VOLUME 34 NUMBER 8
ACCOUNTS of CHEMICAL RESEARCH®
AUGUST 2001

Stereoselective Total Synthesis of Axially Chiral Natural Products via Biaryl Lactones†

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Received March 7, 2001

ABSTRACT
Axially chiral natural products are rewarding synthetic targets, due to their wide distribution, diverse structures, and promising bioactivities. The "lactone concept" provides an efficient strategy for the regio- and stereoselective construction of even bulky biaryls. Key steps are the intramolecular coupling of the ester-prefixed molecular portions to give (mostly configurationally unstable) biaryl lactones and their stereoselective ring cleavage (usually by dynamic kinetic resolution), leading to the one or—optionally—the other atropisomeric product from the same lactone. Stereoisomeric byproducts can be recycled by recyclization back to the lactone. The broad applicability of the method is demonstrated in the total synthesis of selected representatives from five very different classes of natural biaryl products.

1. Introduction

Eighty years after the first observation of axial chirality,[1] this phenomenon is still ambiguously assessed. On one hand, the structures of obviously rotationally hindered new biaryl natural products are—even today—frequently published "flat", without regarding the phenomenon of atropisomerism, so that often not even α_D values are published.[2] On the other hand, axial chirality is of increasing importance, because of the sometimes substantially different bioactivities of atropisomers,[3] and because of its widespread occurrence in nature.[4] Wherever phenolic compounds occur in living organisms, from whatever biosynthetic origin, the corresponding "dimers"—symmetric or unsymmetric—can be expected. Moreover, axial chirality represents one of the stereochemical key features of modern synthetic chemistry. Next to centrochiral compounds, rotationally hindered biaryls with their rigid chiral framework are the most successful reagents, ligands, and catalysts.[5]

Given the importance of chiral biaryls and the high demand for their availability, a number of synthetic approaches, based on oxidative, "redox-neutral", or reductive coupling steps, have been elaborated.[6,7] Still, powerful methods that can actually be applied to the synthesis of concrete natural biaryls are quite rare.[7,8] In particular, there are few practicable regiocontrolled cross-coupling methods that are atropo-divergent (i.e., allowing production of any of the two possible atropisomers from preferably "late" joint precursors), economic (inter alia, permitting reuse of undesired stereoisomeric byproducts), and efficient, giving high chemical and optical yields even for bulky target molecules. In this paper, we present the "lactone method", a conceptually unique and preparatively successful pathway to biaryls that indeed accomplishes the above requirements, and its application to natural product synthesis.

2. The Basic "Lactone Concept"

The general principle of the "lactone method" [9] for the regio- and stereoselective total synthesis of axially chiral biaryls is outlined in Scheme 1. Accordingly, the axis is constructed in a two-step procedure, achieving the two goals of stereoselective biaryl synthesis *consecutively*—the

† Novel Concepts in Directed Biaryl Synthesis 96; for part 95, see ref 42.

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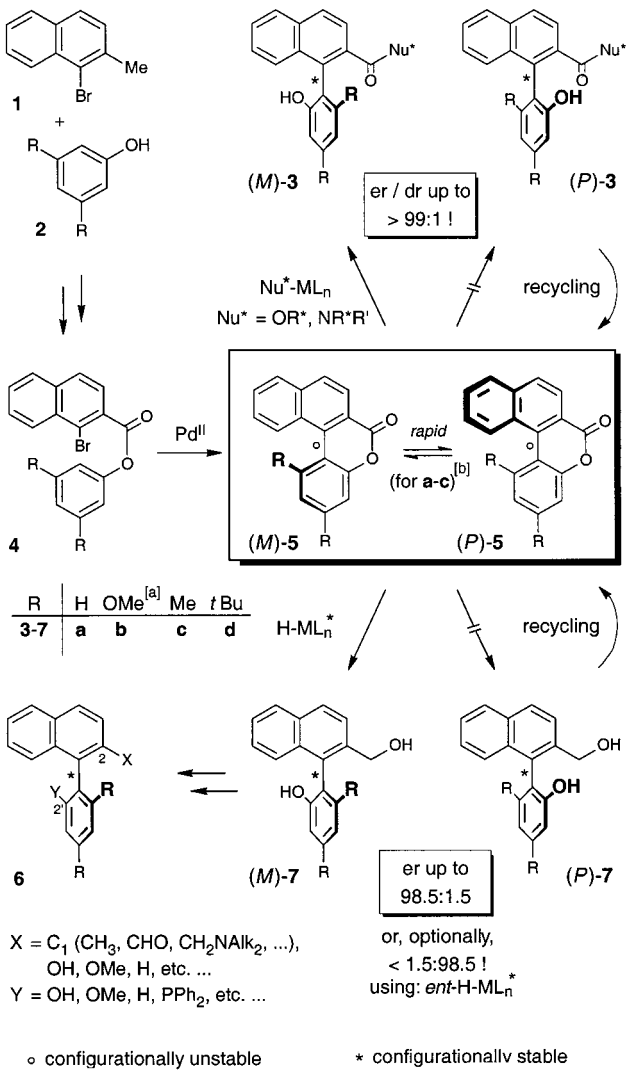
10.1021/ar000106z CCC: $20.00
Published on Web 07/21/2001

Scheme 1. The Basic Principle: Preparation and Atroposelective Ring Cleavage of Configurationally Unstable Lactones[a]



[a] Note that, due to the CIP formalism, biaryls **3** and **7** (but not **5**) with R = OMe have opposite descriptors compared to those with R = H or alkyl. [b] Due to the large ortho *tert*-butyl group, lactone **5d** is configurationally stable at room temperature.[10]

C−C bond formation and the asymmetric induction. The biaryl coupling is performed intramolecularly, after prefixation of the aromatic moieties, **1** and **2**, via an ester type bridge as in **4**. This bridge serves two purposes: it brings together the two building blocks and thus allows the palladium-catalyzed cyclization to proceed smoothly, giving the lactones **4** in excellent yields, even against extremely high steric hindrance (e.g., >80% yield for **4d**, with R = *t*-Bu!).[10] But the most significant (and innovative) function of the ester bridge is that it dramatically lowers the rotational isomerization barrier at the axis, so that, in contrast to the corresponding "open" biaryls (e.g., **3**, **6**, or **7**), six-membered biaryl lactones of type **5** (except for R = *t*-Bu) are still configurationally unstable and exist as racemic mixtures of rapidly interconverting atropo-enantiomers, (*M*)-**5** ⇌ (*P*)-**5**. Thus, starting from the lactone, the axial configuration can now be installed independently, in a separate step. Out of its racemic mixture, **5** can be cleaved with high stereoselectivity by a number of chiral *H*-,[11] *O*-,[12] or *N*-nucleophiles,[13] producing configurationally stable biaryl compounds, such as (*M*)-**3** or (*M*)-**7**. By use of the other nucleophile enantiomer (i.e., *ent*-Nu*-ML$_n$ or *ent*-H-ML$_n$*), the other isomeric products, *ent*-(*M*)-**3** or *ent*-(*M*)-**7** [= (*P*)-**7**], can likewise be obtained, i.e., within an atropo-enantio- or -diastereodivergent reaction. Mechanistically, this ring cleavage reaction represents a dynamic kinetic resolution, and thus—in contrast to a "normal" (i.e., nondynamic) enantiomer-differentiating reaction—permits conversion of virtually all of the starting material into the correspondingly configured product. This favorable option is further complemented by the valuable possibility of recovering the small quantities of the "wrong" isomer, possibly likewise obtained, by cyclization back to the lactone **5** and its renewed atroposelective cleavage—chiral economy in the field of axial chirality!

Although initially elaborated for biaryls containing an OH and a C$_1$ unit in opposite ortho-positions next to the axis, the method is by no means restricted to this target array. By standard transformations, the correctly configured biaryl structure **3** or **7** thus prepared can be transformed into biaryls with virtually any substitution pattern (e.g., into the various forms of **6**), inter alia, by conversion of the C$_1$ unit at C-2 to a methyl,[14] an aminomethyl,[15] or a hydroxy function[16]—or by its complete removal.[16] Exemplary conversions of the OH group at C-2′ are its reductive elimination[17] or substitution, e.g., by a phosphine group.[18]

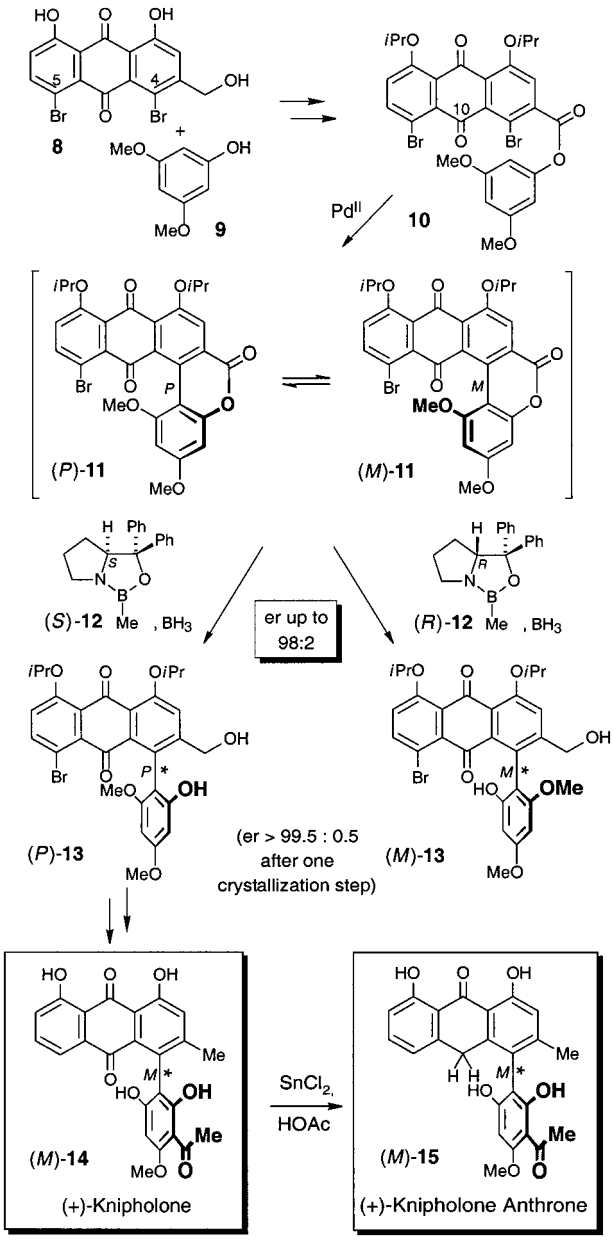
But the most thrilling feature of the method—besides its conceptual novelty—is its applicability to the stereocontrolled synthesis of a variety of target biaryls from quite different classes of natural products, as demonstrated in the following.

3. Applications of the Method to Natural Product Synthesis

3.1. (+)-Knipholone and Related Phenylanthraquinones. One of the most recent applications of the concept in natural product synthesis and an instructive example of the procedure is the first—and atropo-enantioselective—total synthesis of (+)-knipholone [(*M*)-**14**].[19] This phenylanthraquinone from the torch lily *Kniphofia foliosa* and other African plants[20] shows good antimalarial activity in vitro against *Plasmodium falciparum*.[21] Being composed of an anthraquinone (viz. chrysophanol) and a phenyl (viz. xanthoxylline) moiety, it represents one of the rare "true" examples of a constitutionally unsymmetric natural biaryl. It is optically active ($[\alpha]_D^{20}$ +80°) and thus stereochemically stable, and its absolute configuration has recently been elucidated by quantum chemical CD calculations.[22]

One of the characteristics of our synthesis[19] (and of the lactone method in general) is its convergent character, allowing independent preparation of the two molecular portions. The first was carboxylic acid **8** (here more comfortably with *two* bromine substituents rather than just with the required, functional one at C-4), and the second was the phenolic part **9**. Attachment of **8** to **9** was achieved by conversion to the bromoester **10** (Scheme 2).

Scheme 2. (+)-Knipholone: The First Arylanthraquinone To Be Stereoselectively Synthesized



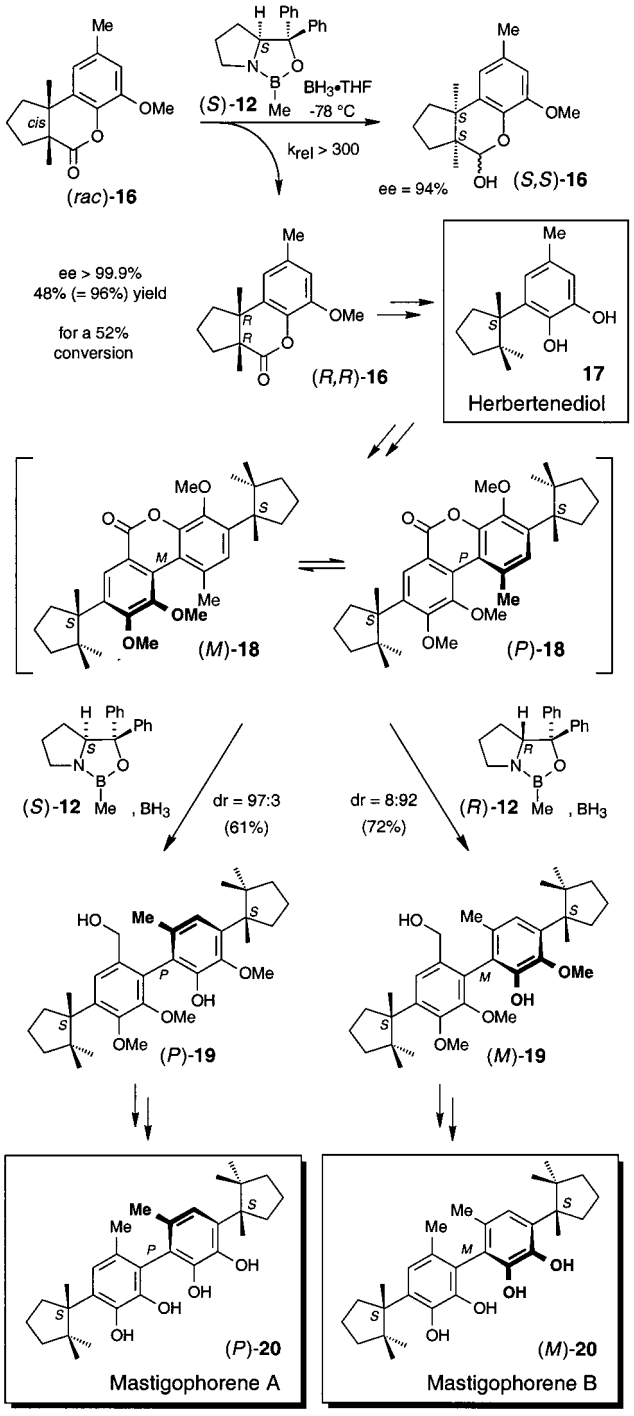
Against the steric hindrance by the C-10 keto function, the Pd-catalyzed intramolecular coupling produced the key intermediate **11** in good yields and without affecting the additional bromo function at C-5. Remarkably, lactone **11** is configurationally unstable, which thus permitted the following ring cleavage as a dynamic kinetic resolution. Likewise luckily, it was possible to reduce the lactone function of the bridge chemoselectively (without attacking the quinoid system)—and also stereoselectively. The reagent of choice to achieve both goals was the oxazaborolidine–borane system, which, initially developed for the enantioface-differentiating attack on carbonyl functions, mainly of ketones,[23] is a powerful reagent for the atropo-enantio- or -diastereoselective ring cleavage of configurationally unstable biaryl lactones.[9,11] Using the oxazaborolidine (*S*)-**12**, the diol (*P*)-**13** can be obtained in high chemical (81%) and optical (er up to 98:2) yields, while, as expected, (*R*)-**12** gives (*M*)-**13** with the same asymmetric induction. The optical purities can be further enhanced by recrystallization of the respective product enantiomers, and the undesired minor atropisomeric byproduct (e.g., from the mother liquor) can be reutilized by recyclization back to the lactone (not shown). In a few steps, including the introduction of the *C*-acetyl group (e.g., by a Fries rearrangement), the first total synthesis of knipholone [(*M*)-**14**], moreover in enantiopure form, was accomplished.[19]

In a similar way, several further phenylanthraquinones were obtained, among them, e.g., (+)-knipholone anthrone [(*M*)-**15**], which shows an even better antiplasmodial activity than **14**.[21] As demonstrated for these previously unattained synthetic targets, the "lactone concept" tolerates high steric hindrance and the presence of various functional groups, like the additional bromine atom or the quinoid system.

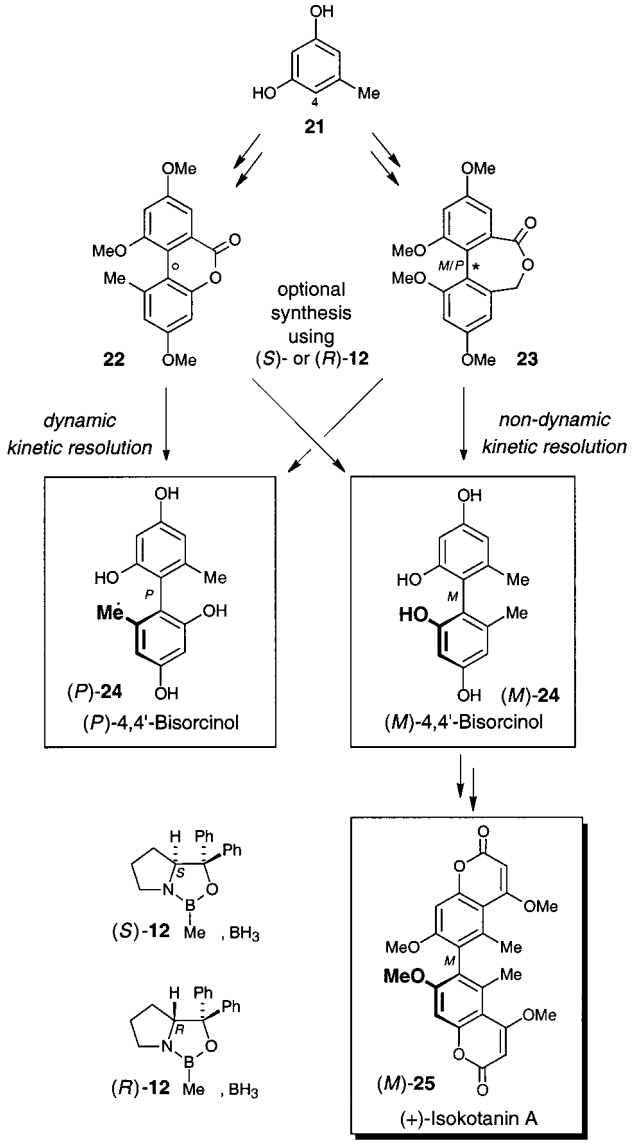
3.2. Mastigophorenes A and B. In contrast to knipholone, the mastigophorenes A [(*P*)-**20**)] and B [(*M*)-**20**)] are constitutionally symmetric and possess two (homochiral) stereocenters, so that they are atropo-*diastereomeric* to each other. These—hence C_2-symmetric—"dimeric" sesquiterpenes from *Mastigophora* liverworts have attracted interest for their nerve growth stimulating activity,[24] triggering numerous synthetic efforts. The first synthesis used a biomimetic oxidative phenolic coupling of their (partially protected) joint monomeric half, herbertenediol (**17**), yielding the two atropisomeric products with unspectacular diastereomeric ratios (dr 40:60).[25] By the oxazoline-mediated asymmetric Ullmann coupling, Degnan and Meyers[26] obtained higher stereoselectivities for mastigophorene A (dr 75:25) and for mastigophorene B (dr 13:87, when starting from a near-enantiomeric oxazoline) in the decisive coupling steps, yet still leaving room for further improvements with respect to atropo-diastereodivergence and asymmetric inductions.

Our mastigophorene synthesis[14] utilizes enantio- and diastereomer-differentiating reactions on lactone intermediates, both for the regio- and stereoselective construction of the biaryl axis (see below), and for the achievement of the correct configuration at the stereocenter. The key substrate for this new modification is the "aromatic–aliphatic" lactone **16**, which is (of course) configurationally stable. It proved to be an ideal substrate for a virtually perfect (k_{rel} > 300!)—now nondynamic—kinetic resolution of (*rac*)-**16**, by the oxazaborolidine–borane system, giving the remaining enantiomer, (*R*,*R*)-**16**, in excellent chemical and optical yields (Scheme 3). After its conversion to the natural[27] monomer herbertenediol (**17**), the biaryl lactone **18** was again obtained via the corresponding bromoester. The (expected) configurational instability of **18** again permitted its ring cleavage to proceed atropo-diastereodivergently, according to the principle of a dynamic kinetic (here diastereomeric) resolution. Reduction of **18** with (*S*)-**12** gave (*P*)-**19** (dr 97:3), while (*R*)-**12** yielded (*M*)-**19** (dr 92:8) in high asymmetric inductions. From these configurationally stable alcohols, (*P*)-**19** and (*M*)-**19**, the atropisomeric mastigophorenes A [(*P*)-**20**] and B [(*M*)-**20**] were

Scheme 3. Controlling Centrochirality and Axial Chirality via Lactones: Synthesis of the Sesquiterpene Herbertenediol and Its "Dimers", the Mastigophorenes A and B



Scheme 4. Dynamic vs Nondynamic Kinetic Resolution: Atropo-Enantiodivergent Synthesis of Bisorcinols and of the Bicoumarin (+)-Isokotanin A

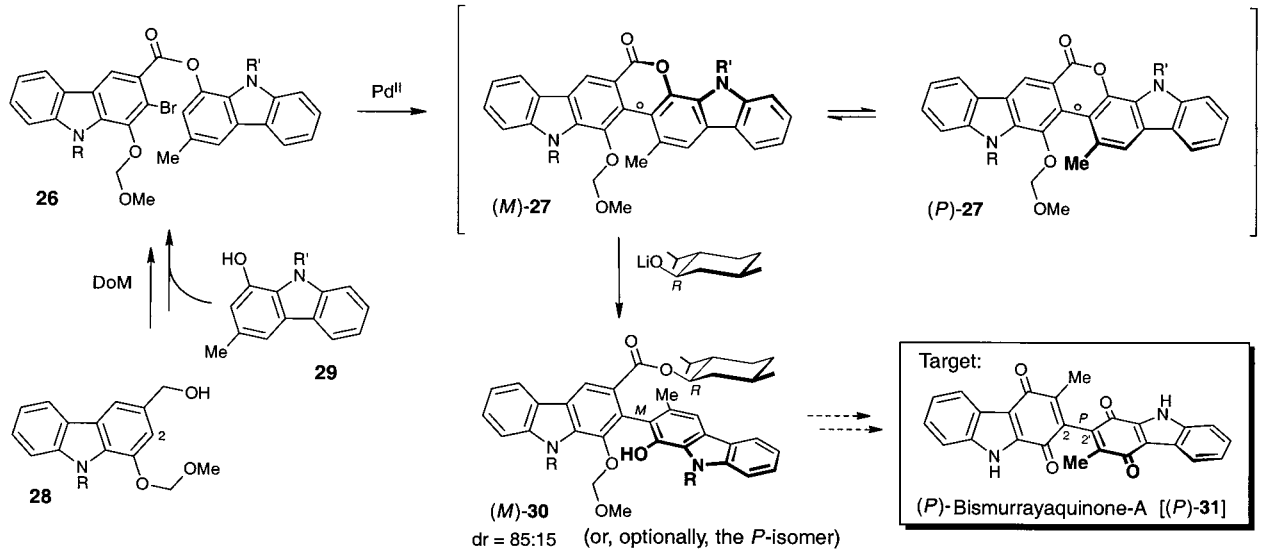


obtained—straightforward and, ultimately, via the same "late" lactone precursor, **18**.

3.3. (+)-Isokotanin A. Again C_2-symmetric, but without any stereocenters, are the—hence atropo-enantiomeric—forms of 4,4′-bisorcinol, (*P*)- and (*M*)-**24**, potential natural precursors to litmus dyes[28] in lichens. Following the lactone concept, the monomeric portion, orcinol (**21**), was enantio-divergently transformed into either (*P*)-**24**—or (*M*)-**24**—via the configurationally unstable six-membered lactone **22** as the joint key intermediate,[29] by the use of the respective oxazaborolidine enantiomer, (*S*)- or (*R*)-**12** (Scheme 4). As yet another novel variant, the lactone methodology was extended to seven-membered lactones such as **23** as likewise useful intermediates.[10,30] Because of the additional methylene group in the bridge, these biaryls are configurationally stable under the reaction conditions. Their atropo-enantioselective reduction with the oxazaborolidine−borane system, hence within non-dynamic kinetic resolution, proceeded with high relative rate constants (k_{rel} = 43). The remaining unreacted enantiomer of **23** can be reused, by brief thermal racemization ($t_{1/2}$ = 6 min, 100 °C) and renewed ring cleavage. Such seven-membered lactones are accessible by an Ullmann coupling → Cannizzaro reaction → cyclization sequence,[30] or (if composed of two different aromatic portions) again by intramolecular coupling of the ester-prefixed molecular parts.[31]

As another application of the lactone method to natural products synthesis, (*M*)-**24** was converted into (+)-iso-

Scheme 5. First Atroposelective Construction of the Biscarbazole Core of Bismurrayaquinone A



kotanin A [(*M*)-**25**],[32,33] an insect antifeedant bicoumarin from an *Aspergillus* mold.[34]

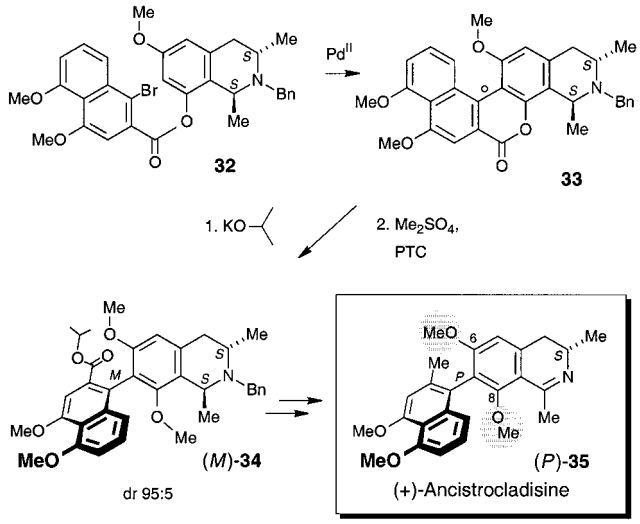
3.4. En Route to Bismurrayaquinone A. C,C- and N,C-bonded biarylic biscarbazoles comprise a class of so far 14 alkaloids, mostly from Asian *Murraya* species.[35] Although, from their substitution patterns, all of them should have a configurationally stable axis, none of the C,C-coupled[36] representatives has so far been assigned stereochemically, and not even α_D values for these natural biaryls are known.[35] Only recently, some enantiopure biscarbazole alkaloids became available synthetically, by (nonstereoselective) oxidative phenolic coupling of the natural monomeric carbazole units and subsequent racemate resolution.[37−40] Because of the lack of stereochemical information on the *natural* biscarbazoles and due to their bioactivities,[41] these compounds are attractive synthetic targets. Moreover, their structures (including the electron-pushing pyrrolic nitrogen) are considerably different from the previous examples and thus might pose a novel challenge to our concept.

As a first synthethic goal, we chose bismurrayaquinone-A (**31**), a 2,2′-coupled biscarbazole. It had already been prepared earlier, by oxidative phenolic coupling with chromatographic resolution of the atropisomeric forms, whose absolute configurations were assigned by quantum chemical CD calculations.[37] Starting from carbazoles **28** and **29**, the synthesis of the ester **26** (Scheme 5) required a regioselective bromination of **28** at C-2. This was achieved by the directed ortho metalation (DOM) methodology, with a hydroxymethyl (for the later carboxy substituent at C-3) and a methoxymethoxy function (for the oxygen function at C-1) as directing groups for the introduction of lithium and then bromine into the 2-position (90% yield).[42] For this exploratory approach, the protection of the carbazole nitrogen was effected by *N*-methylation, despite foreseen difficulties of a presumably impossible later deprotection. Different from all the previous cases, the intramolecular coupling of the ester **26** required stoichiometric quantities of the Pd "catalyst", producing lactone **27**, which, as anticipated, was configurationally unstable. Apparently due to the strongly electron-donating carbazole nitrogen, the carbonyl group was significantly less reactive than for all the examples above. Reductions with chiral H-nucleophiles proceeded slowly and with moderate yields. In this case, O-nucleophiles such as alkali mentholates proved to be the reagent of choice, producing ester (*M*)-**30** with a diastereomeric ratio of up to 85:15, permitting the first *stereoselective* synthesis of the biaryl core of a biscarbazole alkaloid.[42] With the still necessary introduction of a suitable (i.e., eventually cleavable) N-protective group R (e.g., benzyl), the now-started first atropisomer-selective total synthesis of a concrete biscarbazole alkaloid, e.g., (*P*)-bismurrayaquinone-A [(*P*)-**31**], should no longer pose any major problems.

3.5. Naphthylisoquinoline Alkaloids. The target molecules presented so far either were constitutionally symmetric and/or had no stereogenic centers. The naphthylisoquinoline alkaloids,[43] by contrast, are usually equipped with a stereogenic axis *and* with up to three stereocenters. Moreover, they consist of two quite different aromatic portions: a naphthalene part and a di- or tetrahydroisoquinoline moiety. These biosynthetically unprecedented, acetogenic[44] isoquinoline alkaloids furthermore show interesting bioactivities, including strong antimalarial[45] and antileishmanial[46] properties. In addition, high anti-HIV activities of some of their dimers have been found,[47] making these natural biaryls promising lead structures for the development of new medical drugs. The need for an efficient synthetic access to this class of alkaloids has been the initial impetus to develop our lactone concept.[9,43] Out of the ca. 20 naphthylisoquinoline alkaloids readily prepared by this strategy, three instructive examples will be presented here.

One of the earliest applications of the concept was the stereoselective total synthesis of ancistrocladisine [(*P*)-**35**] (Scheme 6). This antileishmanial[48] alkaloid from the Indian liana *Ancistrocladus heyneanus*[49] represents one of the ca. 25 known 7,1′-coupled naphthylisoquinolines.[43,50] Besides

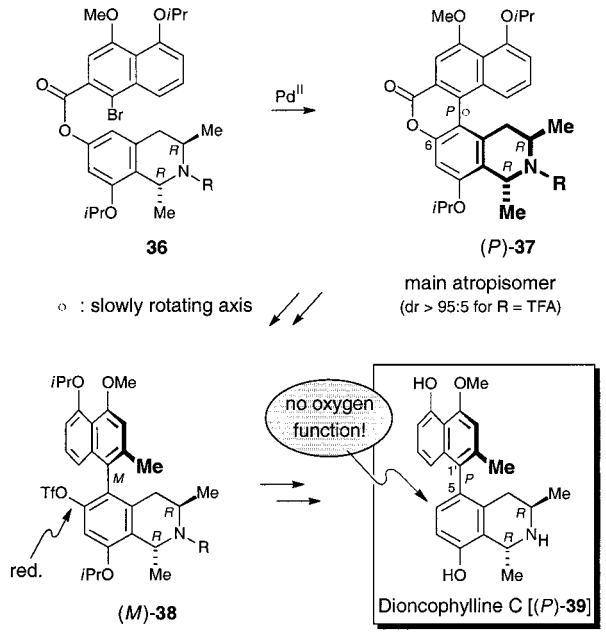
Scheme 6. A Target Molecule with Two Identical Ortho Substituents Next to the Axis: The Naphthylisoquinoline Alkaloid Ancistrocladisine



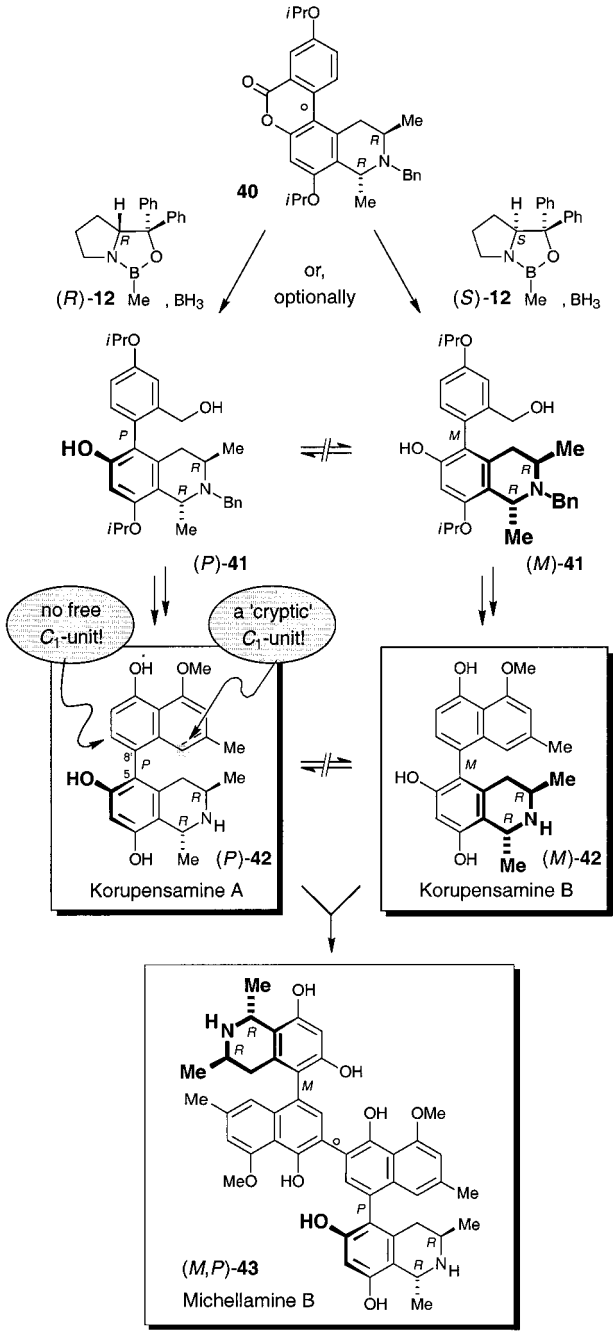
combining centrochirality and axial chirality, (*P*)-**35** is characterized by the presence of two identical ortho substituents next to the axis (6-OMe and 8-OMe). This structural peculiarity should make an achievement of asymmetric inductions by other, direct coupling methods very difficult, if not impossible, but should present no problem for the lactone approach.

As shown in Scheme 6, the basic (but sterically shielded) tertiary amino group of bromoester **32** did not cause any problems in the coupling step to the lactone **33** (87%).[51] This time, because of the stereogenic centers present in **33**, even simple, achiral reagents can be used for the stereoselective ring cleavage reaction, giving high diastereoselectivities (e.g., dr 95:5 for KO*i*Pr).[52,53] Furthermore, the minor ("wrong") atropisomer, (*P*)-**34** (not shown), is easily recovered and can be recycled by cyclization back

Scheme 7. No Oxygen Ortho to the Coupling Site: Synthesis of the Antimalarial Alkaloid Dioncophylline C



Scheme 8. No "Free" C_1 Unit Next to the Axis: Atropo-Divergent Total Synthesis of Korupensamines A and B, as the Molecular Portions of Michellamine B



to the lactone **33**, thus permitting a high degree of chiral economy. Completion of this first[54] synthesis of ancistrocladisine [(*P*)-**35**] was achieved by standard transformations.[51]

Another illustrative example is dioncophylline C [(*P*)-**39**], a 5,1′-coupled naphthylisoquinoline alkaloid from the West African vine *Triphyophyllum peltatum* (Dioncophyllaceae).[55] Within this class of secondary metabolites, it has the as-yet highest antimalarial activity, which has already been successfully employed in vivo to cure malaria-infected mice.[45] The lack of an adjacent ortho oxygen function next to the axis that might serve as a "bridge-

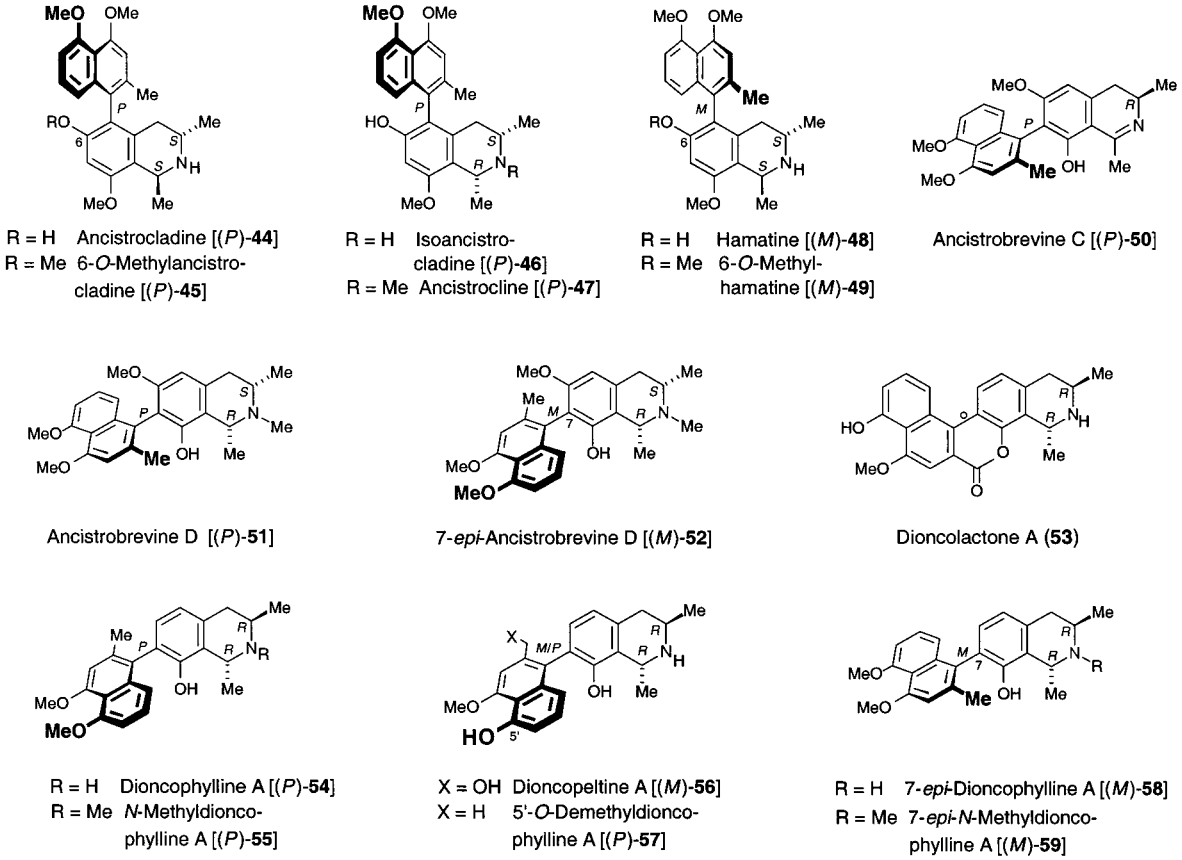


FIGURE 1. Further naphthylisoquinoline alkaloids prepared using the "lactone concept".

head" for an ester tether, however, made (*P*)-**39** a demanding synthetic target.

As shown in Scheme 7, our synthesis[17] did, nonetheless, proceed via a biaryl lactone, viz. **37**, which, in contrast to the target molecule (*P*)-**39**, is indeed equipped with an (unnatural) auxiliary oxygen function next to the axis, at C-6. This extra oxygen thus had to be removed at a later stage of the synthesis. As expected from previous experience,[56] **37** was smoothly obtained from **36** by intramolecular coupling, despite the large steric hindrance. The helically distorted lactone **37** is again configurationally unstable, but its helimerization, compared to the previous examples, is significantly slowed. If equipped with an *N*-TFA residue, the desired atropisomer (*P*)-**37** is by far predominant in the atropisomeric mixture (dr > 95:5).[17] With retention of this thermodynamically controlled diastereomeric ratio, the ring can be reductively cleaved, using cheap, achiral reducing agents (e.g., $LiAlH_4$). Removal of the (no longer required) oxygen function next to the axis succeeded by hydrogenation of *O*-triflate (*M*)-**38**, giving, after a few further standard transformations, dioncophylline C [(*P*)-**39**] in enantiopure form. This as-yet only[57] synthesis of (*P*)-**39**[17] again demonstrates the broad applicability of the lactone concept, even to biarylic target molecules without an oxygen function next to the axis.

The third example, now without a (free) C_1 unit ortho to the axis of the target molecule, are the korupensamines A [(*P*)-**42**] and B [(*M*)-**42**] from the Cameroonian vine *Ancistrocladus korupensis*.[58] These bioactive 5,8′-coupled alkaloids have attracted appreciable interest because they are, simultaneously, the "monomeric" molecular halves of natural naphthylisoquinoline "dimers", like michellamine B [(*M,P*)-**43**], which received high attention as a potent agent against HIV-1 and -2.[47]

This promising activity triggered numerous efforts to develop practicable synthetic pathways to korupensamines and michellamines. An application of the lactone method, however, did not seem feasible for these target molecules at first sight, due to the apparent lack of a potential C_1 bridgehead near the axis. Therefore, all initial synthetic approaches[59]—including the first total synthesis by the authors' group[60]—were based on *intermolecular* coupling steps, giving mostly moderate chemical yields and low asymmetric inductions (always in favor of *P*), with no possibility to direct the stereochemical outcome stereo*divergently*.[61]

A closer look, however, does reveal the presence of an—albeit hidden ("cryptic")—*ortho* C_1 unit next to the axis, as part of the second naphthalene ring, allowing the application of the lactone method even in this case. Our atropo-divergent synthesis of korupensamines A and B[62] was therefore planned to proceed via the respective atropisomers of **41** (Scheme 8). These phenyltetrahydroisoquinolines would, indeed, be equipped with a C_1 unit in the proximity of the axis: for the subsequent construction of the second naphthalene ring and as a "bridgehead" for their synthesis from a joint lactone

precursor, **40**. This lactone, obtained by intramolecular coupling from the corresponding bromoester (not shown), was reductively opened, again the best stereochemical results being obtained with the CBS system. By the use of the appropriate oxazaborolidine enantiomer, (*R*)-**12** or (*S*)-**12**, the two possible atropisomeric products, (*P*)-**41** or, optionally, (*M*)-**41**, were obtained with high asymmetric inductions (dr 94:6 or 4:96) from **40** as the joint precursor. This first atropo-divergent korupensamine synthesis was completed by Stobbe reaction and subsequent ring closure to give korupensamine A [(*P*)-**42**] from (*P*)-**41** and korupensamine B [(*M*)-**42**] from (*M*)-**41**, respectively. Dimerization (or mixed coupling) of these two components by phenolic oxidation to give the corresponding michellamines, e.g., michelamine B [(*M*,*P*)-**43**] has, more recently, been achieved even without any O- or N-protective groups.[63]

Besides the three instructive examples presented above, ancistrocladisine, dioncophylline C, and korupensamines A and B, a broad series of further related naphthylisoquinoline alkaloids have been prepared using the lactone methodology.[64] Figure 1 shows a selection of another 16 such axially chiral biaryl alkaloids, **44**−**59**, synthesized by the method, with different substitution patterns, coupling sites, and configurations at centers and axes.

4. Summary and Outlook

Biaryl lactones have proven to be most valuable intermediates for the stereoselective synthesis of axially chiral natural products. They are easily accessible by intramolecular coupling—even for bulky substrates. A key feature of the concept is that these lactones are, compared to the (unbridged) target biaryls, configurationally unstable and can be cleaved atropo-divergently, by *dynamic kinetic resolution*, thus permitting a virtually complete conversion of the racemic lactone substrate into stereochemically pure products of any desired configuration. By transforming undesired stereoisomeric byproducts back to the lactones, the efficiency of the method is further enhanced. As exemplarily shown for selected, structurally diverse target molecules including phenylanthraquinones, dimeric sesquiterpenes, bicoumarins, biscarbazoles, and naphthylisoquinoline alkaloids, the lactone concept has proven its wide applicability in the atroposelective total synthesis of natural products[65] and (not presented here) in the preparation of C_1-, C_2-, and C_3-symmetric axially chiral reagents and ligands.[9,15,18] As demonstrated, the basic principles of the method have been extended to configurationally stable biarylic and even to aryl-aliphatic lactones, thus opening a wide variety of additional applications to further target molecules with stereogenic axes or centers.

Financial support by the Deutsche Forschungsgemeinschaft (SFB 347), the Bundesministerium für Bildung und Forschung, the Fonds der Chemischen Industrie, and the DAAD (fellowship to D.M.) is gratefully acknowledged. We greatly appreciate the dedicated work of those members of our group who have developed this field of research, fruitful discussions with Dr. Paul Keller (University of Wollongong, Australia), and the stimulating cooperations with our scientific partners—their names can be seen in the literature cited.

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AR000106Z