Nondynamic and Dynamic Kinetic Resolution of Lactones with Stereogenic Centers and Axes: Stereoselective Total Synthesis of Herbertenediol and Mastigophorenes A and B†

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Abstract: The stereoselective total synthesis of the sesquiterpene herbertenediol (**3**) and of its naturally occurring dimers, mastigophorenes A [(*P*)-**1**] and B [(*M*)-**1**], is described. Following the "lactone concept", the configuration at the biaryl axis was atropo-divergently induced to be *P* or, optionally, *M*, by stereocontrolled reductive ring cleavage (diastereomeric ratio up to 97:3) of the configurationally unstable joint biaryl lactone precursor **17** using the oxazaborolidine−borane system, through dynamic kinetic resolution. Mechanistic considerations of the lactone coupling suggested interference by a methoxy group next to the halogen substituent and led to an improvement of the coupling yield from 39 to 87% (to give the lactone **37**). As a new, likewise highly efficient variant of the lactone method, we report for the first time the—now nondynamic—kinetic resolution of a structurally related, but centrochiral "aliphatic−aromatic" lactone, (*rac*)-**10**. Its highly efficient (k_{rel} > 300) enantiomer-differentiating Corey−Bakshi−Shibata reduction delivers the centrochiral building block (*R,R*)-**10** in good chemical yield and with excellent stereochemical purity (enantiomeric excess > 99.9%; enrichment of the starting matrial). The new synthesis of natural herbertenediol (**3**) confirms its absolute stereostructure as well as that of its dimers, (*P*)-**1** and (*M*)-**1**.

Introduction

The natural products mastigophorene A [(*P*)-**1**] and B [(*M*)-**1**] are representatives of a group of axially chiral "dimeric"[1] sesquiterpenes exhibiting nerve growth stimulating activity.[2] Such nonpeptidyl neurotrophic substances are regarded as promising potential therapeutic agents for degenerative diseases of the central nervous system such as Parkinson and Alzheimer.[3] Therefore the total synthesis of (*P*)-**1** and (*M*)-**1** is an attractive target, even more so because the interesting, C_2-symmetric structures involve elements of both axial and centro chirality. In our investigations, we published two different strategies for the construction of the simplified analog **2**,[4] the first one by a (nonstereoselective) biomimetic oxidative phenolic coupling, leading to the likewise neurotrophic[5] mastigophorene analog **2**,[4] and the second one using our "lactone methodology"[6] for the atropo-enantioselective construction of the biaryl axis. An application of the biomimetic strategy to a simple derivative of the authentic monomeric half, **3**, led to the first formal total synthesis of (*P*)-**1** and (*M*)-**1**, albeit with moderate asymmetric inductions.[7] During our ongoing work, Meyers et al. published a synthetic pathway to (*P*)-**1** and (*M*)-**1**, involving a first enantioselective route to (−)-herbertenediol (**3**) and an atropo-diastereoselective Ullmann coupling of chiral aryloxazolines.[8] We report on our highly stereoselective total synthesis of mastigophorenes A [(*P*)-**1**] and B [(*M*)-**1**] by a 2-fold application of the lactone method:[6] first, the novel nondynamic kinetic resolution of "aromatic−aliphatic" lactones for the enantioselective synthesis of the centrochiral molecular "half", herbertenediol (**3**), and second, the dynamic kinetic resolution of a configurationally unstable biaryl lactone for the directed, atropo-diastereodivergent construction of the biaryl array to give, optionally, the *M*- or the *P*-configured product, in high atropo-diastereomeric ratios.

† Part 87 of the series "Novel Concepts in Directed Biaryl Synthesis". For part 86 see ref 18.

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(1) Strictly speaking such "dimers" should be described as "dehydrodimers".

(2) Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737.

(3) Skaper, S. D.; Walsh, F. S. *Mol. Cell. Neurosci.* **1998**, *12*, 179.

(4) Bringmann, G.; Pabst, T.; Busemann, S.; Peters, K.; Peters, E.-M. *Tetrahedron* **1998**, *54*, 1425.

(5) Gille, G.; Pabst, T.; Bringmann, G.; Janetzky, B.; Reichmann, H.; Rausch, W.-D. *Drug Dev. Res.* **2000**, *50*, 153.

(6) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525.

(7) Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett.* **1999**, *40*, 483.

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(9) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett.* **1996**, *37*, 1261.

(10) Weeratunga, G.; Jaworska-Sobiesiak, A.; Horne, S.; Rodrigo, R. *Can. J. Chem.* **1987**, *65*, 2019.

(11) Shiba, T.; Cahnmann, H. J. *J. Org. Chem.* **1964**, *29*, 3061.

(12) Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139.

(13) Klärner, F.-G.; Adamsky, F. *Chem. Ber.* **1983**, *116*, 299. The elimination step to ethyl 1,2-dimethyl-cyclopent-2-enoate was done by azeotropic removal of water with toluene and *p*-toluenesulfonic acid. Subsequent hydrolysis as described gave (*rac*)-**8** in 72% yield (2 steps).

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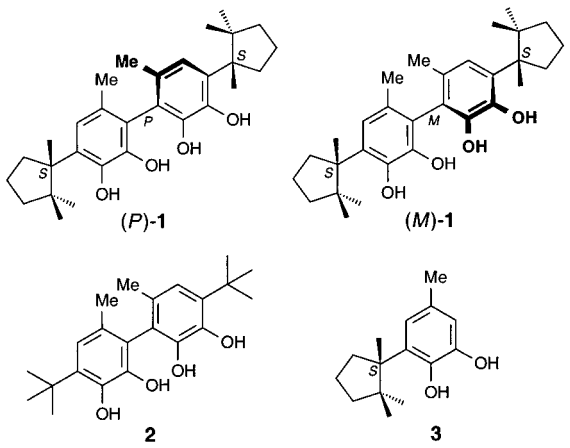
Structure Block



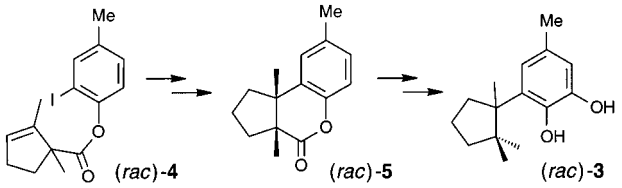
Results and Discussion

Our concept for the enantioselective synthesis of herbertenediol (**3**) was related to a synthetic pathway previously developed—albeit in a racemic form—by Fukuyama et al.[9] (Scheme 1). In that approach the chiral quaternary carbon center had been built up by a diastereoselective intramolecular Heck coupling of (*rac*)-**4** to give lactone (*rac*)-**5**, which was then converted to (*rac*)-**3**, including introduction of the second phenolic oxygen function.

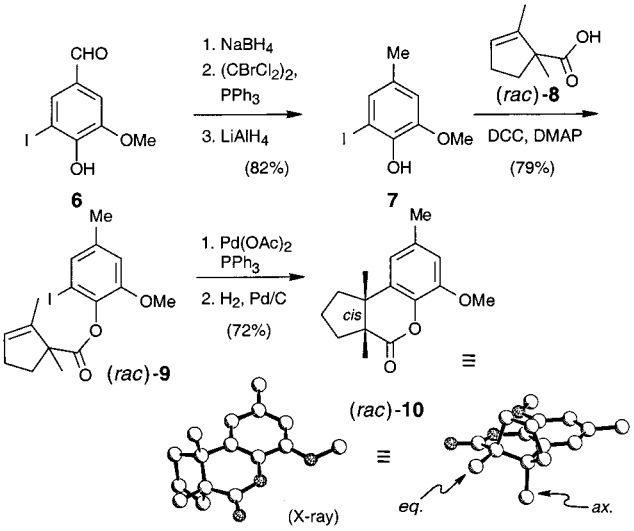
For the directed synthesis of enantiomerically pure **3**, with its *two* oxygen functions, we modified this synthetic concept in two respects. First, to avoid the subsequent introduction of the second phenolic function, we started directly from the dioxygenated aromatic building block **7** (Scheme 2), which might be prepared either according to a method described in the literature[10] or, more easily, from the known[11] 5-iodovanilline (**6**), by reaction with $NaBH_4$ and reductive deoxygenation via the corresponding bromide.[4,12] Esterification of **7** with the known[13] acid (*rac*)-**8** using dicyclohexylcarbodiimide (DCC) as the condensation agent gave (*rac*)-**9**. This iodo ester was, similar to (*rac*)-**4** in the literature, diastereoselectively cyclized by a palladium-catalyzed Heck reaction, to afford, after hydrogenation, the *cis*-configured lactone (*rac*)-**10** in racemic form (of which Scheme 2 arbitrarily shows the *R,R*-enantiomer). The cis-configuration, which could not be assigned by nuclear Overhauser effect (NOE) experiments, was clearly established by X-ray structure analysis of (*rac*)-**10** (see Scheme 2). This analysis further showed the methyl group β to the carbonyl function to be in an axial position, and the α-methyl group in an equatorial position. This conformation avoids 1,3-allylic strain between the β-CH_3 group and the aromatic hydrogen.

The second, even more significant improvement of the synthetic pathway to **10** was development of a route to enantiomerically pure material. The acid **8**, however, which would thus be required in stereochemically homogeneous form, had been synthesized only in an insufficient enantiomeric purity (enantiomeric excess (ee) = 90%) in the literature.[9] Therefore, given our good results with atropisomer-selective cleavage reactions of biaryl lactones, a kinetic resolution at the level of the aromatic−aliphatic lactone (*rac*)-**10** seemed to offer an ideal extension of our lactone method. For this purpose, the rigid structure of **10** might indeed provide a good precondition for efficient stereodifferentiation of the two enantiomers. Given the mostly excellent results with oxazaborolidine-mediated borane reductions (Corey−Bakshi−Shibata (CBS) reaction)[14] in the kinetic resolution of configurationally unstable[6]—or stable[15]—

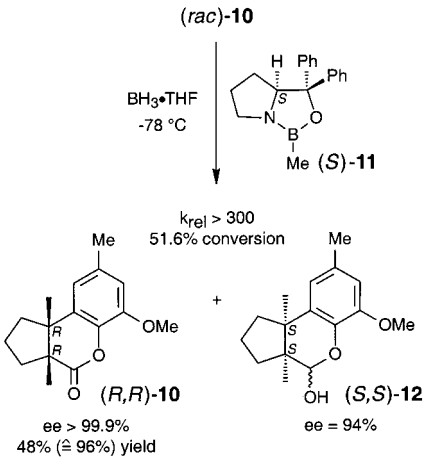
Scheme 1



Scheme 2



Scheme 3



biaryl lactones, we then tried this method also for **10**, i.e., for the first time in the enantiomer-differentiating reduction of nonbiarylic chiral lactones. Initial reduction experiments with (*rac*)-**10** on an analytical scale, even when an excess of **11** was used, revealed the system to be too unreactive to be reduced completely to the diol **14** and the reaction stopped at the lactol **12** (obtained as a diastereomeric mixture) (Scheme 3). Fortunately, this reduction was found to proceed with perfect enantiomer-differentiating selectivity: After 51.5% conversion,[16] the starting material **10** was enriched to an ee > 99%; the other lactone enantiomer was no longer detectable by HPLC analysis on a Chiralcel OD-H phase. Attempts to run the reaction with

(14) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.

(15) Bringmann, G.; Hinrichs, J. *Tetrahedron: Asymmetry* **1997**, *8*, 4121.

(16) The conversion and the relative rate k_{rel} were calculated according to (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

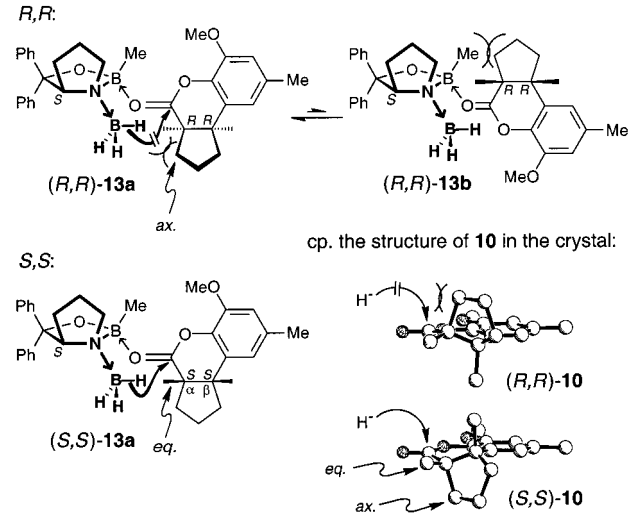


Figure 1. Rationalization of the observed stereodifferentiation and prediction of the stereoisomer expected to be reduced.

catalytic amounts of the oxazaborolidine **11**, however, failed: With 0.1 equivalents of **11**, only 8.4% conversion was observed. Nevertheless, to perform the reaction as economically as possible with respect to the chiral reagent, we used 0.6 equivalents of **11** in preparative reactions and then isolated enantiopure **10** (ee > 99.9%, k_{rel} > 300!)[16] in an excellent 48% chemical yield (= 96% based on the maximum possible yield for that enantiomer).

For a directed synthesis of the correct enantiomer of natural herbertenediol (**3**), independent of a "late" assignment of the product configuration at the level of the stereochemically known[17] monomeric target molecule **3**, the absolute product configuration was already determined for the enantiopure lactone **10**.

From model considerations (Figure 1) based on previous experimental and computational investigations[14,18,19] but also on the crystal structure of **10** (see above), a distinctly preferred attack of the *N*-activated borane to the *B*-activated carbonyl function of **10** should occur from a conformation related to (*R*,*R*)- or, (*S*,*S*)-**13a** [= (*S*)-**11**·BH_3·**10**], thus avoiding a strong heteroallylic strain as, for example, in (*R*,*R*)-**13b**. Of the two isomers of **13a**, (*S*,*S*)-**13a** should react much more easily, because here (assuming a conformation of the lactone part similar to that of **10** in the crystal) the quasi-intramolecular hydride attack would occur syn to the equatorial methyl group, but anti to the propylene bridge, which is axial in the α-position next to the carbonyl function. For (*R*,*R*)-**13a**, by contrast, the attack would have to occur syn to that axial part of the propylene bridge, so that this isomer—and thus (*R*,*R*)-**10** − should remain unreacted with (*S*)-**11**·BH_3.

This assumption was confirmed by quantum chemical circular dichroism calculations.[20] Thus, the circular dichroism (CD) spectrum calculated for (*R*,*R*)-**10** shows good agreement with the experimental spectrum of the product **10** that remained unreacted with (*S*)-**11**, whereas the spectrum calculated for (*S*,*S*)-**10** is virtually opposite to the experimental spectrum (Figure 2), clearly indicating that the product (*R*,*R*)-**10** needed for the synthesis of natural i.e., *S*-configured, herbertenediol (**3**), was

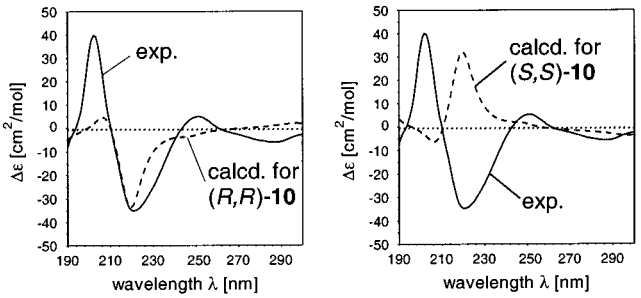
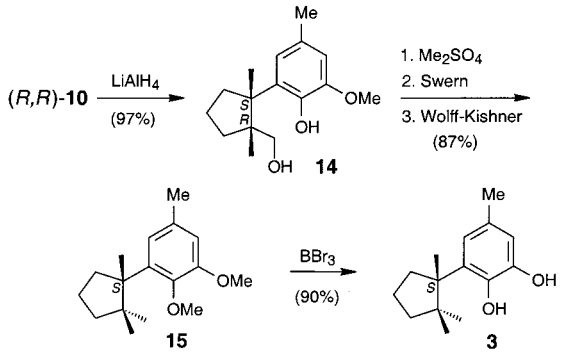
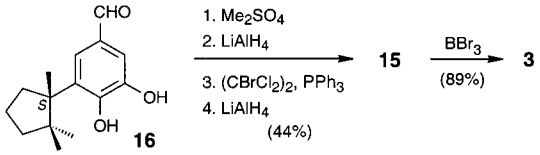


Figure 2. Comparison of the experimental CD spectrum of **10** with the spectra calculated for its two possible enantiomeric forms.

Scheme 4



Scheme 5



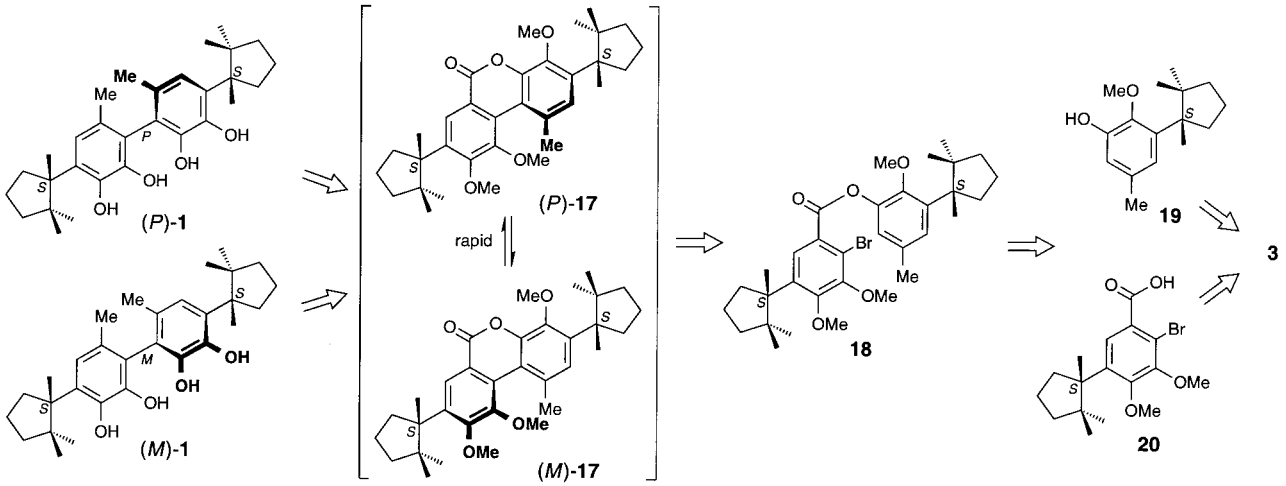
that obtained with (*S*)-**11**. Conversely, with the ultimate outcome of the synthesis (see below), the CD calculations confirm the absolute centrochiral *S*-configuration for both herbertenediol (**3**) and the mastigophorenes A [(*P*)-**1**] and B [(*M*)-**1**] as established earlier.[2,17]

Starting from (*R*,*R*)-**10**, enantiomerically pure herbertenediol (**3**) was synthesized by analogy to the procedure described for racemic material by Fukuyama et al.[9] Reduction with $LiAlH_4$ (LAH) gave the diol **14** (see Scheme 4), which was converted to the still *O*,*O*-dimethylated herbertenediol precursor **15** by *O*-protection with Me_2SO_4, Swern oxidation, and Wolff−Kishner reduction. Deprotection with BBr_3 led to herbertenediol (**3**), which was found to be enantiopure by HPLC analysis on a Chiralcel OD-H phase, and was fully identical to natural material by its physical, chiroptical, and spectroscopic data.[17]

Another approach to enantiomerically pure **3**, recently described in preliminary form,[7] is its partial synthesis from the natural aldehyde **16** (Scheme 5), which co-occurs with herbertenediol (**3**) in the liverwort *Herbertus aduncus* and was isolated as described previously.[21] Protection of the phenolic functions of **16** with Me_2SO_4 and reduction of the aldehyde function with LAH led to the corresponding alcohol, whose reductive deoxygenation via the corresponding bromide[12] gave the dimethyl ether **15**, which was deprotected with BBr_3 to afford (−)-herbertenediol (**3**). This partial synthesis of **3** simultaneously confirms the *S*-configuration of **16**, which had so far been assumed only from its slightly negative α_D.[21]

(17) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.
(18) Bringmann, G.; Hinrichs, J.; Kraus, J.; Wuzik, A.; Schulz, T. *J. Org. Chem.* **2000**, *65*, 2517.
(19) Bringmann, G.; Vitt, D. *J. Org. Chem.* **1995**, *60*, 7674.
(20) Bringmann, G.; Busemann, S. In *Natural Product Analysis*; Schreier, P., Herderich, M., Humpf, H.-U., Schwab, W., Eds.; Vieweg: Braunschweig, 1998; pp 195−212.
(21) Buchanan, M. S.; Connolly, J. D.; Rycroft, D. S. *Phytochemistry* **1996**, *43*, 1245.

Scheme 6



With enantiopure herbertenediol (**3**) in hand by partial and by total synthesis, we could now start building its natural dimers, mastigophorenes A [(*P*)-**1**] and B [(*M*)-**1**], based on previous experience from our model studies.[4] Using our lactone method,[6] both (*P*)-**1** and (*M*)-**1**, optionally, should be synthesizable from the same biaryl lactone **17** (Scheme 6), by atropo-diastereoselective ring cleavage. This key intermediate, expected to be configurationally unstable,[6] should best[22] be synthesized via an intramolecular biaryl coupling of the carboxylic ester **18**, and thus from the phenol **19** and the acid **20**, both ultimately arising from herbertenediol (**3**).

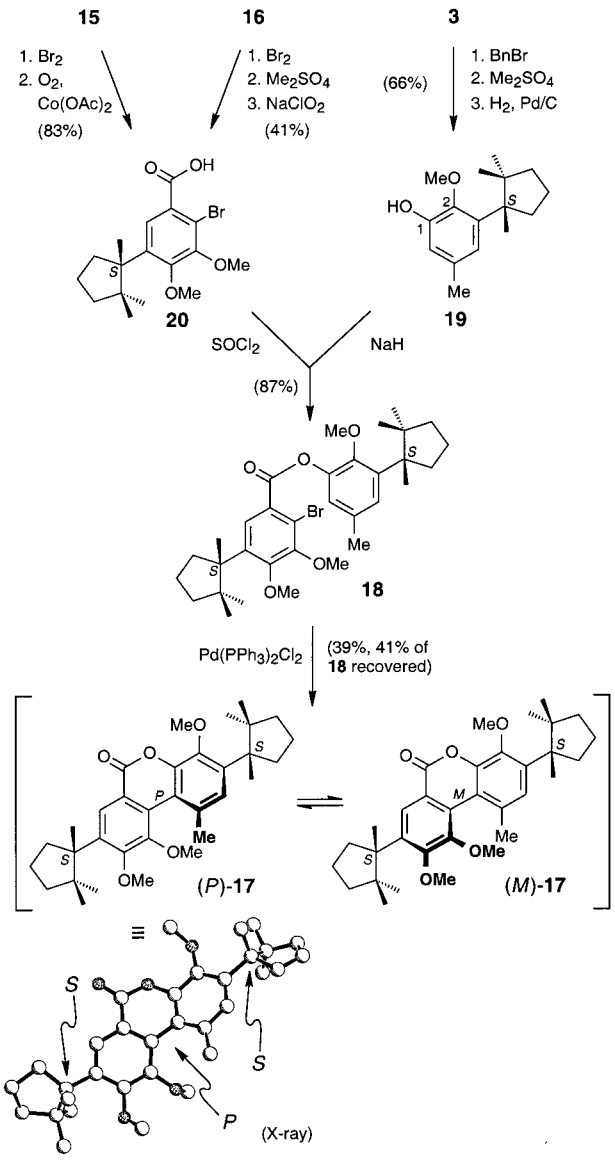
The acid **20** was synthesized from herbertenediol dimethyl ether (**15**) by bromination and cobalt-catalyzed oxidation with O_2 (Scheme 7). Alternatively, a second approach to **20**—by *partial* synthesis—succeeded by bromination of the natural[21] aldehyde **16**, protection with Me_2SO_4, and oxidation with $NaClO_2$. The phenolic precursor **19** was obtained[7] from **3** by selective benzylation of the less hindered oxygen at C-1 and subsequent methylation of the second phenolic function at C-2. Hydrogenolysis of the benzyl group then generated the monophenolic building block **19**.

From the phenol **19** (via its phenolate) and the acid **20** (via its acid chloride) the bromo ester **18** was obtained and submitted to a Pd^0-catalyzed intramolecular biaryl coupling reaction, to give the desired key biaryl lactone **17**, in 39% yield (subsequently improved, see later), together with 41% of recovered substrate. Longer reaction times did not lead to higher yields, but rather to decomposition of the product already formed. As expected, **17** consists of two rapidly interconverting atropo-diastereomers (*P*)-**17** ⇌ (*M*)-**17** in solution, as required for a dynamic kinetic resolution in the ring cleavage reaction. In the crystal however, it occurs as the—*like*-configured—*P*-atropisomer, exclusively, as shown by an X-ray structure analysis (see Scheme 7).

In accordance with the predominance of (*P*)-**17** in the crystal is the observation that LAH reduction of **17** gave the corresponding diols (*P*)-**21** and (*M*)-**21** in favor of the *P*-configured product (diastereomeric ratio (dr) 77:23). Rapid reduction by addition of crystalline **17** to a 1 M solution of LAH in tetrahydrofuran (THF) (−100 → −30 °C) gave an even better dr of 81:19.

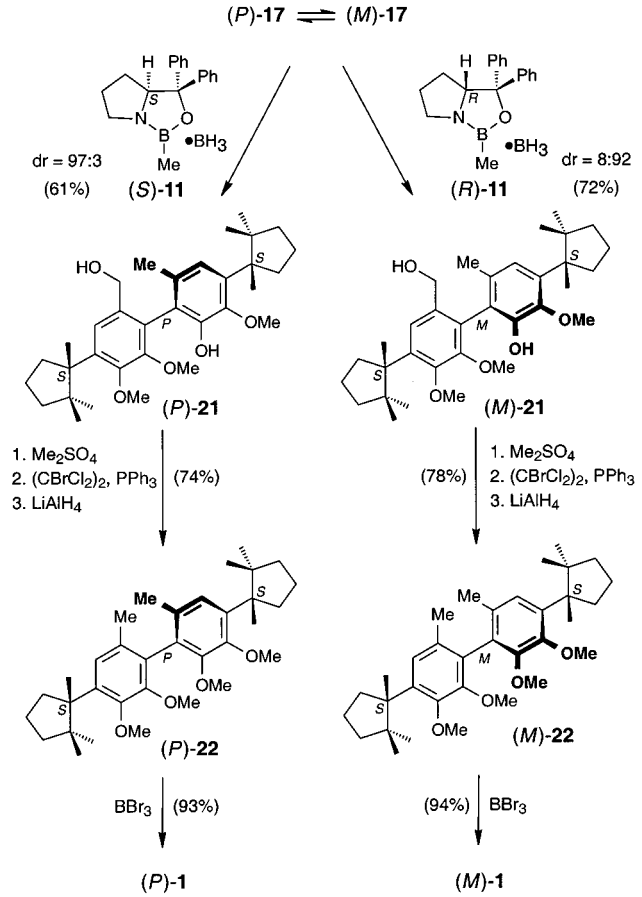
Still better diastereoselectivities and the option of producing *either* of the two atropisomers, (*P*)- or (*M*)-**21**, highly selectively from the same configurationally unstable lactone precursor **17**, within a now dynamic kinetic resolution, were attained using

Scheme 7



(22) For the synthesis of related—albeit sterically less hindered—biaryl lactones by other methods, see: (a) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424. (b) Davies, D. I.; Waring, C. *J. Chem. Soc. C* **1967**, 1639 and references cited therein. (c) de Frutos, O.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 8953.

Scheme 8



techniques developed previously within the lactone methodology.[6] Thus, reaction of (*P*)-**17** ⇌ (*M*)-**17** with (*S*)-**11** gave (*P*)-**21** with an excellent dr of 97:3 (Scheme 8). But even the *M*-configured atropisomer of **21** (less readily produced using achiral reagents, see above) could be obtained with a good dr of 92:8 by using (*R*)-**11**, thus overcoming the molecule-inherent *P*-preference by a strong external asymmetric induction exerted by the CBS system. In both cases diastereomerically pure compounds were obtained by column chromatography.

Further transformation of (*P*)- and (*M*)-**21** to mastigophorenes A [(*P*)-**1**] and B [(*M*)-**1**], respectively (Scheme 8), followed protocols developed previously for related model compounds.[4] Protection of the phenolic function of (*P*)- and (*M*)-**21** by *O*-methylation, and reductive benzylic deoxygenation[12] (via the corresponding bromide) provided the tetra-*O*-methylmastigophorenes (*P*)- and (*M*)-**22**, respectively. Deprotection with BBr_3 gave (*P*)-**1** and (*M*)-**1**, which proved to be identical in all respects with the data published[2] for the natural products.

Within this stereoselective synthesis of the mastigophorenes, their axial configuration was proved rigorously by an X-ray

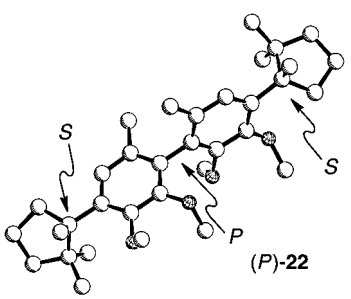
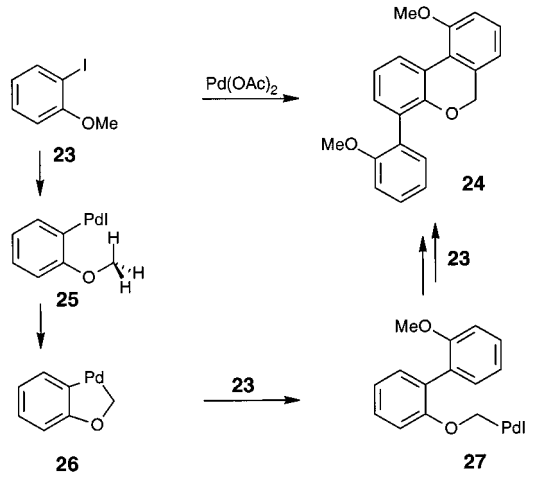


Figure 3. X-ray crystal structure of tetra-*O*-methylmastigophorene A [(*P*)-**22**].

Scheme 9



structure analysis of the tetramethyl ether (*P*)-**22** of mastigophorene A [(*P*)-**1**] (see Figure 3). From the relative configuration of (*P*)-**22** in the crystal, together with the known[17] *S*-configuration in the cyclopentyl residue, as determined above again by the CD calculations, the absolute axial configuration could be established directly to be *P*, which confirms the configurational assignment by Fukuyama et al. based on the exciton chirality rule.[2]

The synthetic approach to the mastigophorenes A [(*P*)-**1**] and B [(*M*)-**1**] presented here is most flexible and efficient, with the exception of the coupling step to the lactone **17**. Unexpectedly and in contrast to so many other related coupling reactions, which gave excellent yields,[6] even against highest steric hindrance (e.g., with a *tert*-butyl group next to the axis),[18] no further optimization was possible by variation of the catalyst, the solvent, or other reaction conditions. The search for a reason for this failure led us to compare the substrate structures of successful coupling reactions in the literature[6,23,24] with those of **17** and others that had previously given insufficient coupling yields.[4,25,26] Strikingly, all the unsuccessful coupling substrates had a methoxy group ortho to the halogen. Indeed, previous investigations by Dyker et al.[27] had shown that Pd^0-catalyzed reactions of substrates such as **23** (Scheme 9) give "trimeric" products of type **24**, apparently by CH activation of the *O*-methyl group of **25**, leading to the five-membered palladacycle **26**, followed by the addition of a second substrate molecule to give **27**. Ring closure and involvement of a third molecule of **23** ultimately produce the observed product **24**.

These results suggested that, in our reaction, intermediates such as **28** and **29** (Figure 4) might play a role and be responsible for the poor coupling yield. However, there was no evidence for such intermediates and consequent byproducts.

Therefore, we performed the reaction with the simplified carboxylic ester **30**, i.e., in the absence of an intramolecular coupling partner (Scheme 10), thus increasing the chance of detecting possibly relevant CH activation products in our system. Indeed, with $Pd(OAc)_2$ as the catalyst, **30** gave the cyclic biaryl ether **31** in 10% yield, consistent with initial oxidative addition

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(24) Bringmann, G.; Ochse, M.; Götz, R. *J. Org. Chem.* **2000**, *65*, 2069.
(25) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977.
(26) Rao, A. V. R.; Chakraborty, T. K.; Joshi, S. P. *Tetrahedron Lett.* **1992**, *33*, 4045.
(27) (a) Dyker, G. *Chem. Ber./Recl.* **1997**, *130*, 1567. (b) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1698. (c) Dyker, G. *Chem. Ber.* **1994**, *127*, 7, 739.

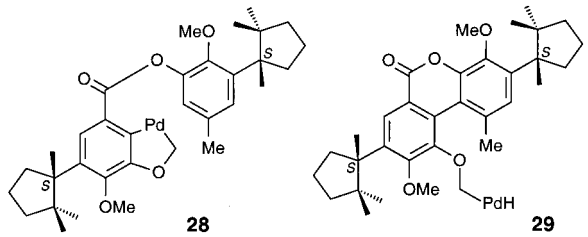
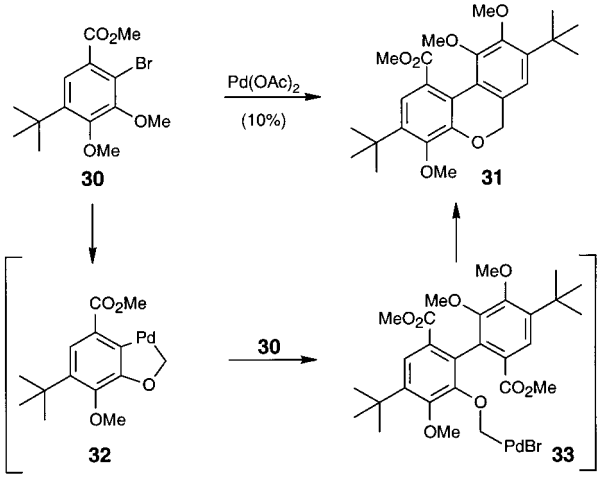


Figure 4. Possible intermediates in the Pd-assisted intramolecular coupling of **18**.

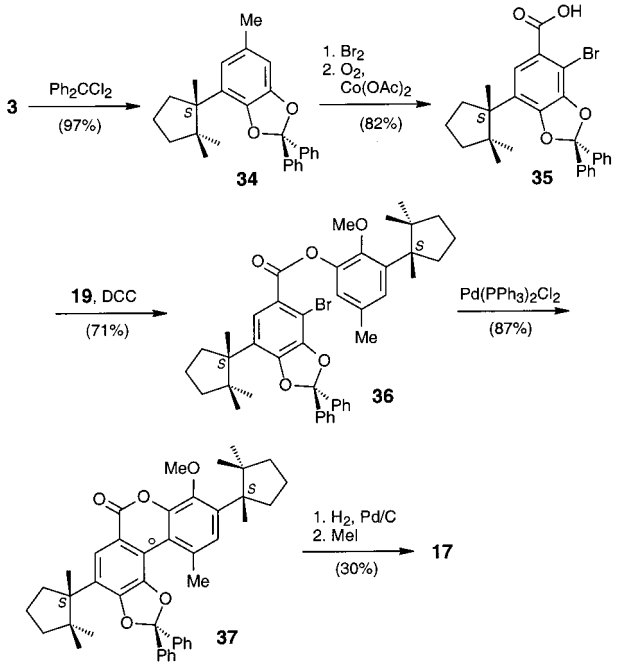
Scheme 10



of Pd^0 and subsequent cyclometalation by CH activation at the neighboring methoxy group to give **32**. Addition of a second molecule of **30** and reductive elimination, with formation of the biaryl axis, apparently then lead to the intermediate **33**, whose ring closure with decarboxylation would produce the ether bridge in **31**. The constitution of **31** was proved, inter alia, by a series of nuclear Overhauser enhancement spectroscopy
(NOESY) interactions. In addition, dynamic nuclear magnetic resonance (DNMR) investigations showed the expected splitting of the signals of the diastereomeric protons in the ether bridge (below ca. −35 °C), and thereby confirmed the chiral (though, at room temperature, configurationally unstable) biaryl structure of **31**.[28]

This experiment demonstrates that in the bromobenzoic acid **18**, it is likely that, after oxidative addition, a CH-activating interaction of Pd with the adjacent ortho-methoxy group will indeed play an important role in diminishing the yield of the desired coupling product. As a consequence of these results, a methoxy group (or any other protecting group that might undergo such CH activation) should be avoided in the immediate neighborhood of the halogen substituent. This condition had been satisfied for our successful substrates, e.g., for 1-bromonaphthalene-2-carboxylic acids and for many precursors of numerous biaryl alkaloid syntheses.[6,24] Therefore, a better coupling substrate than **18** should, for example, be the modified bromo ester **36** (Scheme 11), in which the ortho-methoxy group of **18** is replaced by a diphenylmethylene acetal group for the simultaneous protection of both phenolic hydroxy functions, so that the critical ortho-OCH moieties are absent; moreover, according to experience in the literature,[29,30] its deprotection

Scheme 11



should be achieved very easily, by hydrogenolysis, even at the level of the sensitive lactone **37**.

The required acetal-protected bromo acid **35** [31] was synthesized from herbertenediol (**3**), by reaction with Ph_2CCl_2, bromination, and cobalt-catalyzed oxidation with O_2. Subsequent DCC activation and reaction with the phenol **19** gave the desired bromo ester **36**. Its coupling was now highly efficient under the standard reaction conditions and our considerations presented above were confirmed. The lactone was obtained with an excellent yield of 87% and no side products or even hints of decomposition were observed.

Unexpectedly however, and in contrast to results from the literature,[29,30,32] cleavage of the diphenylmethylene acetal group was more difficult than anticipated. Thus, upon attempted hydrogenolysis with H_2 in THF with Pd/C as the catalyst[29] or by acid-catalyzed hydrolysis,[32] no reaction was observed. Only after further optimization did deprotection succeed hydrogenolytically using THF/concentrated H_2SO_4 (10:1) as the solvent, followed by renewed protection with MeI, to give the lactone **17** in low yield.

Although the overall yield of the total synthesis could not thus be improved, this does not diminish the value of our finding that avoiding an OCH unit next to the palladation site will increase the coupling yields dramatically. This important result should find further applications in other syntheses.

Conclusions

The work presented describes a new synthetic pathway to highly enantiopure herbertenediol (**3**) and its rational conversion to mastigophorene A [(*P*)-**1**] or, optionally, mastigophorene B [(*M*)-**1**] in high diastereoselectivities. Although for the construc-

(28) Line-shape analyses of the ^{1}H NMR spectra at different low temperatures gave the corresponding rate constants k and the activation parameters $\Delta H^{\ddagger} = 43.5 \pm 1.7$ kJ mol^{-1}, $\Delta S^{\ddagger} = -20.8 \pm 7.2$ J K^{-1} mol^{-1}, and $\Delta G^{\ddagger}_{298} = 49.7$ kJ mol^{-1}.

(29) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357.

(30) (a) Lütolf, W. L.; Prewo, R.; Jost, H.; Rüedi, P.; Eugster, C. H. *Helv. Chim. Acta* **1985**, 860. (b) Kawase, M.; Sinhababu, A. K.; McGhee, E. M.; Milby, T.; Borchardt, R. T. *J. Med. Chem.* **1990**, *33*, 2204.

(31) This reaction sequence was first optimized with a simplified model system, bearing a *tert*-butyl group instead of the chiral cyclopentyl residue; for the characterization of these compounds see the Supporting Information.

(32) (a) Feldman, K. S.; Quideau, S.; Appel, H. M. *J. Org. Chem.* **1996**, *61*, 6656. (b) Horie, T.; Tsukayama, M.; Kourai, H.; Nakayama, Y.; Nakayama, M. *Chem. Pharm. Bull.* **1986**, *34*, 30. (c) Bachi, M. D.; Klein, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1925.

tion and atropo-diastereodivergent oxazaborolidine-assisted cleavage of the biaryl lactone **17**, the lactone concept was applied for establishing axial chirality, this methodology was extended here for the first time to the synthesis of enantiomerically pure *centrochiral* compounds, by highly selective (k_{rel} > 300) kinetic resolution of the aromatic−aliphatic lactone **10**. A further improvement of the lactone methodology described here was to recognize and avoid possible side reactions arising from a 2-bromo-3-methoxy benzoate precursor; the methoxy group was replaced by a unit without the critical OCH entity, here a benzylidene acetal, by which the coupling yield was increased from 39 to 87%.

Experimental Section

Kinetic Resolution of (*rac*)-10. From a solution of (*S*)-**11** (9.24 mL, 9.24 mmol, 1 M in toluene) the solvent was removed in vacuo and the residue was dissolved under argon in dry THF (50 mL). Then BH_3·THF (15.4 mL, 15.4 mmol, 1 M in THF) was added and the solution was stirred for 30 min. This solution was added slowly to a cooled (−78 °C) solution of (*rac*)-**10** (4.00 g, 15.4 mmol) in dry THF (200 mL) under argon. This mixture was stirred for 20 h at −78 °C, then acidified with 2 N HCl and the solvent was removed after warming to room temperature. The white precipitate was filtered off and washed with diethyl ether. The filtrate was extracted with diethyl ether, the extract was dried ($MgSO_4$), and the solvent was evaporated. Column chromatography on silica gel (petroleum ether/diethyl ether 2:1) afforded (3a*R*,9b*R*)-cyclopentyl[d]-3a,9b*H*-6-methoxy-*cis*-(3a,9b),8-trimethylcoumarin (*R*,*R*-**10**) (1.91 g, 48%, ee > 99.9%, HPLC) and (*S*,*S*)-**12** (1.90 g) as a diastereomeric mixture. Reduction of a small sample of (*S*,*S*)-**12** with LAH gave (*S*,*S*)-**14** with an ee = 94% (HPLC). (*R*,*R*)-**10**: mp 108 °C; $[\alpha]^{23}_D = -23.8$ (*c* 0.73, $CHCl_3$); CD (ethanol): λ_{max} ($\Delta\epsilon$) 203 (+42), 220 (−34), 251 (+4), 287 (+6).

Atroposelective Ring Opening of 17 with (*S*)-11·BH_3. From 500 μL (500 μmol) of a 1 M solution of (*S*)-**11** in toluene, the solvent was removed in vacuo and the residue was dissolved in 2 mL dry THF. After addition of 400 μL (400 μmol) of BH_3 (1 M solution in THF) and 30 min stirring, this solution was added to a solution of the lactone **17** (62.0 mg, 119 μmol) in 3 mL dry THF at 0 °C. After 4 days of stirring, the reaction was quenched with 2 N HCl, the solvent was removed in vacuo, and the remaining aqueous layer was extracted with diethyl ether. HPLC analysis gave a dr of 97:3. Purification of the dried ($MgSO_4$) extract by column chromatography on silica gel (petroleum ether/diethyl ether 10:1) gave 34.2 mg (55%) of (*P*,1″*S*,1‴*S*)-2-hydroxy-6′-hydroxymethyl-3,2′,3′-trimethoxy-6-methyl-4,4′-di-(1,2,2-trimethylcyclopentyl)biphenyl [(*P*)-**21**] (dr > 99.9:0.1) and (as a late fraction from column chromatography) 4.00 mg (6%) of a mixture of (*P*)- and (*M*)-**21** (dr = 89:11).

Improved Coupling Reaction to (1′*S*,1″*S*)-4-Methoxy-3,8-di-(1,2,2-trimethylcyclopentyl)-1-methyl-9,10-(diphenylmethylidenedioxy)-dibenzo[b,d]pyran-6-one (37). In 50 mL of freshly distilled (over CaH) dimethylacetamide (DMA) **36** (518 mg, 703 μmol), Pd(PPh_3)$_2Cl_2$ (49.3 mg, 70.3 μmol), NaOAc (115 mg, 1.41 mmol), and PPh_3 (14.2 mg, 70.3 μmol) were dissolved under N_2. After heating (130 °C), the reaction mixture was stirred for 16 h, the solvent was removed under reduced pressure, and the residue obtained was purified by column chromatography on silica gel (petroleum ether/diethyl ether 10:1). Crystallization from dichloromethane/petroleum ether gave 402 mg (87%) of **37** as colorless crystals.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds (including unnumberd intermediates), X-ray crystallographical data of (*rac*)-**10**, (*P*)-**17**, (*P*)-**22**, NOESY correlations of **31**, and characterization of the model compounds of **34**−**37** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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