to overcome even the largest steric hindrance at the axis.

In a similar way, the first total synthesis of the antimalarial alkaloid dioncophylline C [(*P*)-**11**] from the West African liana *Triphyophyllum peltatum*[44] was achieved (Schemes 25 and 26). Despite the lack of a "bridgehead oxygen" function next to the biaryl axis in the target molecule—seemingly an inevitable precondition—the lactone method was efficiently applicable.[45] The preparation of the naphthalene precursor **200** started with the known building block **198**, which had previously been used in the total synthesis of the 5,8′-coupled korupensamines and michellamines.[213] The required "shift" of the bromine substituent from the 8- to the 1-position succeeded by hydrogenolytic hydrodebromination of **198**, reduction of the ester function to the alcohol,

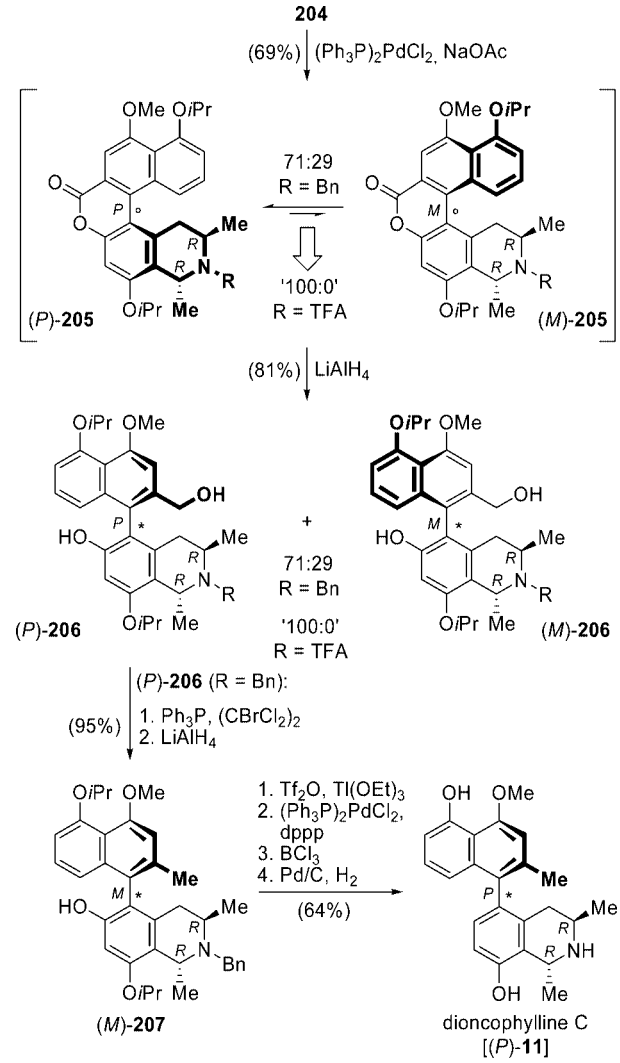
Scheme 25



and subsequent bromination in the 1-position to give **199** in 88% yield. Renewed stepwise oxidation of the alcohol function back to the carboxy group delivered the bromonaphthoic acid **200** (88% yield). The heterocyclic moiety **203** with the required (1*R*,3*R*)-array was obtained from the enantiomerically pure tetrahydroisoquinoline **201**[209] (i.e., the enantiomer of **189**, see Scheme 22), by *O*-isopropylation to give **202** and selective *O*-demethylation to provide **203** in 59% overall yield. The two building blocks, **200** and **203**, were then prefixed via an ester bridge to deliver **204** (71% yield).

Pd-catalyzed intramolecular coupling of **204** provided the 5,1′-linked biaryl lactone **205**, exclusively, in 69% yield (Scheme 26). The two resulting helicene-like distorted diastereomers thus obtained, (*P*)-**205** and (*M*)-**205**, were in a dynamic equilibrium with a ratio of 71:29 in favor of the desired atropisomer (*P*)-**205**. As for the lactone intermediates **196** in the ancistrocladine synthesis described in Scheme 24, this diastereomeric ratio could again be completely shifted toward the (*P*)-atropisomer (dr = 100:0), if, instead of the *N*-Bn substituent, an *N*-TFA protecting group was used. With conservation of this atropisomeric ratio, rapid reductive ring cleavage of **205** with $LiAlH_4$ gave the alcohol (*P*)-**206**, which (in the case of R = Bn) was easily separated from (*M*)-**206**. The configurationally stable alcohol (*P*)-**206** was converted into the methyl compound (*M*)-**207** by hydroxy/bromine exchange and reduction. Hydrodeoxygenation at C6 by catalytic hydrogenation of the respective *O*-triflate removed the previous bridgehead oxygen. Cleavage of the protective groups gave (*P*)-**11** (eight steps, 24% yield from **204**).

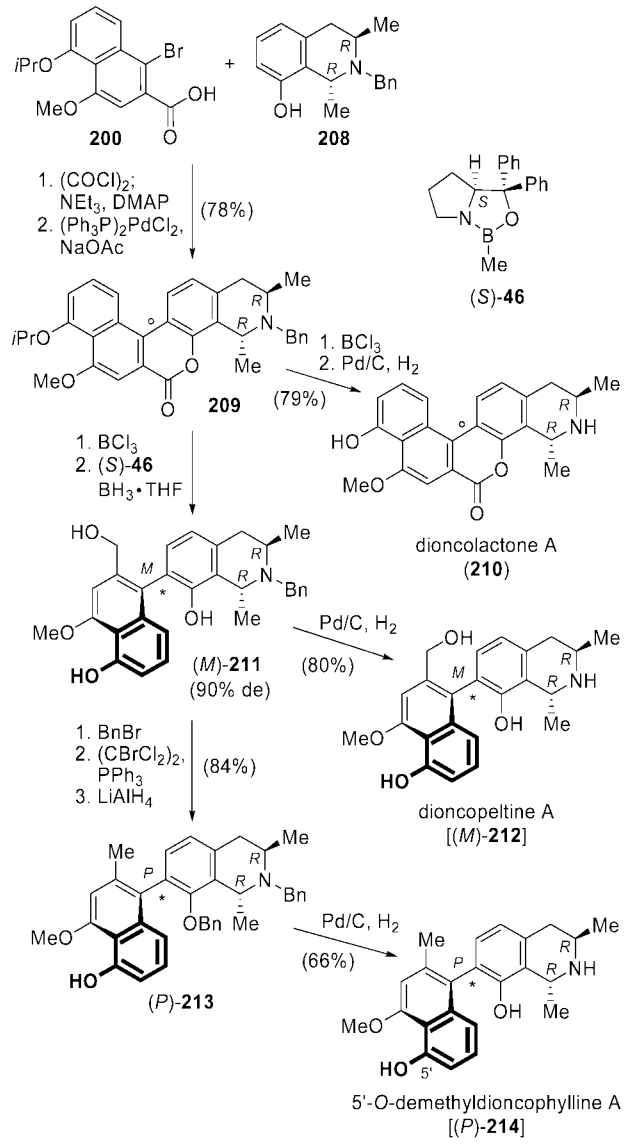
Scheme 26



Likewise in the authors' lab, the directed total synthesis of three further metabolites of *Triphyophyllum peltatum* was accomplished in one joint pathway (Scheme 27),[107] again starting with the bromonaphthoic acid **200** (see Scheme 25). The required enantiopure tetrahydroisoquinoline building block **208** was accessible from the (1*R*,3*R*)-enantiomer of **188** (see Scheme 22) by deoxygenation and *O*-demethylation.[209] Reaction with the acid chloride of **200** provided the respective bromoester,[214] which was intramolecularly coupled with palladium catalysis, to give the biaryl lactone **209** (78% overall yield). Subsequent *O*- and *N*-deprotection (79% yield) already furnished the first of three alkaloids dioncolactone A (**210**), a natural product closely related to the key intermediate of the lactone method and, expectedly, configurationally unstable at the biaryl axis. *O*-Deprotection of **209** and reductive ring-opening using an excess of borane in combination with the CBS reagent[106] (*S*)-**46** gave the benzylic alcohol (*M*)-**211** in 90% de, which, after *N*-debenzylation, provided the natural product dioncopeltine A [(*M*)-**212**] in 80% yield. The third alkaloid resulting via this route, the likewise naturally occurring 5′-*O*-demethyldioncophylline A [(*P*)-**214**)], was obtained from (*M*)-**211** in four steps and 55% overall yield by selective *O*-benzylation of the phenolic hydroxy function, reductive removal of the benzylic hydroxy function to deliver (*P*)-**213**, and *O*- and *N*-debenzylation.

Within the group of naphthylisoquinolines, the korupensamines and their dimers, the michellamines (see Figure 11),

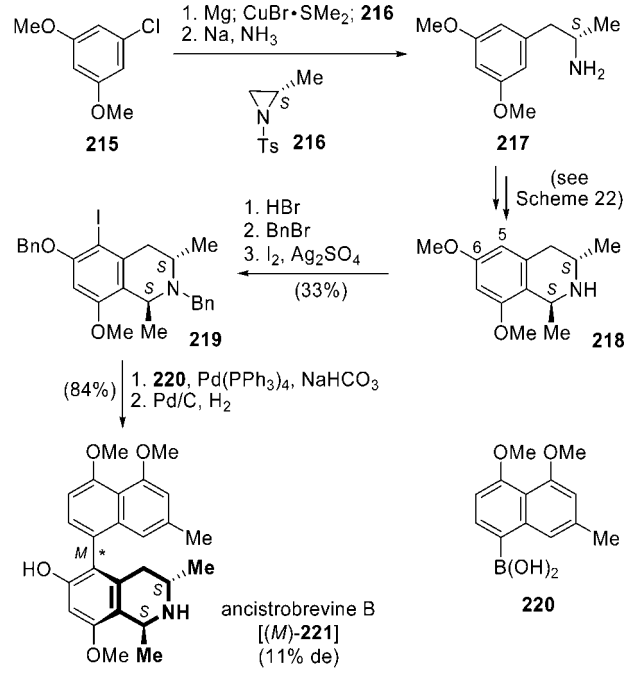
Scheme 27



have received particular attention because of their antimalarial and anti-HIV properties, respectively.[9,190] In 1999, Hoye and co-workers reported the total synthesis of several korupensamine related, likewise 5,8′-coupled naphthylisoquinolines, based on intermolecular coupling methods and on the preparation of some dimeric analogues of the michellamine type.[215,216] In the course of these investigations, his group developed an efficient alternative access to the chiral isoquinoline portion (Scheme 28). This time, the chiral amine **217**, a key intermediate, was obtained not by reductive amination of arylpropanones (see Scheme 22) but through CuBr-catalyzed regioselective ring-opening of the enantiomerically pure aziridine **216**[217] with the Grignard reagent derived from commercially available 1-chloro-3,5-dimethoxybenzene (**215**) followed by reductive removal of the *N*-Ts group. The optically pure tetrahydroisoquinoline **218** was obtained from the primary amine **217** as described in Scheme 22.

Among the different coupling strategies for the construction of the biaryl bond investigated by Hoye et al.,[215] Suzuki coupling of aryl boronic acids or the respective cyclic esters with aryl iodides gave the best results. By this approach, korupensamines A−D, ancistrobrevine B [(*M*)-**221**], and the unnatural *ent*-korupensamine D were synthesized, albeit with

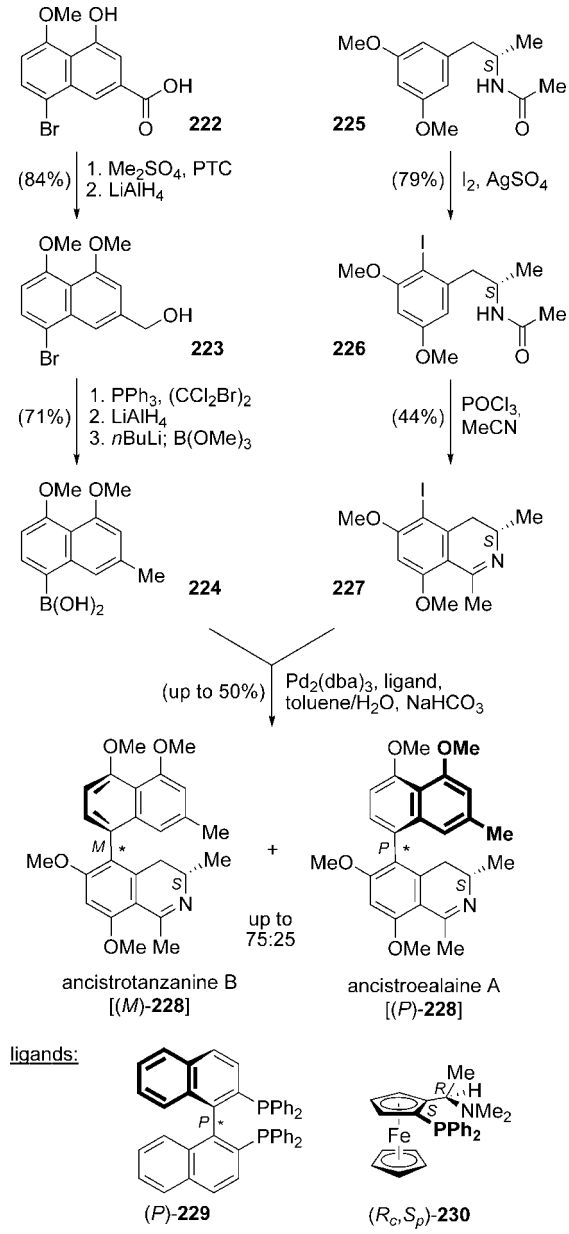
Scheme 28



low atropodiastereoselectivities (up to 20% de, always in favor of the same axial configuration relative to the stereogenic centers in the isoquinoline). The weak asymmetric inductions result from the fact that these stereocenters are far away from the coupling position and do not exert a strong, configuration-specific influence on the transition state of the coupling step.[215] As an example, Hoye's synthesis of ancistrobrevine B [(*M*)-**221**] will be discussed here, which starts from **218** (Scheme 28).[215] This building block was selectively *O*-demethylated at O6 and *O*,*N*-dibenzylated, followed by iodination at C5 to give **219** in 33% overall yield. Pd-catalyzed coupling of the iodotetrahydroisoquinoline **219** with the known[213] boronic acid **220** and subsequent *O*-debenzylation furnished (*M*)-**221**[218] in 84% yield (11% de). Even though this route is highly concise and one of the shortest known today, it is compromised by an unsatisfactory stereocontrol in the decisive coupling step.

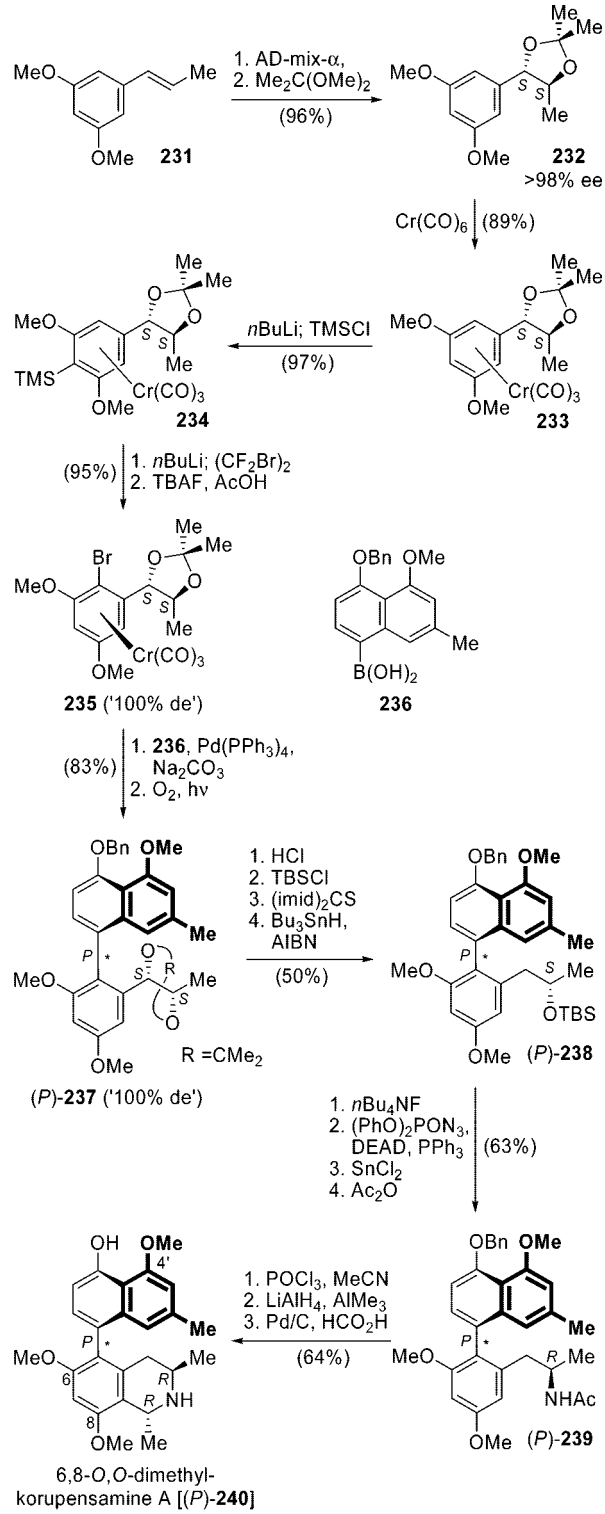
Because of the fact that 5,8′-coupled naphthylisoquinoline alkaloids have a lower degree of steric hindrance at the axis as compared to, e.g., ancistrocladine [(*P*)-**21**, see Scheme 24] or ancistrocladisine [(*P*)-**178**, see Scheme 23], they can also be built up by intermolecular coupling reactions. Thus, for the total synthesis[219] of ancistrotanzanine B [(*M*)-**228**], isolated from *Ancistrocladus tanzaniensis*,[220] and its likewise natural atropodiastereomer, ancistroealaine A [(*P*)-**228**], as found in *Ancistrocladus ealaensis* (Scheme 29),[221] an asymmetric Suzuki cross-coupling reaction has been used by the authors' group. The readily available bromonaphthoic acid **222**[213] was *O*-methylated and reduced to the alcohol **223**. Hydroxy/bromine exchange, hydrodebromination, and formation of the boronic acid function gave the desired naphthalene precursor **224**. The other heterocyclic coupling partner, the dihydroisoquinoline **227**, was prepared from the acetamide **225**,[209] by regioselective iodination to furnish **226** and subsequent Bischler−Napieralski cyclization. The two molecular portions, **224** and **227**, were then subjected to different biaryl coupling conditions. Because reactions without additional chiral reagents resulted in almost no asymmetric induction (i.e., 10% de), different previously successful[222] chiral catalysts were tested. Optimization of the

Scheme 29



reaction parameters revealed the best results for the ferrocene (R_c,S_p)-**230** and (*P*)-BINAP [(*P*)-**229**]. In both cases, ancistroealaine A [(*P*)-**228**] was obtained as the main product (50% de). Interestingly, the use of the respective enantiomeric catalysts did not lead to a preferred formation of the other atropodiastereomer, ancistrotanzanine B [(*M*)-**228**], but just resulted in diminished selectivities [2% de for (S_c,R_p)-**230** and 22% de in the case of (*M*)-**229**]. Even though the impact of the stereogenic centers in the isoquinoline moiety **227** in the PPh_3-mediated coupling step is small, it still exceeds the external asymmetric induction by the latter catalysts, (S_c,R_p)-**230** and (*M*)-**229**. Recently, the authors' group successfully applied a similar approach to the first total synthesis of the alkaloid 5-*epi*-4′-*O*-demethylancistrobertsonine C, i.e., the 1-*epi*-4′-*O*-demethyl-4-*O*-methyl derivative of ancistrobrevine B [(*M*)-**221**], which has been isolated from a Congolese *Ancistrocladus* species.[223] The construction of the biaryl axis was again achieved by an asymmetric Suzuki cross-coupling reaction (24% de), remarkably without the need of protective groups.

Scheme 30



An entirely different concept for the synthesis of the unnatural *O*,*O*-dimethyl analogue (*P*)-**240** of korupensamine A [(*P*)-**182**, see Figure 11] was pursued by Uemura and co-workers,[204,205] on the basis of a diastereoselective Pd-mediated cross-coupling reaction of the naphthylboronic acid **236** with the planar−chiral (arene)$Cr(CO)_3$ complex **235** (Scheme 30) as the stereochemical key step. The synthesis of the latter building block **235** started with the enantioselective dihydroxylation of the styrene **231**, which, after protection of the resulting (*S*,*S*)-diol, delivered the acetonide **232** in 96% yield and >98% ee. This chiral arene was reacted

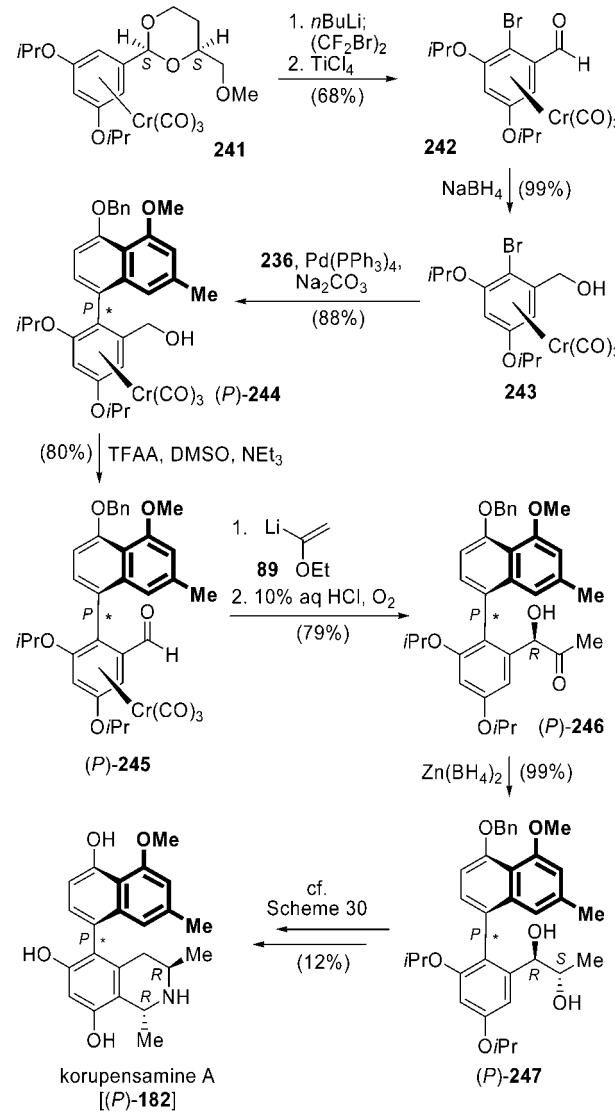
with $Cr(CO)_6$ to form the tricarbonylchromium complex **233** in 89% yield. The planar−chiral η^6-chromium portion was stereoselectively built up by *ortho*-selective bromination of **233** next to the acetal substituent, which simultaneously acted as the internal asymmetric inductor. For this purpose, the *para*-position first had to be blocked by a trimethylsilyl (TMS) group, giving **234** in 97% yield. Stereoselective bromination succeeded by diastereotopos-differentiating lithiation followed by treatment with 1,2-dibromotetrafluorethane. Subsequent removal of the trimethylsilyl group furnished **235** (95%). Atropodiastereoselective Pd-catalyzed biaryl coupling of the planar−chiral building block **235** and the naphthylboronic acid **236**, known from previous work,[224] followed by oxidative demetalation produced the configurationally stable phenylnaphthalene (*P*)-**237** in 83% yield and with complete stereocontrol at the axis.

The construction of the isoquinoline portion required a series of another 11 linear steps. Acetal cleavage, selective protection of the homobenzylic hydroxy group, and removal of the free OH function by the Barton method[225] afforded (*P*)-**238** in 50% yield. The OTBS group was converted into an NHAc function in 63% yield and with inversion of the configuration, by desilylation, hydroxy/azide exchange under Mitsunobu conditions, and reduction of the azide to the primary amine, followed by *N*-acetylation. Bischler−Napieralski cyclization of (*P*)-**239** and reduction of the resulting iminium double bond with $LiAlH_4$ in the presence of $AlMe_3$[210] completed the construction of the isoquinoline portion, thereby establishing the required *trans*-configuration with a good asymmetric induction (86% de). After *O*-debenzylation, the (unnatural) *O*,*O*-dimethyl derivate (*P*)-**240** of korupensamine A [(*P*)-**182**] was obtained in 64% yield from (*P*)-**239**. The true natural product (*P*)-**182** was not prepared via this route because a selective bis-*O*-demethylation (at C6 and C8, but not at C4′) of (*P*)-**240** seemed unlikely.

Further using the concept of inducing chirality at the biaryl axis by using planar−chiral arene complexes, Uemura and co-workers pursued a second approach (Scheme 31)—this time aiming at the synthesis of the genuine alkaloid, korupensamine A [(*P*)-**182**].[202,203]

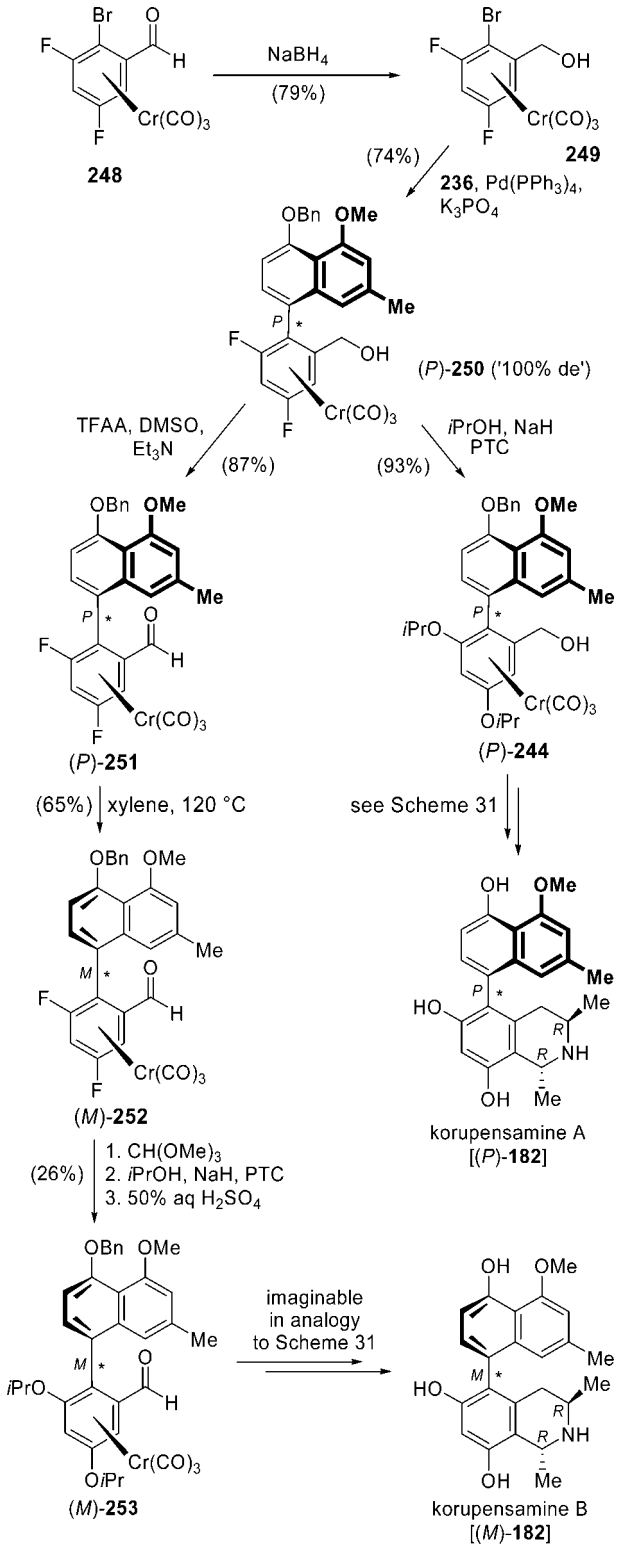
Starting from (3,5-diisopropoxybenzaldehyde)−chromium and (*S*)-1,2,4-butanetriol,[206] the aldehyde **242** was prepared via the "planar−prochiral", exclusively centro−chiral acetal **241** by diastereotopos-differentiating lithiation, bromination, and cleavage of the chiral acetal in two steps and 68% overall yield. Whereas the coupling of **242** with the naphthylboronic acid **236** gave disappointingly low yields, the respective alcohol **243**, prepared from **242** (99% yield), permitted the coupling to proceed smoothly in high 88% yield, with exclusive formation of (*P*)-**244**. Subsequent oxidation gave the aldehyde (*P*)-**245** in 80% yield. The still-required construction of the heterocyclic ring with its two stereogenic centers was achieved diastereoselectively (with internal asymmetric induction by the biaryl system) by elongation of the side chain using α-ethoxyvinyllithium (**89**) to furnish the (*R*)-configured α-hydroxyketone (*P*)-**246** after acidic hydrolysis and oxidative demetalation (79% yield). Diastereoselective reduction of the acyl group, mediated by the chelating effect of the newly created benzylic hydroxy function, provided the (*R*,*S*)-configured *erythro*-diol (*P*)-**247**, which was transformed into korupensamine A [(*P*)-**182**] in 12 further linear steps, in a close analogy to the reaction sequence depicted in Scheme 30 (12% yield).[202,203]

Scheme 31



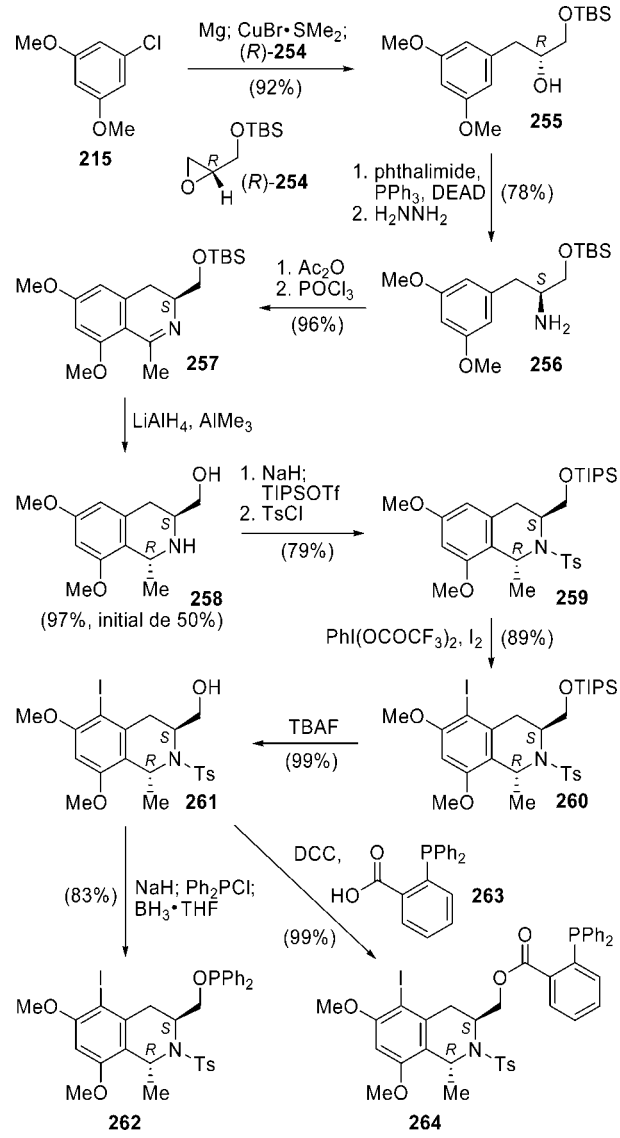
In a third approach, Uemura and co-workers now pursued the atropodivergent synthesis of both korupensamine A [(*P*)-**182**] and its atropodiastereomer korupensamine B [(*M*)-**182**], with the latter one being accessed by a directed thermal axial isomerization of the intermediate difluoro−chromium complex **251** (Scheme 32).[203] Such an atropodiastereomerization had failed in the previous synthesis (see preceding Scheme 31) because of an unexpected migration of the $Cr(CO)_3$ unit to the diastereotopic arene face, leading to a complex with an opposite planar−chiral configuration,[203] and because of the instability of the electron-rich chromium complexes (used so far) under the conditions needed to induce a rotation about the biaryl bond.[226] Thus, the synthesis started with the electron-poor and enantiomerically pure η^6-chromium complex of 2-bromo-3,5-difluorobenzaldehyde **248**, obtained by resolution of its racemate with L-valinol.[227] This planar−chiral aldehyde **248** was reduced to the alcohol **249** and coupled to the naphthylboronic acid **236** to give (*P*)-**250** as a single diastereomer. Nucleophilic substitution of the fluorine atoms with isopropanol under phase-transfer catalysis conditions delivered the biaryl (*P*)-**244**, i.e., the same intermediate as previously used in the preparation of korupensamine A [(*P*)-**182**, see Scheme 31]. Oxidation of (*P*)-**250** to the aldehyde (*P*)-**251**, which is sterically less crowded[226] in the proximity of the axis, now permitted a thermal equilibration with

Scheme 32



inversion of the axial configuration, yielding the more stable atropodiastereomer, (*M*)-**252**, in 65%. Protection of the aldehyde function as its acetal, nucleophilic substitution of fluorine by an isopropoxy group, and deprotection of the carbonyl function delivered (*M*)-**253**. Because this aldehyde is the atropodiastereomer of (*P*)-**245** (see Scheme 31), which had previously been converted into korupensamine A [(*P*)-**182**], it can, in principle, be considered as a precursor for a possible (but not yet realized) further total synthesis of

Scheme 33



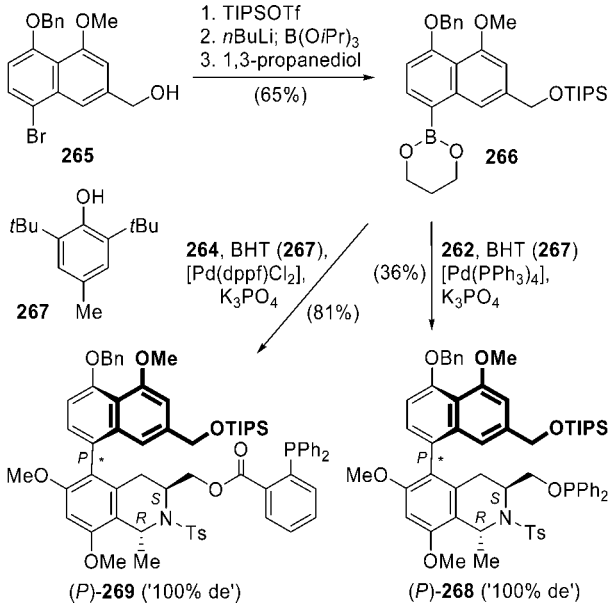
korupensamine B [(*M*)-**182**], following the same synthetic steps as described before.[203]

Even though these routes based on planar chirality offer conceptually novel and highly atroposelective approaches to korupensamines and their analogues, they are hampered by some disadvantages, like the high toxicity of the chromium species used and their possible residues in the final product, the sometimes difficult access to the planar−chiral chromium complexes, and the long linear reaction sequences, which demand, in part, more than 20 consecutive steps.

An intriguing, completely different way to control the configuration at the biaryl axis of korupensamine A [(*P*)-**182**] was developed by Lipshutz and Keith.[207] They enhanced the previously insufficient internal asymmetric induction (see Schemes 28 and 29) through the stereocenter at C3 of the naphthylisoquinoline by covalently linking it to the catalyst in the asymmetric Suzuki coupling step.

The synthesis of the accordingly C3-modified tetrahydroisoquinolines started with the aryl chloride **215** (Scheme 33), which was transformed into the respective organocuprate and reacted with commercially available *tert*-butyldimethylsilyl (TBS)−glycidol (*R*)-**254** to give the alcohol **255**, a suitable precursor for the subsequent Mitsunobu reaction proceeding with phthalimide with inversion of configuration. The enantiopure primary

Scheme 34

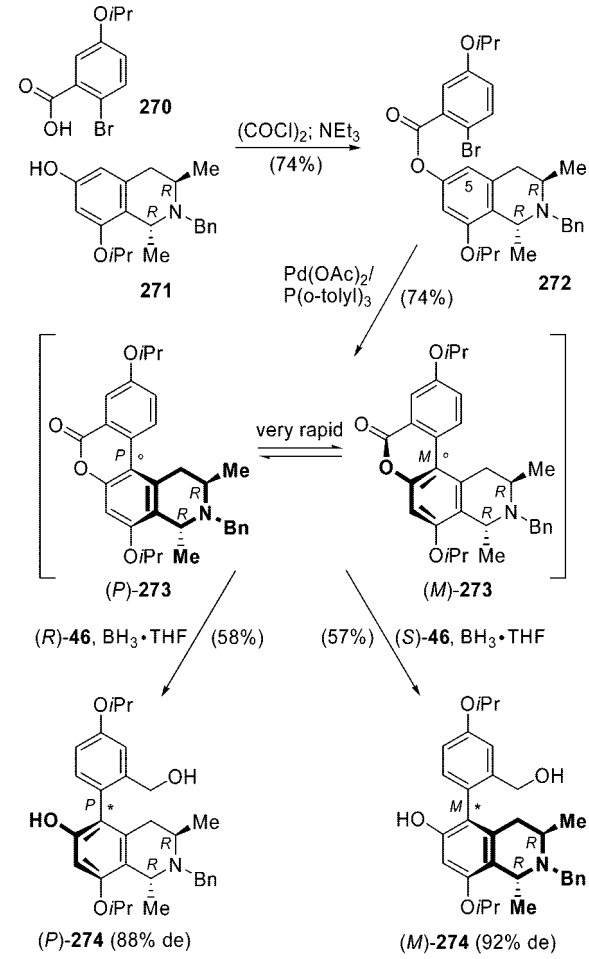


amine **256**, as obtained after hydrazinolysis, was subjected to a Bischler−Napieralski cyclization, affording the dihydroisoquinoline **257**. Careful reduction[210] furnished the respective tetrahydro derivative in 50% de (97% yield) in favor of the desired *trans*-isomer **258**. The reaction was, however, accompanied by a premature loss of the TBS protective group. In order to maximize the size of the stereochemical directing group for the aryl−aryl bond-forming step later in the synthesis, a triisopropylsilyl (TIPS) function was attached to the hydroxy function. Subsequent *N*-tosylation delivered **259**, which was regioselectively iodinated to form **260**. Initial investigations on the decisive biaryl coupling of **260**, with the bulky *O*-TIPS functionality as the only chiral controller, resulted in good chemical coupling yields but suffered from low stereoselectivity. Therefore, the hydroxy function was set free to give **261**, which was then reacted with $ClPPh_2$ to provide **262** or with (2-diphenylphosphinyl)benzoic acid (**263**) to deliver **264**, both now bearing a phosphine function with additional Pd-chelating properties.

The second required coupling partner, **266**, was prepared from the bromonaphthalene **265**[228] by *O*-protection and introduction of the boronate group in 65% yield (Scheme 34). Pd-catalyzed coupling of phosphine **262** with boronic ester **266** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (**267**), which served as an oxygen scavenger, gave the desired diastereomer (*P*)-**268** as the only product, albeit in low chemical yield (36%). By using phosphine **264** in the coupling reaction, the chemical yields were (depending on the amount of Pd catalyst used) dramatically enhanced to up to 81%, without any decrease of the excellent atropodiastereoselectivity. This shows that intermolecular Suzuki coupling reactions can also provide naphthylisoquinoline precursors highly atroposelectively if the chiral isoquinoline portion is equipped with a chelating phosphine substituent. A directed preparation of the respective (*M*)-atropisomers (i.e., potential precursors to korupensamine B [(*M*)-**182**]) or the conversion of the stereochemically pure products (*P*)-**268** and (*P*)-**269** into natural korupensamine A [(*P*)-**182**] was not reported.

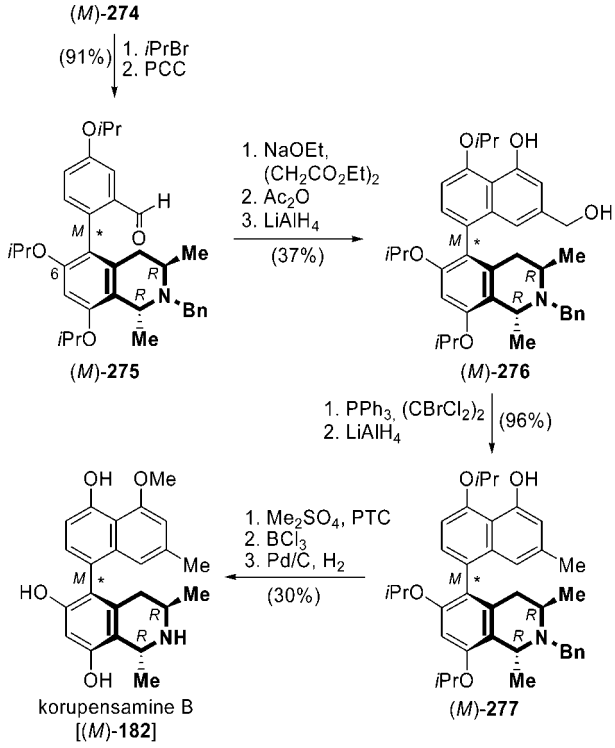
All of the aforementioned korupensamine syntheses based on an intermolecular coupling step gave rise to mainly one particular atropodiastereomeric product, viz. the one with the

Scheme 35



axial configuration of korupensamine A [(*P*)-**182**]. After an earlier korupensamine synthesis,[228] combined with the first preparations of their dimers—anti-HIV active michellamines[213,229]—the as yet only truly atropodivergent total synthesis of either korupensamines A [(*P*)-**182**] or B [(*M*)-**182**] was reported from the authors' group (Scheme 35).[230,231] This succeeded by applying the lactone method—despite the fact that there is no apparent (free) C_1 unit next to the biaryl axis, as required for the ester-type prefixation. At a closer look, such a C_1 unit does, however, exist, it is just hidden, as part of the second ring of the naphthalene moiety (i.e., C1′). The synthetic concept thus was to build up the korupensamines via an axially chiral *phenyl* (instead of naphthyl) isoquinoline precursor. Accordingly, the bromobenzoic acid **270**[232] (instead of a bromonaphthoic moiety) was esterified with the enantio- and diastereomerically pure tetrahydroisoquinoline **271** (prepared in analogy to **188**, as shown in Scheme 22)[45] to give **272**. Intramolecular aryl−aryl bond formation was best done using the "Herrmann-Beller" catalyst,[233] while standard palladium reagents led to low yields only. As in previous cases (see Schemes 24 and 26), the coupling occurred in the 5-position of the isoquinoline portion exclusively, delivering the required biaryl lactone **273** as a mixture of its very rapidly interconverting atropodiastereomers, (*M*)-**273** and (*P*)-**273**, in 50% overall yield. Among a series of different achiral and chiral *H*-nucleophiles for the reductive ring cleavage, Corey et al.'s oxazaborolidine−borane system[106] gave the best asymmetric inductions, leading to the (*P*)-configured product (*P*)-**274** when using (*R*)-**46** (58% yield, 88% de) and to the (*M*)-isomer (*M*)-**274** if

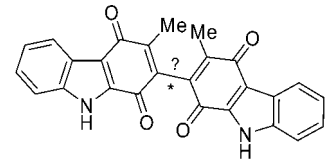
Scheme 36



applying the enantiomeric system, (*S*)-**46** (57% yield, 92% de). Thus, either atropisomeric diol, (*P*)-**274**, precursor to korupensamine A [(*P*)-**182**], or (*M*)-**274**, which leads to korupensamine B [(*M*)-**182**], was atropodiastereo-divergently obtained with high asymmetric inductions from the same late precursor **273**.

The completion of the syntheses (Scheme 36) of both korupensamines A [(*P*)-**182**] and B [(*M*)-**182**] followed similar reaction sequences, here described for (*M*)-**182**, starting from (*M*)-**274**. Prior to the oxidation of the hydroxymethyl side chain to the respective aldehyde, the free hydroxy function at C6 had to be protected by *O*-isopropylation, in order to prevent the formation of a biaryl hydroxy aldehyde, which, by transient cyclization to a lactol-bridged biaryl,[99,234] would be configurationally unstable, thus leading to the loss of the chiral information at the axis. From the intermediate aldehyde (*M*)-**275**, the naphthalene system was completed by Stobbe reaction with diethyl succinate followed by Friedel−Crafts acylation and reduction to give the alcohol (*M*)-**276**. The benzylic hydroxy function was removed reductively to afford (*M*)-**277**, which was *O*-methylated at the phenolic alcohol function under phase-transfer conditions. Final full *O*-deisopropylation and *N*-debenzylation released authentic korupensamine B [(*M*)-**182**] in 10 steps and 10% yield from (*M*)-**274**. In a similar way, but now starting from (*P*)-**274**, the atropodiastereomeric alkaloid, korupensamine A [(*P*)-**182**], was synthesized.[231]

In conclusion, several conceptually different synthetic approaches to naphthylisoquinoline alkaloids have been developed, most of them, however, being suited just for one particular atropisomer of the respective target molecule. The, so far, shortest access to these compounds was elaborated by Hoye et al. in their synthesis of korupensamine A [(*P*)-**182**], albeit with low diastereoselectivities in the Suzuki coupling step and without the option of divergence, i.e., without the possibility to likewise prepare the (*M*)-atropodiastereomer, korupensamine B [(*M*)-**182**]. The good optical yields received by Uemura et al. are compromised by the long required linear reaction sequences. Unfortunately, Lipshutz et al., who also were capable to produce selectively one particular atropodiastereomer, did not complete the total synthesis of the genuine natural product, korupensamine A [(*P*)-**182**]. The lactone method, by contrast, appears to be a quite efficient and flexible synthetic route to this group of secondary metabolites, the only one, so far, permitting the atropodiastereodivergent synthesis of even 4-fold *ortho*-substituted target alkaloids (including the possibility of recycling undesired atropisomeric byproduct). This is shown in the synthesis of the as yet largest number of structurally most diverse natural naphthylisoquinoline alkaloids with respect to coupling types, configurations, and substitution patterns.[95,96]



bismurrayaquinone A (**278**)
(absolute configuration as yet unknown)

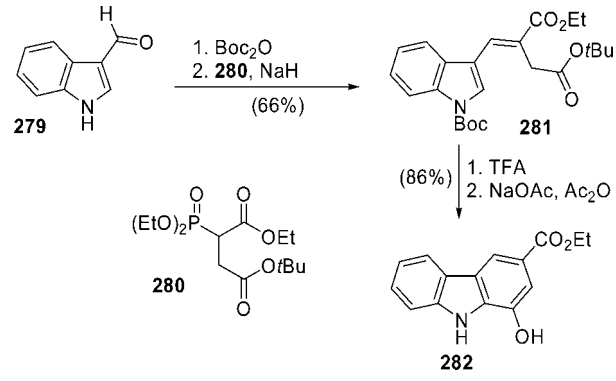
Figure 12.

3.2.5. Biscarbazole Alkaloids

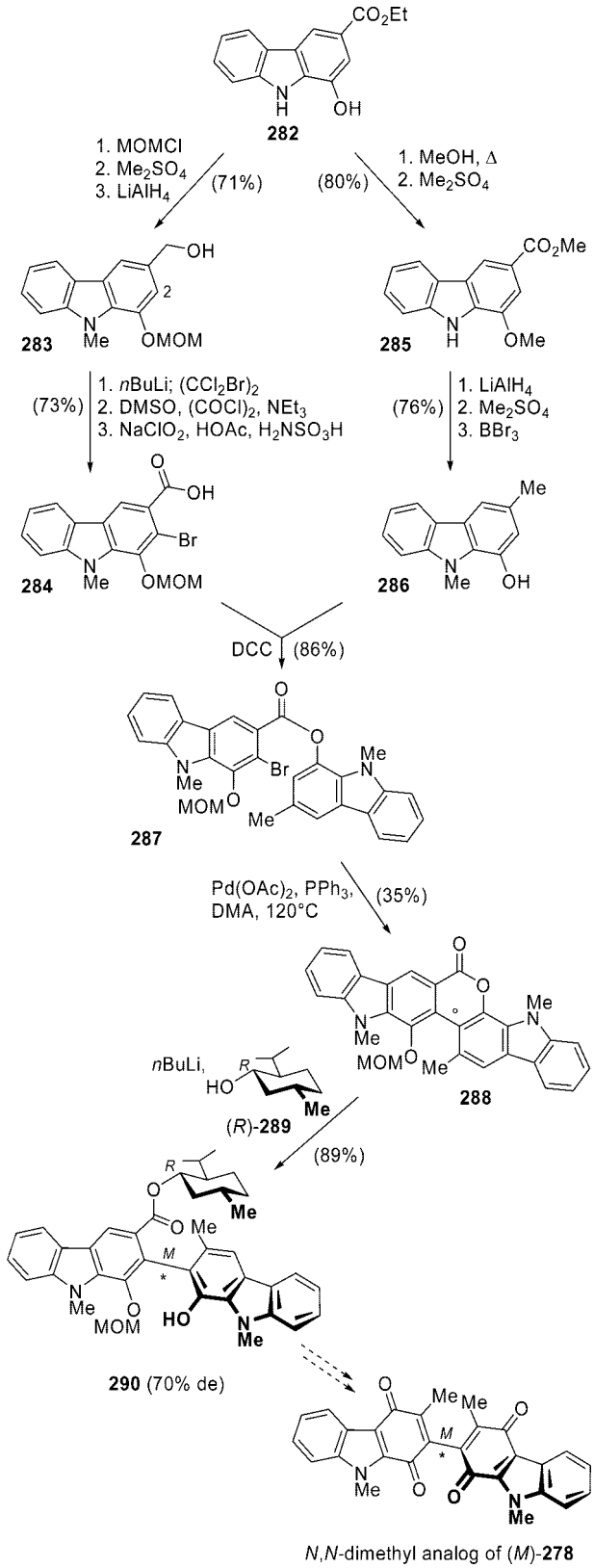
Most of the carbazole alkaloids known so far have been isolated from the plant genera *Murraya* and *Clausena*,[4] among them almost all representatives of the small class of biarylic biscarbazoles, like bismurrayaquinone A (**278**, Figure 12).[51] Despite the fact that monomeric carbazoles exhibit a broad variety of bioactivities,[235] the potential of the respective dimers has been little investigated. In particular, all stereochemical aspects related to their obvious axial chirality were neglected in all of the isolation papers (in most cases, not even α_D values were given),[51,236] and only in connection with subsequent synthetic work have in-depth stereochemical investigations been described, including liquid chromatography−circular dichroism (LC−CD) measurements and quantum chemical CD calculations.[237,238] For the construction of the biaryl linkage, mainly biomimetic, nonenantioselective oxidative couplings of the monomeric carbazole portions have so far been used,[237,239] followed by racemate resolution directly, on a chiral phase, or via the respective atropodiastereomers after derivatization with chiral auxiliaries,[240] but there is as yet no example of a stereoselective total synthesis of an authentic axially chiral biscarbazole.

The only approach toward the atroposelective synthesis of a naturally occurring biscarbazole—bismurrayaquinone A (**278**)—has so far been reported by the authors' group, by

Scheme 37



Scheme 38



applying the lactone method (Scheme 37).[241] After *N*-protection of indole-3-carbaldehyde (**279**) and Horner−Wadsworth−Emmons reaction with the phosphonate **280** to give **281**, removal of the *tert*-butyloxycarbonyl (Boc) protecting group, and cleavage of the *tert*-butyl ester, were achieved in one step.[242] Acid-mediated cyclization furnished the carbazole building block **282** in 57% overall yield.

The further synthesis of the bromoacid **284**, as required for the intramolecular biaryl coupling, from the carbazole ester **282** was achieved by MOM protection of the hydroxy function, *N*-methylation, and reduction to form the benzylic alcohol **283** (71%, Scheme 38).[241] This substrate proved to be well suited for a regioselective DoM (directed *ortho*-metalation) reaction in the 2-position. Treatment of **283** with *n*BuLi and $(CBrCl_2)_2$ followed by Swern and $NaClO_2$ oxidations of the intermediate benzylic alcohol afforded **284** in 73% yield. The other coupling partner, **286**, was synthesized from **282** by methanolysis of the ethyl ester and *O*-methylation to give the alkaloid mukonine (**285**), which was further converted to **286** by reduction, *N*-methylation, and *O*-demethylation (61% yield).[242] The crude (unnatural) *N*-methyl derivative **286** of murrayafoline A thus obtained was esterified with the bromoacid **284** to give the immediate coupling precursor **287** in 86% yield.[241]

The intramolecular "redox-neutral" coupling of **287** turned out to be the most difficult and yield-limiting step of the synthesis.[241] The best results were obtained using 1.5 equiv of $Pd(OAc)_2$ and 3.0 equiv of PPh_3, giving the configurationally unstable biscarbazole lactone (**288**) in 35% yield, together with up to 30% of the respective hydrodebromination product. The low yield is in agreement with similar difficulties observed for other substrates bearing an *ortho*-OCH functionality next to the coupling site,[122,243] but it is certainly also a consequence of the highly electron-rich character of the carbazole systems. This circumstance is also the reason for the low ring-cleavage reactivity of the lactone carbonyl function, which is a phenylogous carbamate. Thus, standard CBS-reduction[106] conditions gave only a low 20−40% yield and a moderate stereoselectivity (64% ee). (*M*)-BINAL−H as the reducing agent led to slightly better chemical yields (58%). The best results were achieved with the lithium alkoxide of (1*R*)-menthol [(*R*)-**289**] as a chiral *O*-nucleophile, furnishing (*M*)-**290** in 89% yield and 70% de. This exploratory reaction sequence, here exemplarily elaborated for *N*-methyl analogues as chemically robust model compounds, now paves the way for the first atropoenantioselective total syntheses of authentic axially chiral biscarbazole alkaloids, using appropriate—and mildly cleavable—*N*-protective groups.

3.3. Multiply Coupled Biaryls: Perylenequinones

Cercosporin [(*M*)-**291**],[244] (−)-phleichrome [(*P*)-**15**],[57] and calphostins A−D [(*P*)-**292**−(*P*)-**295**][245] belong to the perylenequinones, a class of acetate/malonate-derived biquinones (Figure 13).[55] They consist of two polyhydroxynaphthalene units linked together by a "normal" biaryl bond and, in addition, by a double bond between the *peri*-positions of the two quinoid moieties. Despite this multiple binding, the molecular halves are not flat, but twisted, thus giving rise to axially chiral "extended biaryls". A characteristic feature of most perylenequinones is the presence of two chiral side chains, both having the same absolute configuration at the respective stereogenic center, so that these colored substances are usually C_2-symmetric. They mainly occur in molds,[55] like the members of the calphostin family, which are formed in the phytoparasitic fungus *Cladosporium cladosporioides*.[246] There are, however, also some representatives that have been isolated from aphids[55,247] and one example obtained from the higher plant *Diospyros natalensis* subsp. *natalensis*. Perylenequinones possess pronounced photochemical properties, which are of interest for photodynamic cancer therapy

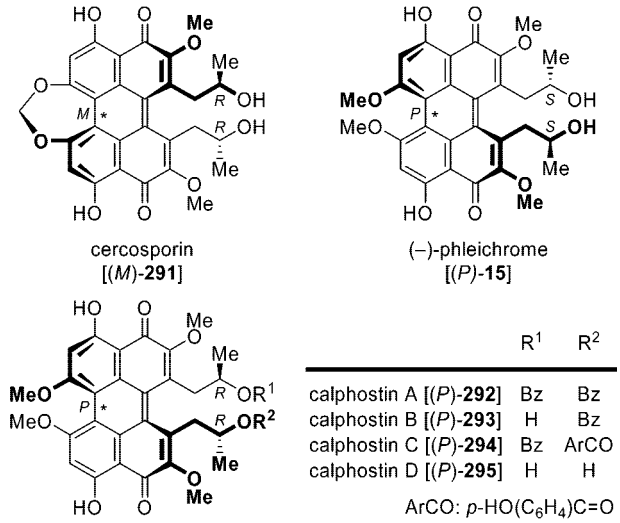


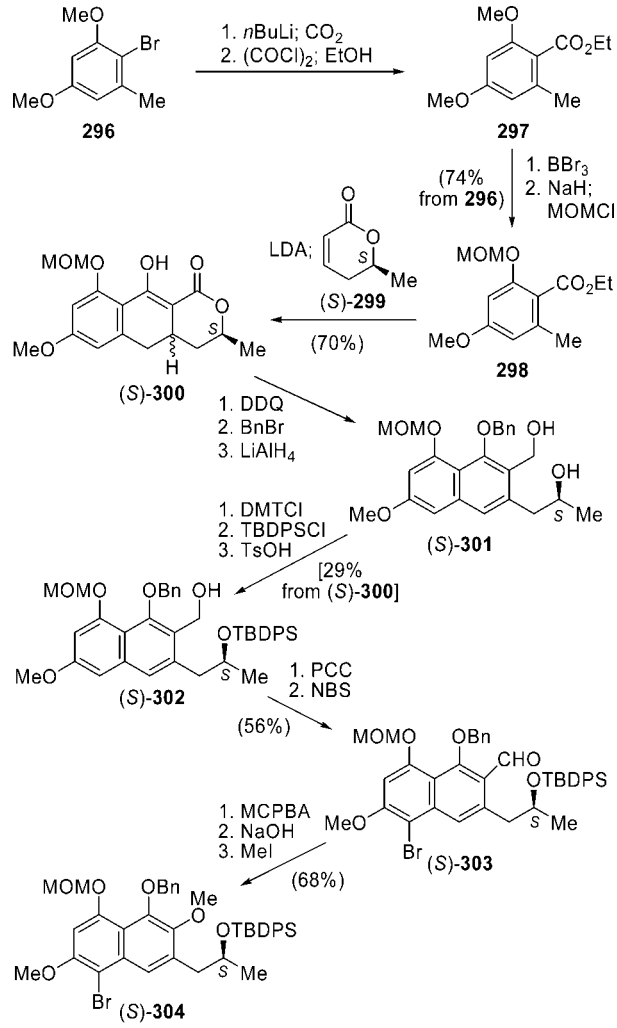
Figure 13.

(PCT).[58,59] They also show light-induced antiviral and antibacterial effects.[59,248] Moreover, because of their strong inhibition of protein kinase C, they constitute potential anti-HIV agents.[246,249] Since 1991 many reports on the total synthesis of perylenequinones have been published, nearly all of them based on the atropodiastereoselective oxidative coupling of chiral 2-naphthols as the stereochemical key step. More recently, efficient atropoenantioselective phenol-oxidative couplings[18] of achiral 2-hydroxynaphthalene-3-carboxylates have been used, too, showing the high potential of this approach.[250]

The first diastereoselective total syntheses of natural perylenequinones were reported by Broka (Scheme 39).[251] The naphthalene core for the synthesis of (−)-phleichrome [(*P*)-**15**] was generated starting from 2-bromo-3,5-dimethoxytoluene (**296**), which was transformed to the ethyl benzoate **297**. Mono-*O*-demethylation followed by renewed protection of the hydroxy function next to the ester moiety gave the MOM ether derivative **298**. The chiral information in the side chain was introduced by condensation of the anion of **298** with enantiomerically pure (*S*)-6-methyl-5,6-dihydropyran-2-one [(*S*)-**299**] in 70% yield to give the tricyclic compound (*S*)-**300**. Reductive ring-opening of the lactone, after oxidative aromatization and *O*-benzylation of the hydroxy group, led to the naphthalene (*S*)-**301**, with the required (*S*)-configured isopropanol side chain. Selective silylation of the secondary hydroxy function was achieved by a three-step procedure, involving the protection of the benzylic OH group as a 4,4′-dimethoxytriphenylmethyl (DMT) ether, treatment with *tert*-butylchlorodiphenylsilane (TBDPSCl), and cleavage of the benzylic ether [29% yield from (*S*)-**300**]. Oxidation of the benzylic hydroxy function in (*S*)-**302** with pyridinium chlorochromate (PCC) to give the aldehyde and subsequent bromination of the naphthalene nucleus *ortho* to the methoxy group delivered (*S*)-**303** in 56% yield. The C_1 side chain of (*S*)-**303** was transformed into the required methoxy group by a Dakin reaction, saponification, and *O*-methylation of the resulting phenolic hydroxy group, to furnish the desired monomeric building block (*S*)-**304** in 16 steps and an overall 4% yield.

Intermolecular oxidative *C*,*C*-coupling of 2 equiv of the naphthalene (*S*)-**304** was accomplished by lithiation with *t*BuLi and in situ treatment with $FeCl_3$ (Scheme 40). The major byproduct was the hydrodebrominated naphthalene (*S*)-**305**, which was recycled to (*S*)-**304** by bromination with

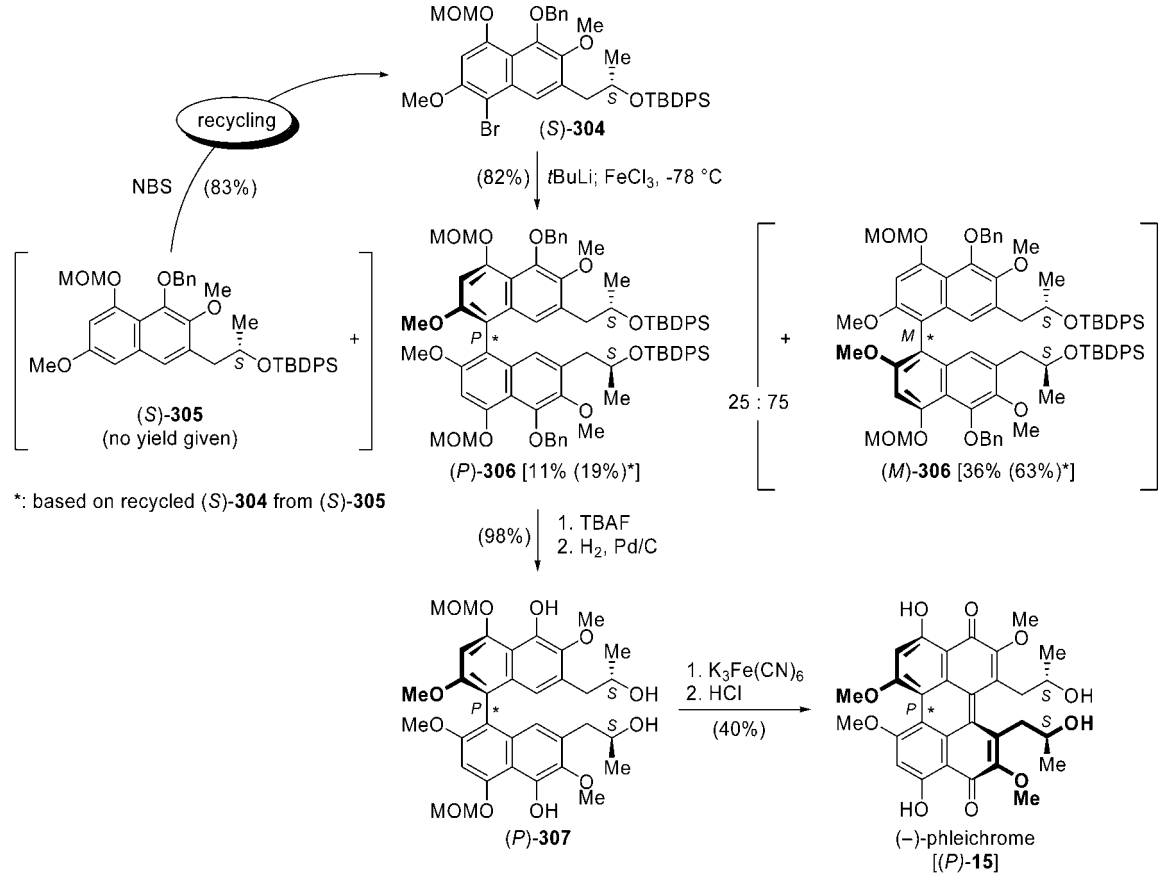
Scheme 39



N-bromosuccinimide (NBS) and renewed submission to the coupling conditions. In this way, the overall yield of the dimerization was raised to 82%. The stereogenic center in the propyl side chain induced the absolute configuration at the rotationally hindered biaryl axis, yet with the "wrong", unnatural configuration at the biaryl axis. Thus, the derivative (*S*)-**304**, with its (*S*)-configured 2-propanol side chain, favored the formation of (*M*)-**306** (50% de). Consequently, for the synthesis of (−)-phleichrome [(*P*)-**15**], the minor (*P*)-atropisomer of **306** had to be separated by preparative thin-layer chromatography on silica gel, giving stereochemically homogeneous (*P*)-**306** in only 19% yield. Removal of the silyl and benzyl protecting groups led to (*P*)-**307**, which afforded the natural perylenequinone (*P*)-**15** by oxidative phenolic coupling with $K_3Fe(CN)_6$ followed by deprotection of the phenol groups *para* to the biaryl axis under slightly acidic conditions. Altogether, this first synthetic approach to the naturally occurring perylenequinone (−)-phleichrome [(*P*)-**15**] required 21 steps providing <1% overall yield.

The preferential formation of the "wrong" atropodiastereomer in the dimerization of (*S*)-**304** was used by Broka[251] for the directed synthesis of calphostins A [(*P*)-**292**] and D [(*P*)-**295**] (Scheme 41). Like (−)-phleichrome [(*P*)-**15**], these two natural products possess a (*P*)-configured biaryl axis; the stereogenic centers in the side chain, however, have the absolute (*R*)-configuration and thus exactly the relative configuration accessible through the above coupling reaction. Therefore, the stereocenter in the propyl side chain in (*S*)-

Scheme 40



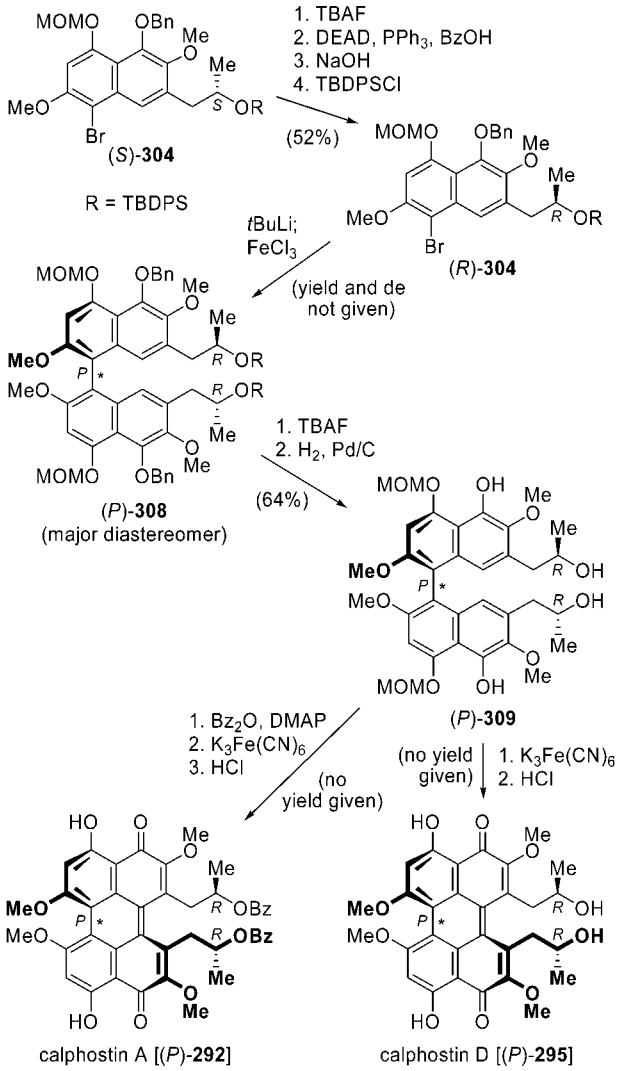
304 was inverted, after TBDPS deprotection of the secondary alcohol function, by a Mitsunobu reaction to deliver (*R*)-**304**. Lithiation of the naphthalene (*R*)-**304** and in situ Fe(III)-mediated oxidative coupling gave the biaryl (*P*)-**308** as the major diastereomer (no yield and diastereomeric ratios are given). Cleavage of the silylether and the benzyl protecting group provided (*P*)-**309** in 64% yield. The total synthesis of calphostin D [(*P*)-**295**] was accomplished by further oxidation with $K_3Fe(CN)_6$ and removal of the two MOM groups. The *O*-benzoylated derivative calphostin A [(*P*)-**292**] was obtained by esterification of the free phenol groups of (*P*)-**309**, followed by oxidation and cleavage of the MOM−ether groups.

Coleman and Grant[252] developed a synthetic approach toward (−)-phleichrome [(*P*)-**15**] and calphostin A [(*P*)-**292**], based on a novel route to chiral naphthyl-2-propanols (Scheme 42). Starting from the benzoic acid **310**, the *ortho*-quinone derivative **311** was obtained in five steps and 35% yield by esterification, *O*-benzylation of the phenol group *meta* to the ester function, protection of the remaining *ortho*-OH group as the methyl ether, cleavage of the benzyl function, and oxidation using $Pb(OAc)_4$.[253] The dienone **311** was subjected to a regio- and chemoselective Diels−Alder reaction with the diene **312** to give the naphthalene **313** in 65% yield. *O*-Benzyl-protection of the free phenolic hydroxy group, followed by reduction of the ester to the alcohol, and renewed oxidation afforded the aldehyde **314**. The optically active precursor (*R*)-**315** (>90% ee) for the chiral 2-propanol side chain was prepared in three steps by addition of α-ethoxyvinyllithium (**89**) to Bu_3SnCl and enol ether cleavage, asymmetric reduction using (*P*)-BINAL−H as a chiral *H*-transfer reagent, and subsequent *O*-alkylation with BOMCl. Nucleophilic addition of the alkoxyalkyllithium reagent, in situ generated from the corresponding stannane (*R*)-**315** by transmetalation with *n*-butyllithium, to the aldehyde **314** gave (*S*)-**316** in 85% yield, with a nearly complete conservation of the optical purity at the stereogenic center at C2′ as compared to that of the building block (*R*)-**315**. Regioselective bromination of the naphthalene core after removal of the benzylic hydroxy group under radical conditions furnished the chiral naphthalene derivate (*S*)-**317**.

For the dimerization of the highly functionalized, electron-rich naphthalenes (*S*)-**317**, Coleman and Grant[252] applied Lipshutz' Cu(I)-promoted biaryl coupling (Scheme 43). Halogen−metal exchange followed by treatment with CuCN generated a higher-order cuprate−naphthalene complex, which afforded the corresponding dimer (*P*)-**318** in 70% yield. The diastereoselectivity of this aryl−aryl bond formation was efficiently governed by the (*S*)-configuration of the stereogenic center of the *O*-protected propanol side chain, inducing a (*P*)-axial chirality in **318** with 78% de. Acid-mediated cleavage of the BOM-protecting group gave (*P*)-**319**, which was converted to (−)-phleichrome [(*P*)-**15**] in nearly 1% overall yield, by hydrogenolysis of the *O*-benzyl function, radical cyclization with $K_3Fe(CN)_6$ to form the perylenequinone system, and removal of the *O*-methyl groups.

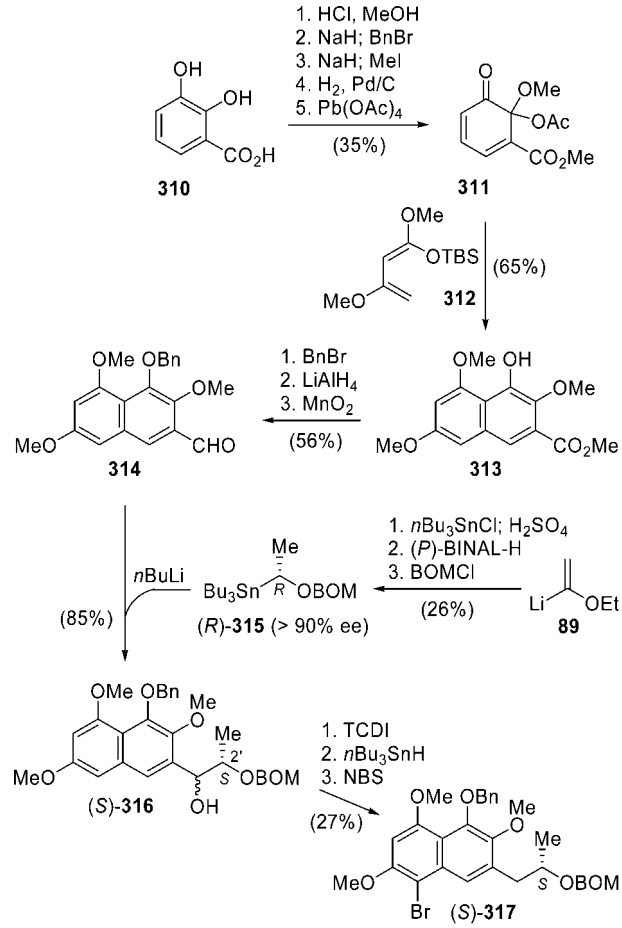
Another perylenequinone, calphostin A [(*P*)-**292**], which differs from (*P*)-**15** in the absolute configuration at C2′, was also prepared from (*P*)-**319**. For this purpose, the stereocenter in the side chain was inverted by a 2-fold Mitsunobu reaction delivering (*P*)-**320**. Cleavage of the benzyl ethers, followed by MnO_2-promoted oxidative cyclization and *O*-demethylation of the methoxy groups *para* to the original biaryl axis, furnished (*P*)-**292** in a total of 24 steps.

Scheme 41



In 2001, a new synthetic route toward the members of the calphostin family was introduced by Merlic et al. featuring a benzannulation of an enantiopure Fischer carbene complex for the construction of the naphthalene core and an atroposelective thermal isomerization to control the axial chirality (Scheme 44).[254] Aromatic bromination of **321** followed by hydroxy−halogen exchange at the benzylic position and treatment with triethylphosphite provided the phosphonic acid diethyl ester **322**. The stereoinformation required in the later 2-propanol side chain of the calphostins, (*P*)-**292**−(*P*)-**295**, was established by a Horner−Wadsworth−Emmons reaction of the enantiopure aldehyde (*R*)-**323** with the phosphonate ester **322** delivering the desired (*E*)-alkene (*R*)-**324**, exclusively (92% yield). Formation of the chromium carbene complex (*R*)-**325** was achieved in 88% yield by addition of $Cr(CO)_6$ to the in situ generated organolithium derivative of (*R*)-**324**, followed by *O*-methylation. Reaction with *t*BuNC delivered the corresponding ketenimine intermediate, which was subjected to a thermal 6π-electrocyclization and a fluoride-induced desilylation, furnishing the aminonaphthalene (*R*)-**326** in 60% yield. The aliphatic hydroxy function in (*R*)-**326** was benzoylated and the electron-rich naphthalene oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide the *ortho*-naphthoquinone (*R*)-**327** (87% yield), the precursor for the oxidative biaryl coupling. Treatment of (*R*)-**327** with TFA

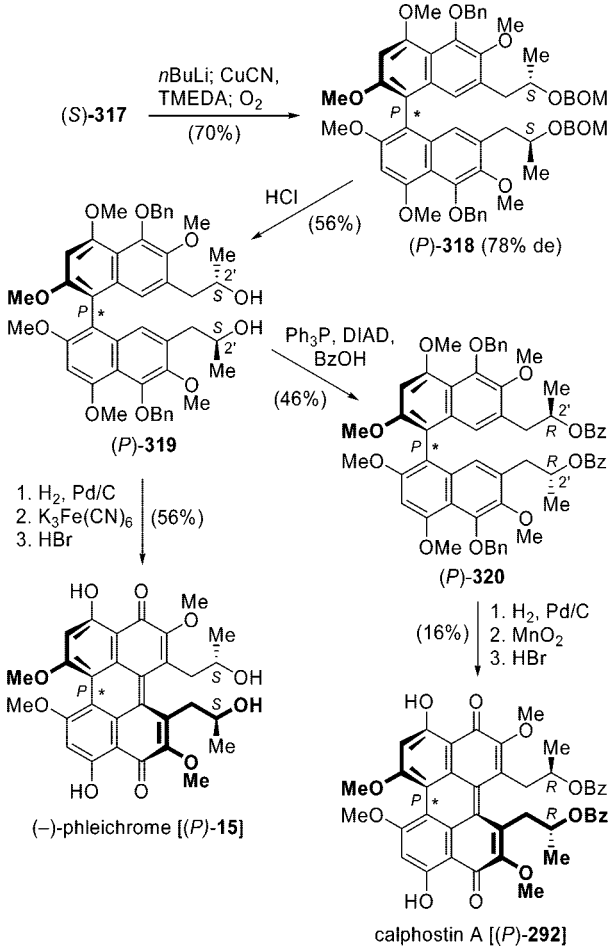
Scheme 42



and air as the oxidant gave the desired perylenequinone derivative (*P*)-**328**, but unfortunately as the minor diastereomer [(*M*)-**328**/(*P*)-**328** = 2:1]. Using the fact that the biaryl axis in **328** is not rotationally stable at high temperatures (isomerization barrier = 21 kcal/mol) and that the required (*P*)-configuration at the axis is thermodynamically favored, **328** was smoothly epimerized in refluxing toluene over 36 h to yield the (*P*)-atropodiastereomer of **328** with 50% de. After column chromatography, stereochemically pure (*P*)-**328** was obtained in 56% yield from (*R*)-**327**. *O*-Methylation of (*P*)-**328** delivered the hexamethoxy−perylenequinone (*P*)-**329**. This provided the basis for the synthesis of all four members of the calphostin family, which only differ in the two substituents R^1 and R^2 on the oxygen functions in the 2-propanol side chain (see Figure 13).

The shortest of these synthetic pathways starting from (*P*)-**329** (Scheme 45) provided calphostin A [(*P*)-**292**] in only one further step, by regioselective *O*-demethylation (92% yield) of the two methoxy groups *para* to the "western" biaryl axis. Additional saponification of both benzoyl esters of (*P*)-**292** gave calphostin D [(*P*)-**295**] in 61% yield over the last two steps. The perylenequinone calphostin B [(*P*)-**293**] was accessible in 60% yield through desymmetrization of the molecule by mono-*O*-debenzylation of the 2-propanol side chain followed by cleavage of the two methylether functions using MgI_2. Methanolysis of only one of the two homotopic ester groups in (*P*)-**329**—as described for the synthesis of (*P*)-**293**—and reaction of the secondary alcohol with phosgene followed by in situ treatment of the intermediate chloroformate ester with 4-acetoxyphenol, regioselective 2-fold *O*-demethylation of the hydroxy groups *para* to the

Scheme 43

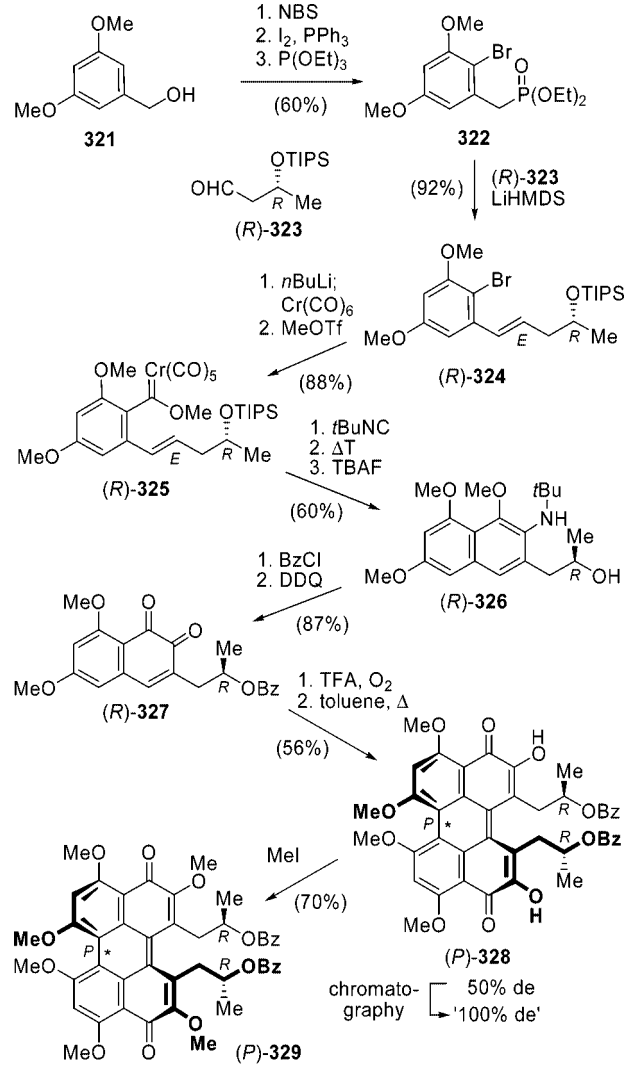


biaryl axis, and liberation of the phenolic OH function in the salicylic acid ester moiety provided calphostin C [(*P*)-**294**] in 60% yield.

Two representatives of a structurally remarkable subclass of the perylenequinones, which are characterized by an additional seven-membered bridge containing two stereogenic centers, are hypocrellin A (**330**) and shiraiachrome A (**331**),[255] both isolates from the fungus *Shiraia bambusicola* (Figure 14).[256]

Because of the additional bridge, which lowers the atropisomerization barrier ($\Delta G^{\ddagger}_{22°C} = 66.5$ kJ mol^{-1}), hypocrellin A (**330**) is not configurationally stable at the biaryl axis, which is different from other perylenequinones like (−)-phleichrome [(*P*)-**15**, see Figure 13].[257,258] It thus exists as a 4:1 mixture of its two atropodiastereomers, (*P*)-**330** and (*M*)-**330**, with the two helical isomers readily interconverting at room temperature (rt) ($k_{22°C} = 15.3$ s^{-1}).[259,260] In shiraiachrome A (**331**), a diastereomer of **330** with a different configuration at the stereogenic centers, the atropisomeric equilibrium is strongly shifted toward the (*M*)-isomer [(*M*)-**331**/(*P*)-**331** > 10:1].[259,261] Even though these two biaryls, **330** and **331**, do not possess a configurationally stable axis, but just a thermodynamically preferred axial conformation, the as yet only total synthesis of hypocrellin A (**330**), in which shiraiachrome A (**331**) was obtained as a side product, is presented here because it has been accomplished via configurationally stable, axially chiral perylenequinone intermediates by Kozlowski and co-workers.[261,262] A key step of this approach was an enantioselective phenol-oxidative homocoupling.[18]

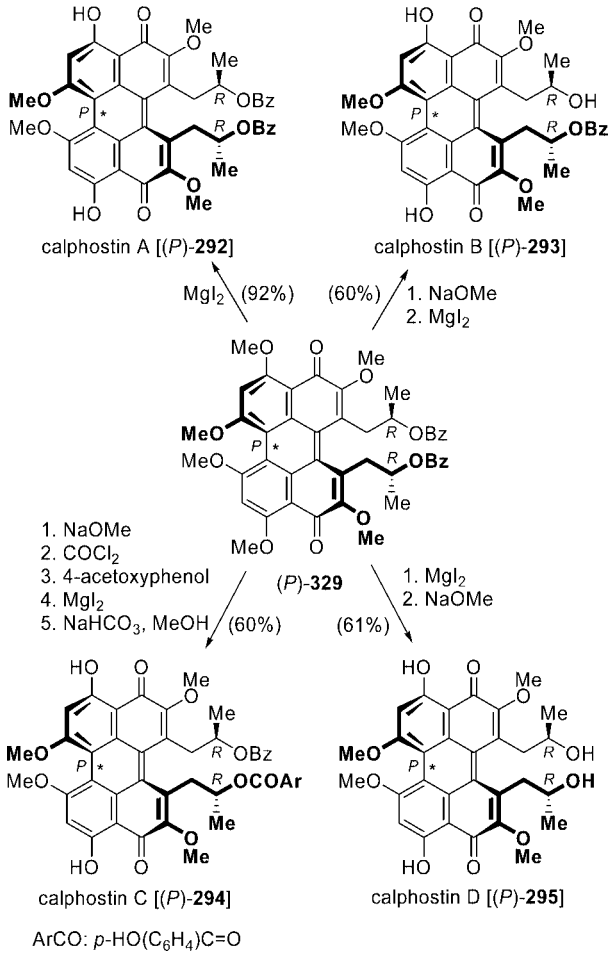
Scheme 44



The synthesis started with naphthalene **333**, which was obtained from phenylacetic acid **332** in three steps (Scheme 46), by regioselective iodination *ortho* to the methoxy group, preparation of the acid chloride, condensation with dimethyl malonate, and acid-catalyzed cyclization. Selective protection of the hydroxy function at C4 was achieved by 2-fold *O*-acetylation and regioselective hydrolysis of the ester function at C2 delivering the naphthol **334** (30% yield over six steps) as the coupling precursor. The stereochemical key step, the enantioselective oxidative "dimerization" of **334** to give (*P*)-**335**, was achieved in good 80% yield and with high stereocontrol (88% ee) using 20 mol % of a chiral Cu catalyst (*R*,*R*)-**49**[263] derived from the respective C_2-symmetric *cis*-diazadecalin and CuI, in combination with oxygen as a stoichiometric oxidant. The enantiomeric excess was enhanced to >99% by trituration from CH_2Cl_2/hexanes.

After deacylation and *O*-methylation of (*P*)-**335**, the allyl side chains at C7 were introduced in 90% yield by Suzuki coupling to give (*P*)-**336** (Scheme 47). Hydroxylation at C5 was accomplished smoothly by oxidation with PhI(O-$COCF_3)_2$. *O*-Benzylation and regioselective Wacker oxidation of the propenyl side chains yielded the diketone (*P*)-**337** in 38% yield. Because of the basic conditions needed for the subsequent steps, the carbonyl functions were protected as acetals. To avoid any loss of optical purity, removal of the unreactive esters at C3 was carried out in a two-step

Scheme 45



procedure using a $NaCN/H_2O$-promoted saponification followed by a mild palladium-mediated decarboxylation, which provided (*P*)-**338** in 54% yield without any racemization. *O*-Debenzylation and oxidation with MnO_2[252] afforded the perylenequinone (*P*)-**339** (88% yield). Because acetal hydrolysis of (*P*)-**339** under acidic conditions was accompanied by decomposition, compound (*P*)-**339** was converted into (*P*)-**340** (89% yield) in a three-step one-pot sequence, by $Na_2S_2O_4$ reduction to the corresponding perylene, deacetal-

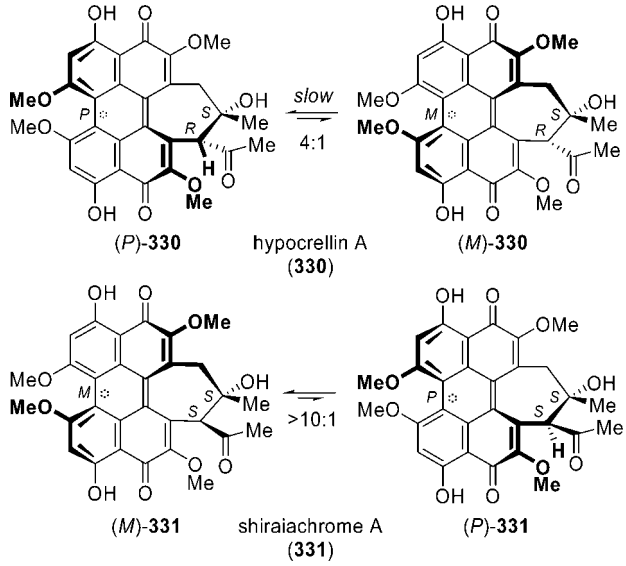
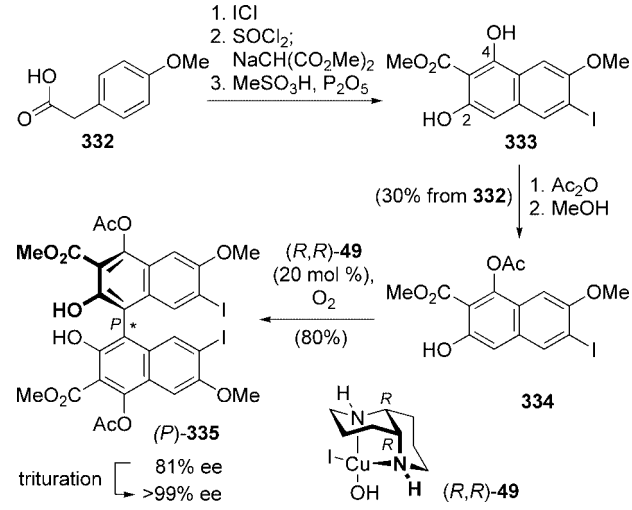
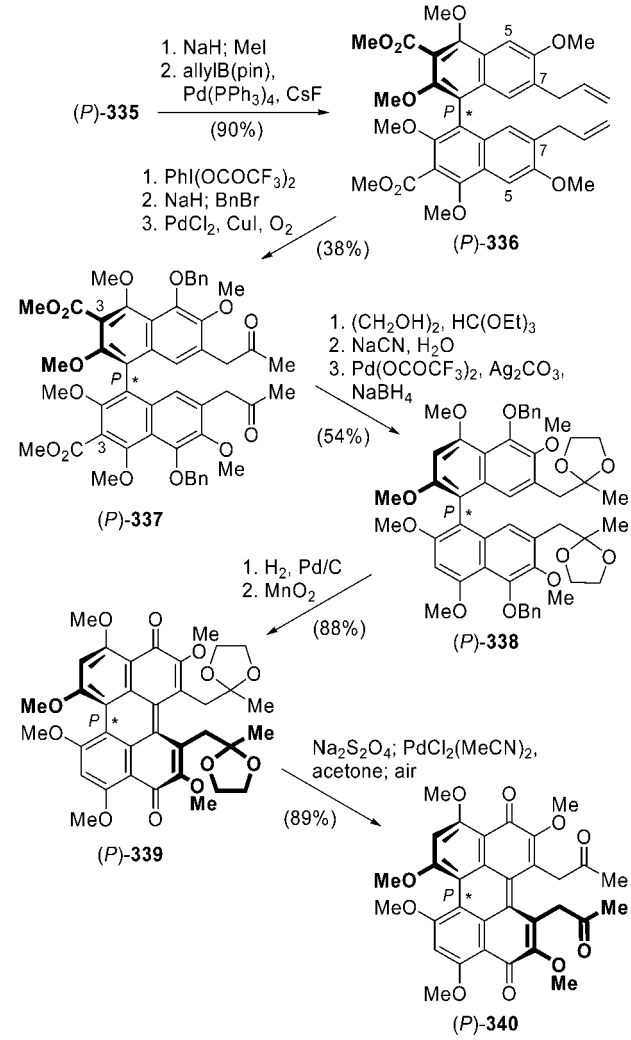


Figure 14.

Scheme 46



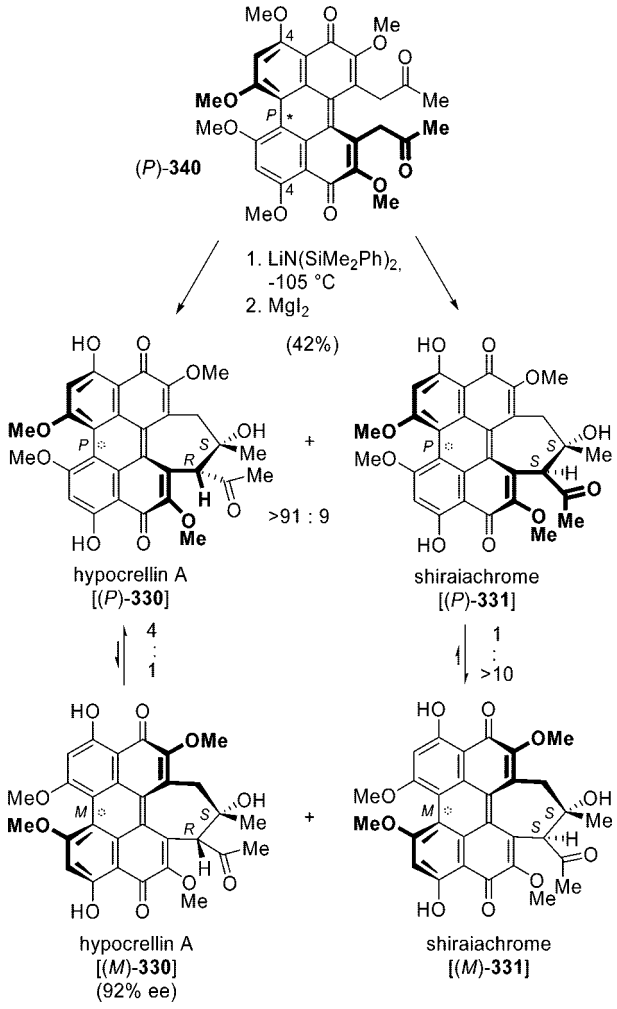
Scheme 47



ization with $PdCl_2(MeCN)_2$ in acetone, and reoxidation to the perylene quinone by exposure to air.

In the final steps toward hypocrellin A [(*P*)-**330**], the correct configuration at the two stereogenic centers in the seven-membered ring was installed by using the helical chirality of the perylenequinone core of (*P*)-**340** as an internal asymmetric inductor, thus applying an efficient—potentially biomimetic—"dynamic chirality transfer reac-

Scheme 48



tion"[261] (Scheme 48). Molecular modeling studies suggested that an intramolecular aldol addition of the *Z*-enolate of one keto function to the remaining one should generate the required stereochemical orientation in the bridge. Treatment of (*P*)-**340** with $LiN(SiMe_2Ph)_2$ as a sterically encumbered base at −105 °C indeed provided the desired stereochemical array in >82% de. Selective *O*-demethylation of the oxygen atoms at C4 using MgI_2 yielded the natural product hypocrellin A (**330**), which is configurationally unstable at the biaryl axis, as a thermodynamically controlled 4:1 mixture of the atropodiastereomers (*P*)-**330** and (*M*)-**330**, along with shiraiachrome A [(*M*)-**331**/(*P*)-**331** > 10:1] as a pair of minor diastereomers. The complete synthesis required 19 steps and delivered hypocrellin A (**330**) in 1.6% overall yield.

The latter synthesis is one of the rare examples in which a chiral biaryl axis is constructed enantioselectively, using a chiral catalyst. Recently, further applications of this method were published.[18,250] The advantage of this approach over all other diastereoselective phenol-oxidative coupling reactions described earlier in this section is obvious: The strategy successfully avoids all problems arising from the formation of the wrong atropodiastereomers, as observed in the preparation of the calphostins from naphthols with chiral side chains.

4. Bridged Biaryl Natural Products

4.1. Lactone-Bridged Biphenyls on a Glucose Matrix: Ellagitannins

The ellagitannins[264] are part of the hydrolyzable tannin class of polyphenolic secondary metabolites derived from higher plants of the families Hamamelidae, Dilleniidae, and Rosidae.[264,265] Characteristic of these gallic acid derivatives is the presence of one or more axially chiral hexahydroxydiphenoyl (HHDP)[266] residues connected to a D-glucopyranose scaffold via ester bridges.[267] Among the monomeric representatives (one HHDP moiety and one glucopyranosyl unit, Figure 15) already, the structural diversity of the ellagitannins is broad with respect to the position and the absolute configuration of the HHDP part, the degree of galloylation, and the configuration at the anomeric center, and it is even larger for dimeric and oligomeric representatives.[66] It has been observed that ellagitannins with a 4,6- or a 2,3-linkage occur exclusively with the (*P*)-configuration at the biaryl axis,[66,268] among them tellimagrandin I [(*P*)-**18**][67] and sanguiin H-5 [(*P*)-**342**],[269] whereas 3,6- or 1,6-coupled compounds like, e.g., corilagin [(*M*)-**343**][270] and davidiin [(*M*)-**344**],[271,272] possess an (*M*)-configured HHDP subunit. The Schmidt−Haslam hypothesis[265,267,268,271,273] proposes that the absolute configuration at the biaryl axis is induced by the conformational preference of the D-glucopyranose core within the intramolecular coupling step in nature. The validity of this prediction was first demonstrated by Feldman et al.[274] in the course of the highly atropodiastereoselective biomimetic oxidative coupling reaction of neighboring galloyl groups attached to a D-glucopyranosyl moiety (see Scheme 49). These simple, "monomeric" ellagitannins are precursors to a large number of oligomeric higher analogues such as coriariin A [(*P*,*P*)-**345**],[272] in which two molecules of (*P*)-**341** are attached to each other via a—likewise oxidatively formed—diphenyl ether bridge connecting the anomeric galloyl moieties. Some of these compounds even possess two HHDP units like, e.g., pedunculagin [(*P*,*P*)-**346**][275] and its atropodiastereomer platycaryanin D [(*M*,*M*)-**346**].[276] The latter ellagitannin derivative is one of the rare exceptions[267] in which the Schmidt−Haslan hypothesis[265,267,268,271,273] is not fulfilled, thus hinting at a different biosynthetic origin (vide supra).[277]

Ellagitannins were identified as the curative and palliative agents in several tannin-containing plants used in folk medicine,[278] especially in China and Japan, which has triggered a high interest in these natural products for the development of new pharmaceuticals. These compounds show remarkable antiviral,[279] antibacterial,[280] and antitumoral[248,281] activities.

Because the isolation of ellagitannins is cumbersome and permits access to the compounds only in small quantities,[282] the development of synthetic methods that provide sufficient material of these bioactive molecules is an important task. The existing synthetic approaches[283] have already been reviewed extensively by Quideau and Feldman[66] and Khanbabaee and van Ree;[268] therefore, this review is confined to the presentation of just one representative example of each of the different possibilities for the stereoselective formation of the aryl−aryl bond. This is the key step in all ellagitannin syntheses and can be achieved in two different ways: intermolecularly, by an independent atroposelective construction of the HHDP unit, with subsequent esterification of a suitably protected D-glucopyranose motif, or intramolecu-

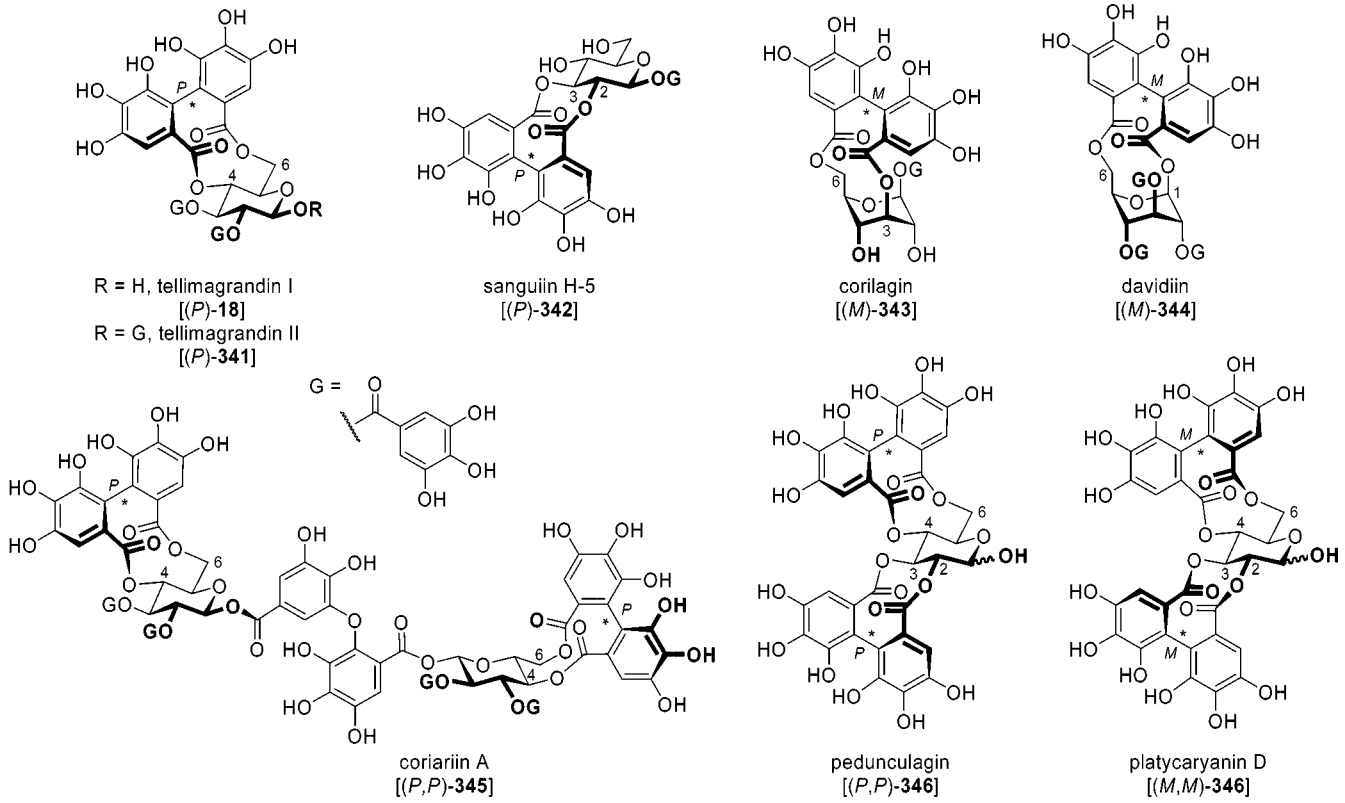
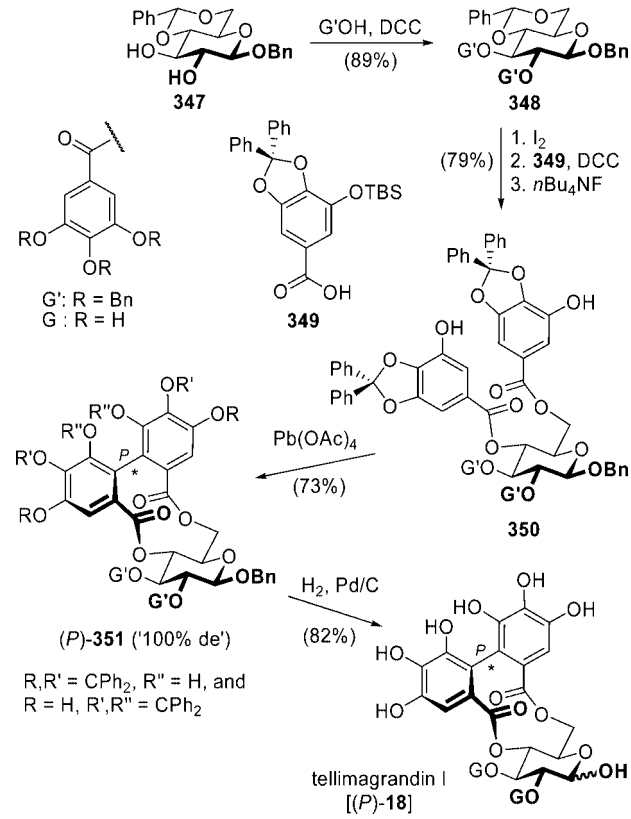


Figure 15.

Scheme 49



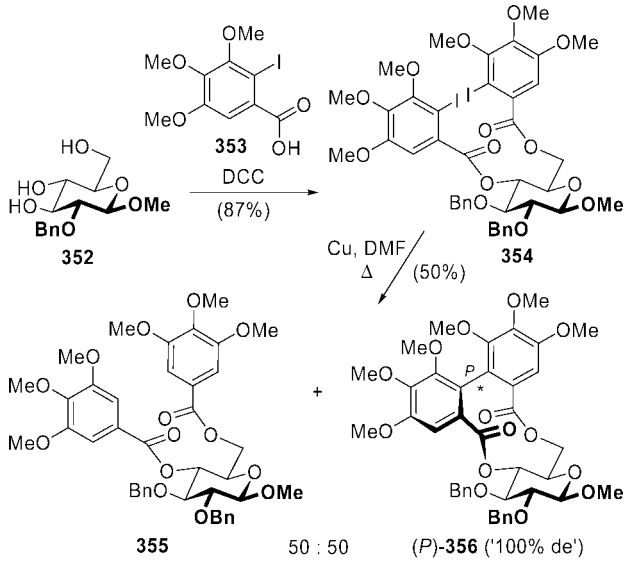
larly, by first connecting the two galloyl moieties to the sugar, with subsequent atroposelective coupling of the aromatic rings.

The latter concept was introduced in 1994 by Feldman et al.,[274] in the course of the first total synthesis of a representative of the ellagitannin family, the 4,6-coupled tellimagrandin I [(*P*)-**18**] isolated from *Tellima grandiflora*[67] (Scheme 49). Starting from the glucopyranose 4,6-benzylidene acetal **347**, the free hydroxy groups at C2 and C3 were esterified with fully *O*-benzylated galloylic acids under Steglich conditions. Deprotection of the 4- and 6-oxygen functions in **348**, linkage of 2 equiv of **349** to the glucose core, and subsequent removal of the silyl group afforded the digalloyl ester **350**. Oxidative aryl−aryl bond formation using $Pb(OAc)_4$ delivered the 4,6-linked product **351** in good chemical yield (73%) and with complete stereocontrol to give exclusively the (*P*)-diastereomer, yet as a mixture of regioisomeric diphenyl ketals. This lacking selectivity, however, remained without consequence, since simple hydrogenolytic deprotection of the phenolic hydroxy groups in the galloyl unit furnished the natural product tellimagrandin I [(*P*)-**18**] free of any isomeric side products in a short six-step synthesis with 42% overall yield. Using this approach, Feldman and co-workers[274,284−286] prepared a series of other ellagitannins, among them sanguiin H-5 [(*M*)-**342**][284] and the dimer coriariin A [(*P*,*P*)-**345**].[286]

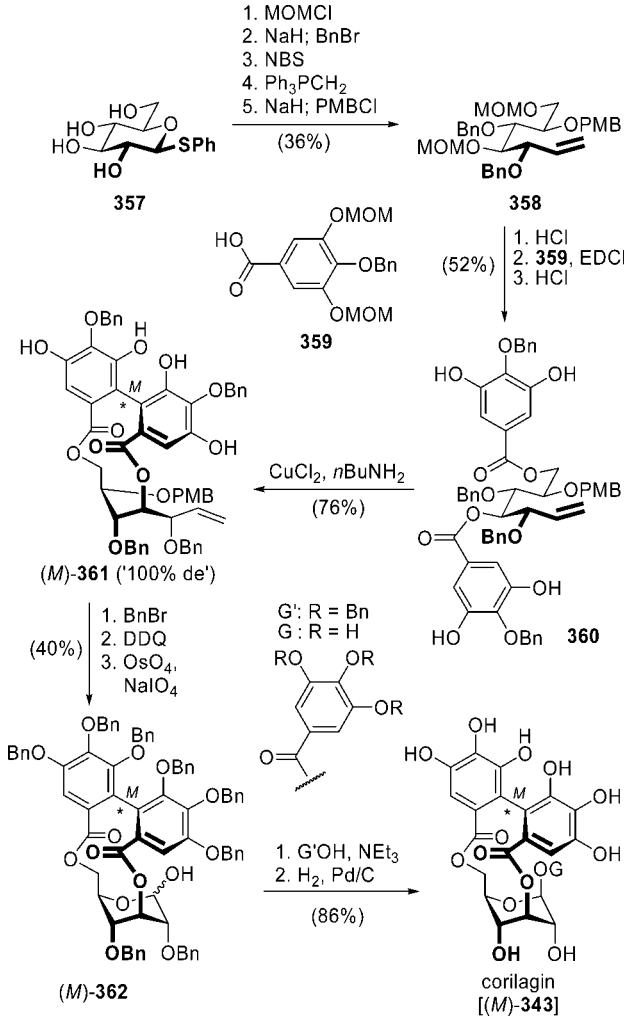
Dai and Martin[287] reported an approach conceptually similar to the one developed by Feldman's group, yet based on an intramolecular Ullmann coupling (Scheme 50). Esterification of **352** with 2 equiv of the methylether-protected iodo galloyl derivative **353**, followed by reductive coupling of the resulting digalloate ester **354** using activated copper, proceeded with complete stereoselectivity, giving the (*P*)-atropodiastereomer of **356**, exclusively (100% de). Unfortunately, hydrodeiodination to give **355** also occurred to a high extent (50%) during the aryl−aryl bond formation, leading to an inseparable mixture of (*P*)-**356** and **355**. Thus, no further attempts to complete this ellagitannin synthesis were reported.

The major challenge in the synthesis of corilagin[288] [(*M*)-**343**, Scheme 51] was the central glucopyranose moiety, which is fixed in a conformation with all substituents in axial

Scheme 50

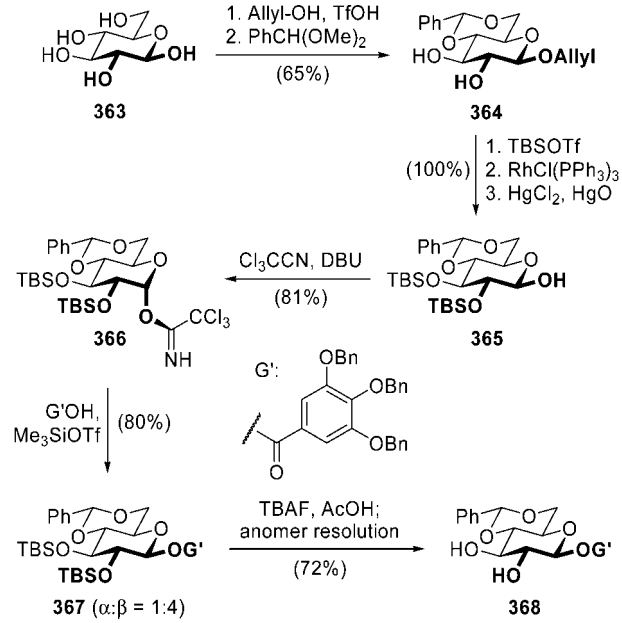


Scheme 51



orientations, due to the 3,6-HHDP bridge. Initial attempts to prepare this compound from a 3,6-digalloyl-substituted glucose derivate by oxidative biaryl coupling or from an 3,6-unprotected glucose derivative by esterification with HHDP acid failed because this would have required a ring-flip at the glucose core from the thermodynamically strongly favored all-equatorial alignment of the substituents into an

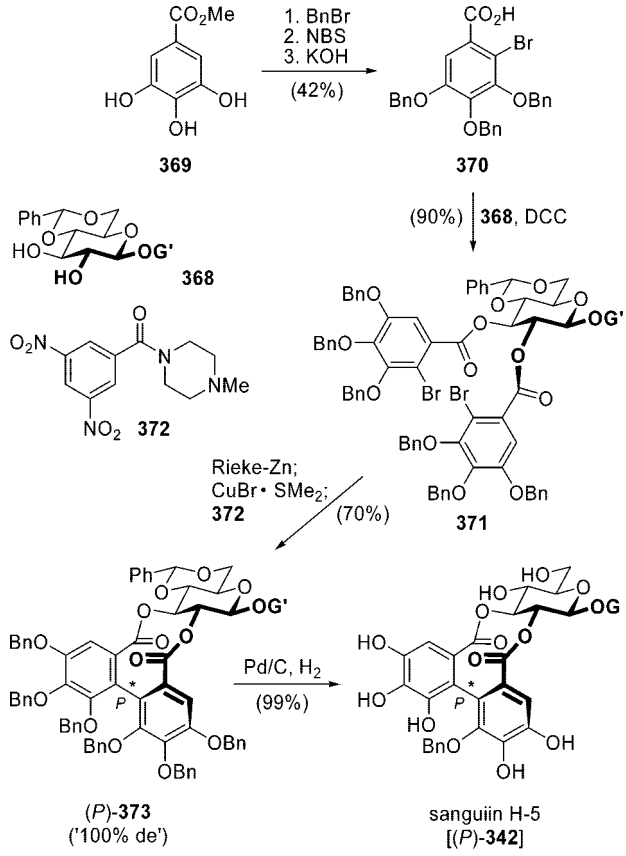
Scheme 52



all-axial array.[289] Yamada et al. solved this problem by choosing a route via a temporarily ring-opened sugar analogue.[290] Starting from the 1-thio-protected glycopyranose **357**, the hydroxy functions at the 2,4- and 3,6-positions were differentiated by selective MOM−ether formation at C3 and C6 and subsequent dibenzylation of the remaining free 2,4-hydroxy groups.[289] Cleavage of the phenylthio moiety at the anomeric carbon atom furnished the starting material for a Wittig olefination, opening the pyranose ring to give the free alcohol. The hydroxy group thus generated at C5 was PMB-protected yielding **358** in 36% yield from **357**. Acidic cleavage of the MOM−ether moieties was followed by esterification of the liberated hydroxy functions with 2 equiv of **359**. Repeated treatment with hydrochloric acid in order to remove the remaining MOM−ether groups delivered the coupling precursor **360**. The atropodiastereoselective formation of the biaryl axis in (*M*)-**361** was accomplished under oxidative conditions using a copper(II) chloride amine adduct at room temperature. The coupling product (*M*)-**361** was obtained as a single diastereomer (100% de), with the asymmetry of the sugar-derived sp^3 carbon atoms being completely transferred to the axial chirality. After protection of the hydroxy functionalities as benzyl ethers, reconstruction of the glycopyranose scaffold by removal of the PMB protecting group, and subsequent oxidative cleavage of the double bond, (*M*)-**362** was obtained in 40% yield. Final galloylation of the anomeric hydroxy function and full debenzylation furnished the natural product corilagin [(*M*)-**343**] in 14 steps and in overall 5% yield.

Recently, Spring and co-workers[291] reported on the synthesis of the 2,3-linked ellagitannin sanguiin H-5 [(*P*)-**342**] utilizing an organocuprate-mediated oxidative biaryl bond formation of the aryl groups attached to the pyranose scaffold. This methodology allows the preparation of sterically hindered biaryls with highly strained medium-sized ring-containing biaryls.[292] By starting from β-D-glucose (**363**), the chiral sugar template **368** for the atroposelective aryl coupling was obtained with stereocontrol at the anomeric carbon atom by a series of protecting group manipulations following a procedure developed by Fujiwara, Murai, and co-workers. (Scheme 52).[293] *O*-Allylation of the anomeric hydroxy functionality and selective protection of the alcohol

Scheme 53

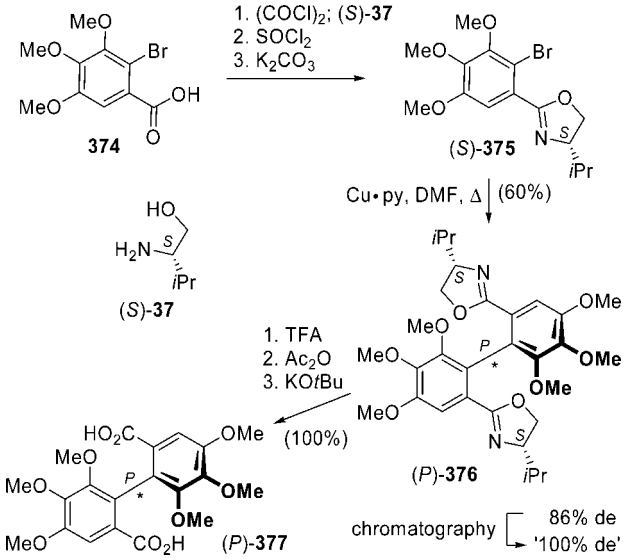


groups at C4 and C6 as the benzylidene acetal afforded diol **364** in 65% yield. After formation of the TBS−silyl ether, the allyl group was isomerized using the Wilkinson catalyst. Hydroxymercuration and hydrolysis gave the lactol **365** almost quantitatively. In analogy to the method of Feldman et al.,[286] the trichloroacetimidate **366** was synthesized using Cl_3CCN and DBU in 81% yield; it was then converted to ester **367** by treatment with benzyl-protected galloylic acid in 80% yield, giving mainly the required β-anomer (β/α = 4:1). After deprotection of the OH functions at C2 and C3, the mixture was resolved by column chromatography, to provide the pure β-galloylglucose derivative **368** in 72% yield.

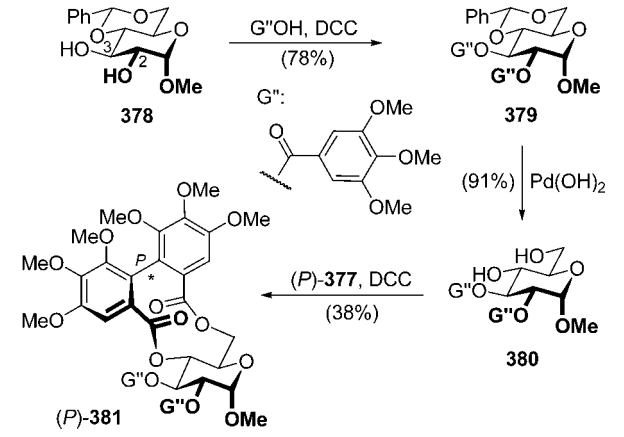
The aryl bromide **370** was accessible in three steps and 42% yield from methyl gallate (**369**) by *O*-benzyl protection, bromination, and subsequent saponification (Scheme 53). Attachment of the aromatic portions **370** to the pyranose scaffold **368** was carried out by double esterification using dicyclohexylcarbodiimide (DCC) in 90% yield. After bromine−zinc exchange and transmetalation into the corresponding copper species, the diaryl ester **371** was submitted to an intramolecular biaryl coupling, accomplished with *m*-dinitrobenzyl amide **372** as the oxidant.[292] In accordance to the Schmidt−Haslam hypothesis,[265,267,268,271,273] the intramolecular coupling generated solely the (*P*)-atropisomer of the benzyl-protected sanguiin H-5 (*P*)-**373** (70% yield). Hydrogenolytic removal of the *O*-benzyl groups finalized the total synthesis of the natural product (*P*)-**342** in 13 steps and good 19% chemical yield from β-D-glucose (**363**).

The intramolecular strategies presented above have their advantage in the economy and efficiency of the biaryl coupling step, since no introduction of additional chiral information is needed and only one atropodiastereomer is

Scheme 54



Scheme 55

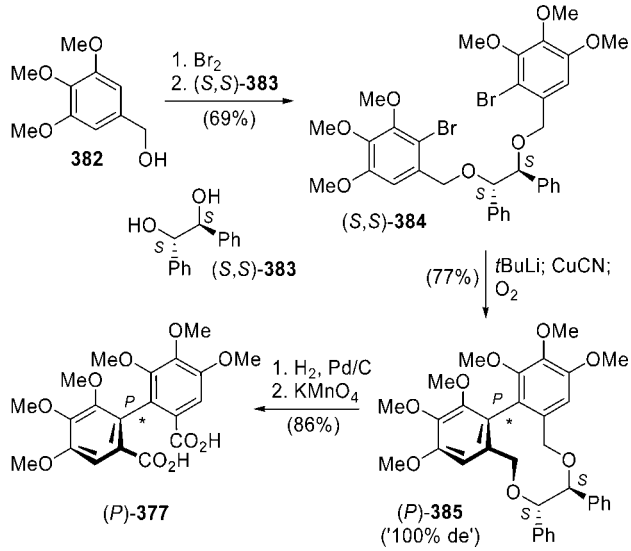


formed depending on the positions of the galloyl residue at the glucose ring, which acts as the chiral template.

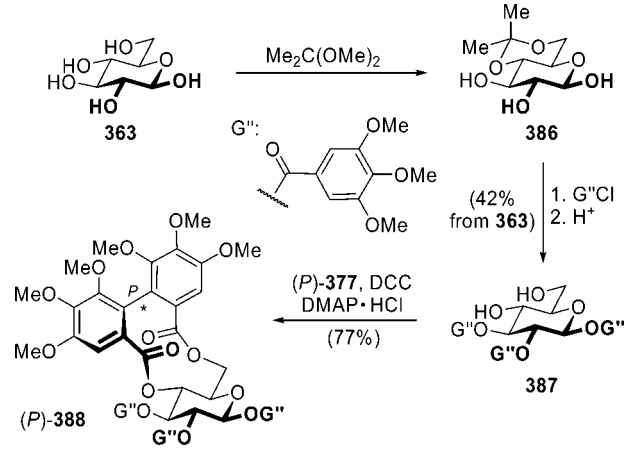
An alternative strategy, in which an independently—*inter*molecularly—prepared axially chiral HHDP−acid derivative is linked to the central D-glucopyranose core, was first realized in the groups of Meyers[294] and Lipshutz.[295] By atropodiastereoselective Ullmann coupling of the two bromoarenes (*S*)-**375** (Scheme 54), which bear an (*S*)-configured oxazoline ring as the chiral auxiliary derived from **374** and (*S*)-valinol [(*S*)-**37**], Nelson and Meyers[294] achieved an—overall enantioselective—preparation of the HHDP moiety.[93] The biaryl bond formation proceeded in 60% chemical yield providing the (*P*)-configured atropodiastereomer (*P*)-**376** in 86% de. After chromatographic removal of the unwanted minor isomer, the oxazoline ring was carefully hydrolyzed to avoid any loss of optical purity at the biaryl axis, by acid-mediated ring-opening, acetylation of the free amino function (to prevent recyclization), and Gassman saponification, quantitatively giving the key intermediate (*P*)-**377**.

Twofold Steglich esterification of the free hydroxy groups at C2 and C3 of the sugar derivative **378** with *O*-trimethylgalloyl acids to give **379** and hydrogenolysis of the benzylidene protecting group released the diol **380** in 71% yield (Scheme 55). Double esterification of **380** with enantiopure (*P*)-**377** completed this overall 10-step synthesis of the (unnatural) per-*O*-methylated derivative (*P*)-**381** of tellimagrandin I.

Scheme 56



Scheme 57

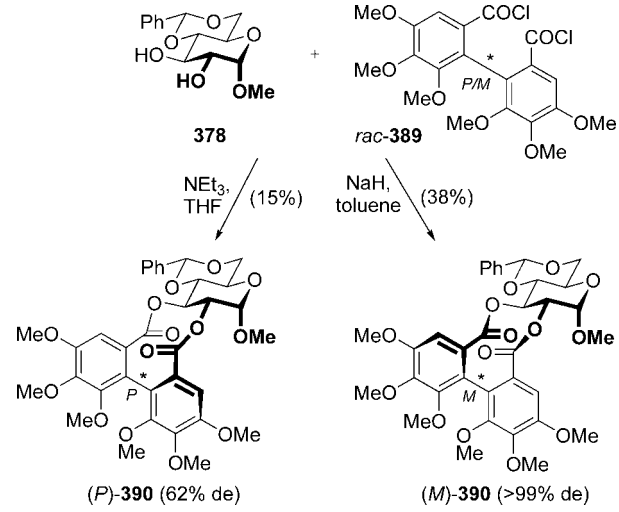


A closely related synthetic approach to ellagitannins was published by Lipshutz et al. in 1994,[295] although accomplishing the key step, the atroposelective preparation of the diacid (*P*)-**377**, by a cyanocuprate-mediated diastereoselective coupling (Scheme 56). Dibromination of **382** followed by nucleophilic substitution of the benzylic bromide with the enantiopure diol (*S*,*S*)-**383** furnished the diether (*S*,*S*)-**384**. The aryl portions, prelinked via a chiral tether as in (*S*,*S*)-**384**, were lithiated, converted into the cyano cuprates, and coupled in the presence of oxygen to give the bridged biaryl (*P*)-**385** in 77% yield. The virtually complete diastereoselectivity (100% de) induced by the chiral tether is clearly superior to that achieved by the approach of Nelson and Meyers[294] (86% de, see Scheme 54). Reductive removal of the tether and oxidation of the resulting benzylic OH functions released the enantiopure diacid (*P*)-**377**.

β-D-Glucose (**363**) was protected as its 4,6-acetonide **386** (Scheme 57), which was reacted with the fully *O*-methylated galloyl acid chloride, delivering the triacid **387** in 42% yield after mild acidic hydrolysis of the acetal. The final step, the attachment of the chiral biaryl diacid (*P*)-**387** to the sugar derivative **388**, afforded (*P*)-**388** in good chemical yield (77%) using the Keck modification of the Steglich esterification conditions.

A particular advantage of the latter strategy (esterification of the sugar with an enantiomerically pure HHDP unit) over the diastereoselective biomimetic oxidative biaryl coupling of sugar-linked galloates (see Schemes 49−53) is the possibility of an atropodiastereodivergent preparation of ellagitannins with (*M*)- or, optionally, (*P*)-configured HHDP moieties starting from the same glycoside. Such an approach was attempted by Itoh and co-workers in the synthesis of the (unnatural) per-*O*-methylated analogues of the 2-fold HHDP-bridged ellagitannins pedunculagin [(*P*,*P*)-**346**] and platycaryanin D [(*M*,*M*)-**346**, see Figure 15],[277] which only differ in the axial configurations at the two biaryl linkages.

Scheme 58

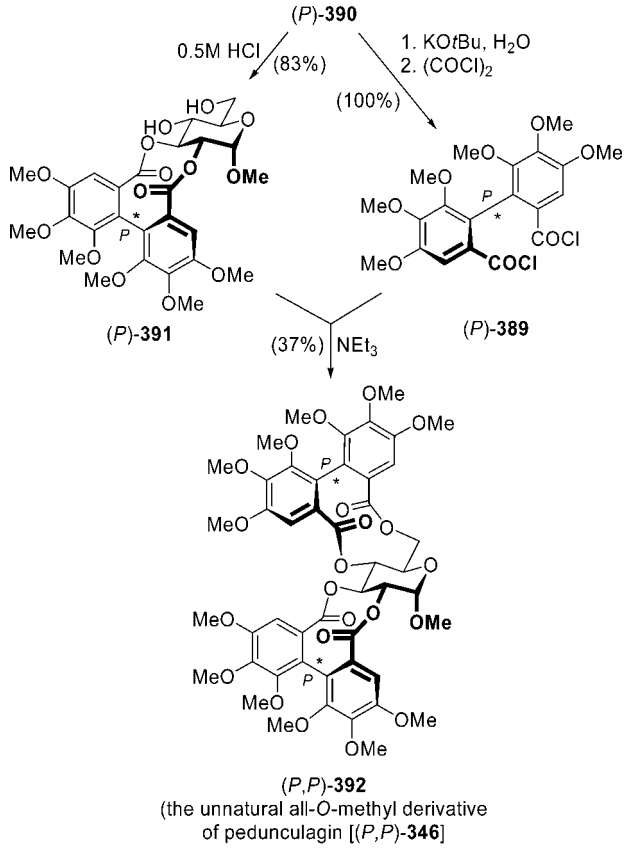


The required intermediates (*P*)-**390** and (*M*)-**390** bearing a 2,3-linked HHDP unit were prepared by kinetic resolution of the racemic acid chloride *rac*-**389**, through esterification with the free hydroxy groups of α-D-glycopyranose **378** as the chiral template (Scheme 58).[277] The choice of solvent and base had a crucial influence on the diastereomeric ratio, leading to (*M*)-**390** in 38% yield and an excellent >99% de when using NaH in toluene. The other atropodiastereomer, (*P*)-**390**, was preferentially (62% de) formed with NEt_3 in THF, albeit in low 15% yield. On the basis of these experiments, it was concluded that the 2-fold (*M*)-configured 2,3-bridged ellagitannins like platycaryanin D [(*M*,*M*)-**346**], which rarely occur in nature, might originate from an esterification process, whereas, in agreement with the Schmidt−Haslam hypothesis,[265,267,268,271,273] the normal (*P*)-configuration at the biaryl axis results from an oxidative biaryl coupling of galloates attached to a glucopyranose template.

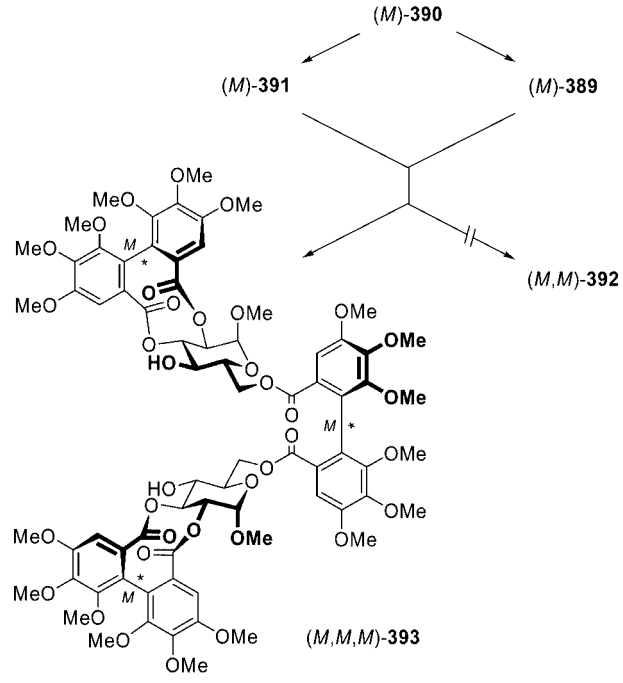
For the completion of the synthesis of the (unnatural) *O*-methyl derivative (*P*,*P*)-**392** of pedunculagin [(*P*,*P*)-**346**], with the natural absolute configuration at the axes, two molecules of (*P*)-**390** were required (Scheme 59). From (*P*)-**390**, the diol (*P*)-**391** was accessed by partial hydrolysis. Under more basic conditions and treatment of the resulting diacid with oxalyl chloride, the enantiomerically pure biaryl acid chloride (*P*)-**389** was obtained, too. Esterification of (*P*)-**389** with (*P*)-**391** delivered (*P*,*P*)-**392** in a total of five steps from **378** and *rac*-**389**.

An extension of this route to the synthesis of the per-*O*-methylated derivative [(*M*,*M*)-**392**] of platycaryanin D [(*M*,*M*)-**346**, see Figure 15], however, failed (Scheme 60).[277] In contrast to the successful preparation of (*P*,*P*)-**392** from (*P*)-**391** and (*P*)-**389**, the chiral building blocks (*M*)-**391** and (*M*)-**389**, as obtained from (*M*)-**390** according to Scheme 59,

Scheme 59



Scheme 60



could not be diesterified in an 1:1 fashion to give [(*M*,*M*)-**392**], leading only to the 1:2 adduct (*M*,*M*,*M*)-**393**, instead.

This preparatively efficient strategy of kinetic resolution was used by Khanbabaee and co-workers[268,296] for the synthesis of a whole series of authentic ellagitannins, like, e.g., pedunculagin [(*P*,*P*)-**346**], now in its natural, i.e., non-*O*-methylated, form. The synthetic pathways differed only by the choice of the protecting groups. The use of *O*-benzyl at the galloyl residues and the photolabile *o*-nitrobenzyl group at the anomeric carbon atom instead of *O*-methyl now did permit the synthesis of the genuine natural products themselves.

Comparing all the above presented synthetic approaches, the "biomimetic" oxidative coupling reaction introduced by Feldman et al. seems to be most suitable for the preparation of naturally occurring ellagitannins, because of the short reaction sequences (see Schemes 49 and 50) and the high diastereoselectivities attained. The chiral information at the biaryl axis is introduced by the natural sugar scaffold, thus avoiding further steps for the introduction and eventual removal of an artificial chiral auxiliary. On the other hand, esterification after atropisomer formation is best if one wants to access all the stereoisomers.

4.2. Dibenzocyclooctadiene Lignans

(+)-Schizandrin [(*M*)-**394**], the first representative of the family of dibenzocyclooctadiene lignans (Figure 16), was isolated in 1961 by Kochetkov and co-workers from *Schizandra chinensis*, a creeping vine native to Northern China.[297] Up to now, >100 of these lignans are known, almost all of them found in plants of the family Schizandraceae, more precisely in only two genera *Schizandra* and *Kadsura*. The lignan-rich extracts of these plants, especially those of the fruits of *Schizandra chinensis*, which produce nearly 40 different dibenzocyclooctadienes, among them (+)-schizandrin [(*M*)-**394**] and its epimer (+)-isoschizandrin [(*M*)-**395**],[298] are used as antitussives, tonics, and antipyretics, as well as for liver-protective purposes in Asian traditional medicine.[299] The large structural variety of the natural dibenzocyclooctadiene lignans is due to the nearly combinatorial permutation of the following structural elements: the substitution patterns of the biaryl unit and of the aliphatic bridge, and the absolute configuration at the biaryl axis and the stereogenic centers of the bridging unit.[4] A small selection of dibenzocyclooctadiene lignans is presented in Figure 16, demonstrating the above-mentioned aspects, such as the change of the absolute configuration at the aryl−aryl bond while keeping the constitution and the stereogenic centers identical, like for the two diastereomers (+)-γ-schizandrin [(*M*)-**396**][300] and gomisin N [(*P*)-**397**].[301] Further structural variations, e.g., an additional ether bridge, are found in the tetrahydrofuranoid product kadsulignan M [(*P*)-**398**].[302] The formation of different esters at the hydroxy functionality of identical dibenzocyclooctadiene skeletons, like benzoyl- or angeloyl groups, can occur, as in the structures of interiotherin A [(*P*)-**399**][303] and angeloylgomisin R [(*P*)-**400**].[304] Another diversifying principle is the formation of annellated butyrolactones resulting in the so-called steganes, e.g., (−)-steganone [(*M*)-**16**] and (−)-steganacin [(*M*)-**401**].[5,60] The latter occur only in *Steganotaenia araliacea* (Apiaceae), the only source of steganes at all, and exhibit a significant cytotoxicity, a strong inhibition of tubulin assembly,[5,61] and in vivo antitumor activity.[60] Structure−activity relationship studies showed that the cytotoxicity and the antimitotic activity of the steganes requires the (*M*)-configuration at the biaryl axis.[62]

Because of the interesting structural elements and the promising biological properties, these biaryl lignans are attractive targets for atroposelective total synthesis. In principle, two general approaches (inter- or intramolecular formation of the biaryl axis) toward dibenzocyclooctadiene lignans are possible, differing only in the order of the creation of the eight-membered ring system and the biaryl coupling

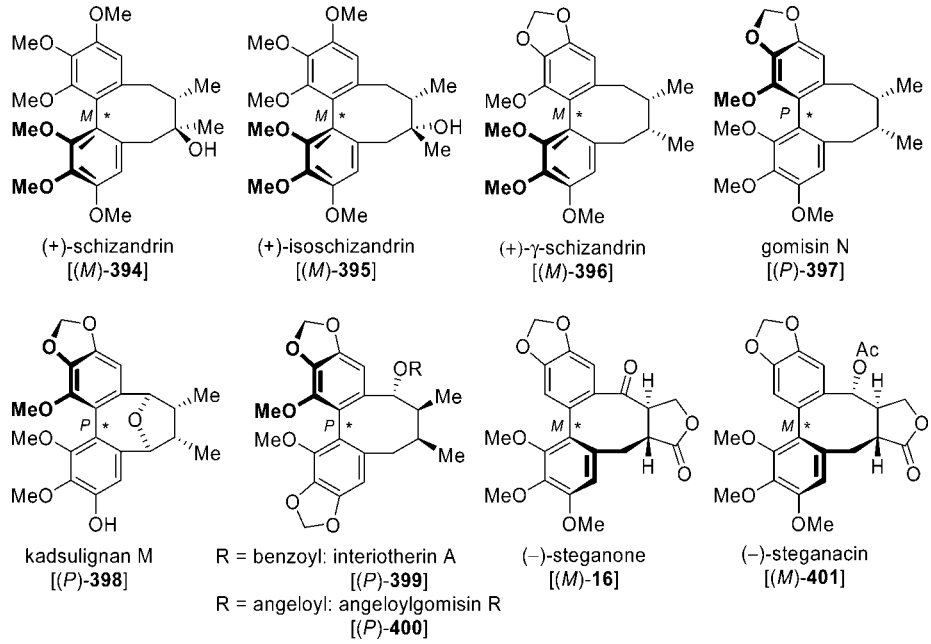


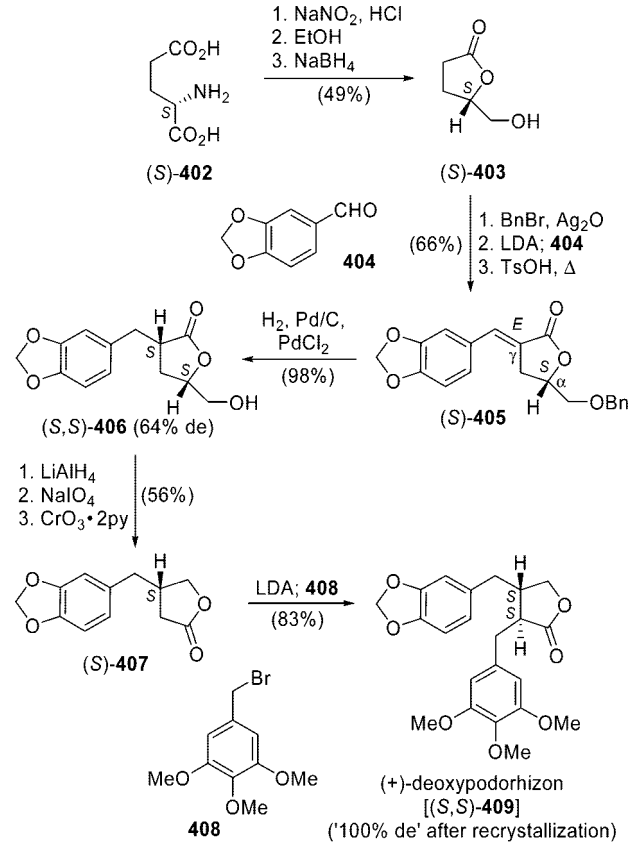
Figure 16.

step. Many stereoselective pathways to dibenzocyclooctadienes have been developed and have, to some extent, already been reviewed.[5,305,306]

The first efforts toward the diastereoselective preparation of steganes were made by the groups of Koga and Robin in the late 1970s in order to establish the absolute configuration of (−)-steganacin [(*M*)-**401**] and (−)-steganone [(*M*)-**16**]. Both groups initially built up the two stereogenic centers of the lactone ring, by using a γ-butyrolactone as a chiral template, which was diastereoselectively alkylated in the stereochemical key step, and then formed the chiral biaryl unit with internal asymmetric induction. Koga and coworkers described two different asymmetric pathways, both via the lactone intermediate (*S*)-**403**, which was obtained in a three-step procedure starting from L-glutamine [(*S*)-**402**] in 49% yield (Schemes 61and 62).[307] The *O*-benzyl ether derivative of the lactone enolate of (*S*)-**403** was condensed with the aldehyde **404** giving the (*E*)-alkene (*S*)-**405** in 84% yield (Scheme 61).[308,309] Hydrogenation of the double bond of (*S*)-**405** occurred mainly from the *Re*-face, as a consequence of a 1,3-asymmetric induction by the stereogenic center in the γ-lactone, yielding the (*S*)-configured lactone (*S*,*S*)-**406** in nearly quantitive yield and 64% de. Reductive opening of the lactone, followed by oxidative glycol cleavage using $NaIO_4$, and Collins oxidation translocated the carbonyl function in the newly formed lactone (*S*)-**407** to the previous γ-position (56% yield). Diastereoselective alkylation with 3,4,5-trimethoxybenzylbromide (**408**) took place from the less-hindered *Si*-face, giving (+)-deoxypodorhizon [(*S*,*S*)-**409**] in 11 steps and 15% overall yield. After recrystallization, optically pure material was obtained.

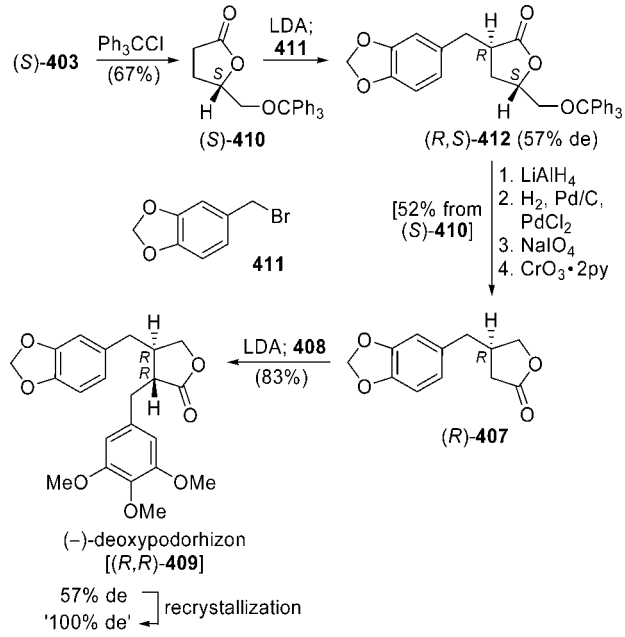
Another strategy (Scheme 62), also using the 1,3-induction of the stereocenter at the γ-position of the lactone ring, comprised the alkylation of the anion of the *O*-trityl protected chiral template (*S*)-**410** with piperonylbromide (**411**), giving (*R*,*S*)-**412** in 57% de.[309,310] A formal carbonyl displacement was achieved by reduction of the lactone, hydrogenolytic removal of the trityl-protecting group, oxidative cleavage of the 1,2-diol unit, and oxidation of the resulting hemiacetal intermediate. According to the reaction sequence described above (see Scheme 61), the lactone (*R*)-**407** was converted

Scheme 61

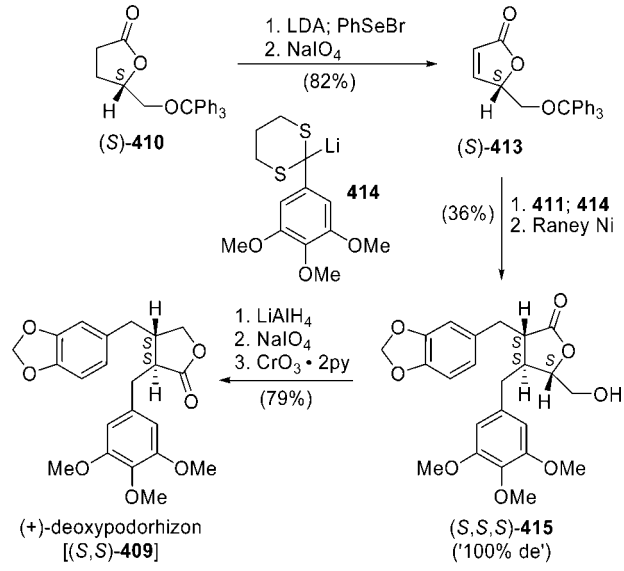


to (−)-deoxypodorhizon [(*R*,*R*)-**409**]. The two approaches impressively demonstrate that it is possible to get either of the two enantiomers, (+)-(*S*,*S*)- and (−)-(*R*,*R*)-**409**, atropoenantiodivergently from the same chiral precursor (*S*)-**403**. A very similar approach toward both (+)- and (−)-steganacin [(*P*)- and (*M*)-**401**] is based on a 1,2-asymmetric induction in the diastereoselective addition to the chiral butenolide (*S*)-**413** (Scheme 63).[311,312] For this purpose, the *O*-trityl protected lactone (*S*)-**410** was transformed into (*S*)-**413** by addition of phenylselenium bromide to the α-position of the lactone

Scheme 62

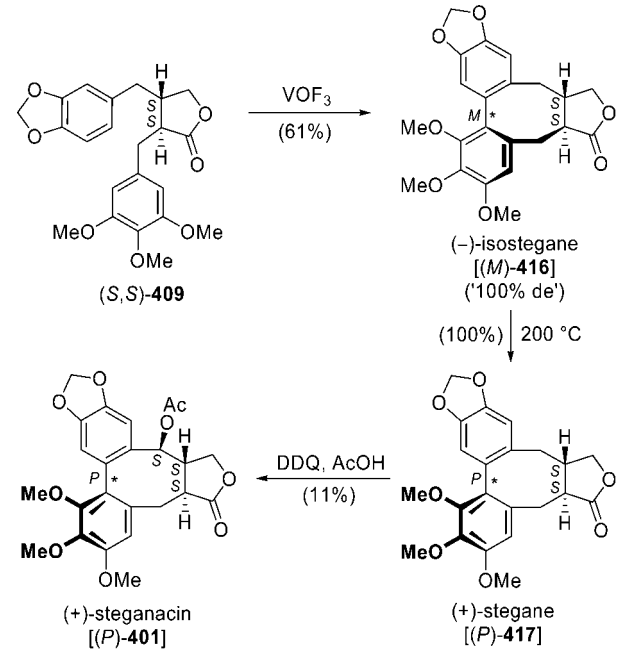


Scheme 63

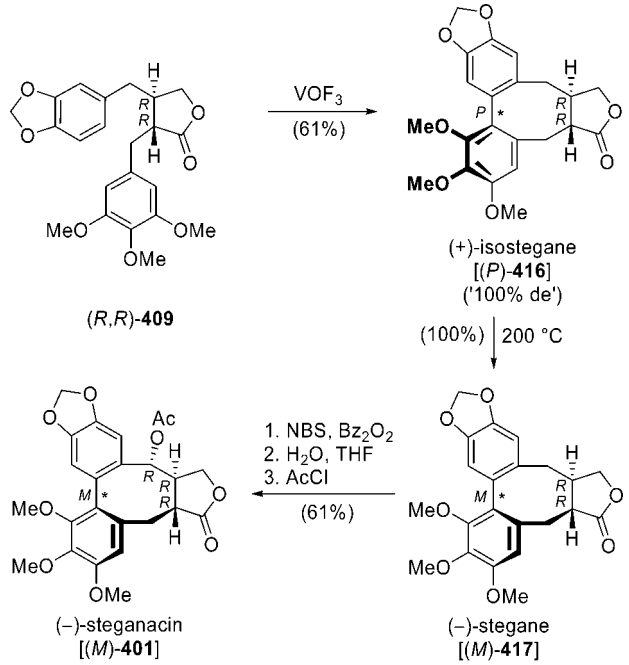


followed by oxidative elimination (82% yield). Michael addition of the lithiated thioacetal **414** occurred from the less-hindered *Si*-face of the lactone (*S*)-**413**, and the in situ formed enolate anion was, in turn, trapped by piperonylbromide (**411**, see Scheme 62), this time *anti* relative to the newly generated stereogenic center, furnishing only one diastereomer, (*S*,*S*,*S*)-**415**, in 36% yield over the last three steps. "Shifting" of the lactone carbonyl function as described above (see Scheme 61) resulted in (+)-deoxypodorhizon [(*S*,*S*)-**409**] in three further steps (79% yield). For the synthesis of unnatural (+)-steganacin [(*P*)-**401**], Koga and co-workers[312] applied the nonphenolic, intramolecular biaryl coupling of (*S*,*S*)-**409** (Scheme 64), as developed earlier by Schlessinger and co-workers,[313] for racemic material. (−)-Isostegane [(*M*)-**416**] was obtained as the (*M*)-configured product exclusively in 61% yield, evidencing a strong intramolecular asymmetric induction by the chiral lactone tether. That this impressive diastereoselectivity is the result of merely kinetic control can be seen from the fact that isomerization at the biaryl axis to the thermodynamically more stable (*P*)-diastereomer (+)-

Scheme 64



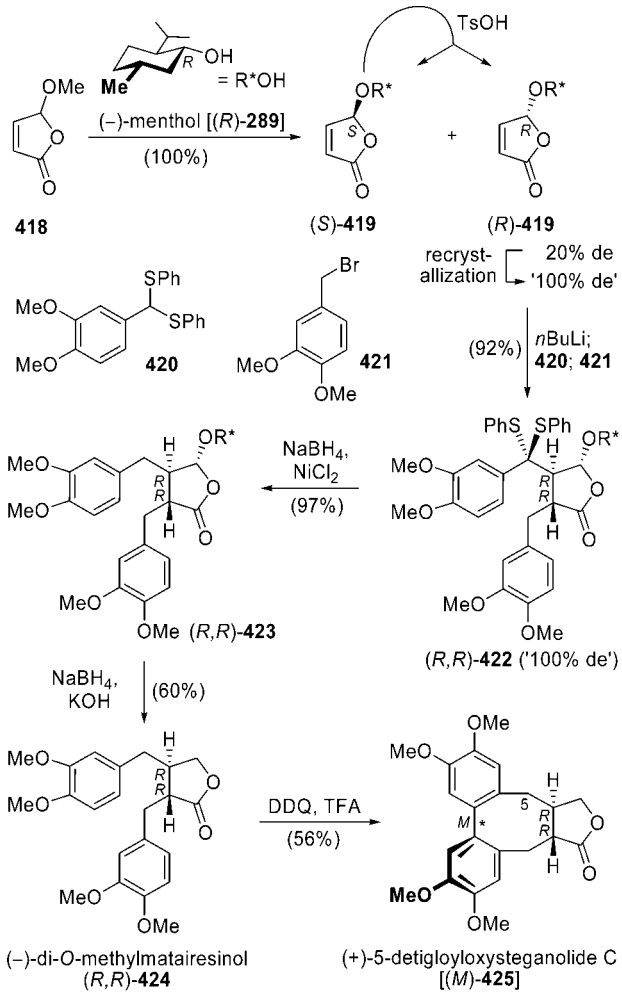
Scheme 65



stegane [(*P*)-**417**] was achieved in quantitative yield by heating at 200 °C. Oxidation of (*P*)-**417** at the benzylic position using DDQ[314] completed the first stereoselective total synthesis of (+)-steganacin [(*P*)-**401**], albeit in a very low yield (7% over the last three steps). Comparison of the natural product[60] with synthetic (+)-steganacin [(*P*)-**401**] showed an opposite sign of the optical rotation value. On the basis of this fact, the incorrect previous assignment of the absolute configuration of the natural product was revised.[312]

To firmly prove the newly established absolute configuration of natural (−)-steganacin [(*M*)-**401**], Koga and co-workers synthesized the enantiomer (*M*)-**401** now starting from (−)-deoxypodorhizon [(*R*,*R*)-**409**, Scheme 65].[312] Oxidative biaryl coupling using VOF_3 and subsequent thermal isomerization of the axis led to (−)-stegane [(*M*)-**417**] in the same chemical and optical yields as described before (see

Scheme 66

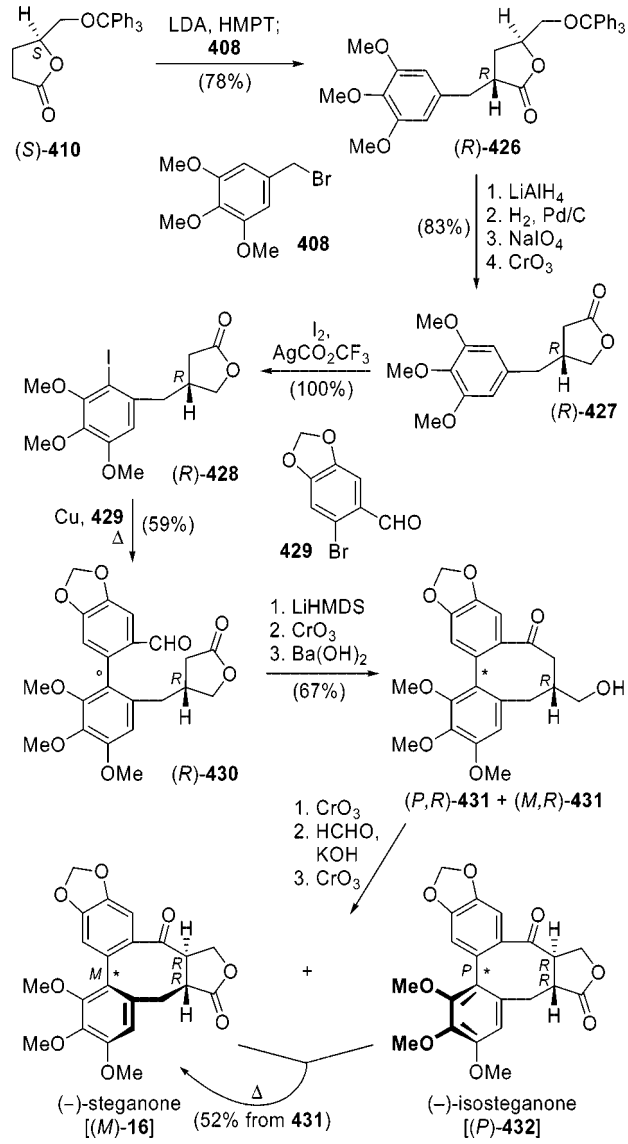


Scheme 64). Bromination followed by an S_N2-type bromine−hydroxy exchange provided the (*R*)-configured stereo center at the benzylic position. Final *O*-acetylation gave (−)-steganacin [(*M*)-**401**], with the same sign of the optical rotation as the natural product, in an overall yield of 37% from (*R*,*R*)-**409**.[60]

Starting from the commercially available racemic butenolide **418**, Pelter, Ward, and co-workers developed another efficient and straightforward synthetic pathway toward lignans, again by applying a tandem addition/alkylation procedure (Scheme 66).[315] The chiral information was introduced by the formation of the menthyloxy butenolide (*R*)-**419** in 20% de. The two diastereomers were separated by recrystallization and the undesired product (*S*)-**419** was reequilibrated and crystallized again.[316] Lithiation of the thioacetal **420**, Michael addition to (*R*)-**419**, and trapping of the in situ formed enolate with the benzyl bromide **421** gave *trans* (*R*,*R*)-**422** as the only diastereomer in 92% yield. Desulfurization using $NaBH_4$ and $NiCl_2$ yielded (*R*,*R*)-**423** in almost quantitative yield. Removal of the chiral menthyloxy auxiliary under reductive conditions led to the lignan (−)-di-*O*-methylmatairsinol [(*R*,*R*)-**424**], which was oxidatively coupled to complete the synthesis of (+)-5-detigloyloxysteganolide C [(*M*)-**425**].

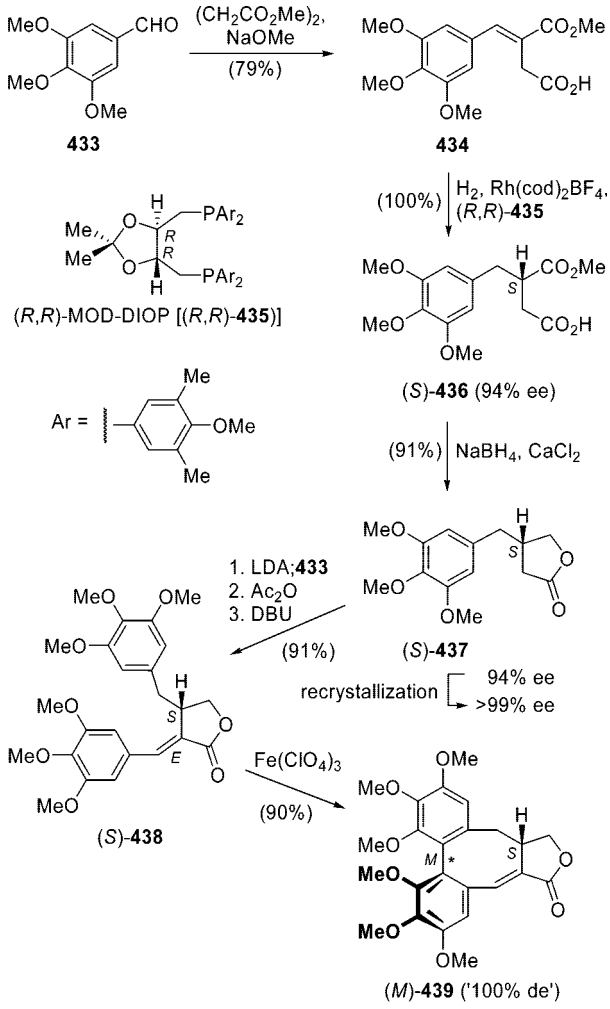
In parallel to Koga's group (see Scheme 62), Brown, Robin and co-workers[317] described the asymmetric synthesis of (−)-steganone [(*M*)-**16**], also starting from the chiral lactone (*S*)-**410**,[307] but using a classical Ullmann coupling (Scheme 67). Applying Kogas's "self-immolative" tech-

Scheme 67

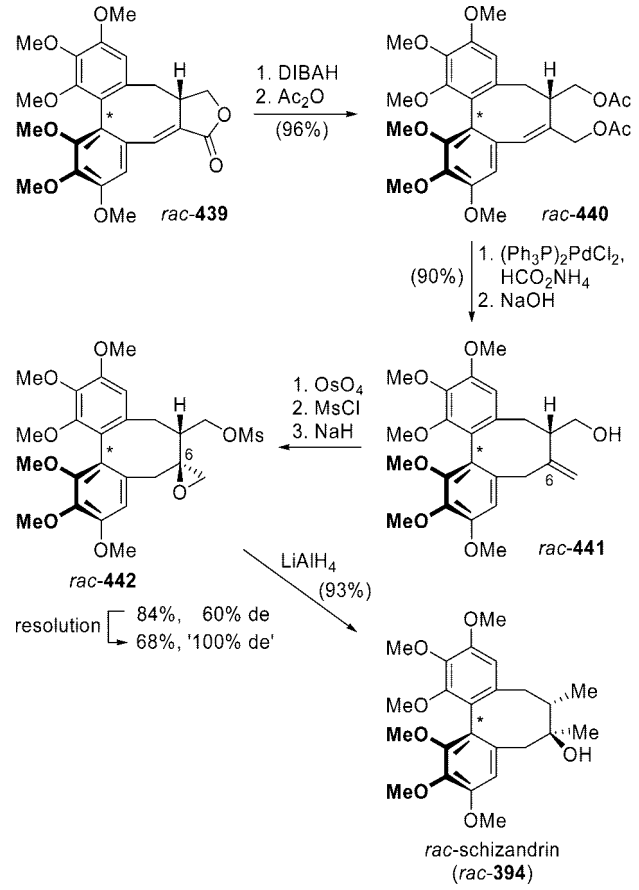


nique,[310] alkylation of the enolate of (*S*)-**410** with **408** followed by translocation of the carbonyl function (see Scheme 62) delivered (*R*)-**427** as a single enantiomer in 83% yield. After regioselective iodination of the aromatic ring, (*R*)-**428** was subjected to an Ullmann reaction with the bromo benzaldehyde **429**, to give the biaryl (*R*)-**430** (59% yield) bearing a rotationally unstable biaryl axis. Intramolecular aldol condensation of the lactone enolate with the aldehyde function furnished the required eight-membered ring. This raised the rotational barrier at the biaryl axis, so that the alcohols (*M*,*R*)-**431** and (*P*,*R*)-**431**, which were prepared in 67% over the last three steps by subsequent oxidation and decarboxylation, were obtained as a mixture of (separable) atropodiastereomers. The lactone functionality was reinstalled by Jones oxidation, hydroxymethylation, and oxidative lactonization. Thermal isomerization of the biaryl axis quantitively converted the initially resulting mixture of (+)-isosteganone [(*P*)-**432**] and (−)-steganone [(*M*)-**16**] into the pure (*M*)-isomer (−)-steganone [(*M*)-**16**, 52% yield]. This synthetic pathway constituted the first total synthesis of (*M*)-**16**, which, together with the synthesis of (−)-steganacin [(*M*)-**401**] by Koga and co-workers[312] (see Scheme 65), confirmed the absolute configuration of the natural product. Wakamatsu, Tanaka, and co-workers[318,319] showed that the methodology

Scheme 68



Scheme 69



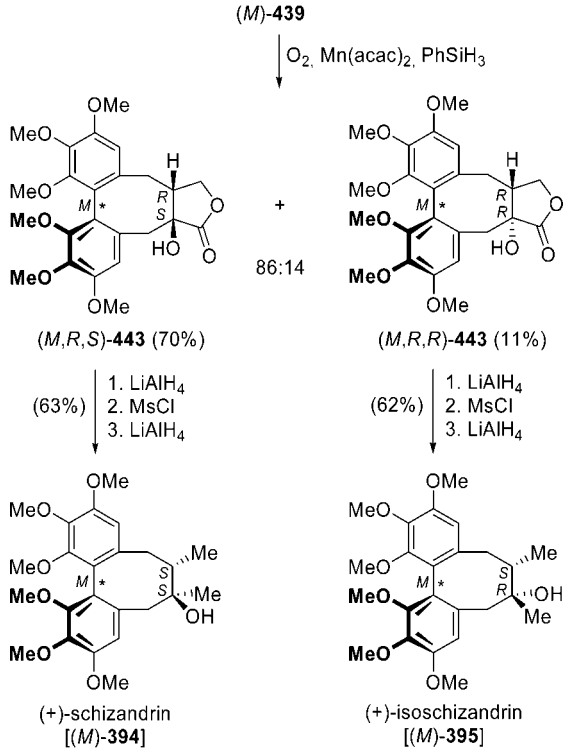
of using a butyrolactone as a chiral template is also applicable to the total synthesis of other lignans, even if devoid of a lactone ring. In the syntheses of (+)-schizandrin [(*M*)-**394**], (+)-isoschizandrin [(*M*)-**395**], and (+)-gomisin A [(*M*)-**447**; for the structures see Figure 16 and Scheme 71], the enantiomerically pure bridged biaryl (*M*)-**439** was used as a key intermediate (Scheme 68). Stobbe condensation of dimethyl succinate with the benzaldehyde **433** delivered the itaconic acid derivative **434** (79% yield), which was enantioselectively hydrogenated using a rhodium catalyst with (*R*,*R*)-MOD-DIOP [(*R*,*R*)-**435**] as the chiral ligand, quantitatively affording the succinate (*S*)-**436** in an excellent 94% ee.[306] Reductive ring closure gave (*S*)-**437**, which was recrystallized to provide enantiomerically pure material and subjected to a three-step aldol condensation sequence with 3,4,5-trimethoxybenzaldehyde (**433**) to provide the (*E*)-benzylidene lactone (*S*)-**438** in 91% yield. In the oxidative biaryl coupling reaction, the highest yields in combination with a short reaction time and a cheap oxidation reagent were achieved with $Fe(ClO_4)_3$,[319] delivering the (*M*)-configured biaryl lactone (*M*)-**439**, in 90% yield and with a complete central-to-axial chirality transfer.

The first route to schizandrin (**394**)[319] was performed with racemic **439**, but should also be applicable to enantiomerically pure material and is, therefore, discussed here. After quantitative cleavage of the lactone ring of *rac*-**439** with DIBAH, the resulting allylic diol was bis-*O*-acetylated to give *rac*-**440** in 96% yield (Scheme 69). Palladium-catalyzed Tsuji reduction of the allyl acetate moiety followed by alkaline hydrolysis afforded the *exo*-methylene compound *rac*-**441** (90% yield). The oxygen function at C6 was introduced by dihydroxylation of the double bond with OsO_4, *O*-mesylation of the primary hydroxy functions, and epoxide formation with NaH, furnishing *rac*-**442** as a 4:1 mixture of the C6-epimers. Resolution of the diastereomers by column chromatography and reduction with $LiAlH_4$ provided racemic schizandrin (*rac*-**394**) in overall eight steps and 55% yield from *rac*-**439**.

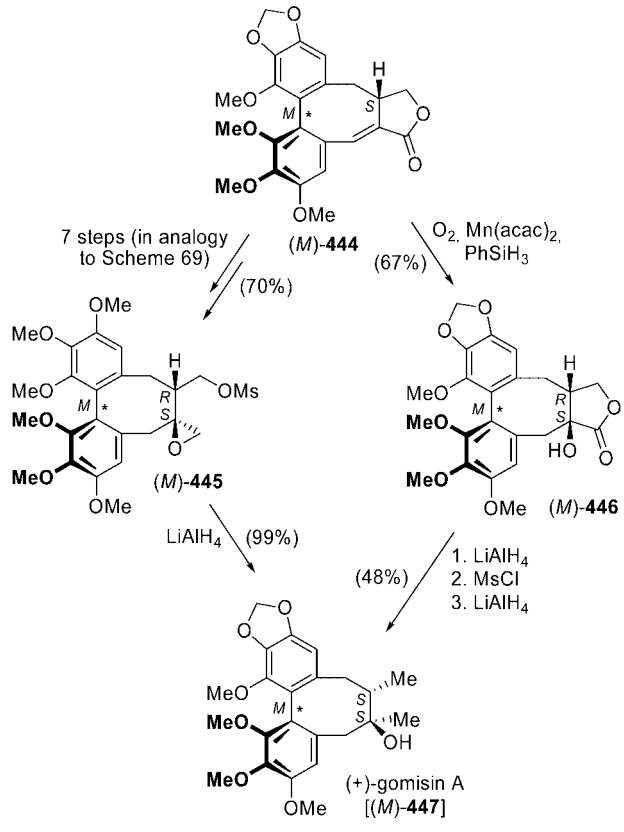
Because this route was lengthy [eight steps from (*M*)-**439**] and suffered from the low stereoselectivity of the introduction of the hydroxy function at C6, Wakamatsu, Tanaka, and co-workers explored several other approaches to (now enantiomerically pure) (+)-schizandrin [(*M*)-**394**].[319] The shortest synthesis of (*M*)-**394** from (*M*)-**439** is shown in Scheme 70.[319] Formal addition of water to the endocyclic double bond in (*M*)-**439** according to the Mukaiyama protocol[320] provided an 86:14 mixture of the diastereomeric alcohols (*M*,*R*,*S*)-**443** and (*M*,*R*,*R*)-**443**, which were separated by column chromatography. The major isomer, (*M*,*R*,*S*)-**443**, was transformed into the natural product by a three-step reduction of the lactone moiety into two methyl groups. Even though this route required just four steps from the key intermediate (*M*)-**439** and although the hydroxylation of C6 occurred with a better diastereoselectivity as compared to the former (racemic) approach, the overall yield was lower (44% vs 55%). (+)-Isoschizandrin [(*M*)-**395**] was obtained in an analogous way from the minor diastereomer, (*M*,*R*,*R*)-**443**.

Wakamatsu, Tanaka, and co-workers also applied the two synthetic pathways toward (*M*)-**394** (see Schemes 68−70) to the preparation of the closely related lignan (+)-gomisin A [(*M*)-**447**],[319] which differs from (+)-schizandrin [(*M*)-

Scheme 70

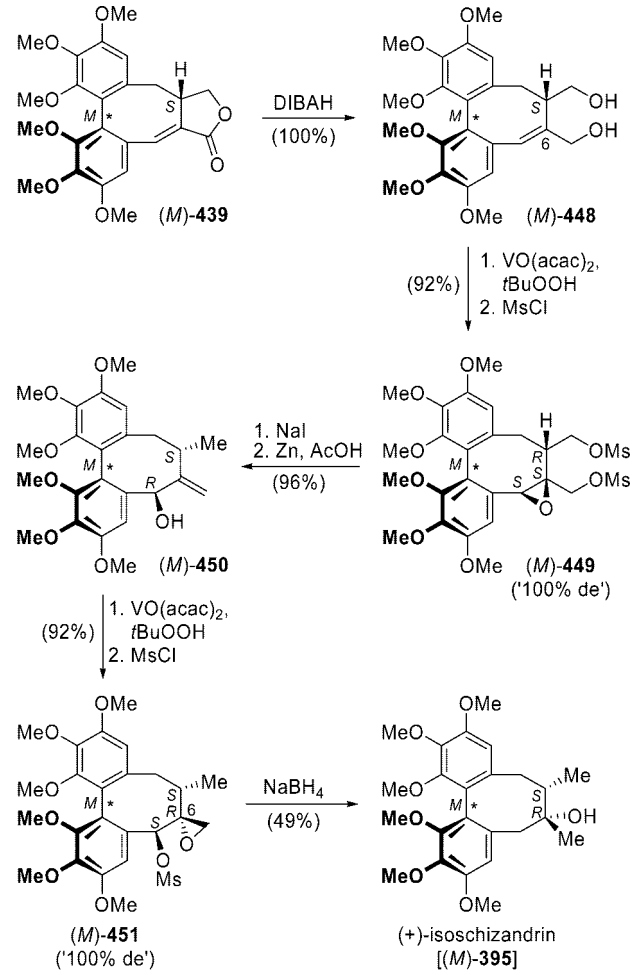


Scheme 71



394] only in the substitution pattern of the "northern" aryl moiety (Scheme 71). The natural product (*M*)-**447** was thus accessible from (*M*)-**444** either in eight steps (69% yield) via the epoxide (*M*)-**445** or via the α-hydroxy lactone (*M*)-**446**, with an overall yield of 32% (four steps). For the directed synthesis of (+)-isoschizandrin [(*M*)-**395**], which had already been obtained as a minor product in the

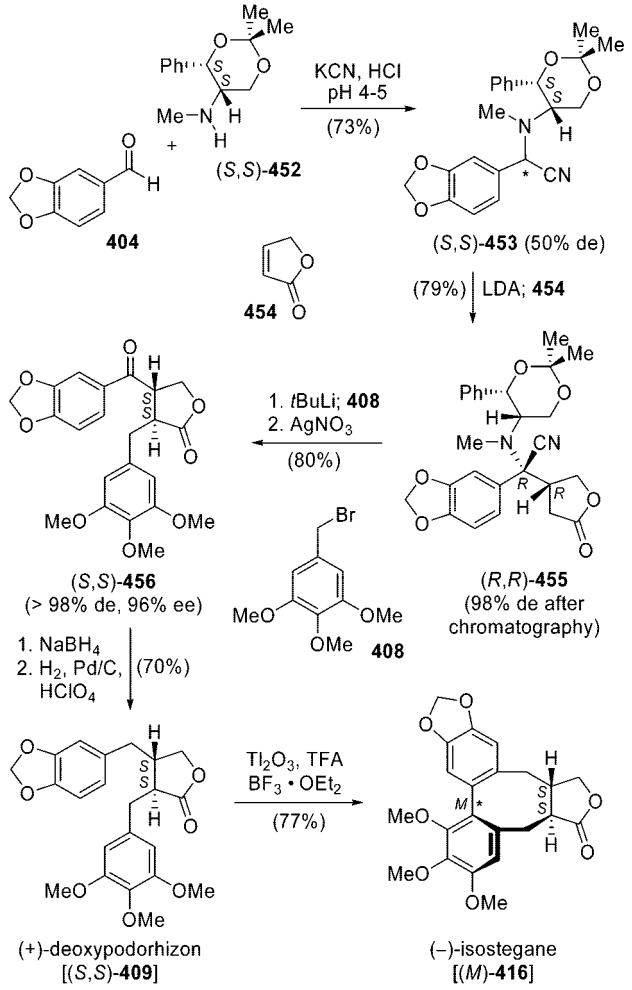
Scheme 72



preparation of (+)-schizandrin [(*M*)-**394**, see Scheme 70)], the OH function at C6 had to be introduced with the opposite configuration (Scheme 72).[319] For this reason, after quantitative reductive cleavage of the lactone ring of (*M*)-**439**, the double bond of the resulting diol (*M*)-**448** was diastereoselectively epoxidized with $VO(acac)_2$ and *t*BuOOH and *O*-mesylated, providing only compound (*M*)-**449** in 92% yield. Mesyloxy−iodine exchange followed by reductive elimination of the iodine with concomitant opening of the epoxide resulted in the exocyclic alkene (*M*)-**450**. Renewed diastereoselective epoxidation using $VO(acac)_2$ and *t*BuOOH, now of the exocyclic double bond, followed by *O*-mesylation, gave (*M*)-**451** in 92% yield as a single diastereomer. Molecular-mechanics calculations suggested that the excellent diastereoselectivity of this epoxidation step is due to the preferred conformation of the eight-membered ring of (*M*)-**450**, with the benzylic hydroxy group below the plane of the double bond, which directs the epoxidation reagent to the *Si*-face of the ene function, thus resulting in the desired (*S*)-configuration at C6. Final reductive epoxide cleavage and benzylic deoxygenation provided (+)-isoschizandrin [(*M*)-**395**] in 15 steps from **433** (see Scheme 68) and with an overall yield of 24%.

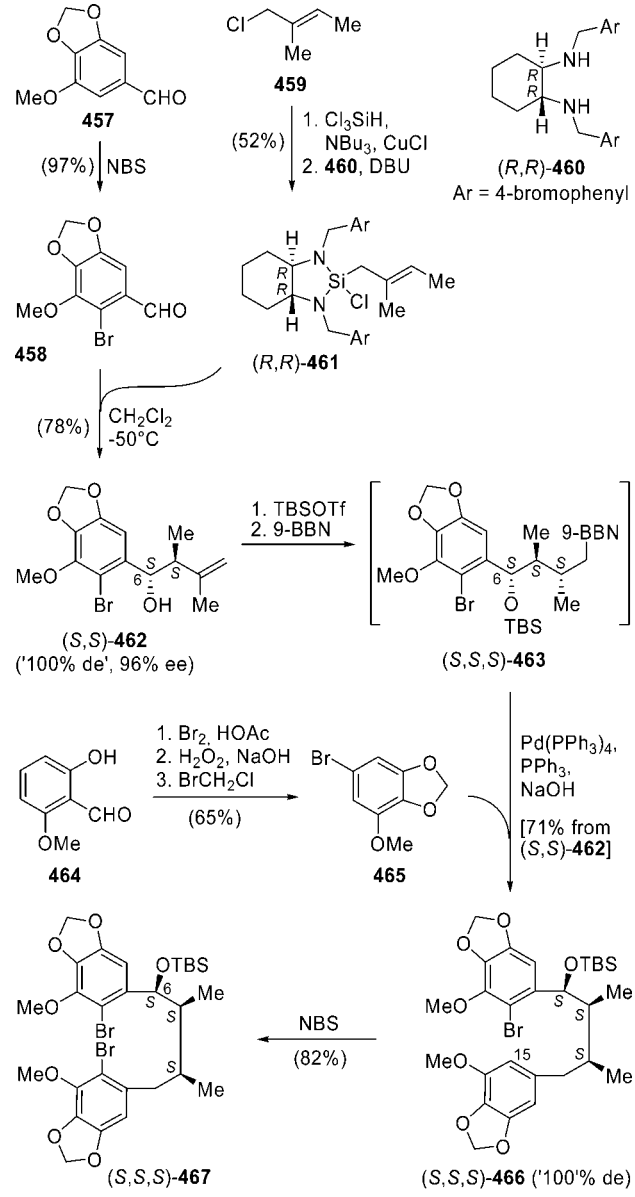
In 2002, Enders et al.[321] described a synthetic pathway toward the lignan (−)-isostegane [(*M*)-**416**] via the α-aminonitrile (*S*,*S*)-**453** (Scheme 73), which is accessible by an asymmetric Strecker reaction[321] from piperonal (**404**) and the optically pure secondary amine (*S*,*S*)-**452**,[321] in 73% yield and 50% de. Lithiation of (*S*,*S*)-**453** and Michael addition to furan-2(5*H*)-one (**454**) gave the 1,4-adduct (*R*,*R*)-**455** in

Scheme 73



79% chemical yield and 98% de, after enrichment of the *like*-diastereomer by column chromatography. After deprotonation of the butyrolactone (*R*,*R*)-**455** with *t*BuLi, the electrophilic addition of 3,4,5-trimethoxybenzylbromide (**408**) occurred *trans* to the amino nitrile moiety, exclusively. Oxidative cleavage of the chiral auxiliary succeeded without loss of stereochemical purity (>98% de, 96% ee), giving the 2,3-disubstituted γ-butyrolactone (*S*,*S*)-**456**. Formation of the dibenzylbutyrolactone (+)-deoxypodorhizon [(*S*,*S*)-**409**] was achieved by reduction of the keto function to the corresponding alcohol followed by its catalytic hydrogenolysis. Oxidative (*M*)-atropodiastereoselective biaryl coupling using Tl_2O_3 and $BF_3 \cdot EtO_2$ completed the short (seven steps) and highly efficient (25% overall yield) synthesis of the lignan (−)-isostegane [(*M*)-**416**]. More recently, Coleman and coworkers reported on their first asymmetric total syntheses of interiotherin A [(*P*)-**399**], angeloylgomisin R [(*P*)-**400**], gomisin O [(*P*)-**475**], and gomisin E [6-*epi*-gomisin O; (*P*)-**474**] using an atroposelective intramolecular biaryl coupling with a cyclooctane bridge as the chiral template.[322,323] The preparation of (*P*)-**399** and (*P*)-**400** started with myristinaldeyde (**457**), which was regioselectively brominated to give **458** in 97% yield (Scheme 74). For the asymmetric construction of the side chain between the two aryl portions (i.e., the "eastern" part of the latter cyclooctane ring in the natural products), a diastereo- and enantioselective methylcrotonylation of **458** was used, with Leighton's diamine (*R*,*R*)-**461**[324] as the chiral reagent. This tiglylsilane amine was prepared in two steps from tiglylchloride **459** and the

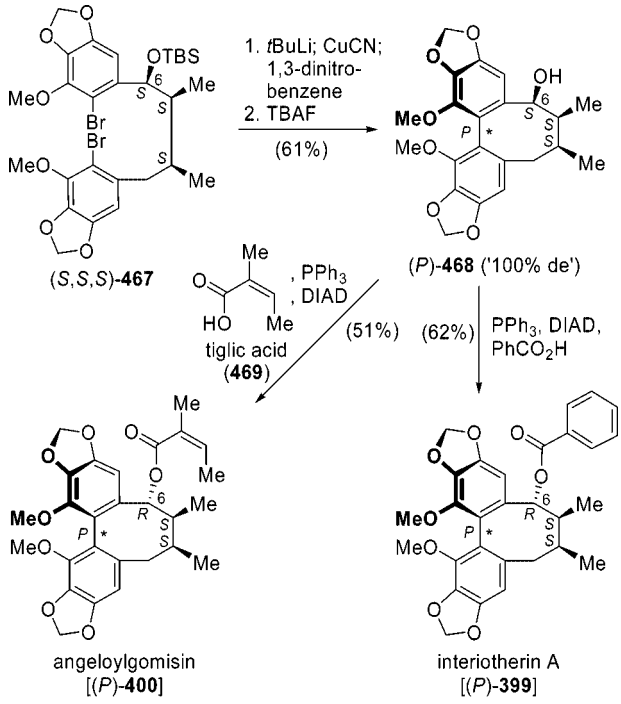
Scheme 74



diamine (*R*,*R*)-**460**. Enantioselective addition of (*R*,*R*)-**461** to the bromoaldehyde **458** at low temperatures proceeded in good chemical yields (78%) and excellent enantio- (96% ee) and diastereoselectivities (100% de), giving the *anti*-configured stereoisomer (*S*,*S*)-**462** exclusively. After protection of the hydroxy function at C6 of alkene (*S*,*S*)-**462** as a silyl ether, hydroboration using 9-BBN occurred with complete diastereofacial selectivity. The intermediate trialkylborane (*S*,*S*,*S*)-**463** was reacted in situ under standard Suzuki−Miyaura coupling conditions with bromide **465**, obtained in three steps and 65% yield from *ortho*-vanillin (**464**).[325] This domino hydroboration/cross-coupling sequence provided 1,4-diarylbutane (*S*,*S*,*S*)-**466** in 72% yield and as a single diastereomer. Subsequent regioselective bromination at C15 furnished the coupling precursor (*S*,*S*,*S*)-**467** in 82% yield.

The biaryl coupling of the dibromo compound (*S*,*S*,*S*)-**467**, with formation of the characteristic eight-membered ring, was accomplished using Lipshutz' protocol (Scheme 75).[322,323] Bislithiation and in situ treatment with CuCN at low temperatures followed by smooth oxidation and deprotection of the alcohol function at C6 gave (*P*)-**468** in 61%

Scheme 75



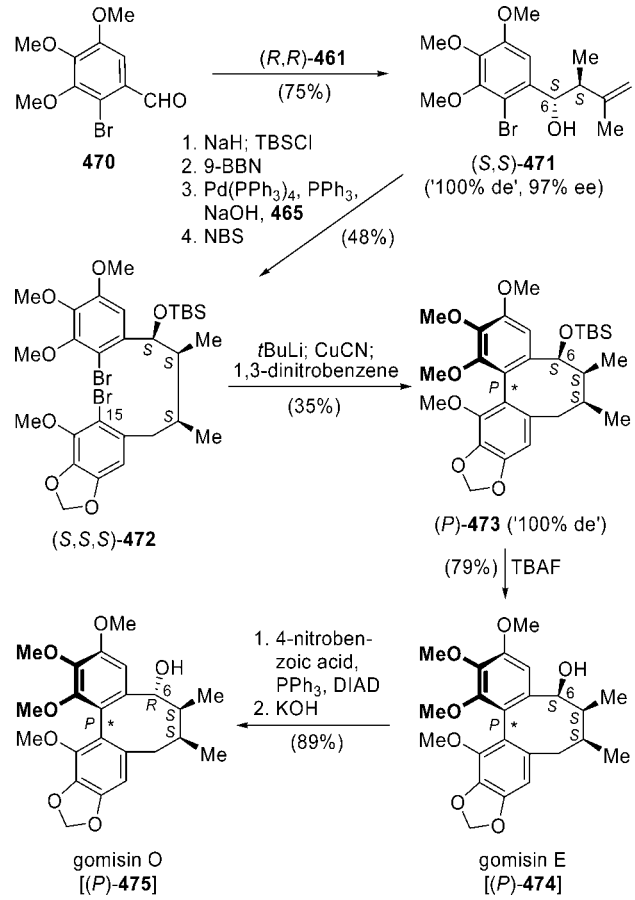
yield and as a single atropodiastereomer. Esterification with tiglic acid (**469**) and benzoic acid under Mitsunobu conditions yielded the natural products interiotherin A [(*P*)-**399**] and angeloylgomisin [(*P*)-**400**], respectively, in nine steps and 17% and 14% overall yields from **457**.

The same approach was also used by Coleman and coworkers for the preparation of two other dibenzocyclooctadiene lignans, gomisins E [i.e., 6-*epi*-gomisin O, (*P*)-**474**] and O [(*P*)-**475**] (Scheme 76).[323] Starting from the benzaldehyde **470**, the butenyl side chain of (*S*,*S*)-**471** was attached diastereo- and enantioselectively by addition of the enantiopure tiglylsilyl reagent (*R*,*R*)-**461** (see Scheme 74). The coupling precursor (*S*,*S*,*S*)-**472** was obtained in four steps and 48% yield by protection of the benzylic OH group as a silyl ether, hydroboration/Suzuki−Miyaura reaction, and regioselective bromination of the "southern" aromatic ring *ortho* to the methoxy function. Intramolecular copper-catalyzed cross-coupling of (*S*,*S*,*S*)-**472** gave the biaryl (*P*)-**473** in a low 35% yield, but with complete central-to-axial chirality transfer. Deprotection of the hydroxy substituent at C6 provided the natural product gomisin E [(*P*)-**474**] in 79% yield. Mitsunobu inversion of the stereogenic center at C6 using 4-nitrobenzoic acid as the *O*-nucleophile followed by saponification delivered gomisin O [(*P*)-**475**] in overall nine steps and 9% yield from **470**.

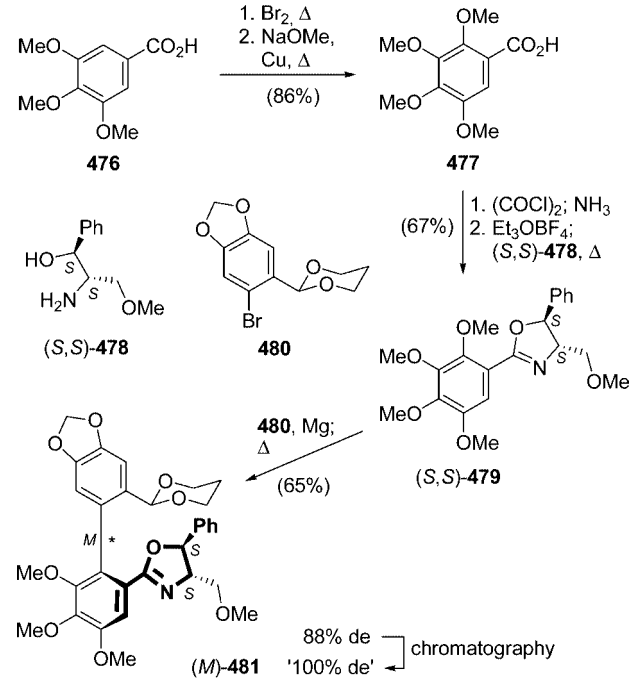
The first example of an atroposelective intermolecular aryl−aryl bond formation, prior to the construction of the central cyclooctadiene moiety, was published by Meyers et al. in 1987.[326] This route toward the dibenzocyclooctadiene lignan (−)-steganone [(*M*)-**16**] involved a highly stereoselective aryl−aryl coupling step but suffered from the occurrence of intermediates with low atropisomerization barriers, which resulted in a partial loss of optical purity even with careful handling (see Schemes 77 and 78). These drawbacks were addressed in the later syntheses of (*M*)-**16** by the groups of Uemura[205,327] (Scheme 79) and Molander (Scheme 80).[328]

Meyers' synthesis[326] of (−)-steganone [(*M*)-**16**] started with 3,4,5-trimethoxybenzoic acid (**476**), which was converted into the tetramethoxybenzoic acid **477** by bromination and copper-mediated displacement of the bromo substituent by a methoxy group (Scheme 77). The oxazoline substituent in (*S*,*S*)-**479**, which served as the chiral inductor in the following biaryl bond formation, was constructed from **477** and the chiral β-amino alcohol (*S*,*S*)-**478** in two steps. Applying the nucleophilic substitution strategy (see section 2.3),

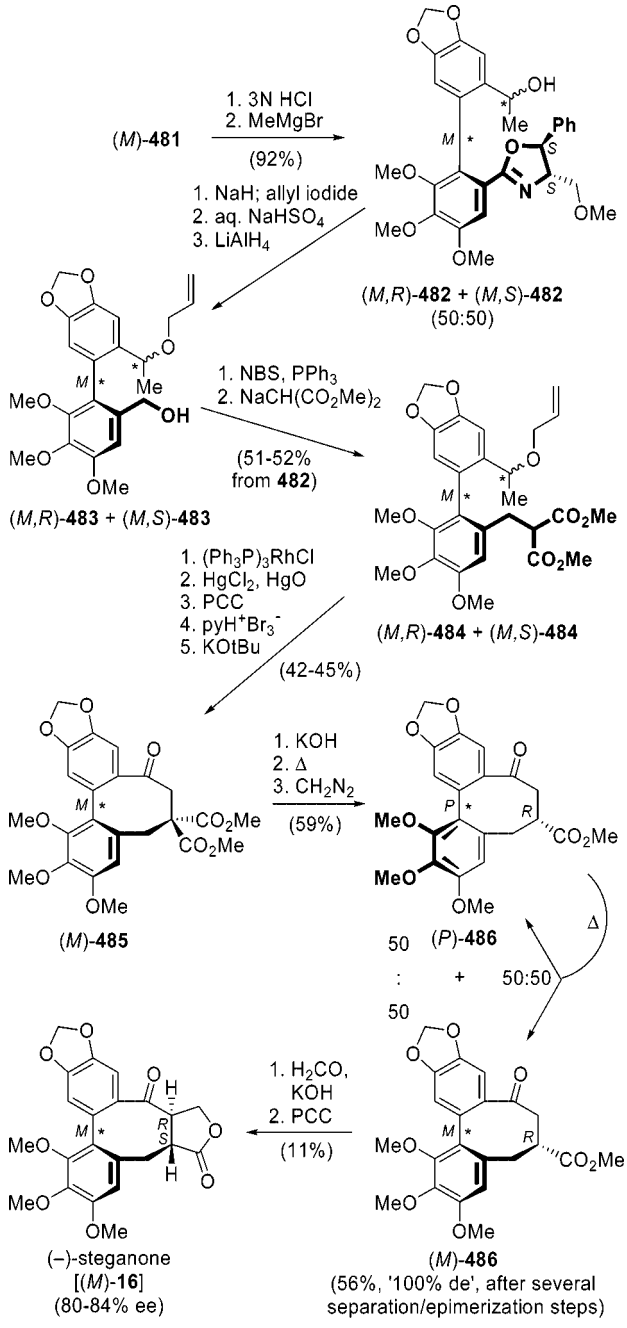
Scheme 76



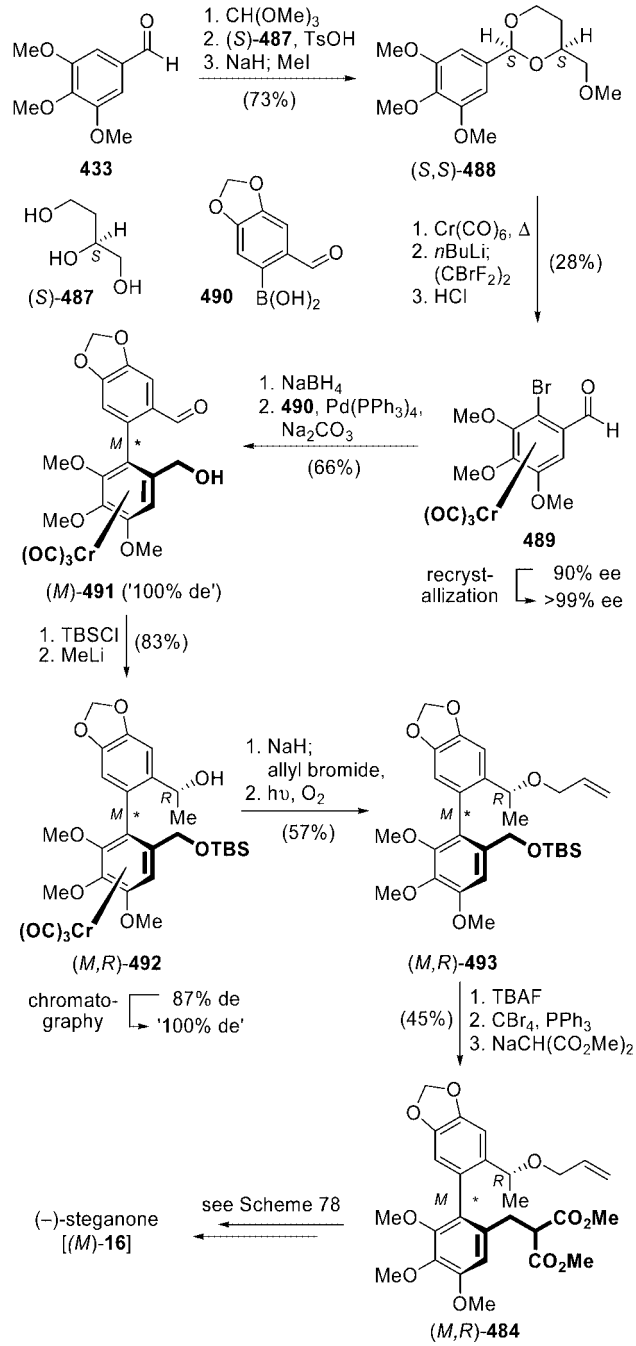
Scheme 77



Scheme 78



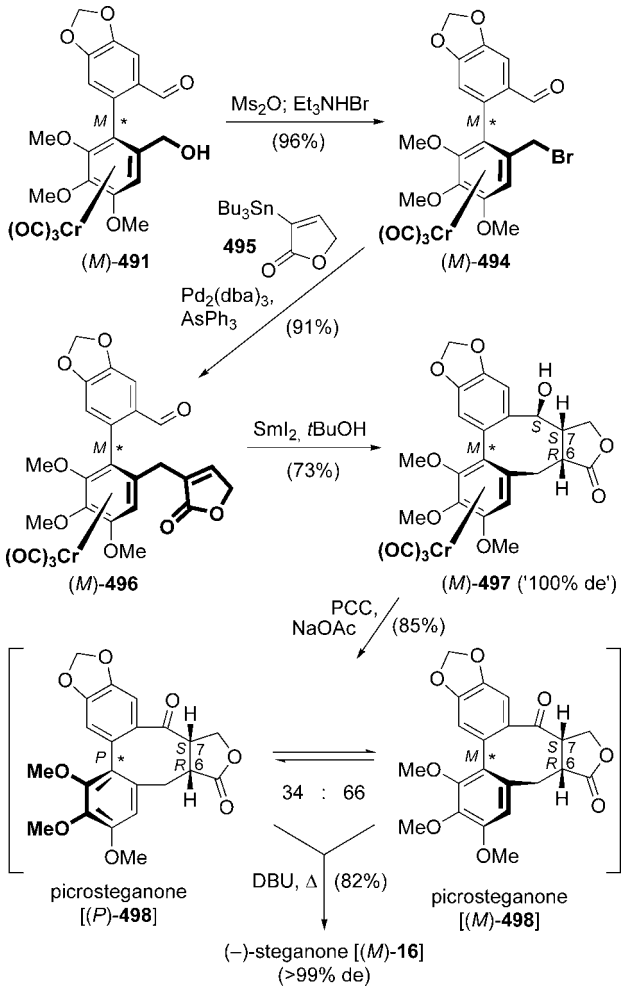
Scheme 79



the *ortho*-methoxy group of (*S*,*S*)-**479** was replaced by an aryl substituent using the respective Grignard reagent (generated in situ from the aryl bromide **480** and magnesium[329,330]), to give the configurationally stable biphenyl (*M*)-**481** in 65% yield and good 88% de. Stereochemically homogeneous (*M*)-**481** was obtained after column chromatography.

Further functionalization of the enantiopure biaryl (*M*)-**481** had to be performed very carefully in order to avoid any unwanted epimerization at the aryl−aryl bond, which would lead to atropisomeric mixtures. Since carbonyl groups next to the biaryl axis can significantly lower the rotational barrier,[77,330] the acetal group in (*M*)-**481** had to be cleaved at −5 °C and the resulting, configurationally semistable aldehyde was immediately reacted with methylmagnesium bromide to afford the alcohol (*M*)-**482** as a 50:50 mixture of epimers with respect to the benzylic stereogenic center (Scheme 78). Even though the diastereomers (*M*,*R*)-**482** and (*M*,*S*)-**482** were separately carried through the next steps, the occurrence of stereoisomeric products was not of relevance since the benzylic stereogenic center was destroyed in one of the following steps anyhow, thus permitting recombination of the two fractions at the stage of the intermediate (*M*)-**485**. After protection of the alcohol functions in (*M*,*R*)-**482** and (*M*,*S*)-**482** as allyl ethers, the oxazoline ring was hydrolyzed under mild conditions using aqueous sodium bisulfate. The ester formed was reduced with $LiAlH_4$ to afford the benzylic alcohols (*M*,*R*)-**483** and (*M*,*S*)-**483**. Hydroxy−bromine exchange followed by treatment with sodium dimethyl malonate delivered the esters (*M*,*R*)-**484** and (*M*,*S*)-**484** in 51−52% yield over the last five steps. To remove the allyl protective group, the two diastereomers of (*M*,*S*)-**484** were subjected to a Rh-catalyzed isomerization and hydrolysis of the resulting vinyl ether. The now solely axially chiral cyclic keto diester (*M*)-**485** was obtained in

Scheme 80



42−45% yield, by oxidation of the alcohol using PCC, immediate bromination in the α-position relative to the carbonyl group, and base-induced ring closure. Saponification of the methyl esters, thermal decarboxylation, and esterification with diazomethane diastereoselectively provided the (*R*)-configured ketoester **486** in 59% yield, albeit as a 50:50 mixture of the two atropodiastereomers (*M*)-**486** and (*P*)-**486**, due to thermal axial epimerization in the decarboxylation step. Although the previously established chiral information at the axis was lost, the yield of (*M*)-**486** could be raised to 56% by repeated chromatographic separation and thermal atropisomerization of the undesired diastereomer (*P*)-**486**. Final formation of the fused lactone ring by addition of formaldehyde in α-postion to the keto function and Jones oxidation (possibly for reinstalling the ketone function) proceeded in poor 11% yield, giving (−)-steganone [(*M*)-**16**] in 22 steps and <1% overall yield. Comparison of the optical rotation values of synthetic and natural (−)-steganone, however, indicated that some racemization had occurred in the course of the synthesis, leading to (*M*)-**16** with just 80−84% ee. The authors presume that the stereochemical homogeneity was lost in one of the last two steps of the preparation of (*M*)-**485**, in which nonbridged α-keto biaryls with a lowered configurational stability at the axis were involved.[331]

A second route to the chiral intermediate (*M*,*R*)-**484** of the Meyers synthesis (vide infra) and, thus, a formal total synthesis of (−)-steganone [(*M*)-**16**] was realized by Uemura and co-workers,[205,327] who utilized a Pd(0)-mediated cross-coupling reaction of a planar−chiral chromium complex as the stereochemical key step (Scheme 79). The preparation of the enantiopure precursor **489** started with 3,4,5-trimethoxybenzaldehyde (**433**), which was converted into its dimethyl acetal. *trans*-Acetalization with (*S*)-1,2,4-butanetriol [(*S*)-**487**] and *O*-methylation affored solely the 1,3-diequatorially substituted dioxane (*S*,*S*)-**488** in 73% yield. Thermal complexation of $Cr(CO)_6$ to (*S*,*S*)-**488** set the stage for a diastereotopos-differentiating *ortho*-lithiation−bromination sequence, which, after acidic removal of the chiral auxiliary, provided the planar−chiral chromium complex **489** in low 28% yield. The enantiomeric excess of **489** was raised from 90% to >99% by recrystallization. Reduction of the aldehyde and Suzuki−Miyaura cross-coupling reaction with the phenyl boronic acid **490** atropodiastereoselectively produced the axially chiral biphenyl (*M*)-**491** in 66% chemical yield and with virtually complete stereocontrol. In contrast to the Meyers approach (see Scheme 78), the configurational stability of the biaryl axis in (*M*)-**491** is guaranteed by the steric demand of the bulky chromium group, despite the presence of a neighboring aldehyde function. After *O*-TBS protection of the benzylic alcohol in (*M*)-**491**, the addition of methyllithium to the aldehyde occurred predominantly from the *Re*-face, thus providing the alcohol (*M*,*R*)-**492** in 83% yield and 87% de. *O*-Allylation of diastereomerically pure (*M*,*R*)-**492**, obtained by column chromatography, was followed by oxidative demetalation to furnish the biaryl (*M*,*R*)-**493** in 57% yield. Further functional group manipulations such as desilylation, Appel reaction, and substitution of the introduced bromide by dimethylmalonate led to (*M*,*R*)-**484**, the intermediate of the Meyers synthesis (see Scheme 78),[326] which can be transformed into (−)-steganone [(*M*)-**16**] in 10 further steps.

The main improvement of this synthesis was the introduction of the bulky chromium tricarbonyl moiety, which raised the rotational barrier of the biaryl axis, thus avoiding any epimerization during functional-group manipulations.

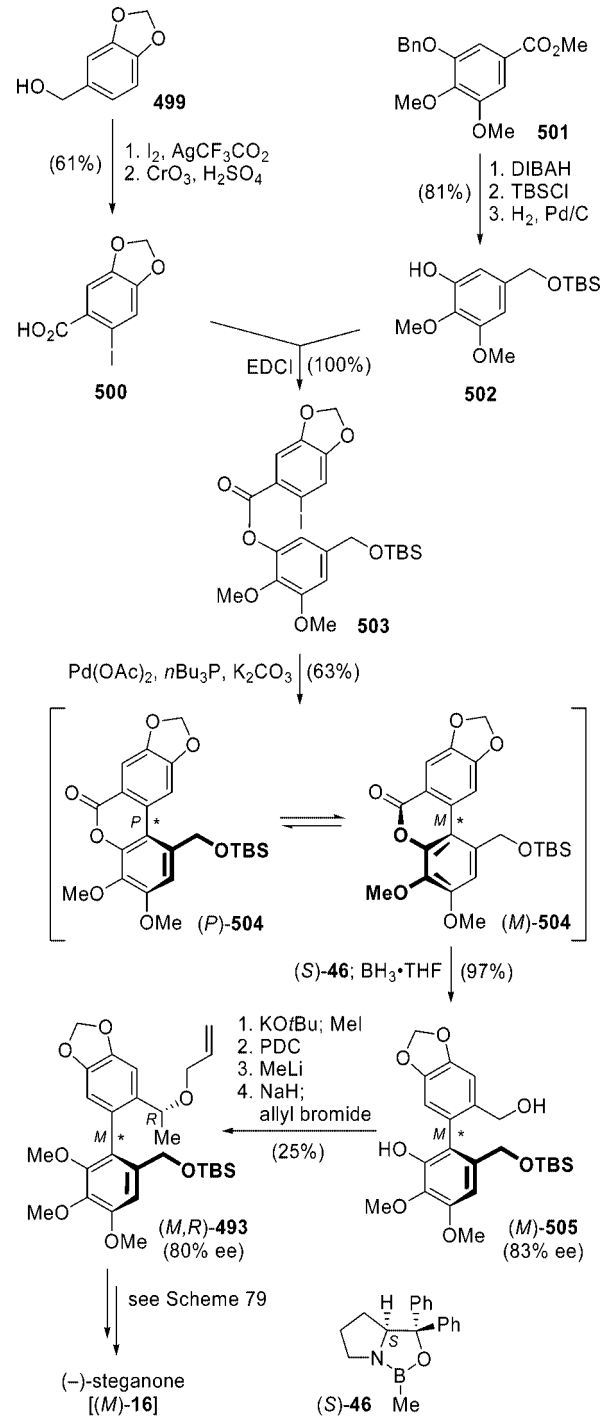
The remaining problem, the loss of optical purity in the late stages of Meyers' synthesis (see Scheme 78), was solved in 2000. Molander and co-workers[328] developed a novel sequence for the final steps to (−)-steganone [(*M*)-**16**], beginning with Uemura's configurationally stable biaryl-(chromium) complex (*M*)-**491**[205,327] (see Scheme 79). After transformation of the benzylic alcohol (*M*)-**491** into the corresponding bromide (*M*)-**494** (96% yield), the later butenolide moiety of (*M*)-**16** was introduced by a Stille coupling of (*M*)-**494** with the stannylated furanone **495**, giving (*M*)-**496** in excellent 91% yield. An 8-*endo* ketyl−olefin radical cyclization promoted by SmI_2 and with *t*BuOH as the proton source was used to construct the central cyclooctadiene core and delivered chromium-complexed isopicrosteganol (*M*)-**497** as a single diastereomer in 73% yield, albeit with a *cis*-array at the ring junctures C6 and C7. Decomplexation of the $Cr(CO)_3$ fragment and oxidation of the secondary alcohol to the corresponding ketone was accomplished in one pot with sodium acetate-buffered PCC, giving picrosteganone (**498**), which exists as a 34:66 mixture of its rapidly interconverting atropodiastereomers, (*M*)-**498** and (*P*)-**498**. The final conversion of **498** into its stereoisomer (−)-steganone [(*M*)-**16**] required an inversion of the stereocenter at C7, which, due to the larger rigidity of the *trans*-annelated γ-lactone ring in **16**, would also reestablish the "lost" axial configuration. Treatment of **498** with DBU in refluxing THF effected a smooth epimerization at C7 through

retro-Michael/Michael reactions, without affecting the stereocenter at C6, simultaneously fixing the chiral information at the biaryl axis, to give the thermodynamically most stable relative configuration, i.e., based on the fixed (*R*)-configuration at C6, (*M*,6*R*,7*R*), thus providing the natural product (*M*)-**16** in 82% yield and with excellent >99% ee. This approach, in combination with Uemura's synthesis of the biaryl(chromium) complex (*M*)-**491**,[205,327] constitutes a relatively short and highly efficient pathway (13 steps, 6% overall yield) to (−)-steganone [(*M*)-**16**], avoiding all problematic stereochemical leakages.

In 2004, Abe and co-workers[98,103] pursued an entirely different concept for their atroposelective formal total synthesis of (−)-steganone [(*M*)-**16**], based on Bringmann's lactone concept[95−98] (see section 2.3). For the preparation of the key lactone intermediate **504**, the precursors **500** and **502** were required (Scheme 81). Of these, **500** was available from the benzyl alcohol **499** by regioselective iodination and oxidation, while **502** was prepared from the benzoic ester **501** by reduction, *O*-TBS protection, and hydrogenolytic *O*-debenzylation. Linkage of the two building blocks **500** and **502** by esterification quantitatively afforded the phenylbenzoate **503**, which was submitted to an intramolecular Pd(II)-catalyzed aryl−aryl bond formation providing the rapidly interconverting lactones (*P*)-**504** and (*M*)-**504** in moderate 63% yield. Dynamic kinetic resolution of **504** by reductive ring-opening with borane in the presence of 3.0 equiv of the oxazaborolidine[106] (*S*)-**46** delivered the configurationally stable biaryl alcohol (*M*)-**505** in excellent 97% yield and with an acceptable atroposelectivity (83% ee). The known biaryl (*M*,*R*)-**493**, an intermediate of Uemura's synthesis (see Scheme 79),[326] was accessed from (*M*)-**505** in 25% yield and with conservation of the stereogenic information, by selective *O*-methylation of the phenolic hydroxy substituent, oxidation of the benzylic alcohol to the aldehyde, substrate-controlled methyllithium addition, and *O*-allylation. Any attempts to increase the enantiomeric purity of (*M*,*R*)-**493** were not reported. The final steps toward (−)-steganone [(*M*)-**16**] can, in principle, be accomplished by following Uemura's and Meyers' procedures (see Schemes 78 and 79).

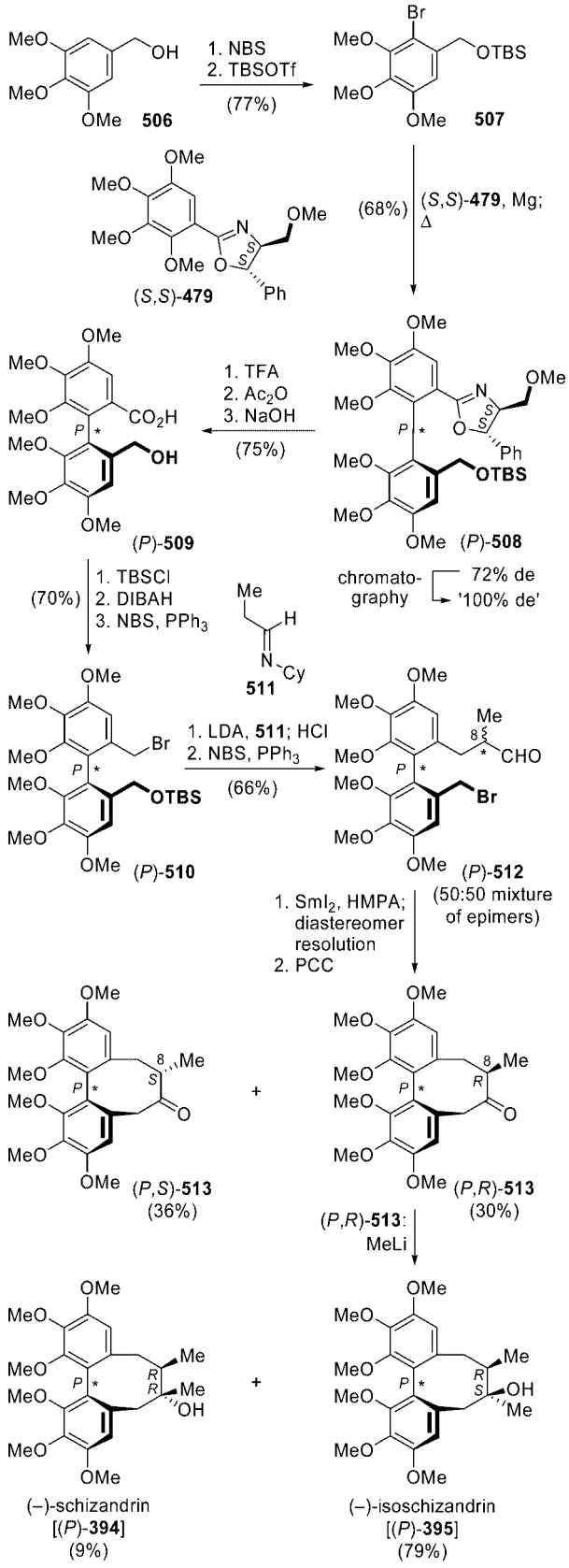
Atropoenantioselective intermolecular biaryl coupling reactions were also used in the preparation of other dibenzocyclooctadiene lignans. Already in 1983, Meyers et al. applied their oxazoline-based nucleophilic substitution methodology to the synthesis of the unnatural stereoisomers (−)-isoschizandrin [(*P*)-**395**] and (−)-schizandrin [(*P*)-**394**].[332] Starting with 3,4,5-trimethoxybenzyl alcohol (**506**, Scheme 82), the coupling precursor **507** was available in two steps and 77% yield by bromination and *O*-silylation. Regioselective nucleophilic displacement of the methoxy functionality adjacent to the oxazoline ring of (*S*,*S*)-**479** (see Scheme 77) by a Grignard reagent (prepared in situ from the bromobenzene **507** and magnesium) delivered the tetra-*ortho*-substituted biphenyl (*P*)-**508** in 68% yield and 72% de. After radial chromatography to give stereochemically pure (*P*)-**508** and removal of the chiral auxiliary and the silyl ether, the hydroxy acid (*P*)-**509** was resilylated, reduced to the corresponding benzylic alcohol, and converted into the bromide (*P*)-**510** by hydroxy−bromine exchange (six steps, 53% yield). Side chain elongation was accomplished by reaction of (*P*)-**510** with the lithiated analogue of the imine **511**. Acidic hydrolysis of the imino function was accompanied by cleavage of the silyl ether to give, after

Scheme 81



hydroxy−bromine exchange, the aldehyde (*P*)-**512** in 66% yield and as a 50:50 mixture of C8 epimers. The central cyclooctadiene ring was formed by treatment of (*P*)-**513** with SmI_2 in the presence of HMPA. The resulting epimeric alcohols were separated by chromatography and oxidized with PCC to furnish the unwanted ketone, (*P*,*S*)-**513**, and the required one, (*P*,*R*)-**513**, in 36% and 30% yield, respectively. The final addition of methyllithium to (*P*,*R*)-**513** occurred mainly in *anti*-position to the C8 methyl group, thus affording unnatural (−)-isoschizandrin [(*P*)-**395**] in 79% yield and its natural diastereomer, (−)-schizandrin [(*P*)-**394**], in 9% yield. This first and atroposelective total synthesis of (*P*)-**395** led to a revision of the originally published,[298]

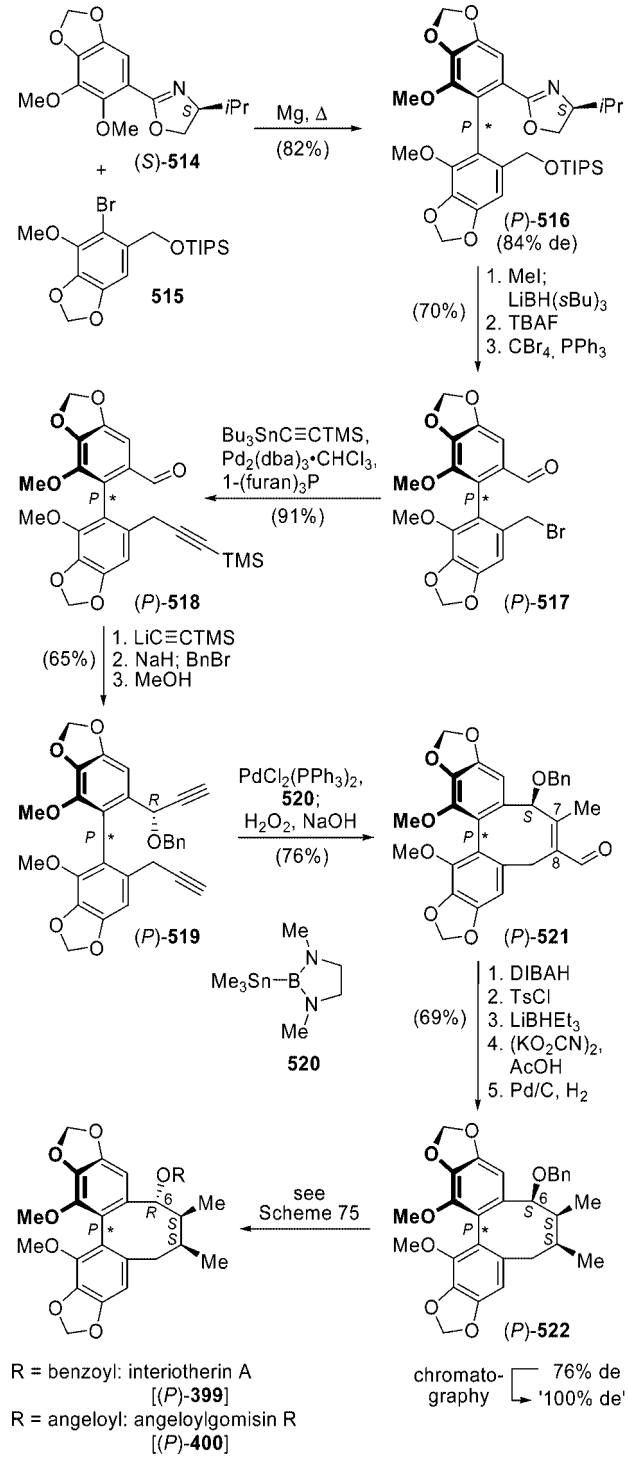
Scheme 82



stereochemically incorrect structure of natural (+)-isoschizandrin [(*M*)-**395**].[332]

In the recently published formal synthesis of the lignans interiotherin A [(*P*)-**399**] and angeloylgomisin [(*P*)-**400**], Singidi and RajanBabu[333] also used Meyers' oxazoline

Scheme 83

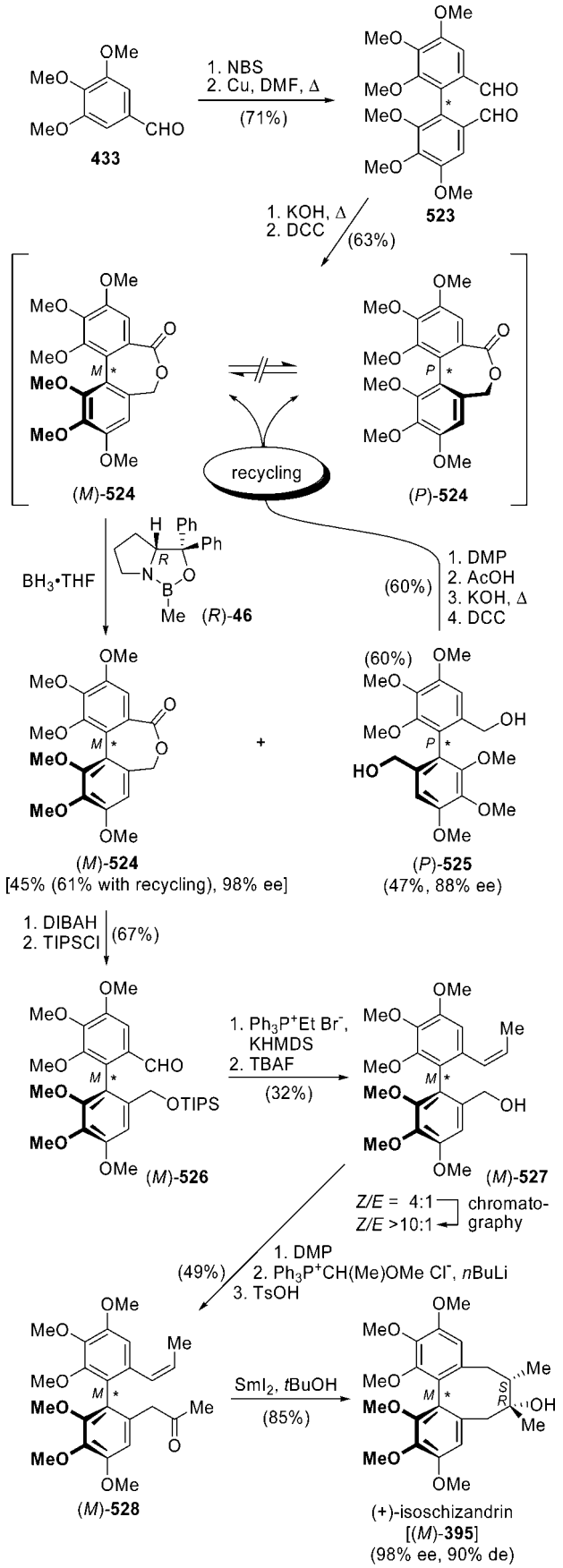


method for the atroposelective preparation of the biphenyl (*P*)-**516**, but applied a novel, highly regioselective [B−Sn]-mediated α,ω-diyne cyclization for the construction of the cyclooctadiene ring (Scheme 83). The synthesis started with the coupling of the Grignard reagent derived from the known arylbromide **515**[334] with the chiral aryloxazoline (*S*)-**514** giving the biaryl (*P*)-**516** in 82% yield and 84% de. After reductive cleavage of the chiral auxiliary, *O*-desilylation, and hydroxy−bromine exchange, which furnished the aldehyde (*P*)-**517**, the alkyne moiety in the southern portion of (*P*)-**518** was installed by Stille coupling of (*P*)-**517** with tri-*n*-butylstannyltrimethylsilylacetylene (64% yield over four steps). Substrate-controlled addition of lithium trimethylsi-

lylacetylide occurred solely to the *Si*-face of the aldehyde functionality of (*P*)-**518**, thus inducing the (*R*)-configuration at the new stereocenter. *O*-Benzylation and desilylation of both alkyne groups delivered the axially chiral diyne (*P*)-**519** (65% yield), which was subjected to a Pd(II)-catalyzed borostannylation-cyclization in the presence of the stannyl diazaborolidine **520**. In situ oxidation of the resulting dienylborane with basic H_2O_2 delivered the enal (*P*)-**521** in good 76% yield and as a single diastereomer. The crotonyl moiety of (*P*)-**521** was stereoselectively transformed into the chiral C_4 bridge of (*P*)-**522** by aldehyde reduction, conversion of the vinyl alcohol into a methyl group, and diimide reduction of the alkene function (five steps, 69% yield, 76% de). Final *O*-debenzylation and chromatographic removal of a minor diastereomer delivered the known biaryl (*P*)-**522**, the late-stage intermediate of Coleman's approach to interiotherin A [(*P*)-**399**] and angeloylgomisin [(*P*)-**400**] (see Schemes 74 and 75),[322] which are available from (*P*)-**522** by simple Mitsunobu esterification with benzoic acid and tiglic acid. Gomisin E [(*P*)-**474**] and gomisin O [(*P*)-**474**] (for the structures, see Scheme 76) were also prepared following this route, by using the tetramethoxy analogue of (*S*)-**514** instead of (*S*)-**514** itself, but no details were given by the authors.[333]

In 2003, a new synthetic route toward the C8-hydroxylated natural lignan (+)-isoschizandrin [(*M*)-**395**] was presented by Molander et al.[102] featuring a kinetic resolution of a conformationally stable biaryl lactone, a concept originally developed in the authors' group (see section 2.3),[95] to control the axial chirality and a SmI_2 promoted 8-*endo* ketyl−olefin cyclization for the construction of the cyclooctadiene moiety (Scheme 84). Bromination of the arylaldehyde **433** followed by a nonstereoselective Ullmann coupling provided the racemic biaryl dialdehyde **523** (71% yield), which was subjected to a Cannizzaro disproportionation with subsequent lactone ring formation. The resulting biaryl lactone **524**, which exits as a racemic mixture of its configurationally stable atropodiastereomers, (*P*)-**524** and (*M*)-**524**, was treated with borane in the presence of the chiral CBS reagent (*R*)-**46** to trigger a kinetic resolution through a atropoenantiomer-differentiating reduction. The diol (*P*)-**525** was obtained with good 88% ee (47% yield), while the unreacted lactone (*M*)-**524** was recovered with an excellent enantiomeric excess of 98% in 45% yield. The undesired diol (*P*)-**525** was recycled to the racemic lactone **524** by oxidation of the benzylic alcohols, thermal equilibration, Cannizzaro reaction, and ring closure. By renewed kinetic resolution of **524**, the overall yield of the highly enantiomerically enriched lactone (*M*)-**524** was raised to 61%. Ring-opening of (*M*)-**524** with DIBAH and *O*-TIPS protection of the alcohol afforded the aldehyde (*M*)-**526** in 67% yield. Installation of the *Z*-propylene side chain at the "northern" phenyl ring was accomplished in a 4:1 *Z*/*E*-selectivity by Wittig reaction using ethyltriphenylphosphonium bromide and KHMDS as the base. Chromatography on silica gel enriched the *Z*/*E* ratio to >10:1. Subsequent *O*-desilylation delivered the alcohol (*M*)-**527** in 32% yield over the last two steps. Benzylic oxidation using Dess-Martin periodinane and Wittig reaction of the aldehyde with (α-methoxyethyl)triphenylphosphonium chloride/*n*BuLi produced the respective enol ether, which was carefully hydrolyzed to give the alkenyl ketone (*M*)-**528**, the precursor for the final 8-*endo* ketyl−olefin cyclization. Treatment of (*M*)-**528** with SmI_2 furnished the natural product (+)-isoschizandrin [(*M*)-**395**] in 85% yield and excellent stereo- and regioselectivities (90% de, 98% ee). In conclusion, dibenzocyclooctadiene lignans have been the challenging target of many semi- and total-synthetic ap-

Scheme 84



proaches. A large number of different strategies, such as intra- and intermolecular coupling reactions with internal or external asymmetric induction, were successfully employed to introduce the chiral information at the biaryl axis, making this class of natural products a test case for the applicability of existing or novel methods. The stereoselectivities attained, in particular those in the earlier approaches, were not always satisfying, but some of the more recent routes have shown efficient solutions to overcome these stereochemical drawbacks.

4.3. Lactam-Bridged Biaryls

4.3.1. (−)-Rhazinilam

(−)-Rhazinilam [(*M*)-**529**], first isolated by Linde in 1965 from the Apocynaceae species *Melodinus australis*,[335] is a representative of the small family of phenylpyrrole lactams (Figure 17). It is not, as initially claimed, a natural product, but is formed during the isolation process by oxidative aromatization of the nonbiarylic 5,21-dihydrorhazinilam (**530**).[336,337] The tetracyclic structure of (*M*)-**529** is unprecedented because it includes a rotationally hindered heterobiaryl axis between a phenyl and a pyrrole subunit, although it is flanked by only two *ortho*-substituents. This, at first sight, unexpected occurrence of axial chirality is a consequence of the rigidity of the strained nine-membered lactam bridge. Likewise remarkable are the in vitro antimitotic properties of (−)-rhazinilam [(*M*)-**529**],[337−340] even though no in vivo activity was observed.[337,341,342] It induces a nonreversible spiralization of tubulin, thus inhibiting its assembly, and it protects microtubules from cold-induced disassembly.[337,338] This is the first combination of the two modes of action, which have been previously found only separately in the two well-known antimitotic drugs, vinblastine and Taxol, respectively.[5,338,343,344] The other enantiomer, by contrast, with (*P*,*S*)-configuration, does not show any bioactivity at all.[337,339,341] In-depth structure−activity relationship (SAR) studies,[339,340,342,345−347] aiming at the search for simpler analogues with improved tubulin-binding properties in vitro and in vivo, led to the discovery that the rigid 9-membered ring and the (*M*)-configuration at the biaryl axis are important for the antimitotic activity. The most promising analogue resulting from the SAR studies was the biphenyl carbamate (*M*)-**531**, which owes its configurational stability to the presence of the quaternary α-substituent at C5′, despite the formal presence of only two *ortho*-substituents next to the axis.[340,346,348] It is twice as active as (*M*)-**529** in inhibiting microtubules assembly and disassembly, while the cytotoxicities on human cancer cell lines were not enhanced.[340,346] The antimitotic activities of rhazinilam [(*M*)-**529**] and its derivatives, their semi- and total syntheses, and accompanying SAR studies have been the topic of three previous reviews.[5,344,349] Herein, the enantioselective total synthesis of (*M*)-**529** is described because of the unique structure of this compound, even though it is not a true natural product. Furthermore, with the axial configuration just being fixed by the lactam bridge, the following approaches are representative for all syntheses of axially chiral biaryls in which this stereoelement is not separately introduced but is a consequence of a preferred configuration of a macrocycle relative to configurationally stable stereogenic centers.

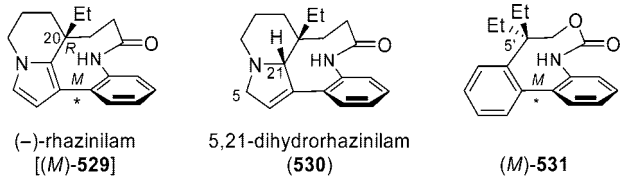
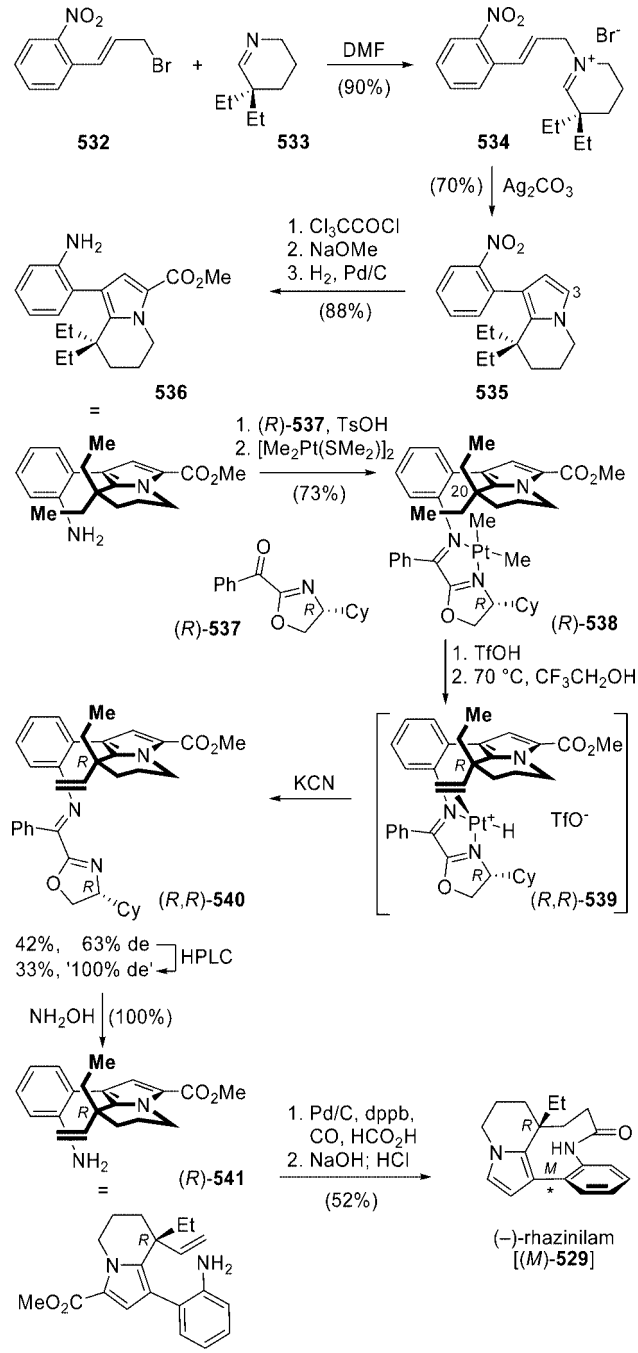


Figure 17.

Scheme 85

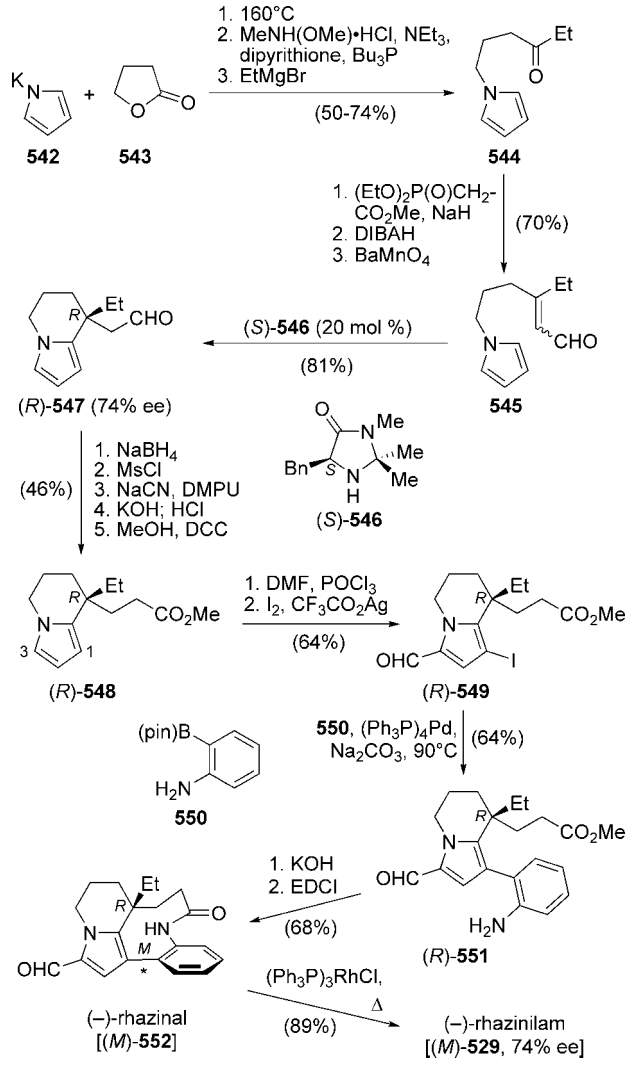


After several semi-[339,347,350] and total-synthetic[343,350,351] pathways to racemic **529** by different groups, Sames and co-workers[352] reported on the first atroposelective preparation of (−)-rhazinilam [(*M*)-**529**] in 2002, based on three key steps, a pyrrole annulation, an asymmetric C−H bond functionalization using a chiral Pt complex, and a macrolactamization (Scheme 85). The pyrrole ring of **535** was generated by heating the allyliminium salt **534**, which was readily available from the imine **533** and the *o*-nitrocinnamyl bromide **532** in the presence of Ag_2CO_3, thus accomplishing the cyclization and oxidative aromatization in a single step. Protection of the nucleophilic C3 position in the heterocycle by a methyl carboxylate group and reduction of the aromatic

nitro function furnished the amine **536** in 88% yield. Attachment of the chiral oxazolinyl ketone (*R*)-**537** with imine formation and subsequent complexation with the dimethylplatinum reagent $[Me_2Pt(SMe_2)]_2$ made the (initially enantiotopic) ethyl groups of the piperidine ring diastereotopic in the resulting chiral platinum complex (*R*)-**538**, thus permitting their differentiation. Exposure of (*R*)-**538** to TfOH followed by thermolysis at 70 °C generated the stereogenic center at C20 by asymmetric dehydrogenation of the *Si* ethyl group to a vinyl substituent, leading to the platinum alkene−hydrido complex (*R*,*R*)-**539**. After demetalation with aqueous KCN, the metal-free oxazoline Schiff base (*R*,*R*)-**540** was obtained in a moderate 42% yield and 63% de. Lower temperatures in the dehydrogenation step (e.g., 60 °C) or sterically more demanding chiral auxiliaries such as the *t*Bu-derivative of (*R*,*R*)-**540** allowed better diastereoselectivities, albeit at the price of reduced yields (≤20%). Separation of the correct diastereomer by high-performance liquid chromatography (HPLC) and cleavage of the chiral auxiliary from (*R*,*R*)-**540** delivered the enantiopure vinyl compound (*R*)-**541**. Formation of the nine-membered lactam ring was achieved by a one-step palladium-catalyzed carbonylation−cyclization process. Removal of the methyl ester protecting group eventually gave enantiopure (−)-rhazinilam [(*M*)-**529**] in 12 steps and 7% overall yield. In 2006, Banwell et al. presented a second enantioselective total synthesis of (−)-rhazinilam [(*M*)-**529**],[353] using an intramolecular organocatalytic Michael addition to construct the quaternary stereocenter in the tetrahydroindolizine ring system (Scheme 86). The preparation of the key precursor, the acrolein derivative **545**, started with the thermal ring-opening of γ-butryolactone (**543**) by potassium pyrrolate (**542**).[343] Conversion of the resulting carboxylate into the Weinreb amide and then into a propionyl moiety afforded the ketone **544**,[343] from which **545** was available by Horner−Wadsworth−Emmons reaction, DIBAH reduction, and oxidation. The enantioselective 1,4-addition of the pyrrole to the *N*-tethered acrylate was performed in the presence of the MacMillan catalyst (*S*)-**546**[354] (20 mol %) under previously optimized conditions,[355] delivering the (*R*)-configured tetrahydroindolizine (*R*)-**547** in 81% yield and 74% ee. Transformation of the acetaldehyde side chain into the methyl propionate group of (*R*)-**548** was accomplished in five further standard steps. After protection of the reactive C3 position as an aldehyde under Vilsmeier−Haack conditions and regioselective iodination at C1 to give (*R*)-**549**, the pyrrole−aryl axis was built up in 64% yield by Suzuki−Miyaura cross-coupling with the boronic ester **550**. Saponification of the methyl ester in (*R*)-**551** followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)-mediated lactamization furnished (−)-rhazinal [(*M*)-**552**] with simultaneous fixation of the axial configuration. Final decarbonylation by heating (*M*)-**552** with a stoichiometric amount of the Willkinson catalyst $[(Ph_3P)_3RhCl]$ accomplished the total synthesis of (−)-rhazinilam [(*M*)-**529**] in overall 18 steps, nearly 5% yield, and 74% ee.

Likewise in 2006, S. G. Nelson and co-workers reported on a third total synthesis of (−)-rhazinilam [(*M*)-**529**], this time via an axially chiral allene as the stereochemically decisive precursor (Scheme 87).[356] Starting with 2-pentynal (**553**) and propionyl chloride, the chiral β-lactone (*R*,*R*)-**554** was prepared in 72% yield and excellent 98% de and 99% ee by an acyl halide−aldehyde cyclocondensation catalyzed by *O*-TMS−quinine (10 mol %).[357] S_N2'-type ring-opening

Scheme 86



of (*R*,*R*)-**554** with the Grignard reagent **555** in the presence of CuCN afforded the allene (*P*,*R*)-**556** as a single diastereomer after esterification of the carboxylate. An efficient chirality transfer was observed in the pyrrole−allene annulation step if $Ph_3P{\cdot}AuOTf$ (5 mol %) was used as the catalyst, providing (*R*,*R*)-**557** in 92% yield and 94% de. After protection of the C3 position of the tetrahydrobenzopyrrole as a carboxylic acid, the alkenyl side chain was converted via (*S*)-**558** into a propionyl moiety by oxidative cleavage, Wittig olefination, and hydrogenation. Iodination of (*R*)-**559** at C1 and $Pd_2(dba)_3$-cataylzed Suzuki−Miyaura cross-coupling with the boronic ester **560** in the presence of Buchwald's SPhos ligand **561**[358] delivered the arylated pyrrole (*R*)-**562**, from which the lactam (*M*,*R*)-**563** was accessed by saponification, *N*-Boc deprotection, and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)-mediated ring closure. Final decarboxylation of (*M*,*R*)-**563** gave the target molecule (−)-rhazinilam [(*M*)-**529**] in overall 14 steps, excellent 22% yield, and 94% ee.

4.3.2. Macrocyclic Indole Bisoxazole: Diazonamide A

The marine natural product diazonamide A [Figure 18, initially proposed structure (*P*,*M*,*M*)-**564**, revised structure (*P*,*M*,*M*)-**20**], isolated in 1991 from the colonial ascidian *Diazona angulata* by Clardy, Fenical, and co-workers,[69]

Scheme 87

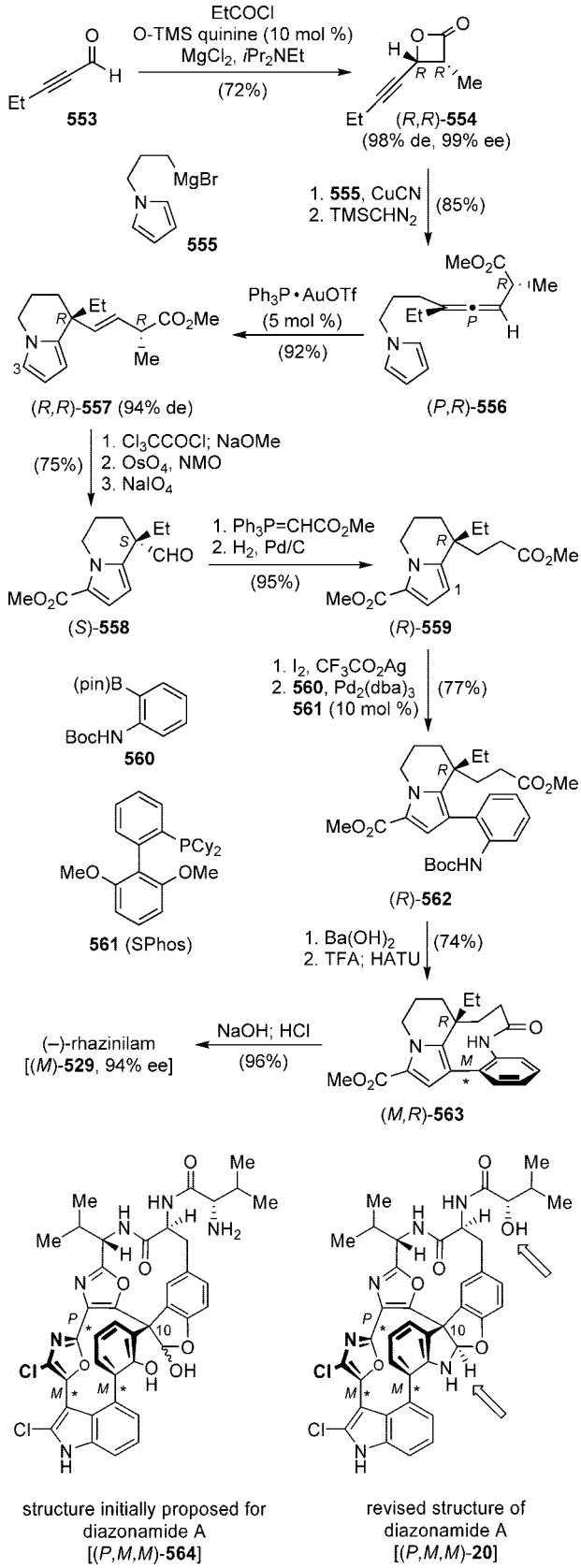


Figure 18.

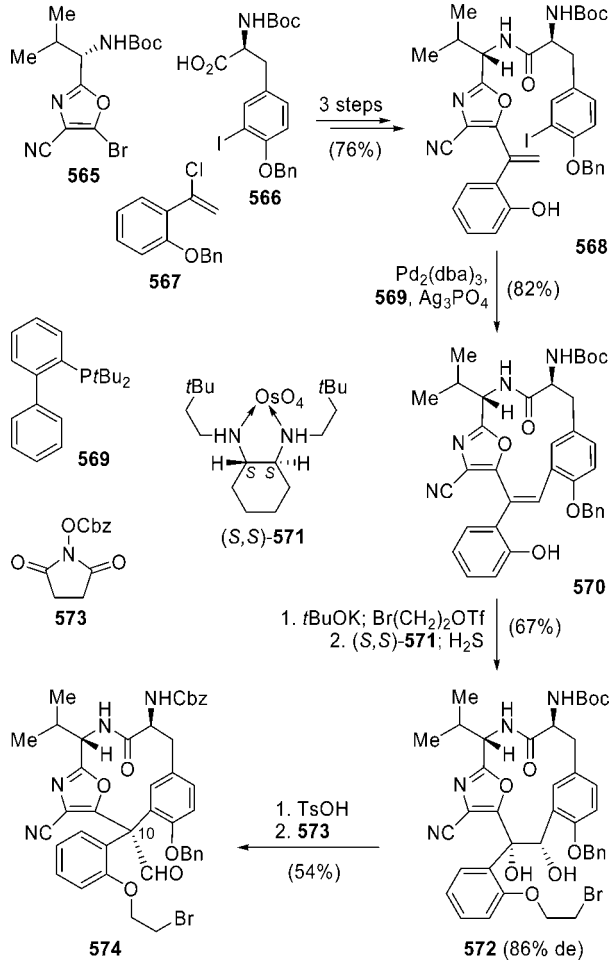
comprises a unique, highly complex molecular framework, including three stereogenic axes, which owe their configurational stability to the rigidity of the bismacrocyclic skeleton. Two of them join together five-membered aromatic heterocycles, a combination that is rarely found in axially chiral biaryls of natural or synthetic origin. These unusual structural features of diazonamide A and its promising in vitro activity against a variety of human cancer cell lines in the nanomolecular range[69−71] triggered intense efforts toward its total synthesis. In 2001, just 10 years after its discovery, Harran and co-workers were the first to report a total synthesis of the initially reported molecular framework.[72] Although the structure of diazonamide A had seemed to be firmly established in the isolation work, even supported by X-ray crystallographic data of a *p*-bromobenzamide derivative,[69] the compound (*P*,*M*,*M*)-**564** synthesized by Harran and co-workers turned out not to be identical with the natural product.[72] Reinvestigation of the spectroscopic and crystallographic data of the natural product finally led to a structural revision of diazonamide A as (*P*,*M*,*M*)-**20**, i.e., with a bicyclic *N*,*O*-acetal instead of a monocyclic hemiacetal and an L-α-hydroxyisovaleric acid side chain instead of an L-valine one as in (*P*,*M*,*M*)-**564**.[73] The identity of (*P*,*M*,*M*)-**20** with the natural product diazonamide A was later unequivocally proven by two total syntheses from the Nicolaou lab[71,74,75] and a third one by Harran and co-workers.[76]

The complex frameworks of both (*P*,*M*,*M*)-**564** and (*P*,*M*,*M*)-**20** inspired the development of a number of highly innovative synthetic strategies.[359] The stereoselective preparation of the biaryl-containing macrocycle, in particular, led to the elaboration of different cyclization strategies, among them Pinacol-type cyclizations by Nicolaou and co-workers,[360] an imino-Dieckmann cyclization by Vedejs and Zajac,[361] and a photo-Fries rearrangement by Magnus and Lescop.[362] These synthetic achievements, together with the above-mentioned total synthetic approaches, have already been subject to excellent reviews recently by Ritter and Carreira[363] and Lachia and Moody.[364] Herein we will, therefore, only outline the successful total syntheses, concentrating on the respective key steps to construct the axially chiral biaryl portion.

In the total synthesis of the originally proposed structure (*P*,*M*,*M*)-**564** of diazonamide A, Harran and co-workers avoided the problem of dealing with atropodiastereomeric intermediates throughout the synthesis by first building up the chiral macrolactam portion of the molecule and subsequently using the stereochemical information of this rigid unit for asymmetric induction in the final biaryl coupling step.[72] Key to this strategy was the stereoselective construction of the C10 quaternary center. The synthesis made use of the readily available precursors **565**, **566**, and **567**, which were linked in a three-step sequence to give the iodoolefin **568** in 76% overall yield (Scheme 88). Heck endocyclization of **568** in the presence of $Pd_2(dba)_3$ and the phosphine **569** furnished **570**, whose phenolic OH function was protected, thus permitting a stereoselective dihydroxylation of the double bond. In the presence of stoichiometric quantities of the chiral osmium−diamine complex (*S*,*S*)-**571**, the oxygenation occurred from the correct face, giving **572** with a good selectivity (86% de, 67% yield). This step already completes the introduction of external stereochemical information into the growing diazonamide framework. Diastereoselective pinacol rearrangement of **572** with ring contraction and renewed protection of the resulting primary amine by carbamoylation with **573** furnished **574**, which comprised the fully assembled carbon skeleton of the macrolactam unit of (*P*,*M*,*M*)-**564**.

Compound **574** was further converted into the aryl bromide **575** in 10 steps (8% yield, Scheme 89), involving a

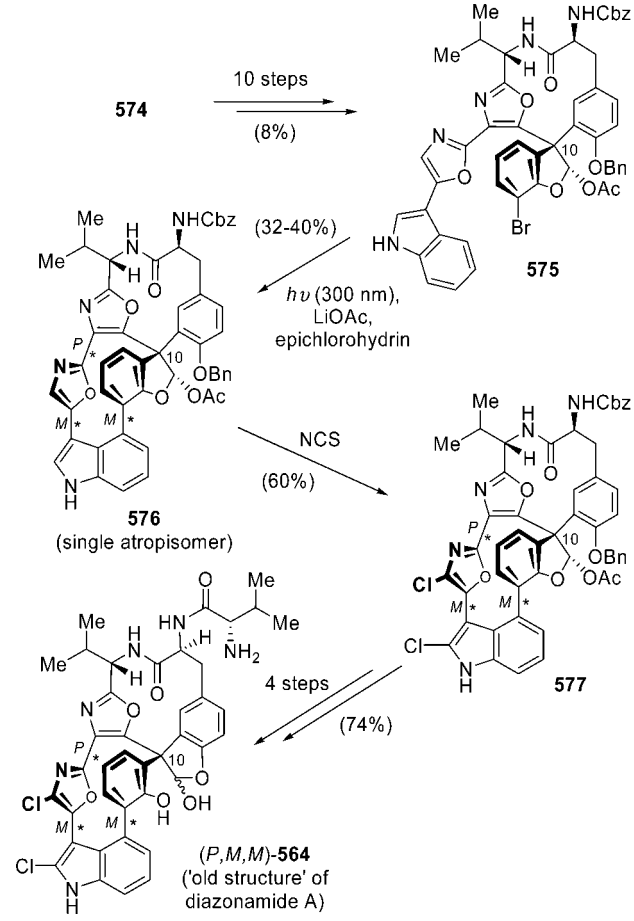
Scheme 88



nucleophilic addition of tryptamine, a photolytic hemiacetal formation, and an oxidation/dehydration sequence to give the bis(oxazolyl)indole segment.[72] The second macrocycle was established by a photoinduced Witkop-type cyclization[365] in the presence of epichlorohydrin, which served as an acid scavenger, providing the desired biaryl **576** as a single regio- and stereoisomer in 32−40% yield, along with some not cyclized, but hydrodebrominated side product.[72] In the course of this biaryl coupling step, the configurations of all three biaryl axes were simultaneously established, fully controlled by an internal asymmetric induction through the rigid chiral macrocycle. Regioselective 2-fold chlorination of **576** with *N*-chlorosuccinimide (NCS) delivered **577** (60% yield), which was transformed into (*P*,*M*,*M*)-**564**, i.e., the structure originally proposed for diazonamide A, in four more steps and 74% yield.[72] The observed differences in the spectroscopic data and in the physical and chemical properties between the synthetic compound (*P*,*M*,*M*)-**564** and the isolated metabolite diazonamide A finally led to the revision of the structure of diazonamide A from (*P*,*M*,*M*)-**564** to (*P*,*M*,*M*)-**20**.[73]

Only one year later, Nicolaou et al. finalized the first total synthesis of the authentic natural product (*P*,*M*,*M*)-**20**, diazonamide A (Scheme 90).[74] As in the synthetic strategy described before,[72] the macrolactam portion was first built up and then used as the chiral environment for the stereoselective formation of the critical biaryl linkage. The intermediate **581** with its stereogenic quaternary center, C10, was prepared in three steps and 11% yield by a sequential bisarylation of the isatin derivative **580** with the oxazole **578**

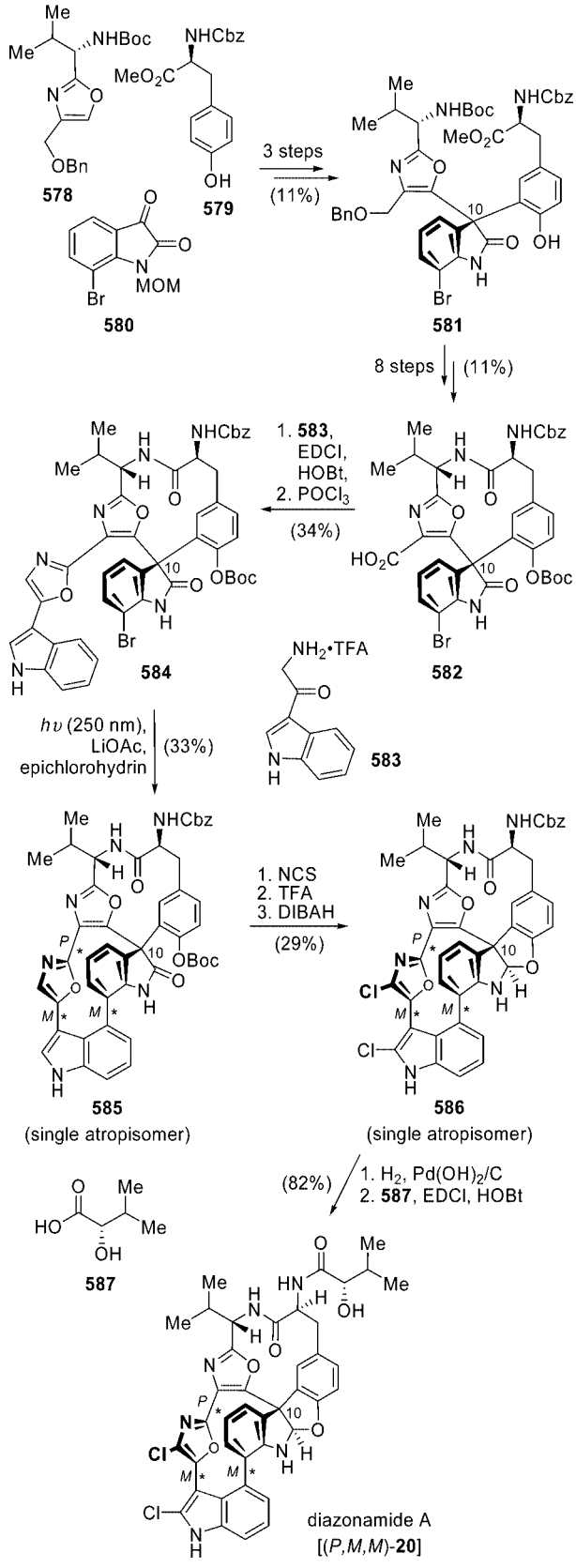
Scheme 89



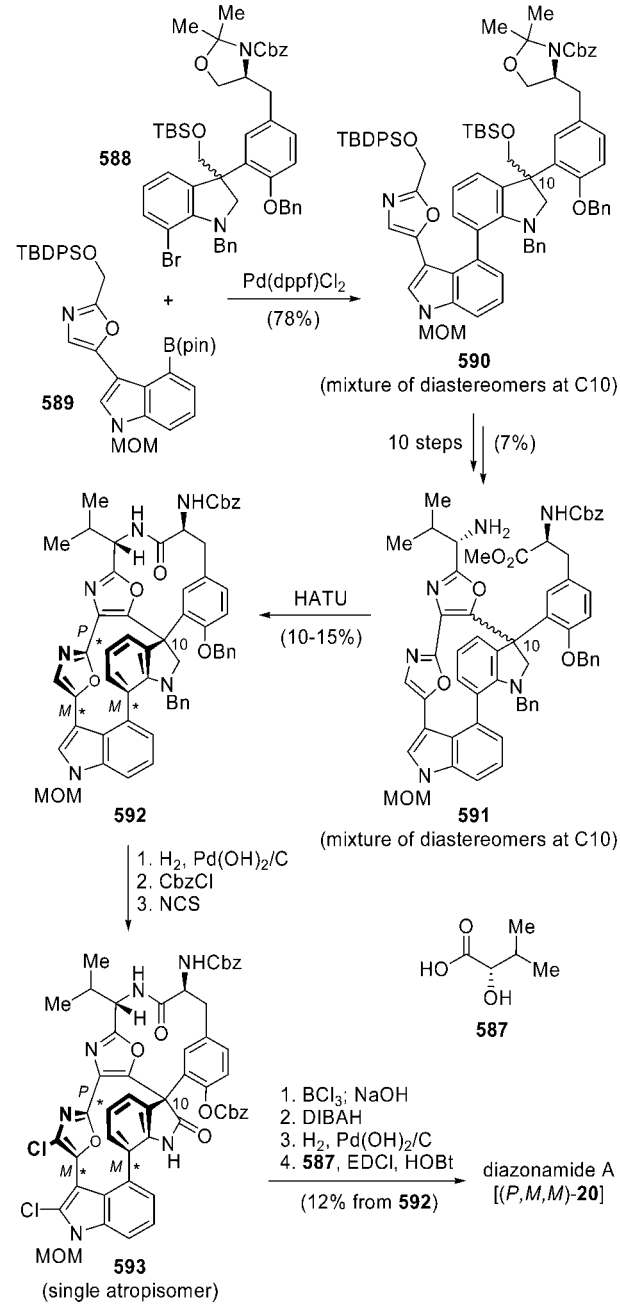
and the protected tyrosine **579**, followed by diastereomeric resolution.[74] Conversion of **581** into the advanced intermediate **582** required a series of functional-group transformations and a macrocyclization (8 steps, 11% yield). It should be noted that in 2007 Magnus and Lescop had succeeded in preparing a close precursor to **582**, by applying a novel photo-Fries rearrangement[362] to construct the stereogenic quaternary C10 carbon atom.[366] Following the Nicolaou synthesis,[74] the second oxazole moiety in **584** was installed by condensation of **582** with the oxo tryptamine **583**, thus paving the way for a Witkop-type photocyclization. In analogy to the Harran synthesis of (*P*,*M*,*M*)-**564** (see above), the biaryl bond formation proceeded with a high stereoselectivity, delivering exclusively the desired atropoisomer **585** in 33% yield. Twofold chlorination of **585** followed by *O*-deprotection, reduction of the oxindole to the iminium salt, and in situ cyclization afforded aminal **586** in three steps and 29% overall yield. Final hydrogenolytic removal of the *N*-carbamate protective group and condensation of the intermediate primary amine with L-2-hydroxyisovaleric acid (**587**) gave diazonamide A [(*P*,*M*,*M*)-**20**] in overall 19 steps from **578**−**580**. With the spectroscopic data in full agreement to those reported for the natural product,[69] this impressive first total synthetic access to (*P*,*M*,*M*)-**20** now confirmed the revised[73] structure of diazonamide A.

A short time after the first total synthesis of (*P*,*M*,*M*)-**20**, Nicolaou and co-workers succeeded in developing yet another synthetic route to this intriguing secondary metabolite, using a different order of macrocycle constructions.[71,75] In this approach, the biaryl bond was constructed by Suzuki coupling of **588** (obtained as a 50:50 mixture of diastereo-

Scheme 90



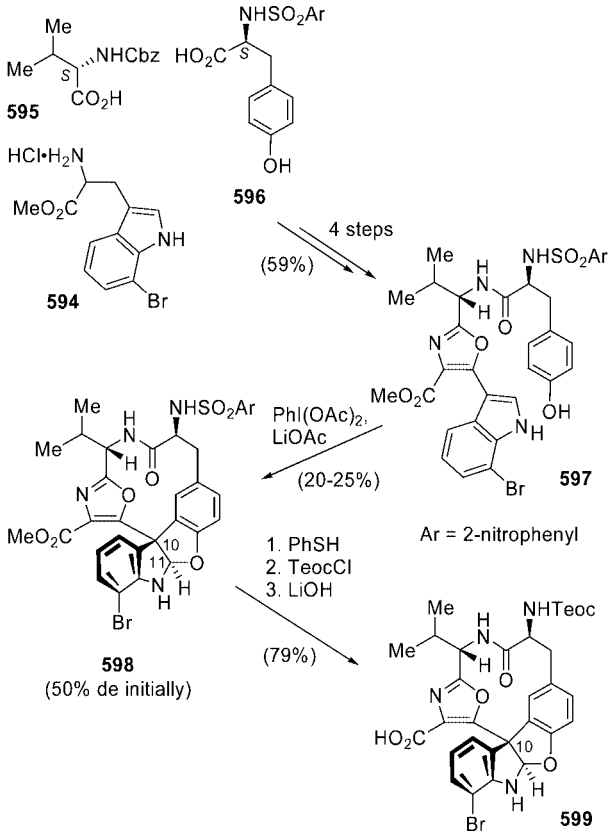
Scheme 91



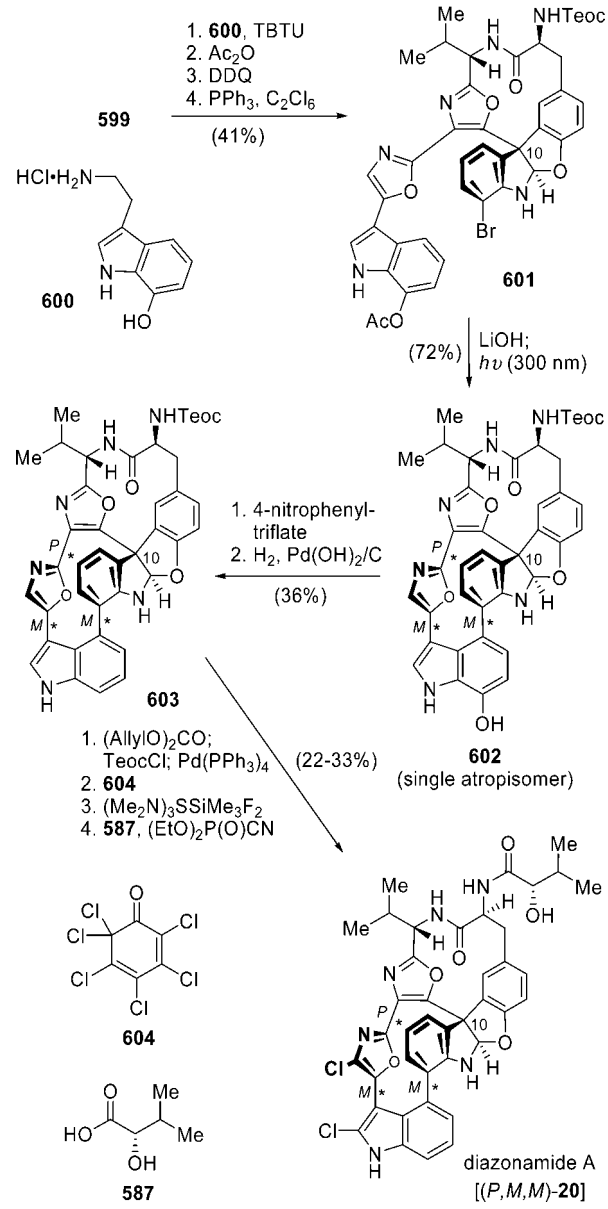
mers by Friedel−Crafts reaction of an *N*-protected tyrosine with 7-bromoisatin followed by a series of reduction and protection steps) and the boronic ester **589** leading to the rotationally unstable biaryl **590** in 78% yield (Scheme 91). Compound **590** was further converted to the bisoxazole **591** (10 steps, 7% overall yield), which was submitted to a HATU-mediated lactam formation giving the bicyclic intermediate **592**, with kinetic resolution of the diastereomeric mixture at C10, because only the "correct" isomer was able to undergo this ring closure. Hydrogenolytic debenzylation, which was accompanied by an oxidation at C11, and Cbz protection of the phenolic hydroxy group set the stage for the chlorination, which delivered **593** with complete atropodiastereoselectivity due to the constraints of the macrocyclic system. Deprotection, reduction, aminal formation, and attachment of the side chain **587** finally afforded diazonamide A (*P*,*M*,*M*)-**20** in overall 31 steps (longest linear sequence from commercially available starting materials).

In 2003, Harran and co-workers likewise succeeded in assembling the authentic natural product (*P*,*M*,*M*)-**20**.[76] The strategy chosen in this route was inspired by its proposed biosynthesis, involving an oxidative formation of both the central aminal and the biaryl bond.[73] As in Harran and co-workers' earlier synthesis of (*P*,*M*,*M*)-**564**[72] (see Schemes

Scheme 92



Scheme 93



88 and 89) and Nicolaou and co-workers' first approach toward (*P*,*M*,*M*)-**20**[74] (see Scheme 90), the initial goal was the formation of the lactam-containing macrocycle, but in contrast to Nicolaou's work, the potentially unstable aminal was planned to be introduced at an early stage of the synthesis. The tripeptidic precursor **597** (Scheme 92) was prepared in four steps and 59% overall yield from 7-bromotryptophan (**594**), *N*-Cbz L-valine (**595**), and the tyrosine **596**. Biomimetic cyclization by intramolecular oxidative coupling of the indole- and tyrosine-derived residues using $PhI(OAc)_2$ afforded the desired macrolactam **598** in 20−25% yield, along with 7−8% of the C10,C11-diastereomer (corresponding to 50% de in favor of **598**) and 15% of spirodienone side products. Adjustment of protective groups in three steps furnished the acid **599** in 79% yield.

Peptide coupling of **599** with 7-hydroxytryptamine (**600**), followed by acetylation of the phenolic hydroxy group, DDQ oxidation, and cyclodehydration gave bisoxazole **601** in 41% yield (Scheme 93).[76] Photoinduced macrocyclization, after deacetylation of **601** by LiOH, furnished biaryl **602** as a single atropodiastereomer in an excellent 72% yield, in particular when compared to the similar cyclization reactions as carried out by the groups of Harran and Nicolaou in their total syntheses of (*P*,*M*,*M*)-**564** (32−40% yield, see Scheme 89) and (*P*,*M*,*M*)-**20** (33% yield, see Scheme 90). Given the likely mechanism of the coupling reaction, starting with a photoinduced electron transfer between the indole chromophore (electron donor) and the bromoarene (electron acceptor) leading to a radical ion pair, which internally collapses with mesolytical elimination of bromide, the increased yield can be explained by the higher electron density in the indole moiety due to the phenoxy group. This benefit clearly justifies the transient introduction of the additional hydroxy group, which is not part of the final target molecule (*P*,*M*,*M*)-**20**, into the system, also because its subsequent removal was easily achieved by simple triflation-hydrogenation in 83% yield to give **603**. The synthesis of (*P*,*M*,*M*)-**20** was completed in four more steps, including the attachment of the *N*-terminal side chain and the bischlorination with perchloro-2,4-cyclohexadien-1-one (**604**). The complete sequence to (*P*,*M*,*M*)-**20** from **594**−**596** required 19 steps, thus having the same length as the first approach by Nicolaou (see Scheme 90), but giving a significantly improved overall yield (ca. 0.4% vs ca. 0.03%).

In conclusion, the synthetic work toward (*P*,*M*,*M*)-**564** and (*P*,*M*,*M*)-**20** shows the importance of total synthesis for the development of novel reactions and strategies[363,364] and, despite the availability of sophisticated modern analytical methods, for structural elucidation, in this case leading to a structure revision of (*P*,*M*,*M*)-**20**. In addition, Nicolaou and co-workers impressively demonstrated the power and speed of modern total synthesis, by developing two different approaches to the newly established structure in an extremely short time span. Harran and co-workers' total synthesis of (*P*,*M*,*M*)-**20** illustrates how biosynthetic inspirations can lead

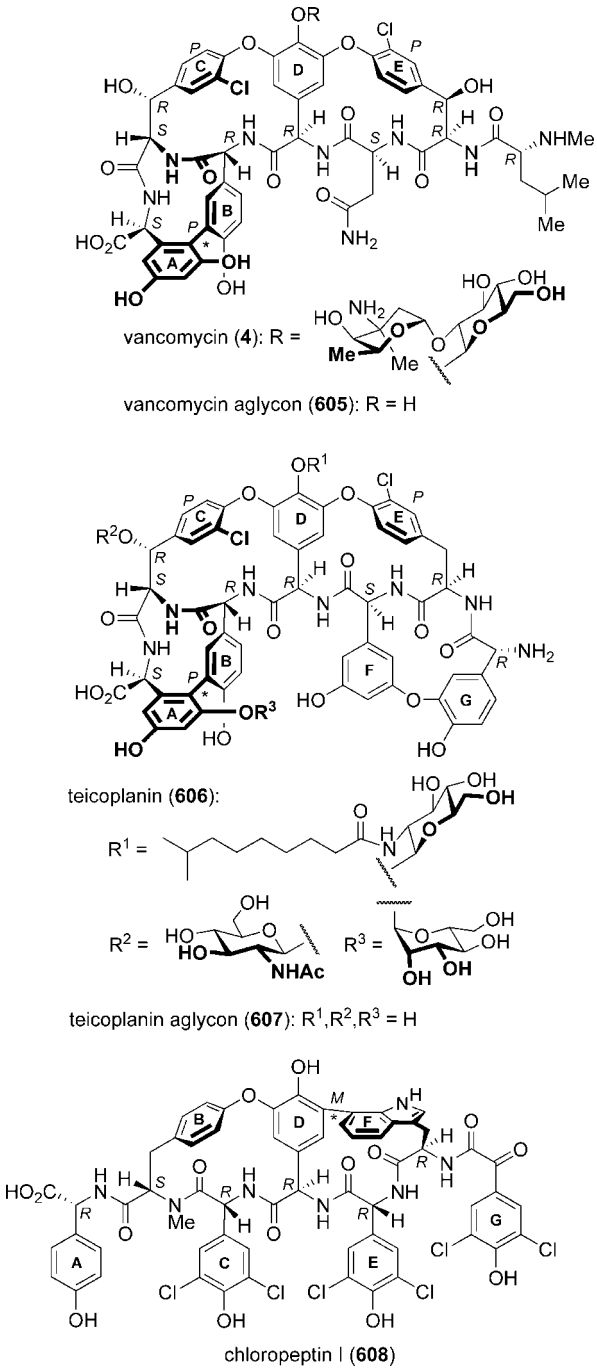


Figure 19.

to remarkably short and efficient routes to highly complex natural products.

4.3.3. Heptapeptide Antibiotics: Vancomycin and Related Compounds

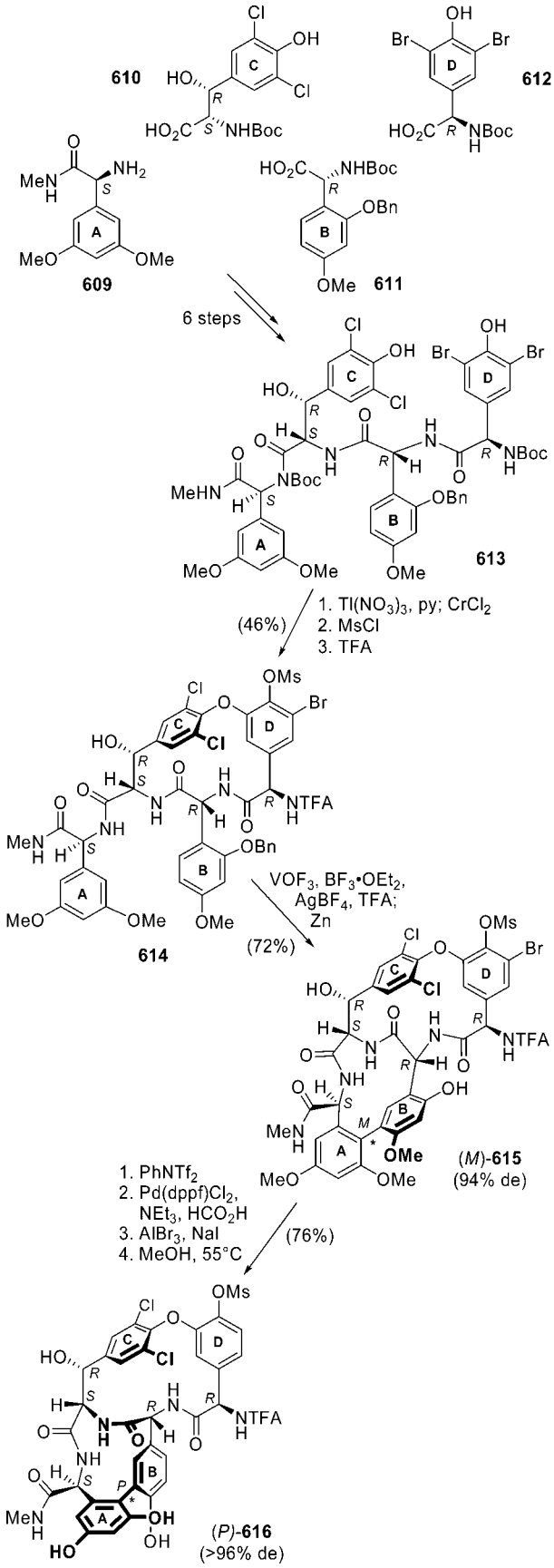
The glycopeptide antibiotics, as produced by actinomycetes and streptomycetes, constitute one of the most intensively studied class of natural products of the past years.[12−14,348] All members of this family, like the well-known representatives vancomycin (**4**; aglycon, **605**, Figure 19), teicoplanin (**606**; aglycon, **607**), and chloropeptin I (**608**), are characterized by a complex heptapeptidic backbone equipped with several stereogenic centers and, more importantly, with two to four elements of axial and planar chirality, including biaryl bonds (AB in **4** and **606** and DF in **608**) and diaryl ether functions (CD and DE in **4**, CD, DE, and FG in **606**, and BD in **608**). The five "western" amino acids are aromatic and identical in almost all such metabolites, while the remaining two "eastern" amino acid modules can be used for the classification of these natural products into distinct categories.[13,367] In the vancomycin-type subfamily, the latter two amino acids are aliphatic, typically leucine and asparagine, whereas avoparcin-type glycopeptides bear 4-hydoxyphenylglycines in these positions. Compounds such as teicoplanin (**606**), belonging to the ristocetin family, possess another 14-membered diaryl ether macrocycle in the western part formed between the two aromatic amino acids (FG junction) and, in addition, a long fatty-acid side chain attached to a sugar moiety. Members of a further group, here represented by chloropeptin I (**608**), typically contain a tryptophan moiety linked to the central amino acid (DF biaryl bond, instead of the DE diaryl ether in **4** and **606**), and they lack the AB connection.

From a medicinal point of view, these glycopeptides are valuable drugs of last resort for the treatment of resistant bacterial strains of *Staphylococcus aureus* and other Gram-positive organisms and constitute agents for the therapy of patients allergic to β-lactam antibiotics.[13]

The intriguing biological properties combined with the unique and challenging structures of these glycopeptide antibiotics have triggered vigorous efforts of several working groups toward the development of a total-synthetic access to selected representatives. In this section, we will describe the synthesis of **608** and of the aglycons **605** and **607** of **4** and **606**, respectively, with particular emphasis on the preparation of the most prominent member of this class, the aglycon **605** of vancomycin (**4**). On the basis of these approaches, the most important features of the syntheses of teicoplanin (**606**) and chloropeptin I (**608**) will then be described.[368] Because the work performed by the groups of Evans, Nicolaou, and Boger has already been comprehensively reviewed,[13,79,367,369,370] focus will only be given to the key steps of the syntheses.

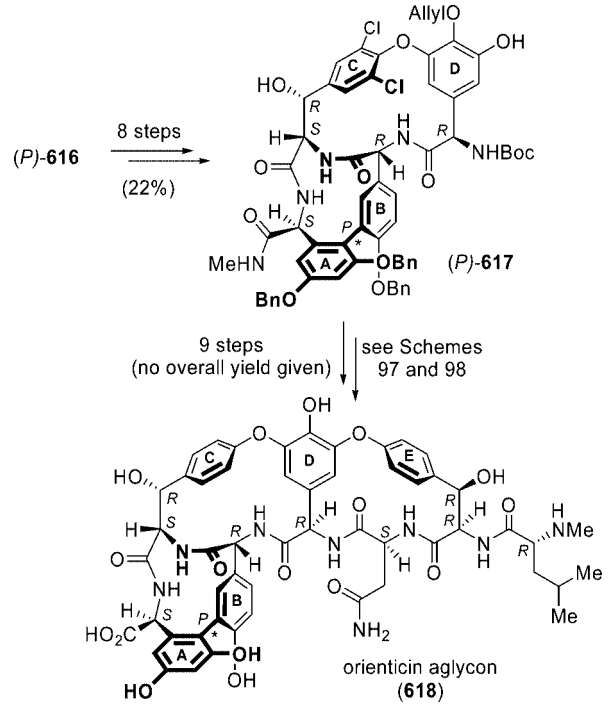
Evans and co-workers were the first to complete the total synthesis of an aglycon of this group of peptides, namely, of the orienticin C aglycon (**618**, for the structure, see Scheme 95), in 1997.[371,372] In contrast to **605**, this bisdechloro analogue of the vancomycin aglycon **605** does not possess any elements of planar chirality and is therefore one of the less challenging members of this class of glycopeptides. Sequential peptide coupling of the amino acid precursors **609**−**612** (Scheme 94) afforded the tetrapeptide **613** in good yields.[372] Thallium nitrate-induced oxidative coupling of the C- and D-ring, followed by reduction of the intermediate with $CrCl_2$, *O*-mesylation, and replacement of the *N*-Boc residue by an *N*-TFA protective group, furnished the monocyclic diaryl ether **614** in three steps and up to 46% yield. Renewed oxidative cyclization, this time with VOF_3, and reductive workup closed the AB−biaryl bond with concomitant *O*-debenzylation, delivering the highly strained bicycle (*M*)-**615** in 72% yield and 94% de, unfortunately in favor of the undesired (*M*)-atropodiastereomer. The stereochemical outcome of this step was triggered by the joint influence of the unnatural hydroxy group at ring B, which was introduced to facilitate the oxidative biaryl coupling step, and the neighboring stereocenter at C_α; the latter effect was demonstrated by the cyclization of the unnatural C_α epimer, which provided the biaryl with the natural (*P*)-configuration (see also the vancomycin synthesis below). After reductive removal of the free phenolic OH group of (*M*)-**615**, which

Scheme 94



was accompanied by an unwanted loss of the bromine substituent, and full *O*-demethylation, the wrong axial (*M*)-configuration was thermally "corrected", providing the desired, thermodynamically more stable (*P*)-configured atropodiastereomer (*P*)-**616** in >96% de.

Scheme 95



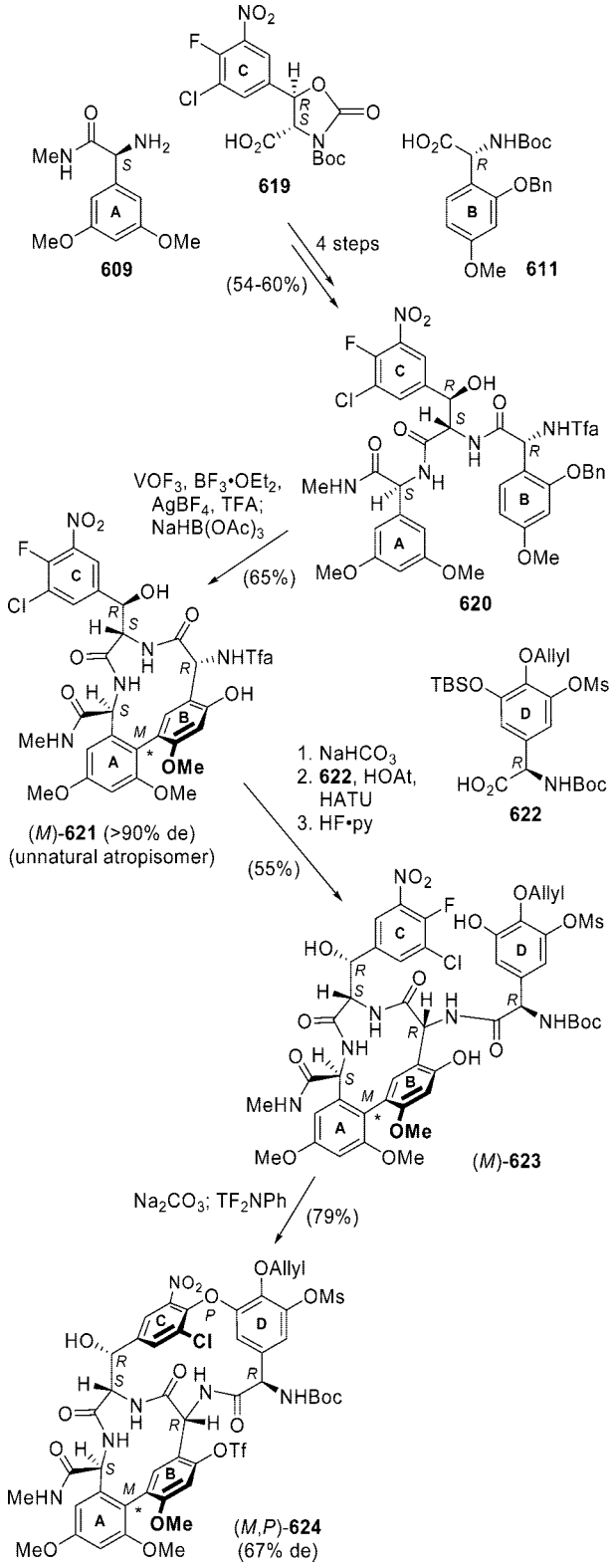
The macrobicycle (*P*)-**616** was then transformed into (*P*)-**617** in eight steps and 22% yield (Scheme 95), involving a renewed introduction of a halogen function on ring D and its conversion into a hydroxyl group, as required for the oxidative formation of the second diaryl ether bond. Because the following steps in the synthesis of the orienticin C aglycon (**618**) are very similar to those of the preparation of the vancomycin aglycon **605** from (*P*,*P*)-**626** (see Schemes 97 and 98),[373] these transformations will be described later.

For the first total synthesis of the aglycon **605** of vancomycin (**4**) in 1998, Evans et al.[373] utilized intramolecular S_NAr-macrocyclizations and changed the order of the diaryl−ether bridge formations, as compared to the synthesis described above, in order to improve the stereocontrol in the decisive coupling steps by using the already existing stereogenic centers as chiral inductors.[373,374]

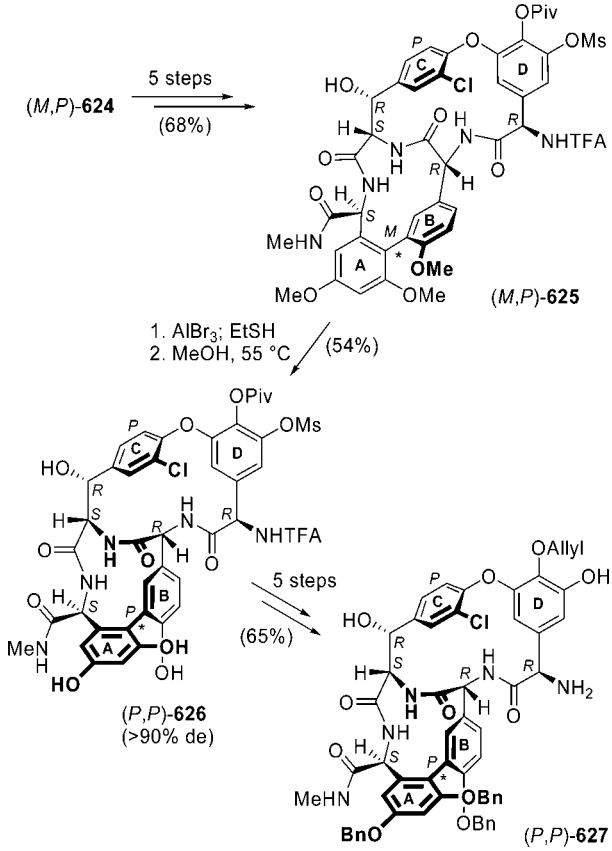
The tripeptide **620** was assembled from the amino acid building blocks **609**, **611**, and **619** in four steps and 54−60% yield (Scheme 96). Oxidative cyclization with VOF_3 and reductive workup, this time with $NaBH(OAc)_3$ instead of zinc dust in order to avoid a reduction of the nitro function of ring C, provided the AB macrocycle in 65% yield and with excellent stereocontrol (>90% de), albeit again with the unnatural atropodiastereomer (*M*)-**621** prevailing. After cleavage of the *N*-TFA protecting group, attachment of **622**, and desilylation of the phenolic hydroxy function thus introduced, (*M*)-**623** was obtained in 55% yield. Formation of the CD diaryl ether bond was achieved by an S_NAr reaction providing the bicyclic tetrapeptide (*M*,*P*)-**624** in 79% yield and 67% de in favor of the desired planar−chiral configuration.

After removal of the nitro group and adjustment of the protective groups affording (*M*,*P*)-**625** (Scheme 97, five steps, 68% yield), the three phenolic methyl ethers were cleaved and the (*M*)-configuration of the AB ring system was inverted to (*P*) by thermal atropisomerization to give

Scheme 96



Scheme 97

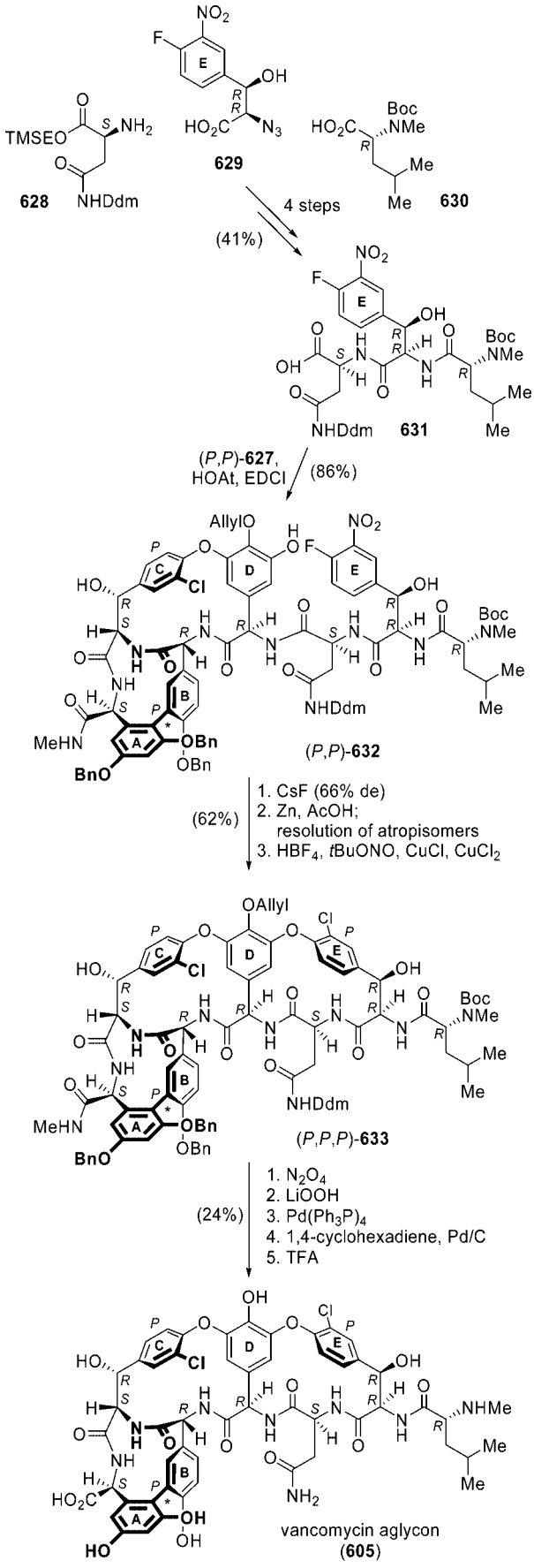


the natural western bicyclic framework (*P*,*P*)-**626** in 54% yield and with an excellent stereocontrol (>90% de). Five further steps exchanging the protective groups provided (*P*,*P*)-**627** in 65% yield.

The yet lacking eastern tripeptide building block **631** was constructed from its three precursors **628**−**630** in four steps and in 41% overall yield (Scheme 98). Peptide coupling of **631** to (*P*,*P*)-**627** provided the heptapeptide (*P*,*P*)-**632** (86% yield), which was subjected to an intramolecular S_NAr cyclization with CsF as a base to give the fully assembled tricyclic core **605** of vancomycin (**4**) as a 83:17 mixture of atropisomers in favor of the natural configuration, in a high 95% yield. Reduction of the nitro function with zinc afforded a mixture of atropisomeric anilines, which were easily resolved. In the required (*P*)-isomer, the chloro substituent at ring E was introduced by Sandmeyer reaction providing (*P*,*P*,*P*)-**633** in 62% yield from (*P*,*P*)-**632**. Five deprotection steps eventually delivered the vancomycin aglycon (**605**) in 24% yield. The expectedly difficult transformation of the *N*-methyl amide moiety at the carboxyl terminus into the carboxylic acid function was smoothly accomplished by selective nitrosation—in the presence of seven other amide functions—followed by exposure to lithium hydrogen peroxide (68% yield for two steps). The total synthesis of **605** thus succeeded in 40 steps (longest linear sequence) from 3,5-dimethoxybenzyl alcohol. The closely related eremomycin aglycon (C-ring dechloro vancomycin aglycon) was prepared by applying the same strategy.[373]

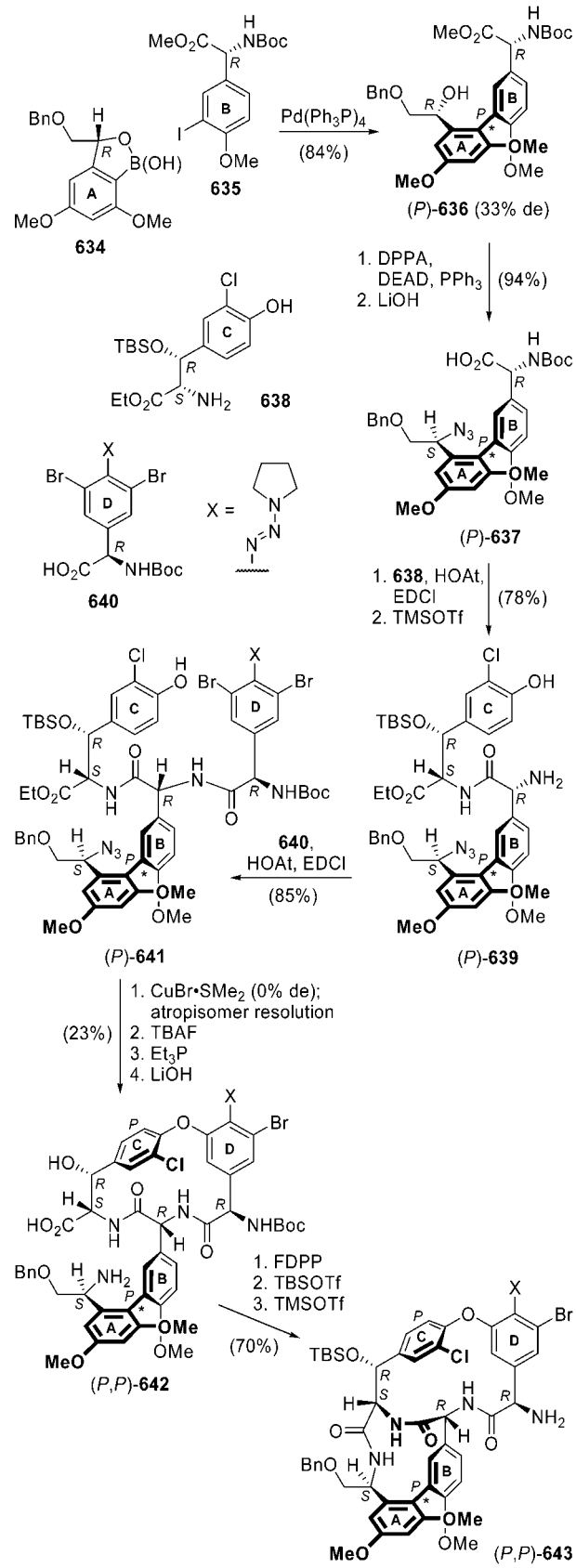
A short time after this first approach, the Nicolaou group published a second total synthesis of **605** (Scheme 99),[375−378] by using totally different strategies for the construction of the biaryl and diaryl ether bonds (an intermolecular Suzuki coupling and the use of the triazene method, respectively) and varying the order in which the macrocycles were constructed.[375] Thus, first the AB fragment was built up by Pd-mediated intermolecular coupling of **634** and **635** to give **636** in 84% yield and 33% de in favor of the naturally occurring (*P*)-atropodiastereomer.[376,377] After chromatographic purification of (*P*)-**636**, introduction of the azide function with inversion of configuration, and saponification of the methyl ester, (*P*)-**637** was obtained in 94% yield. Attachment of **638** using HOAt and EDCI and cleavage of the *N*-Boc protective group gave (*P*)-**639** (78% yield), which

Scheme 98



was subjected to peptide bond formation with the triazene **640** to deliver (*P*)-**641** in 85% yield. CuBr·SMe_2-mediated

Scheme 99



ring closure of (*P*)-**641** provided the tetrapeptide in a 50:50 ratio of its C-ring epimers in 67% yield. Despite some exploratory work toward the thermal isomerization of the undesired stereoisomer, the stereochemically pure product finally had to be gained by chromatography. Removal of the

O-TBS group, reduction of the azide, and hydrolysis of the ethyl ester furnished (*P*,*P*)-**642** (23% yield from (*P*)-**641**), which was cyclized using pentafluorophenyl diphenylphosphinate (FDPP), followed by silylation at the benzylic hydroxy function and *N*-deprotection to give the bicyclic building block (*P*,*P*)-**643** in an overall 70% yield.

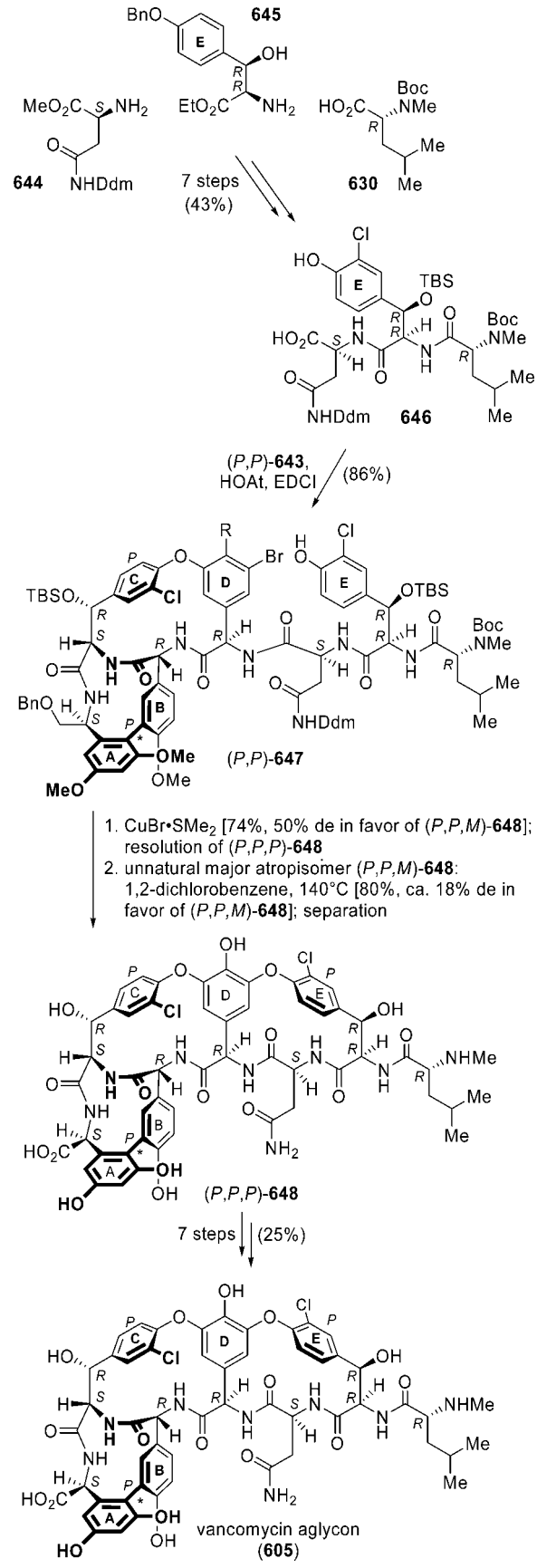
The eastern tripeptide **646** of the vancomycin aglycon (**605**) was independently prepared from the amino acids **644**, **645**, and **630** in seven consecutive steps with an overall yield of 43% (Scheme 100).[376] Amide bond formation between **646** and (*P*,*P*)-**643** delivered the heptapeptidic precursor (*P*,*P*)-**647** in 86% yield, even in the presence of the free phenolic hydroxy group of **646**. The macrocylization was again achieved with $CuBr \cdot SMe_2$, providing a 25:75 mixture of the (*P*,*P*,*P*)- and (*P*,*P*,*M*)-**648** epimers, unfortunately in favor of the unnatural (*M*)-configuration at the new planar−chiral element. This "wrong" epimer is, however, not lost, but can be recycled by renewed conversion into a 41:59 mixture of (*P*,*P*,*P*)-**648** and (*P*,*P*,*M*)-**648** (80% yield) by heating to 140 °C, thus giving rise to the possibility of a nearly complete (iterative) transformation of the material into the desired isomer (*P*,*P*,*P*)-**648** by repeated chromatographic resolution and thermal atropisomerization. The vancomycin aglycon (**605**) was obtained in seven more steps, including the cleavage of the triazene moiety and full deprotection.

In 1999, Boger et al. published a third approach to **605**,[379] integrating strategies successfully applied in the former total syntheses, such as the AB ring closure by amide bond formation and the construction of the CD and DE diaryl ether linkages by S_NAr reactions. Despite these similarities, the new access to the aglycon **605** differed remarkably from the previous syntheses. In-depth studies on the thermodynamics of the equilibria of the subunits bearing planar and axial chirality[380,381] resulted in a new strategy of the construction of the respective bonds, eventually permitting an—in principle complete—transformation of all intermediate atropodiastereomers into the natural product.

Tripeptide **652** was synthesized from the building blocks **649**−**651** in a three-step sequence with 72% yield and cyclized with K_2CO_3 and $CaCO_3$, generating the CD ring system as a 50:50 mixture of the epimers (*P*)-**653** and (*M*)-**653** in 60% yield (Scheme 101).[379,382] After chromatographic resolution, the unnatural isomer (*M*)-**653** was thermally reequilibrated to yield a 48:52 mixture, thus permitting a stepwise transformation of (*M*)-**653** into the desired (*P*)-configured building block.[379,380] Conversion of the nitro derivative (*P*)-**653** into the chloride (*P*)-**654** and Suzuki coupling of (*P*)-**654** with the boronic acid **655** provided the axially chiral biaryls (*P*,*P*)-**656** and (*M*,*P*)-**656** in good 88% yield, albeit as a 43:57 mixture of the atropoepimers.[379] As for **653**, repeated resolution and thermal equilibration of (*M*,*P*)-**656** at 120 °C, which furnished a 75:25 atropodiastereomeric mixture of (*P*,*P*)-**656** and (*M*,*P*)-**656**, permitted an accumulation of the required diastereomer (*P*,*P*)-**656**. Under these conditions, the configurational stability in the CD ring portion was not affected, since the activation barrier for the latter process was significantly higher (30.4 vs 25.1 kcal mol^{-1}).

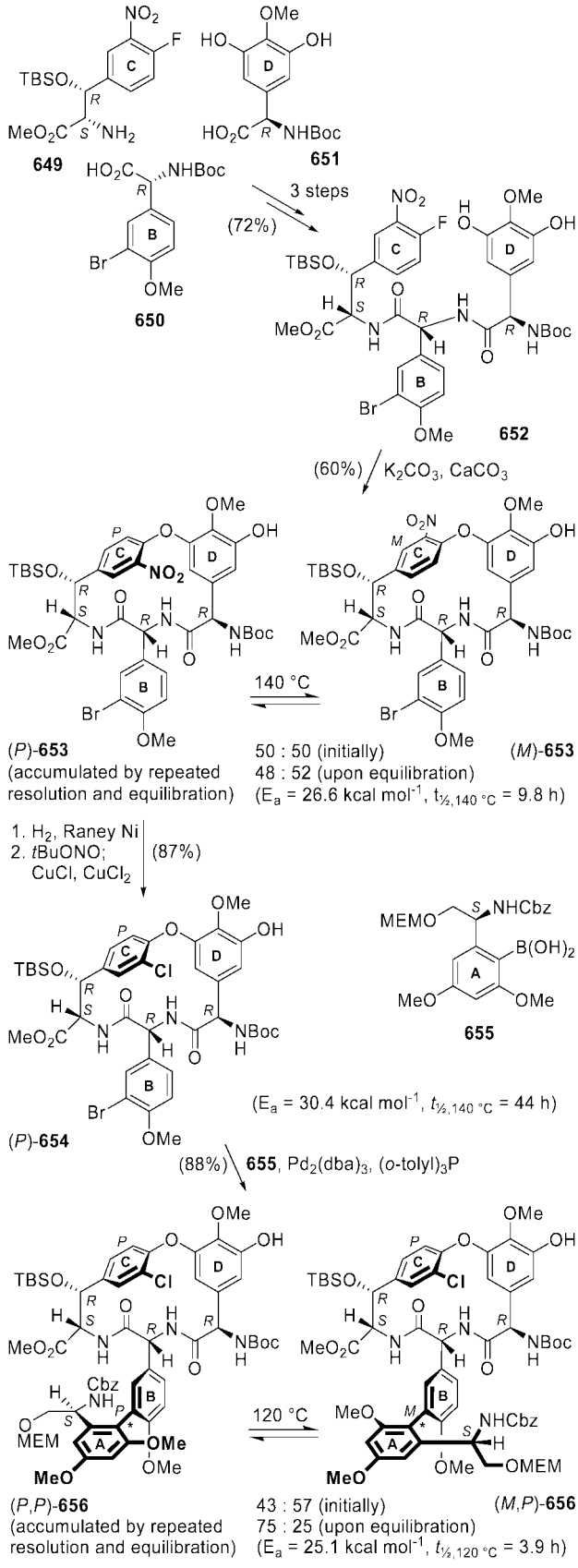
Cleavage of the *O*-TBS group of (*P*,*P*)-**656**, saponification of the methyl ester, and removal of the *N*-Cbz protective group paved the way for macrolactamization by treatment with HOBt and EDCI to furnish the bicyclic tetrapeptide (*P*,*P*)-**657** in 47% yield after removal of the Boc protective group (Scheme 102).[379] Attachment of the eastern tripeptide

Scheme 100

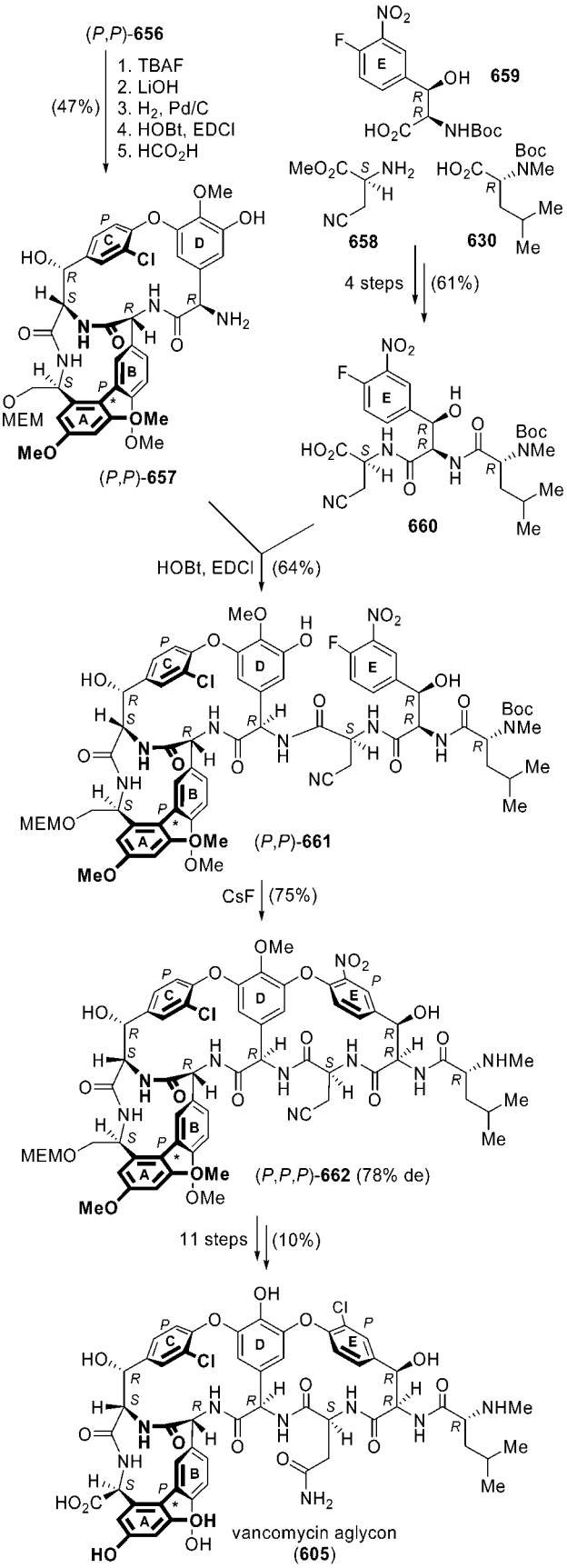


660, which was accessible from **658**, **659**, and **630** in four steps,[382,383] to the bicycle (*P*,*P*)-**657** gave the nitro compound (*P*,*P*)-**661**, which was cyclized by renewed S_NAr reaction using CsF to afford (*P*,*P*,*P*)-**662** (75%) with a good kinetic

Scheme 101



Scheme 102



diastereoselection (78% de). Although the final deprotection and functional group interconversion reactions needed 11 more steps, Boger et al.'s convergent atropoenantioselective synthesis of the vancomycin aglycon (**605**) required just 24 steps from the respective amino acids (thermal isomerizations not included) and provided an excellent overall performance (ca. 1% yield).

After the successful total syntheses of the vancomycin aglycon (**605**), the three groups turned to related, but different

projects. Nicolaou and co-workers succeeded in building a glycopeptide library with different sugar moieties attached[13] and achieved the total synthesis of the fully functionalized glycopeptide itself.[384] The groups of Boger and Evans, by contrast, switched to the synthesis of the structurally even more complex teicoplanin aglycon (**607**), both applying a convergent approach with analogues of their respective ABCD fragments as used in their syntheses of **605** and the independently obtained "eastern" tripeptide.

Evans et al. synthesized the tripeptide **666** from the amino acids **663**−**665** in five steps and 57% yield (Scheme 103).[385] After *N*-deprotection with TFA, macrolactamization was achieved utilizing HATU and HOAt to give **667**. Hydrolysis of the terminal *N*-methyl amide moiety via the nitrosamide intermediate and peptide bond formation with (*P*,*P*)-**668**, a bicyclic tetrapeptide closely related to the precursor (*P*,*P*)-**627** (see Scheme 97) already used in Evans' vancomycin synthesis, gave the fluorophenol (*P*,*P*)-**669**, which was cyclized by nucleophilic aromatic substitution to furnish the tetracycle (*P*,*P*,*P*)-**670** with a very good diastereoselection (>88% de). Final functional group manipulation and cleavage of all protective groups delivered the aglycon **607** of teicoplanin (**606**) in five further steps and 25% yield.

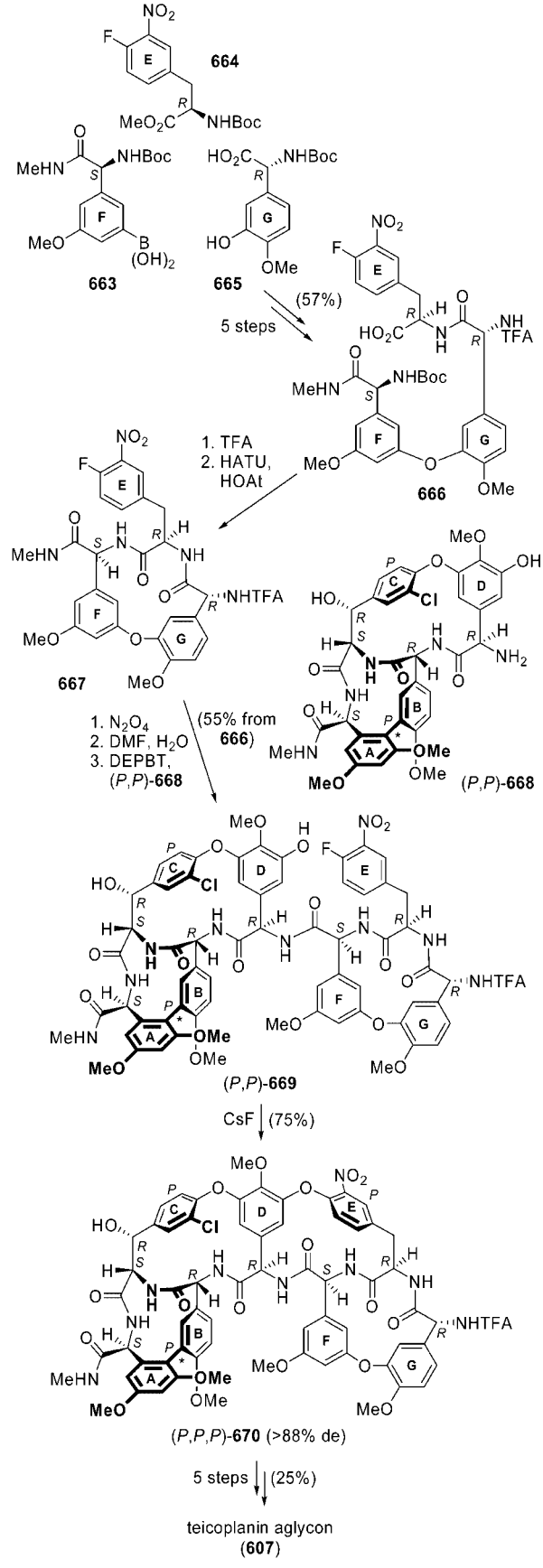
Boger and co-workers elaborated two different approaches to the teicoplanin aglycon (**607**),[370,386−388] with both strategies taking advantage of the late precursor (*P*,*P*)-**657** (see Scheme 102) of their previous vancomycin synthesis. In the first of these routes, the diaryl ether **674** was synthesized from the building blocks **671**−**673** in 10 steps and 36% yield (Scheme 104).[386] Amide bond formation with the western part (*P*,*P*)-**657** by using the peptide coupling agent 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) delivered the heptapeptide (*P*,*P*)-**675** (83% yield), which was subjected to an S_NAr reaction giving the tetracycle (*P*,*P*,*P*)-**676** in 80% yield, albeit with a moderate stereocontrol (50% de in favor of the required diastereomer).

(*P*,*P*,*P*)-**676** was converted into (*P*,*P*,*P*)-**677** in a seven-step sequence in 38% yield (Scheme 105). Final macrolactamization of the "southeastern" cycle by utilizing PyBop delivered the fully functionalized precursor (*P*,*P*,*P*)-**678** (66% yield), which was transformed into the aglycon (*P*,*P*,*P*)-**607** of the natural product in four more steps and 29% yield.

In their more convergent, second-generation approach, Boger et al. first built up the complete FG macrolactam subunit **680** by cyclization of the tripeptide **679**, which is structurally closely related to their open-chain precursor **674** as utilized in the synthesis described above (see Scheme 104), in 95% yield (Scheme 106).[387] Conversion of **680** into its acid derivative **681** in four steps and 86% yield paved the way for the DEPBT-mediated peptide bond formation with the known amine (*P*,*P*)-**657** to give (*P*,*P*)-**682** in 72% yield. Ring closure by nucleophilic aromatic substitution delivered the tetramacrocycle (*P*,*P*,*P*)-**683** in 76% yield and with >82% de. The substantially increased diastereoselection for this ring closure over that from (*P*,*P*)-**675** to (*P*,*P*,*P*)-**676** (see Scheme 104, 50% de) is a consequence of the intact FG ring system. The aglycon **607** of teicoplanin (**606**) was attained in eight further steps and an overall yield of 16%.

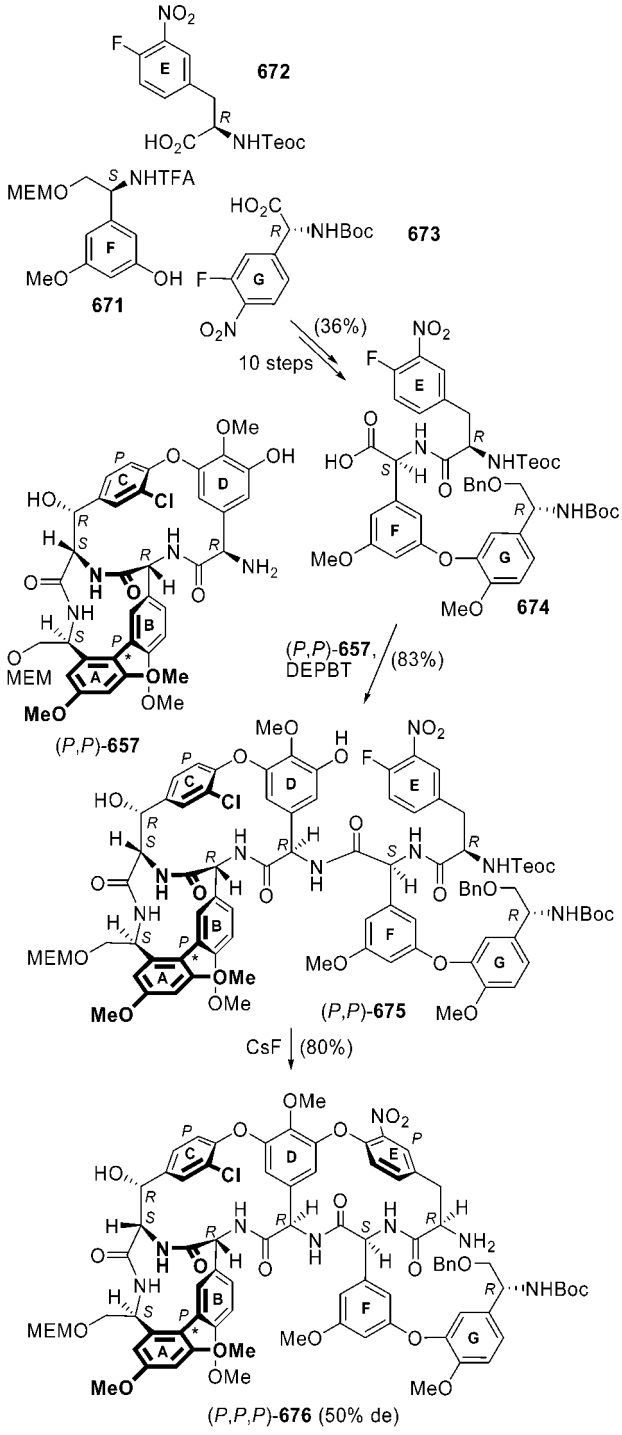
In 2004, Boger and co-workers also succeeded in the first total synthesis of the structurally closely related ristocetin aglycon (which lacks the chloro substituents and bears an additional benzylic hydroxy function next to ring E and an aromatic methyl group on ring F as compared to the teicoplanin aglycon **607**).[389] The key steps of this pathway

Scheme 103



are almost identical to those of the second approach toward **607** described in Scheme 106 and will thus not be discussed here separately. It is worth mentioning that the diastereose-

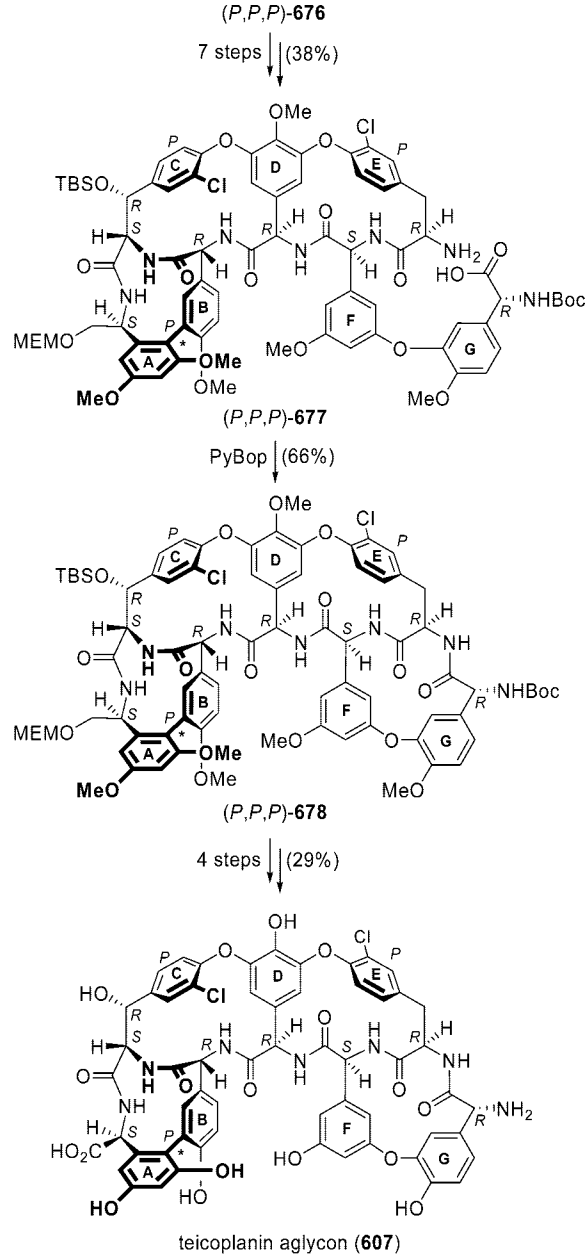
Scheme 104



lectivity in the last S_NAr cyclization was even further improved to >88% de in favor of the natural configuration.

In 2003, Hoveyda, Snapper, and co-workers reported the first total synthesis of the bicyclic heptapeptide chloropeptin I (**608**),[390,368] which, compared to vancomycin (**4**) and teicoplanin (**606**), possesses a stereogenic biaryl bond between the rings D and F, but no AC biaryl bond. The key step for the formation of the BD diaryl ether bond was a Cu-mediated coupling, whereas the DF biaryl bond was constructed using a Pd-catalyzed cross-coupling reaction. Tripeptide **687** was obtained from the chiral building blocks **684**−**686** in four steps and 62% overall yield (Scheme 107). $NaIO_4$-induced cleavage of the pinacol boronic ester to release the corresponding boronic acid and copper-mediated

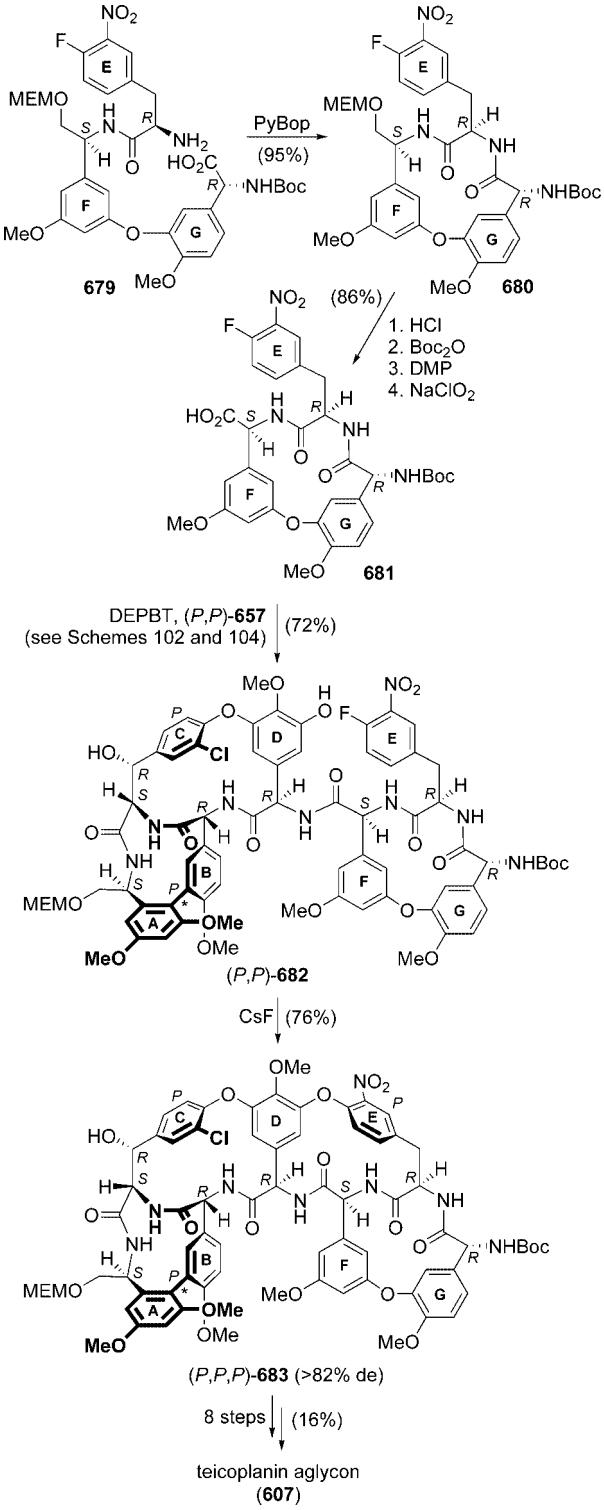
Scheme 105



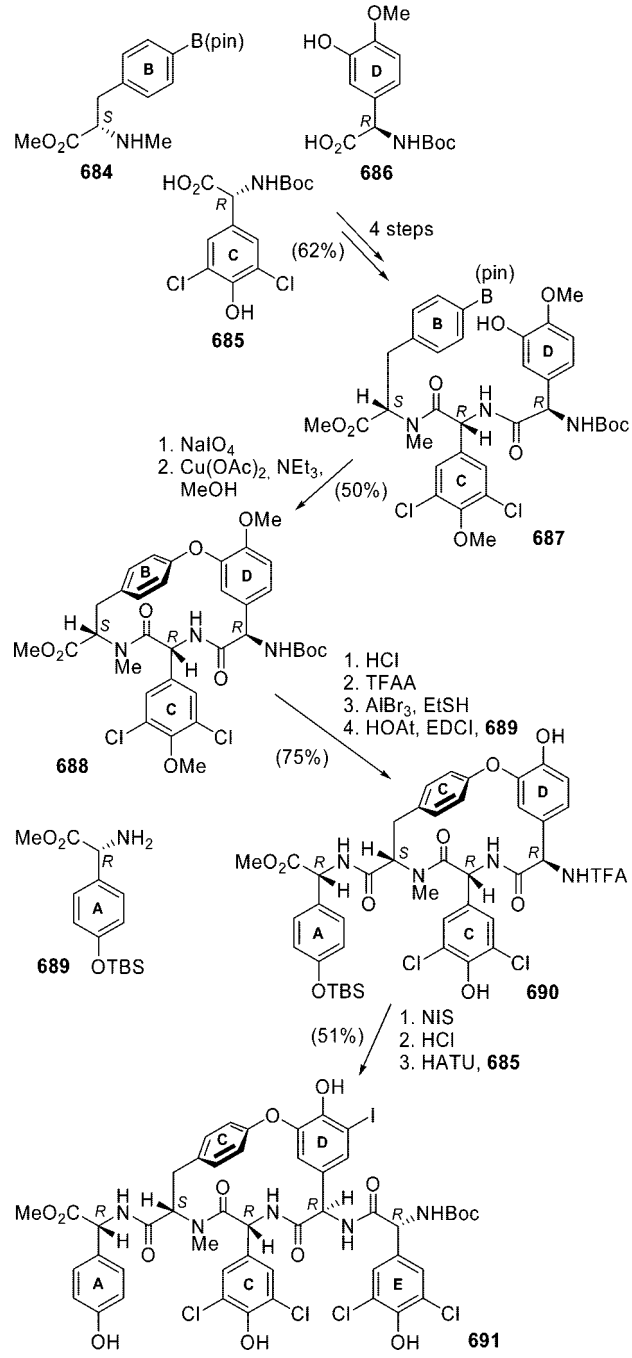
coupling in the presence of an excess of MeOH and NEt_3 (both being crucial for the success of the coupling reaction) gave the diaryl ether **688** in 50% yield. Protective group exchange at the terminal amino function, demethylation of the two phenolic ethers, and saponification of the methyl ester set the stage for the peptide coupling with **689** providing the intermediate **690** (75% overall yield), which was equipped with an iodo substituent at ring D, as needed for Pd-mediated cross-coupling later in the synthesis. Acid-mediated removal of the TBS and TFA protective groups with subsequent installment of the second dichlorophenylglycine unit **685** furnished the cyclic pentapeptide **691** in 51% yield.

Cleavage of the *N*-Boc group of **691** and amide bond formation with the sodium salt **692** gave **693** (Scheme 108), which was directly subjected to a $Pd(PtBu_3)_2$-catalyzed Stille coupling to deliver the bicyclic product (*M*)-**694** in 38−42% overall yield and as a single isolated diastereomer. The final three steps were the cleavage of the *N*-Boc group, the coupling of the resulting amine to the α-ketoacid **695**, and

Scheme 106



Scheme 107

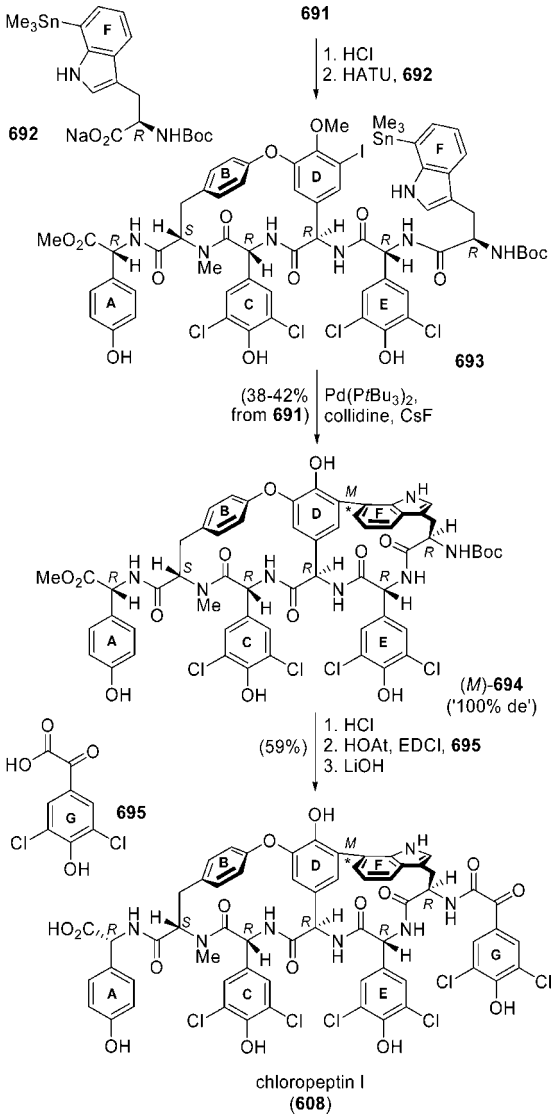


the saponification of the methyl ester, leading to the target molecule chloropeptin I (**608**) in 59% yield over the last three steps (19 steps and 4% overall yield from the amino acids **684**−**686**).

Following this first total synthetic access to **608**, Hoveyda, Snapper, and co-workers also succeeded in the preparation of isocomplestatin, an (*M*)-configured DF coupling regioisomer of chloropeptin I (**608**).[391] Further—non-natural—diastereomeric derivatives of these types of cyclic peptides have recently been synthesized by Zhu's group.[392]

In conclusion, the synthesis of the aglycon **605** of vancomycin (**4**) by Nicolaou et al. was developed in a remarkably short time but has some drawbacks concerning the atropisomeric selectivity. These problems have been solved more conveniently by the approaches of Evans' and Boger's groups, who used their synthetic knowledge in the atroposelective preparation of even more complex glycopeptides, like, e.g., the aglycon **607** of teicoplanin (**606**). The total synthesis of chloropeptin I[368] (**608**) by Hoveyda, Snapper, and co-workers also made this subgroup of cyclic peptides synthetically available. In contrast to the other, more convergent syntheses described, it is based on a strictly linear reaction sequence. Although "only" atropodiastereoselective methods were used to establish the chiral information at the biaryl axis, all approaches toward the different members of this group of natural products impressively demonstrate the

Scheme 108



power of modern synthetic concepts for the construction of even highly complex biaryl natural products.

5. Conclusions

During the past decades, axially chiral biaryl natural products have received particular attention, due to their often promising pharmacological profiles and their exceptional architectures created by the element of axial chirality. The structural variety in this class of naturally occurring substances is broad and ranges from simple biphenyls to highly complex glycopeptides with numerous further stereogenic elements. As a consequence, the challenges associated with their total syntheses are often manifold, beginning with the preparation of suitable aromatic building blocks over the atroposelective aryl−aryl coupling reaction (or other methods that establish the axial configuration) to the final steps toward the natural product. Quite a number of powerful and reliable methods have been developed for the construction of the chiral biaryl axis, which is, in most cases, the stereochemically decisive key step. Diastereoselective biaryl coupling reactions that use already existing stereoelements, artificial bridges, or chiral *ortho*-substituents nowadays belong to the standard repertoire, giving good to excellent chemical and optical yields. A particularly successful approach is provided by the dynamic kinetic resolution of configurationally unstable biaryl lactones, as demonstrated in a large number of applications in natural product synthesis. Atropoenantioselective methods, however, are still rare, but good progress has been made in developing strategies for the enantioselective oxidative coupling of naphthols. This biomimetic approach might receive increasing importance if it can be extended to phenolic substrates in general.

With the steadily growing number of natural products possessing a chiral biaryl axis, both the further refinement of the existing methods and the development of novel strategies, e.g., for atropoenantioselective, redox-neutral, and direct biaryl coupling reactions, are necessary to simplify the often lengthy total syntheses. Nevertheless, it is astonishing how rapidly the atroposelective total synthesis of some of the most complex representatives of this class of natural products has been recently achieved. Still, many subgroups of axially chiral natural products have not yet been synthetically accessed, and it will be rewarding to meet this challenge.

The total synthesis of axially chiral biaryl natural products is much more than a mere playing field for organic chemists. It can be pivotal for structural elucidation or conformation (as seen in the case of diazonamide A) and, in particular for pharmacologically active substances, to get sufficient material and modified analogues for in-depth biological testing, elucidation of the mode of action, and, eventually, for the development of more potent derivatives with less side effects.

6. Abbreviations

Ac	acetyl
acac	acetylacetonate
9-BBN	9-borabicyclo[3.3.1]nonane
(*P*)-BINAL-H	(*P*)-(−)-2,2′-dihydroxy-1,1′-binaphthyllithium aluminum hydride
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
Bz	benzoyl
DCC	dicyclohexylcarbodiimide
Ddm	4,4′-dimethoxydiphenylmethyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DIBAH	diisobutylaluminum hydride
dipyrithione	2,2′-dithiobis(pyridine-*N*-oxide)
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DMTCl	4,4′-dimethoxytriphenylmethyl chloride
dppb	1,4-bis(diphenylphosphino)butane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FDPP	pentafluorophenyl diphenylphosphinate
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HHDP	6,6′-dicarbonyl-2,2′,3,3′,4,4′-hexahydroxybiphenyl
HMPA	hexamethylphosphoric triamide
HOAt	*N*-hydroxy-7-azabenzotriazole
HOBt	*N*-hydroxy-1*H*-benzotriazole
LDA	lithium diisopropylamide

MCPBA	3-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NSu	succinimidyl
PCC	pyridinium chlorochromate
pin	2,3-dimethyl-2,3-butanediol
PMB	4-methoxybenzyl
PTC	phase-transfer catalysis
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TCDI	*N*,*N*′-thiocarbonyldiimidazole
TEBACl	triethylbenzylammonium chloride
Teoc	2-(trimethyl)ethoxycarbonyl
Tf	triflate (trifluoromethylsulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
TIPS	triisopropylsilyl
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
Ts	tosyl (4-methylphenylsulfonyl)

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8. Note Added after ASAP Publication

This paper was published on the Web on October 12, 2010 with an incorrect Figure 19 due to publisher error. The corrected version was reposted on November 2, 2010.

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