From Dynamic to Non-Dynamic Kinetic Resolution of Lactone-Bridged Biaryls: Synthesis of Mastigophorene B†

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Dedicated to Prof. Max Schmidt, on the occasion of his 75th birthday.

Abstract: The atroposelective ring cleavage of configurationally unstable biaryl lactones, by dynamic kinetic resolution, is an efficient tool for the stereoselective synthesis of axially chiral biaryl target molecules. The recent extension of this methodology to the kinetic resolution of configurationally stable biaryl lactones and its application to natural product synthesis is described herein, exemplarily for the preparation of the nerve-growth stimulating dimeric sesquiterpene mastigophorene B.

Key words: axial chirality, biaryl natural products, lactone-bridged biaryls, kinetic resolution, total synthesis

Introduction and Background

Rotationally hindered, stereogenic biaryl axes are, besides stereocenters, the most commonly found and utilized elements of chirality. During the past years, stereochemically pure biaryl compounds have become increasingly important as effective chiral reagents and catalysts in stereoselective synthesis[1] and as widespread natural products.[2] Such naturally occurring biaryls constitute a large class of structurally most divergent substances, among them antimalarial[3] naphthylisoquinoline alkaloids[4,5] like dioncopeltine A (**1**)[6] and dioncophylline C (**2**),[7] the anti-HIV quateraryl alkaloid michellamine B (**3**),[8] the insect antifeedant bicoumarin (+)-isokotanin A (**4**),[9] the antimalarial phenylanthraquinone knipholone (**5**),[10] and the nerve-growth stimulating biphenyl mastigophorene A (**6a**)[11] (Figure 1).

Due to the increasing importance of axially chiral biaryls, the availability of atropo-enantio- or -diastereomerically pure material is a challenging task. For the elaboration of efficient methods for the stereoselective synthesis of such biaryl target molecules, quite a couple of methods have been developed based on oxidative,[12,13] 'redox-neutral',[14,15] or reductive[16] coupling reactions, following inter- and intramolecular strategies.[17] Still, many of these methods suffer from low chemical and/or optical yields as soon as sterically crowded target molecules are involved.[15,17,18] Moreover, most of them do not permit an atropo-enantio- or -diastereo-*divergent* synthesis, i.e., the directed preparation of any desired atropisomeric product from a joint general precursor, and thus few applications to natural products biaryl synthesis have as yet been described in the literature.[19]

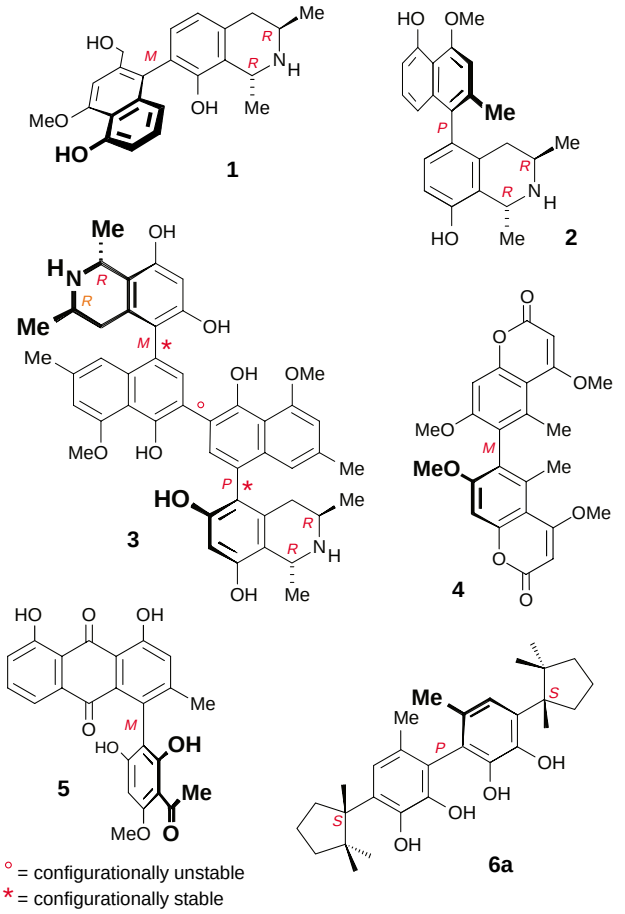


Figure 1 Axially chiral biaryl natural products with pronounced biological activities

The Basic 'Lactone Concept': Atropisomer-Selective Cleavage of Configurationally Unstable Biaryl Lactones with Dynamic Kinetic Resolution

For the regio- and stereoselective construction of even sterically highly hindered biaryls, we have developed a fundamentally novel approach, the 'lactone concept'.[20] It differs from the other existing coupling methods in solving the two formal partial goals of atropisomer-selective synthesis: the *C,C*-bond formation, and the asymmetric

Biographical Sketches

From left to right:
Bringmann, Henschel, Hinrichs, Pabst

Gerhard Bringmann was born in 1951. He studied chemistry in Gießen und Münster, where he obtained his diploma in 1975. In addition, he performed a basic study of biology ('Vordiplom', 1977). He received his Ph.D. with B. Franck (1978), for research in the field of porphyrin chemistry and related cyclic and linear oligopyrroles. From 1978 to 1979, he worked as a postdoctoral fellow with Sir Derek H. R. Barton's group in Gif-sur-Yvette (France) studying radical-induced hydrodeamination reactions of relevance to aminoglycoside chemistry. After his 'habilitation' on biomimetic syntheses of acetogenic isoquinoline alkaloids (1984), he was offered chairs in Vienna (1986) and Würzburg (1987), and has since been a full professor and director at the Institute of Organic Chemistry of the University of Würzburg. In 1998, he received a call for a chair of natural products chemistry at the Institute of Plant Biochemistry (a Gottfried Wilhelm Leibniz Institute) in Halle. He was awarded, *i.a.* the 'Otto Klung Prize' in 1988 and the Prize for Good Teaching by the Bavarian Ministry of Culture and Research in 1999. His research interests lie in the fields of analytical, synthetic, and computational natural products chemistry, some particular fields being mono- and dimeric naphthylisoquinoline alkaloids, bioassay-guided search for new bioactive compounds from tropical medical plants, novel concepts in regio- and stereoselective biaryl synthesis, computational chemistry including the calculation of structures, dynamics, and chemical reactivities of molecules and the prediction of CD spectra as well as QSAR investigations, and ‘endogenous alkaloids in Man’, their in vivo formation, metabolism, and medicinal relevance for neurodegeneration.

Petra Henschel, born in 1970, received her education as a technical assistant from 1991 to 1993 at the Naturwissenschaftlich-Technische Akademie Prof. Dr. Grübler in Isny, Germany. She joined the Bringmann group in 1993 and has since then worked in various synthetic and analytical fields, likewise involving cell tissue culture techniques.

Jürgen Hinrichs, born in 1970, received his diploma in 1996 under the supervision of Prof. Bringmann at the University of Würzburg. His research interests are the development of new methodologies in stereoselective organic synthesis and their applications to the preparation of complex natural products. He received part of his undergraduate education in Glasgow, Scotland, and spent three months (Autumn, 1998) as an intern at Merck in Rahway, NJ, where he developed an automated protocol for the rapid screening of new catalysts. For his Ph. D. thesis, he examined the kinetic resolution of configurationally stable biaryl lactones and prepared the axially chiral target molecules, (+)-isokotanin A and mastigophorene B. From 1997 to 1999 he was supported by a fellowship of the State of Bavaria. He was also among the prize winners at Drug Discovery 99 held by Pfizer. After receiving his Ph.D., he recently joined Professor Nicolaou's group at Scripps as a postdoctoral fellow.

Thomas Pabst, born in 1969, received his diploma in 1996 under the guidance of Prof. Bringmann at the University of Würzburg for work focused on the development of a new methodology for stereoselective oxidative biaryl coupling by using carbohydrates as chiral templates. He received his Ph. D. in 2000 for the atroposelective synthesis of the nerve-growth stimulating mastigophorenes A and B, as well as structurally simplified analogs, via configurationally labile biaryl lactones.

induction, *separately*. Firstly, and independent of the final axial chirality, the coupling is achieved intramolecularly, after pre-fixation of the two aromatic portions via an ester bridge as in **7** (Scheme 1). This bridge is of manifold crucial importance within the concept:

It brings together the reaction partners, i.e., the two aromatic rings, thus guaranteeing the coupling to 6-membered lactones of type **8** to be achieved in excellent yields, even against highest steric hindrance (e.g., R = *t*-Bu).

Moreover, by dramatically lowering the atropisomerization barrier at the newly created biaryl axis, it allows the establishment of the required axial configuration separately, by atropisomer-selective cleavage of lactone **8**, for which a variety of different nucleophilic reagents can be used. For this purpose, the bridge with its reactive C=O group again provides the site of stereocontrolled attack and thus constitutes a useful "Achilles' heel" for the directed opening of the lactone ring of **8**. This cleavage can be brought about with high stereocontrol; atropo-diastereoselectively to esters or amides **9** using *O*- or *N*-nucleophiles[21,22] (e.g., sodium 8-phenylmentholate (**11**), giving drs of up to > 99:1), or atropo-enantioselectively with *H*-nucleophiles[23,24] (e.g., with borane activated by the oxazaborolidine (*S*)-**12**, to provide alcohols **10** with up to er 98.5:1.5 (Scheme 1). In each case, the other respective atropisomer can be obtained, too, just by the use of the other reagent enantiomer, starting from the same 'late' lactone precursor **8**, in the sense of an atropisomer-divergent procedure.

And finally, even minor atropisomeric byproducts are not lost, but can be re-used; literally a recycling by re-cyclization back to the configurationally unstable lactone, and renewed stereocontrolled ring cleavage.[24,25]

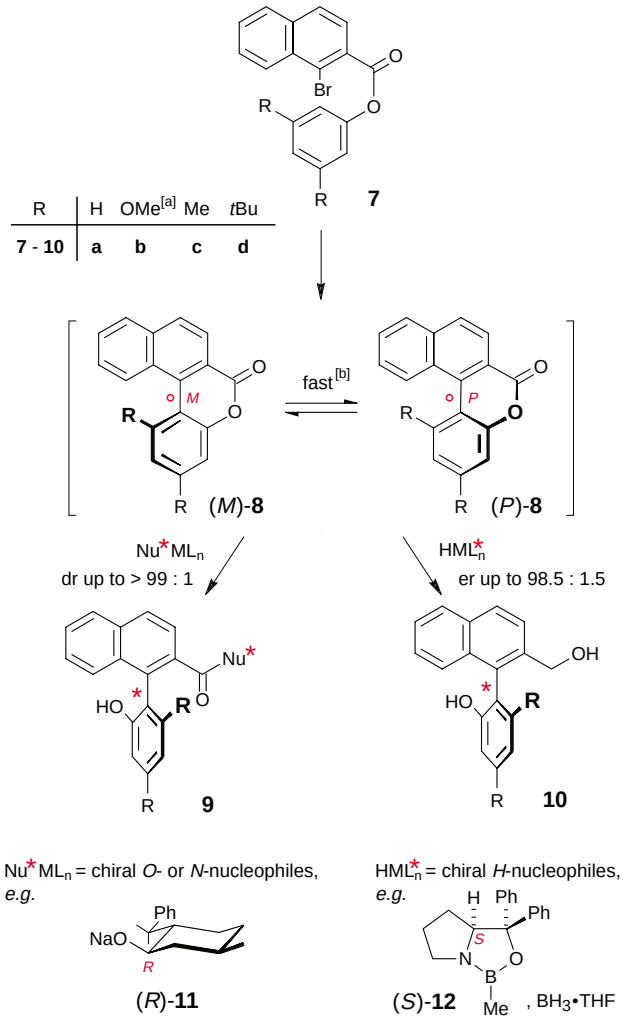
This lactone method is not only conceptually novel and thus of intellectual and mechanistic interest, but has proven its efficiency and practicability already in the total synthesis of more than 25 natural biaryl target molecules, among them all of the natural products shown in Figure 1.[25-30] Furthermore, quite a series of useful axially chiral reagents and ligands like the aminophenol (*P*)-**13**[31] (Figure 2), the monodentate phosphine reagent (*P*)-**14**,[32] and the as yet unprecedented C_3-symmetric tripod ligand (*M*,*M*,*M*)-**15**,[33] which has three homochiral biaryl axes, have been prepared by this efficient methodology.

The target molecules to be prepared by the lactone methodology do not necessarily have to be equipped with C_1- and *O*-substituents next to the axis because of the possibility of further modifying the substitution pattern after the ring cleavage reaction. Besides subsequently transforming the phenolic oxygen function into hydrogen (cf. structure **2**) or into a phosphorous substituent (cf. **14**), the C_1-'bridgehead' can be used to build up further ring systems (cf. **3**), or it can be replaced by an oxygen function, or again just by hydrogen.[34]

Biographical Sketches

Karl Peters, born in 1940, received his doctorate degree in inorganic chemistry for work on single-crystal structure determinations, under the direction of H. G. von Schnering. Since 1975 he has been a senior research associate at the Max-Planck-Institut für Festkörperforschung in Stuttgart, and his research interests concentrate on the application of X-ray crystallography.

Eva-Maria Peters, born in 1948, extended her chemical profession to the computational management of crystal structure determinations at the Max-Planck-Institut für Festkörperforschung, where she has been working since 1975.



[a] Note that for formal reasons of the CIP denotation, biaryls with R = OMe have opposite descriptors compared to those with R = H or alkyl

[b] Due to the large *ortho* substituent, lactone **8d** (R = *t*Bu) is configurationally stable at room temperature

Scheme 1 The basic principle of the 'lactone concept' for the atroposelective synthesis of axially chiral biaryls like **9** or **10**: the dynamic kinetic resolution of configurationally unstable biaryl lactones **8**[20]

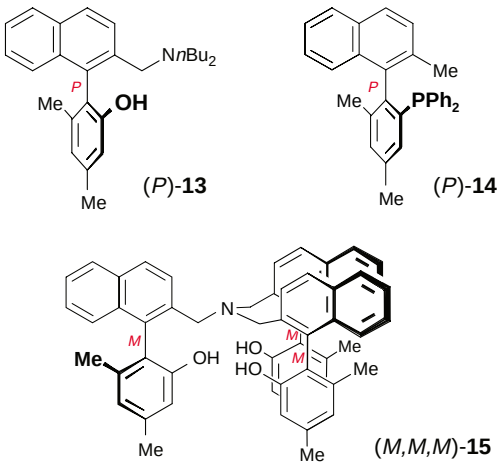
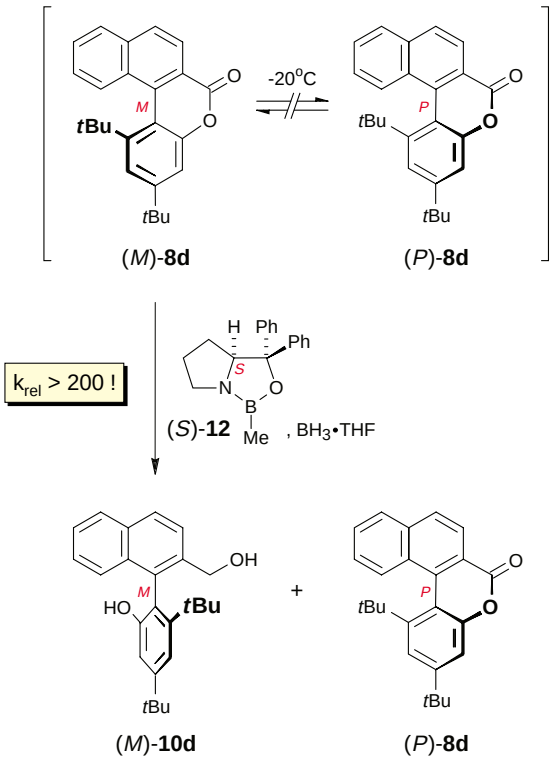


Figure 2 A selection of useful biaryl ligands already prepared by the lactone methodology[31-33]

'Non-Dynamic' Kinetic Resolution of Configurationally *Stable* Lactones

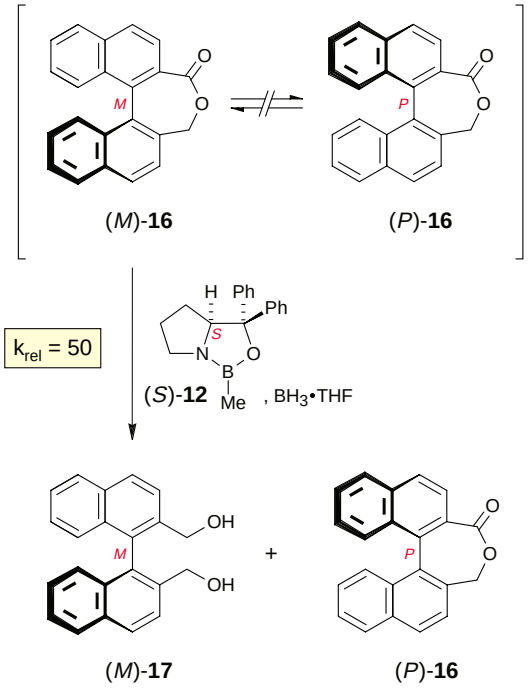
More recently, the lactone method has been further extended to the atropisomer-selective ring cleavage of configurationally *stable* lactones,[35,36] which have thus proved to be valuable substrates for such enantiomer-differentiating reactions, too. Configurational stability for lactone-bridged biaryls can be attained in two different ways: by placing even more steric hindrance into the *ortho*-position next to the biaryl axis (which is easily tolerated in the coupling step), or by utilizing a bridge that will not, as in the previous cases, lead to a 6-membered lactone, but to a 7-membered one. The first of these two cases is exemplified by the *tert*-butyl substituted lactone **8d**. The fact that it can, as all the other (less hindered) lactones of type **8**, again be prepared by the intramolecular coupling of the corresponding bromo ester, despite the now enormous steric hindrance, emphasizes the efficiency of this coupling step, which provides **8d** in more than 80% yield.[36] Lactone **8d** is a drastically distorted, helicene-like chiral molecule,[37] and of course initially racemic. Application of the reductive cleavage reactions as above leads to a 'here non-dynamic' kinetic resolution. Due to the strain-induced enhanced reactivity of **8d**, this resolution can be performed even at −78 °C, now proceeding with a nearly immeasurably high relative rate constant $k_{rel} > 200$[36] (Scheme 2). The remaining unreactive atropisomer, (*P*)-**8d**, in the case of the *S*-configured oxazaborolidine (*S*)-**12** can again be recycled, this time not in situ, but separately,



Scheme 2 Highly efficient non-dynamic kinetic resolution of the configurationally stable biaryl lactone **8d** using oxazaborolidine-activated borane[36]

by thermal equilibration, followed by renewed reduction of the racemic lactone; a most efficient pathway to even highly hindered biaryls, proceeding in excellent chemical and optical yields.[36]

Turning from 6-membered lactones of type **8** to larger, e.g., to 7-membered rings as in **16**, the atropisomerization barrier at the axis is less efficiently lowered by the bridge: thus, in contrast to its 6-membered analog,[38] **16** is configurationally stable up to well above 120 °C (Scheme 3). This makes a dynamic kinetic resolution impossible, but under reductive conditions using borane activated by the oxazaborolidine (*S*)-**12**, the diol (*M*)-**17** is obtained through a 'normal' kinetic resolution, again with high relative rate constants (up to $k_{rel} = 50$).[35] During the reaction, (*P*)-**16** is enriched up to complete optical purity.

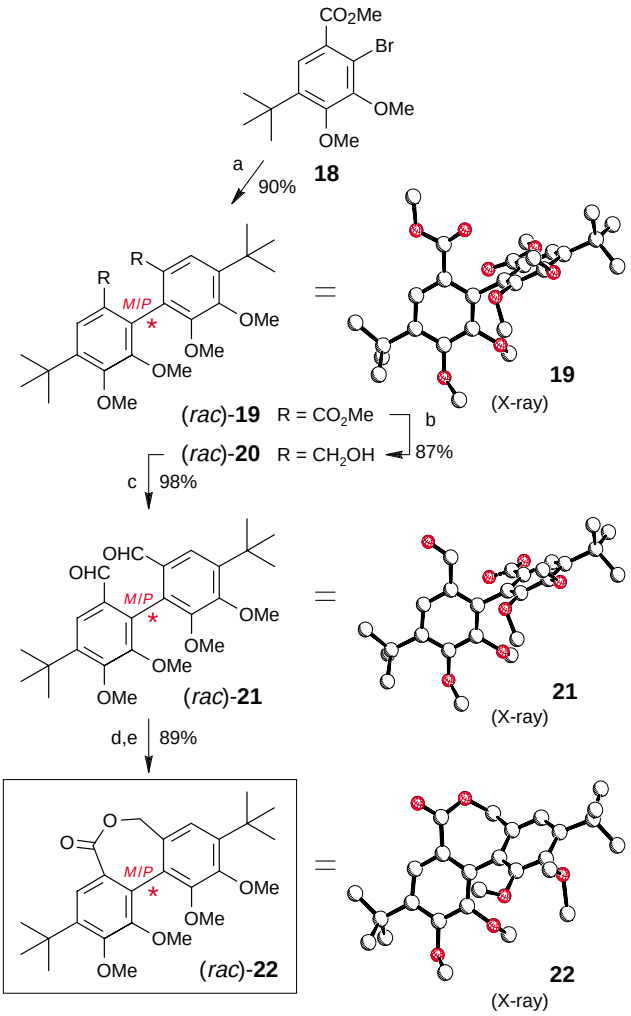


Scheme 3 Another successful example of the new principle: kinetic resolution of the 7-membered lactone **16** with two C_1 units next to the biaryl axis[35]

Configurative instability at the axis and the resulting possibility of achieving *dynamic* kinetic resolutions has to be considered as a major advantage when using 6-membered lactones, while 7-membered lactones can be cleaved only by a normal, non-dynamic kinetic resolution and thus require a separate recycling of the unreacted enantiomer. On the other hand, the 7-membered lactones bear the inherent advantage of complementing the substitution pattern initially attained in the primary ring cleavage process of 6-membered lactones (one C_1- and one *O*-substituent) by producing molecules with two C_1-units next to the biaryl axis, which is a valuable enrichment of the basic lactone methodology.

Application of the 7-Membered Lactone Methodology to Natural Product Synthesis: Preparation of Mastigophorene B (4)

With this new methodology in hand, the synthesis of mastigophorene B (**6b**), the atropo-diastereomer of mastigophorene A (**6a**), via a configurationally stable biaryl lactone was envisaged and is described herein. Reaction conditions were first optimized for a simplified analog **23** (vide infra), in which the two chiral cyclopentyl residues of **6** are replaced by *tert*-butyl groups. Previous studies had shown that, like the mastigophorenes **6** themselves,[11] this model compound also has neurotrophic properties.[39] Starting from the known[28] ester **18**, the required lactone **22** was obtained in five smooth reaction steps as outlined in Scheme 4. Ullmann coupling of **18** gave racemic **19**, whose structure was fully confirmed by X-ray structure analysis;[40] reduction of **19** and oxidation of the resulting

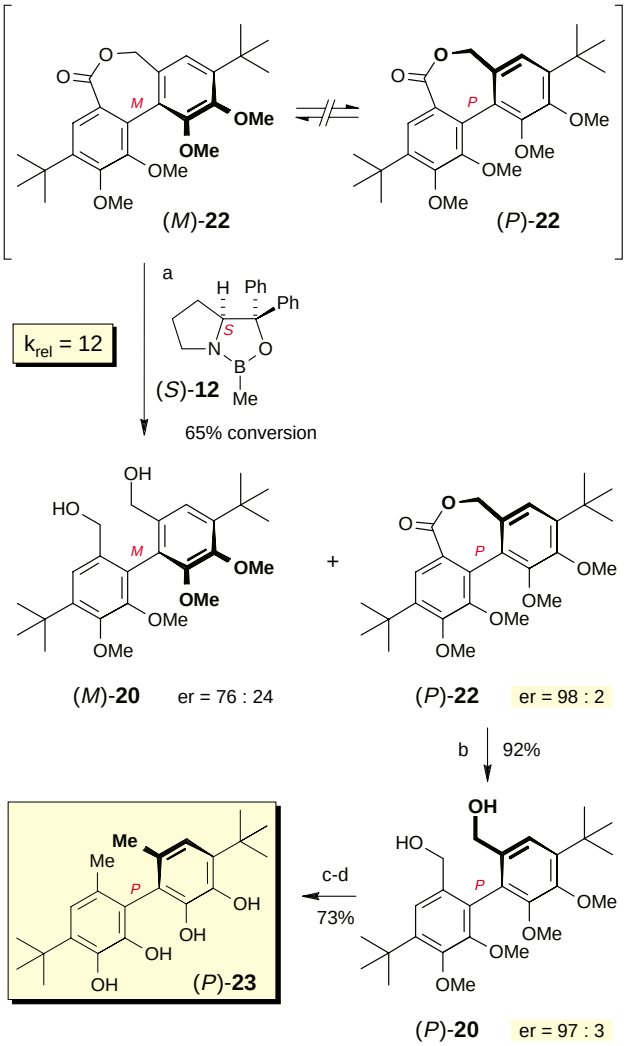


Reagents and conditions: (a) Cu, DMF, 160 °C, 48 h (90%); (b) $LiAlH_4$, THF, 2 h (87%); (c) MnO_2, CH_2Cl_2, 3 days (98%); (d) KOH, EtOH, reflux, 24 h; (e) DCC, DMAP, CH_2Cl_2, reflux, 4 h (89%, two steps)

Scheme 4 Preparation of the configurationally stable model lactone **22**

diol **20** yielded the dialdehyde **21**,[40] which was transformed into the corresponding hydroxy acid under Cannizzaro conditions. Ring closure with DCC gave the key lactone **22**.

This lactone-bridged biaryl **22** was found to be configurationally stable at room temperature by HPLC on a chiral stationary phase (Chiralcel OF, Daicel Chem. Ind.). An X-ray crystallographic analysis of **22** (Scheme 4)[40] revealed that the lactone bridge as compared to that of the 6-membered lactones **8**[37] is long enough to let the two molecular portions adopt a 'relaxed', near-orthogonal position, without distortion of the aromatic rings, which, besides additional steric interactions in the atropisomerization transition state,[36] results in the observed higher rotational barrier. Kinetic resolution under the conditions previously optimized for lactone **16**[35] proceeded with moderate selectivity (k_{rel} = 12) in this case (Scheme 5), making it necessary to use the enantiomerically enriched unreacted lactone (*P*)-**22**[41] for further transformations. Reduction of (*P*)-**22** with $LiAlH_4$ yielded the alcohol (*P*)-**20** without significant loss of stereochemical purity.

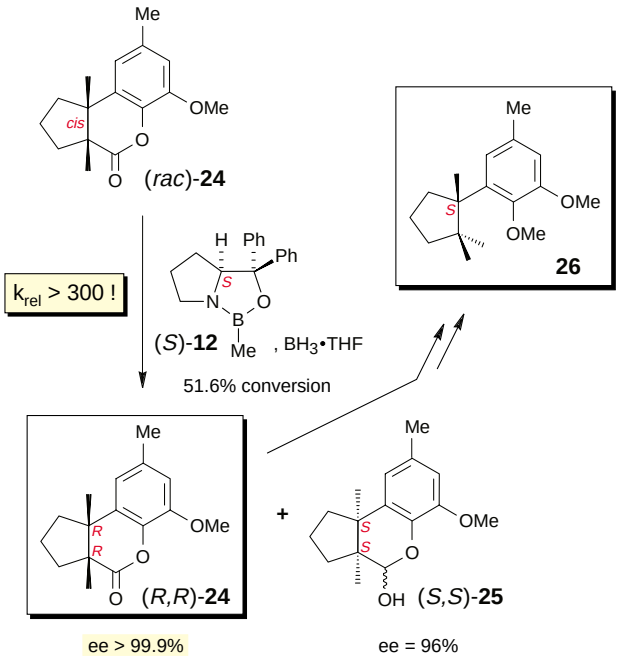


Reagents and conditions: (a) (*S*)-**12**, BH_3·THF, THF, −20°C, 3 h [33% (*P*)-**22** and 58% (*M*)-**20**]; (b) $LiAlH_4$, THF, 2 h (92%); (c) $(CBrCl_2)_2$, PPh_3, CH_2Cl_2, 4 h, then $LiAlH_4$, CH_2Cl_2/Et_2O, 24 h; (d) BBr_3, CH_2Cl_2, 1 h (73%, three steps)

Scheme 5 Kinetic resolution of lactone **22** by enantiomer-differentiating reduction and further transformation of (*P*)-**22** to give the mastigophorene A analog (*P*)-**23**

In order to avoid unnecessary tedious separation work on synthetic intermediates, the final steps in the synthesis of the mastigophorene A analog (*P*)-**23**, the hydroxy-bromo exchange, the $LiAlH_4$ reduction, and the subsequent removal of the protecting groups were all achieved in situ, yielding (*P*)-**23** in an overall 73% yield, fully identical with material previously prepared.[42]

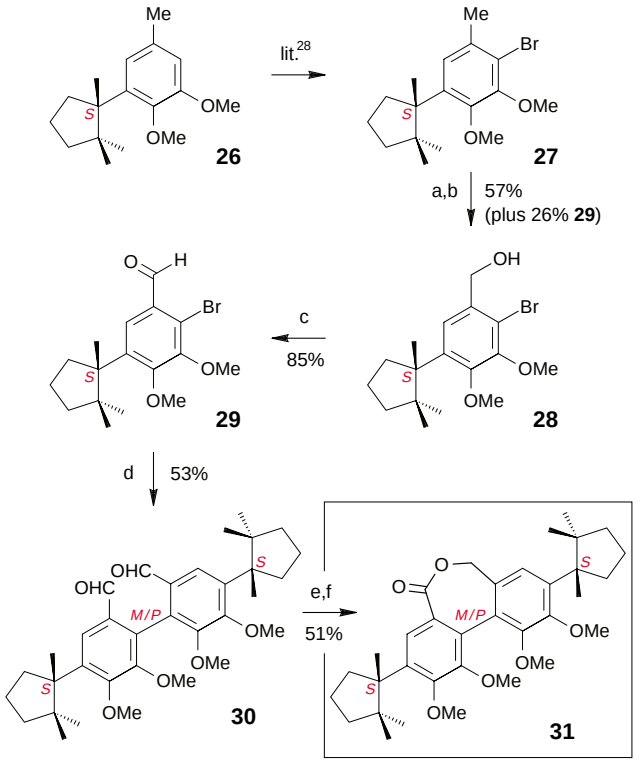
This procedure was then applied to the total synthesis of the related authentic natural product mastigophorene B (**6b**). As a starting material, we chose herbertenediol dimethyl ether (**26**),[28] which had previously been obtained by a novel modification of the lactone method, as outlined in Scheme 6: by an again – non-dynamic – kinetic resolution of a configurationally stable lactone, here the 'aliphatic-aromatic' **24**, with borane activated by oxazaborolidine (*S*)-**12**, resulting in a highly efficient (k_{rel} > 300!) enantiomer-differentiating reduction, which underlines that the extension of the basic lactone concept described here is not limited to biaryl lactones. This high selectivity made it possible to obtain unreacted, stereochemically pure (*R*,*R*)-**24** (ee > 99.9%) already after less than 52% conversion.[28] Standard transformations of (*R*,*R*)-**24** then gave herbertenediol dimethyl ether (**26**), the *O*-protected 'monomer' of the mastigophorenes **6**.



Scheme 6 Another efficient extension of the lactone methodology: the highly selective (k_{rel} > 300) production of the enantiomerically pure 'monomer', herbertenediol dimethyl ether (**26**), by reduction of the 'aliphatic-aromatic' lactone **24** with kinetic resolution[28]

Bromination of **26** according to the literature[28] gave compound **27** (Scheme 7), which was oxidized in a three-step

procedure (74% overall yield) to furnish the bromo aldehyde **29**, fully identical to material previously obtained by semisynthesis from a natural precursor.[28] In an improvement compared to the synthesis of the mastigophorene A analog (*P*)-**23** presented above, aldehyde **29** was directly subjected to the Ullmann coupling conditions; not as its ester derivative. Although this gave rise to the biaryl dialdehyde **30** in an only moderate yield (53%), it reduced the number of steps significantly. Cannizzaro reaction of **30** and ring closure with DCC gave the 7-membered biaryl lactone **31** as a mixture of its two configurationally stable atropisomers, in a diastereomeric ratio of 58:42.



Reagents and conditions: (a) NBS, $(t\text{-BuO})_2$, $CHCl_3$, reflux, 4 h; (b) $CaCO_3$, H_2O/dioxane, reflux, 16 h (57% and 26% **29**, two steps); (c) MnO_2, CH_2Cl_2, 1 day (85%); (d) Cu, DMF, 165 °C, 16 h (53%); (e) KOH, EtOH, reflux, 1.5 h; (f) DCC, DMAP, CH_2Cl_2, 8 h (51%, two steps)

Scheme 7 Preparation of the configurationally stable lactone **31**, a key intermediate in the synthesis of mastigophorene B (**6b**)

Comparison of the CD spectrum of this mixture with that of the related lactone (*P*)-**32**, a compound from the synthesis of the configurationally well known natural product, (+)-isokotanin A (**4**)[30] (Figure 3), clearly revealed that (*M*)-**31** must be the predominant atropisomer in the mixture. This made it rewarding to pursue the following strategy: Since the enantiomer-differentiating selectivities in the model studies (see above) had been unexpectedly moderate, the remaining, stereochemically enriched lactone, in that case (*P*)-**22**, was used for further transformations. For the actual mastigophorene synthesis, it thus seemed desirable to rather try to remove as much as possible of the minor ('wrong') (*P*)-isomer of lactone **31**, through reduction to the corresponding alcohol by kinetic resolution. For this, by analogy to the stereochemical outcome of previous ring cleavage reactions (see *i.a.* above), the (*R*)-oxazaborolidine enantiomer, (*R*)-**12**, should be the required reagent of choice. The resulting enriched (*M*)-enantiomer of the unreacted lactone (*M*)-**31** would then be used for completing the synthesis of mastigophorene B (**6b**), which is likewise (*M*)-configured.

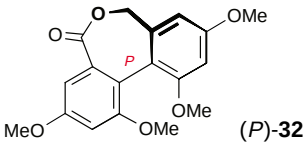


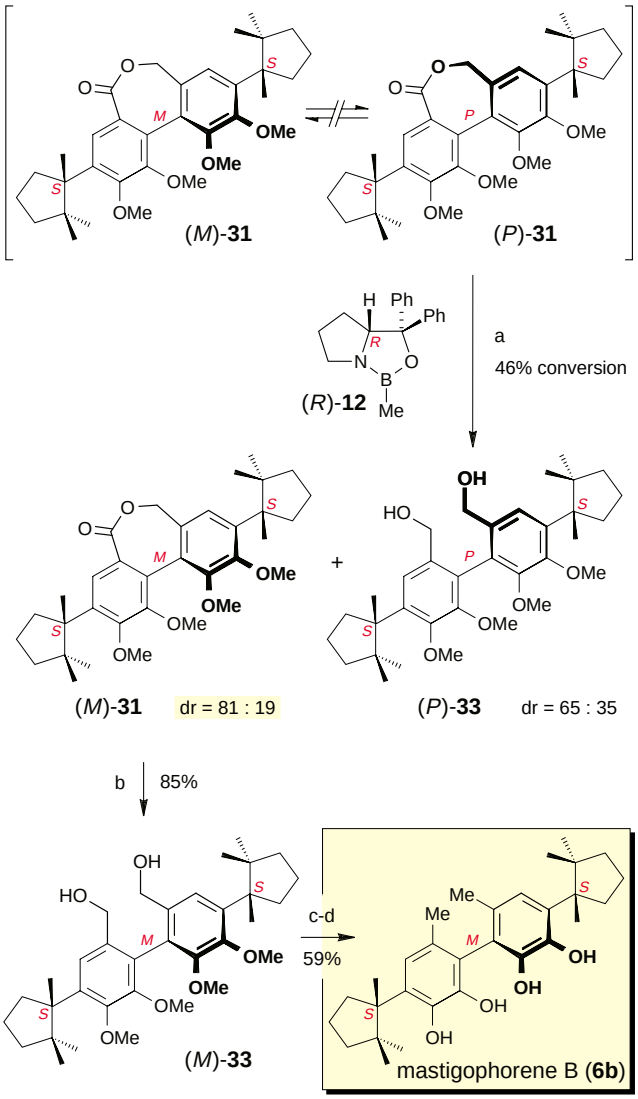
Figure 3 Biaryl lactone (*P*)-**32**, an axially chiral compound from the synthesis of (+)-isokotanin A (**4**)[30]

Following this strategy, partial reduction of (*M/P*)-**31** with (*R*)-**12**·BH_3 gave stereochemically enriched lactone (*M*)-**31** with a diastereomeric ratio of 81:19. Further reduction of (*M*)-**31** with $LiAlH_4$ (85% yield) and application of the above three-step procedure; reduction of the two benzylic alcohol functions in (*P*)-**33** to methyl groups and subsequent removal of the protecting groups gave stereochemically pure mastigophorene B (**6b**) after chromatographic purification, in an overall yield of 5.1% starting from the herbertenediol derivative **26** (Scheme 8). It proved to be identical in all respects with the natural product **6b**,[11] by which the previous assumption (see above) that the (*M*)-atropisomer of lactone **31** had been formed predominately in the coupling step, was confirmed.

Although the atropisomer-differentiating selectivity in the resolution step is only moderate, the strategy elaborated here represents the as yet shortest and most convergent synthesis of mastigophorene B (**6b**), compared both to Meyers' oxazoline approach[43] and to our previous synthesis via a configurationally unstable six-membered lactone.[28]

Conclusion

The kinetic resolution of configurationally stable lactones, both biarylic and 'aliphatic-aromatic' ones, has proven to provide an efficient pathway to both axially chiral and centrochiral compounds. The new protocol has been used for the first time in a diastereomer-differentiating reaction, for a short synthesis of the nerve-growth stimulating bis-sesquiterpene mastigophorene B (**6b**). In comparison to our lactone method via configurationally unstable biaryl lactones, it is especially well-suited for constitutionally *symmetric* biaryls, since it avoids the need of first building up two different aryl compounds (a bromo acid and a phenolic portion) for the construction of a 6-membered lactone, thus significantly reducing the number of required reaction steps.



Reagents and conditions: (a) (*R*)-**12**, BH_3·THF, THF, −20 °C, 2 h [51% (*M*)-**31** and 43% (*P*)-**33**]; (b) $LiAlH_4$, THF, 2 h (85%); (c) $(CBrCl_2)_2$, PPh_3, CH_2Cl_2, 4 h, then $LiAlH_4$, CH_2Cl_2/Et_2O, 4 h; (d) BBr_3, CH_2Cl_2, 1 h (59%, three steps).

Scheme 8 kinetic – here diastereomeric – resolution of **31** by oxazaborolidine-assisted borane reduction and final steps of the synthesis of mastigophorene B (**6B**).

Experimental

Mps were determined on a Reichert−Jung Thermovar hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin−Elmer 1420 spectrometer and are reported in wave numbers (cm^{-1}). Optical rotations were measured on a Perkin−Elmer 241 MC polarimeter. CD spectra were taken on a Jasco J-715 spectropolarimeter, using EtOH as solvent. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 (200 and 50 MHz), AC 250 (250 and 63 MHz), and AMX 400 (400 and 101 MHz) machines. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. As the internal reference, the solvent signal [^1H: δ ($CDCl_3$) = 7.26, ^{13}C: δ ($CDCl_3$) = 77.01] was used. EI mass spectra (70 eV) were measured on Finnigan MAT 90 and MAT 8200 mass spectrometers, the relative intensities are given in brackets. Microanalyses were performed by the microanalytical laboratory of the Inorganic Institute of the University of Würzburg, Germany (Leco CHNS-932).

THF was freshly distilled from K, Et_2O from Na wire, DMF from CaH_2, and CH_2Cl_2 from P_2O_5. All air or moisture sensitive reactions were carried out with dry glassware under N_2 or Ar atm. Column chromatography was performed on silica gel 63−200 μm (Merck). Oxazaborolidines (*S*)-**12** and (*R*)-**12** (1 M in toluene, which was removed in vacuo prior to use) and BH_3·THF (1 M in THF) were obtained from Aldrich.

HPLC analyses were carried out with a combination of a Waters HPLC pump 510, a 20 μl injection loop and Chiralcel OF and OD-H columns (0.46 × 25 cm, Daicel Chem. Ind.) with UV detection at 254 nm. The atropisomers of lactone **22** were separated on the OF column with hexane/*i*-PrOH (85:15; 1.0 mL/min) as the eluent, the t_R for (*P*)-**22** and (*M*)-**22** were 11 and 15 min, respectively. For diol **20**, the OD-H column was used with hexane/*i*-PrOH (98:2; 1.0 mL/min) as the eluent, with t_R of 9 and 15 min for (*M*)-**20** and (*P*)-**20**, respectively. The diastereomeric ratios of compounds **31** and **33** were determined by ^1H NMR.

(*rac*)-Dimethyl 4,4′-Di-*tert*-butyl-5,5′,6,6′-tetramethoxy-1,1′-biphenyl-2,2′-dicarboxylate (19)

A mixture of methyl 2-bromo-5-*tert*-butyl-3,4-dimethoxybenzoate (**18**)[28] (3.00 g, 9.06 mmol) and activated copper[44] (4.40 g) in DMF (10 mL, degassed) was heated to 160 °C for 48 h under N_2. After the mixture had cooled to r.t., the copper was filtered off and washed with CH_2Cl_2, and the solvent was removed in vacuo. Column chromatography (petroleum ether/Et_2O 10:1) gave **19** (2.05 g, 4.08 mmol, 90%) as colorless crystals from petroleum ether, mp 161−165 °C.

IR (KBr): ν = 2980, 2930, 2890, 2840 (C-H), 1710 (C=O), 1300, 1040 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.43 [s, 18H, $C(CH_3)_3$], 3.55, 3.56, 3.90 (3 × s, each 6H, each OCH_3), 7.75 (s, 2H, 3-H, 3′-H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 30.36 [$C(CH_3)_3$], 35.12 [$C(CH_3)_3$], 51.59, 59.50, 59.84 (OCH_3), 123.8, 124.4, 132.1, 142.3, 150.8, 155.9, 167.4 (C=O).

MS (70 eV): *m/z* (%) = 502 (21) [M^+], 455 (20) [$M^+-CH_3OH-CH_3$], 149 (100), 57 (47) [$C_4H_9^+$].

Anal. Calcd for $C_{28}H_{38}O_8$ (502.60): C, 66.91; H, 7.62. Found: C, 66.64; H, 7.52.

(*rac*)-4,4′-Di-*tert*-butyl-6,6′-dihydroxymethyl-2,2′,3,3′-tetramethoxy-1,1′-biphenyl (20)

At 0 °C under Ar, a solution of diester **19** (2.00 g, 3.98 mmol) in THF (50 mL) was treated with $LiAlH_4$ (605 mg, 15.9 mmol) in portions. After 2 h, the reaction mixture was carefully hydrolyzed by slow addition of H_2O (10 mL) and 2 N HCl (20 mL), the organic solvent was removed in vacuo, and the aqueous phase was extracted with Et_2O. The organic phase was dried ($MgSO_4$), the solvent evaporated, and the residue crystallized from Et_2O/petroleum ether to give colorless crystals of **20** (1.54 g, 3.45 mmol, 87%), mp 183−185 °C.

IR (KBr): ν = 3420 (OH), 2980, 2940, 2850 (C-H), 1370, 1290, 1220, 1000 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.43 [s, 18H, $C(CH_3)_3$], 3.62 (s, 6H, 2- and 2′-OCH_3), 3.87 (s, 6H, 3- and 3′-OCH_3), 4,17 (s, 4H, CH_2OH), 7.21 (s, 2H, 5-H, 5′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.53 [$C(CH_3)_3$], 35.14 [$C(CH_3)_3$], 59.91 (OCH_3), 63.76 (CH_2OH), 123.3, 128.1, 134.3, 143.7, 150.6, 152.2.

MS (70 eV): *m/z* (%) = 446 (10) [M^+], 428 (100) [M^+-H_2O], 57 (81) [$C_4H_9^+$].

Anal. Calcd for $C_{26}H_{38}O_6$ (446.58): C, 69.93; H, 8.58. Found: C, 69.46; H, 8.40.

(*rac*)-4,4′-Di-*tert*-butyl -5,5′,6,6′-tetramethoxy-1,1′-biphenyl-2,2′-dicarbaldehyde (21)

A solution of compound **20** (1.54 g, 3.45 mmol) in CH_2Cl_2 (50 mL) was stirred with MnO_2 (3.00 g, 34.5 mmol) for 3 days at 30 °C with ultrasonic assistance. The mixture was filtered over silica (2 cm Celite on top of column). After evaporation of the solvent, the crude product (1.49 g, 3.37 mmol, 98%) was obtained, which was used in the next step without purification. An analytical sample was crystallized from petroleum ether, mp 181−182 °C.

IR (KBr): ν = 2980, 2940, 2840, 2800 (C-H), 1670 (C=O), 1290, 1220, 1040 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 [s, 18H, $C(CH_3)_3$], 3.56 (s, 6H, 5- and 5′-OCH_3), 3.95 (s, 6H, 6- and 6′-OCH_3), 7.81 (s, 2H, 3-H, 3′-H), 9.61 (s, 2H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.22 [$C(CH_3)_3$], 35.44 [$C(CH_3)_3$], 59.70, 60.15 (OCH_3), 122.3, 129.6, 130.0, 144.7, 151.2, 157.9, 190.6 (CHO).

MS (70 eV): *m/z* (%) = 442 (56) [M^+], 413 (41) [M^+−CHO], 385 (73), 57 (100) [$C_4H_9^+$].

Anal. Calcd for $C_{26}H_{34}O_6$ (442.55): C, 70.56; H, 7.74. Found: C, 70.15; H, 7.64.

(*rac*)-4,4′-Di-*tert*-butyl-2′-hydroxymethyl-5,5′,6,6′-tetramethoxy-1,1′-biphenyl-2-carboxylic Acid (22)

A mixture of dialdehyde **21** (1.49 g, 3.37 mmol) and KOH (2.80 g, 50.6 mmol) in EtOH (100 mL) was refluxed for 24 h. The solvent was removed in vacuo, H_2O (20 mL) was added, and the mixture was acidified with 2 N HCl. Extraction with Et_2O (drying with $MgSO_4$) gave the hydroxy acid **22** as a colorless solid, which was used in the next step without purification. An analytical sample was crystallized from EtOAc, mp 189−191 °C.

IR (KBr): ν = 3400 (OH), 2980, 2920, 2840 (C-H), 1690 (C=O), 1290, 1240 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 [s, 18H, $C(CH_3)_3$], 3.50, 3.57 (2 × s, each 3H, 6-OCH_3, 6′-OCH_3), 3.78, 3.91 (2 × s, each 3H, 5-OCH_3, 5′-OCH_3), 4.21, 4.22 (2 × br s, each 1H, CH*H*OH, C*H*HOH), 7.15, 7.75 (2 × s, each 1H, 3-H, 3′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.25, 30.53 [$C(CH_3)_3$], 35.08, 35.20 [$C(CH_3)_3$], 59.40, 59.73, 59.85, 60.24 (OCH_3), 64.40 (CH_2OH), 122.9, 124.9, 125.0, 128.5, 131.1, 132.8, 143.1, 143.3, 150.5, 150.9, 152.1, 156.6, 171.3 (CO_2H).

MS (70 eV): *m/z* (%) = 460 (47) [M^+], 442 (100) [M^+−H_2O], 427 (28) [442−CH_3], 57 (87) [$C_4H_9^+$].

Anal. Calcd for $C_{26}H_{36}O_7$ (460.57): C, 67.80; H, 7.88. Found: C, 67.51; H, 7.94.

(*rac*)-3,9-Di-*tert*-butyl-1,2,10,11-tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one (22)

To a solution of crude hydroxy acid **22** (vide supra) in CH_2Cl_2 (150 mL), DCC (832 mg, 4.04 mmol) and DMAP (206 mg, 1.68 mmol) were added, and the mixture was refluxed. After 4 h, the solvent was removed in vacuo and the residue was purified by column chromatography (petroleum ether/Et_2O, 5:1). Crystallization from Et_2O/petroleum ether gave the lactone **22** (1.33 g, 3.01 mmol, 89% over two steps) as colorless crystals, mp 196−197 °C.

IR (KBr): ν = 2960, 2920, 2840 (C-H), 1690 (C=O), 1360, 1220, 1140, 1040 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.41, 1.43 [2 × s, each 9H, each $C(CH_3)_3$], 3.56, 3.64 (2 × s, each 3H, 1-OCH_3, 11-OCH_3), 3.93, 3.94 (2 × s, each 3H, 2-OCH_3, 10-OCH_3), 4.80 (d, 1H, *J* = 11.8 Hz, CH*H*), 4.96 (d, 1H, *J* = 11.9 Hz, C*H*H), 7.11, 7.56 (2 × s, each 1H, 4-H, 8-H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 30.27, 30.38 [$C(CH_3)_3$], 35.18, 35.38 [$C(CH_3)_3$], 60.10, 60.21, 60.23 (OCH_3), 69.99 (CH_2), 121.6, 123.9, 126.3, 126.5, 126.7, 130.8, 144.1, 144.6, 151.0, 152.8, 153.6, 155.6, 170.5 (C=O).

MS (70 eV): *m/z* (%) = 442 (100) [M^+], 427 (25) [M^+−CH_3], 397 (18) [M^+−CO_2H], 383 (32), 341 (55).

Anal. Calcd for $C_{26}H_{34}O_6$ (442.55): C, 70.56; H, 7.74. Found: C, 70.56; H, 7.46.

Kinetic Resolution of (*rac*)-3,9-Di-*tert*-butyl-1,2,10,11-tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one (22)

To a solution of oxazaborolidine (*S*)-**12** (133 mg, 480 µmol) in THF (4 mL), BH_3•THF (1 M in THF, 640 µl, 640 µmol) was added at 0 °C under an Ar atm. After stirring for 30 min at r.t., the solution was cooled to −20 °C and added dropwise during 5 min to a solution of lactone **22** (71.0 mg, 160 µmol) in THF (4 mL) at −20 °C. After 3 h, the mixture was hydrolyzed by careful addition of H_2O (5 mL) and acidified with 2 N HCl (5 mL). After removal of the organic solvent in vacuo, the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was chromatographed on silica gel (petroleum ether/Et_2O, 1:2), leading to alcohol (*M*)-**20** [41.8 mg, 93.6 µmol, 58%, er = 76:24; after crystallization: enrichment to er = 90:10 in the mother liquor] and lactone (*P*)-**22** (23.2 mg, 52.4 µmol, 33%, er = 98:2). The relative rate constant K_{rel} was determined[45] to be 12 (65% conversion).

(*M*)-4,4′-Di-*tert*-butyl-6,6′-dihydroxymethyl-2,2′,3,3′-tetramethoxy-1,1′-biphenyl [(*M*)-**20**]

Colorless needles, mp 182−184 °C (CH_2Cl_2/petroleum ether).

$[\alpha]^{23}_D$ −54.7° (*c* 0.20, $CHCl_3$).

CD (EtOH): $\Delta\varepsilon_{194}$ +29.8, $\Delta\varepsilon_{218}$ −14.4.

(*P*)-3,9-Di-*tert*-butyl-1,2,10,11-tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one [(*P*)-**22**]

Colorless crystals, mp 198 °C (CH_2Cl_2/petroleum ether).

$[\alpha]^{24}_D$ = +23.3° (*c* 0.95, CH_2Cl_2).

CD (EtOH): $\Delta\varepsilon_{196}$ +12.3, $\Delta\varepsilon_{212}$ −7.1, $\Delta\varepsilon_{228}$ +2.7, $\Delta\varepsilon_{266}$ −4.0.

(*P*)-4,4′-Di-*tert*-butyl-6,6′-dihydroxymethyl-2,2′,3,3′-tetramethoxy-1,1′-biphenyl [(*P*)-20]

$LiAlH_4$ (3.87 mg, 102 µmol) was added in portions at 0 °C to a solution of (*P*)-**22** (37.9 mg, 85.6 µmol) in THF (6 mL) under Ar atm. After stirring for 2 h at r.t., the reaction was quenched by addition of 2 N HCl (1 mL), the organic solvent was removed in vacuo, and H_2O (10 mL) was added. This mixture was extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column filtration (petroleum ether/Et_2O, 1:2). Crystallization from Et_2O/petroleum ether gave (*P*)-**20** (35.2 mg, 78.8 µmol, 92%, er = 97:3) as colorless crystals, mp 182−183 °C.

$[\alpha]^{23}_D$ +64.1° (*c* 0.93, $CHCl_3$).

CD (EtOH): $\Delta\varepsilon_{197}$ −21.3, $\Delta\varepsilon_{221}$ +14.8, $\Delta\varepsilon_{240}$ +2.1.

(*P*)-4,4′-Di-*tert*-butyl-2,2′,3,3′-tetrahydroxy-6,6′-dimethyl-1,1′-biphenyl [(*P*)-23]

Under an atm of dry Ar, 1,2-dibromotetrachloroethane [$(CBrCl_2)_2$, 67.7 mg, 208 µmol] and PPh_3 (54.6 mg, 208 µmol) were added to (*P*)-**20** (33.1 mg, 74.1 µmol) in CH_2Cl_2 (3 mL). After stirring for 4 h at r.t., Et_2O (3 mL) and $LiAlH_4$ (11.8 mg, 311 µmol) were added, and the reaction was stirred at r.t. for 1 day. After addition of H_2O (8 mL) and 2 N HCl (4 mL), extraction (CH_2Cl_2, drying over Na_2SO_4), and removal of the solvent in vacuo gave a colorless residue,[46] which was dissolved in CH_2Cl_2 (4 mL) and treated with BBr_3 (49.1 µL, 519 µmol) at 0 °C under Ar. After stirring for 1 h at r.t.,

excessive BBr_3 was destroyed by addition of MeOH (1 mL), and the solvent was removed in vacuo. Purification of the residue by column chromatography (cyclohexane/EtOAc, 5:1) yielded (*P*)-**23**, which was obtained from EtOAc/cyclohexane as colorless crystals (19.5 mg, 54.4 µmol, 73% over three steps), identical to material obtained previously,[42] mp 244 °C (Lit.[42]: mp 242−243 °C); $[\alpha]^{23}_D$ −33.6° (*c* 0.53, $CHCl_3$) [Lit.[42]: $[\alpha]^{23}_D$ −33.3° (*c* 0.61, $CHCl_3$)]. During this reaction, $Ph_3P{\cdot}BBr_3$[47] was formed, which could be easily separated by column chromatography. On contact with air, $Ph_3P{\cdot}BBr_3$ slowly hydrolyzed, so that, after treatment of the recovered adduct with H_2O and extraction with Et_2O, PPh_3 (47.2 mg, 180 µmol, 86%) could be recycled.

(1′*S*)-2-Bromo-3,4-dimethoxy-5-(1′,2′,2′-trimethylcyclopentyl)phenyl-1-methanol (28)

Bromo compound **27**[28] (150 mg, 440 µmol) was refluxed with NBS (156 mg, 876 µmol) and (*t*-BuO)$_2$ (50 µL) in $CHCl_3$ (10 mL). After 2 h, another portion of NBS (117 mg, 657 µmol) and (*t*-BuO)$_2$ (50 µL) was added to ensure complete consumption of the starting material. The reaction was stirred at reflux for another 2 h. After cooling to r.t., H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting solid was dissolved in H_2O/dioxane (9 mL each) and refluxed with $CaCO_3$ (222 mg, 2.22 mmol) overnight. After acidification with 2 N HCl, the mixture was extracted with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting residue was purified by column chromatography (petroleum ether/Et_2O, 5:1), yielding, besides the aldehyde **29** (40.0 mg, 113 µmol, 26%), the bromo alcohol **28** (90.0 mg, 252 µmol, 57%) as a colorless oil.

$[\alpha]^{23}_D$ −13.9° (*c* 0.75, $CHCl_3$).

CD (EtOH): $\Delta\varepsilon_{195}$ −3.3, $\Delta\varepsilon_{208}$ +7.8, $\Delta\varepsilon_{234}$ −4.9.

IR (KBr): ν = 3090 (Ar-H), 2920, 2845, 2805 (C-H), 1535 (C=C), 1375, 1020, 1005 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68, 1.12, 1.34 (3 × s, each 3H, each CH_3), 1.44−1.84 (m, 5H, 3′-H, 4′-H, 5′-C*H*H), 2.51−2.63 (m, 1H, 5′-CH*H*), 3.81, 3.83 (2 × s, each 3H, each OCH_3), 4.68 (br s, 2H, CH_2OH), 7.21 (s, 1H, 6-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.34 (CH_2), 23.88, 25.23, 26.84 (CH_3), 39.12, 40.96 (CH_2), 44.83, 51.68 (C-1′, C-2′), 59.87, 60.27 (OCH_3), 65.46 (CH_2OH), 115.7, 124.5, 133.9, 140.5, 150.8, 153.4.

MS (70 eV): *m/z* (%) = 358/356 (100/100) [M^+], 327/325 (13/22) [M^+-CH_3O], 288/286 (62/61) [$M^+-C_5H_{10}$], 277 (7) [M^+−Br], 276/274 (62/76) [$M^+-C_6H_{10}$], 275/273 (65/89) [$M^+-C_6H_{11}$], 259 (51), 245/243 (46/55).

Anal. Calcd for $C_{17}H_{25}BrO_3$ (357.29): C, 57.15; H, 7.05. Found: C, 56.89; H, 7.18.

(1′*S*)-2-Bromo-3,4-dimethoxy-5-(1′,2′,2′-trimethylcyclopentyl)benzaldehyde (29)

To a solution of benzyl alcohol **28** (74.5 mg, 209 µmol) in CH_2Cl_2 (10 mL), MnO_2 (72.7 mg, 836 µmol) was added, and the mixture was stirred at r.t. for 1 day. After removal of the insolubles by filtration, the solvent was evaporated and the residue was subjected to column chromatography (petroleum ether/Et_2O, 5:1), to give **29** (63.2 mg, 178 µmol, 85%) as a colorless oil, identical to material previously obtained by semisynthesis,[28] $[\alpha]^{23}_D$ −38.5° (*c* 1.26, $CHCl_3$) [Lit.[28]: $[\alpha]^{23}_D$ −37.6° (*c* 1.01, $CHCl_3$)].

(1″*S*)-5,5′,6,6′-Tetramethoxy-4,4′-bis(1″,2″,2″-trimethylcyclopentyl)-1,1′-biphenyl-2,2′-dicarbaldehyde (30)

Bromo aldehyde **29** (89.7 mg, 252 µmol) was dissolved in degassed DMF (0.25 mL) and treated with activated copper[44] (176 mg) under Ar at 165 °C for 16 h. After the mixture had cooled to r.t., the copper was filtered off and washed with CH_2Cl_2 and the solvent was removed in vacuo. Column chromatography (cyclohexane/EtOAc, 8:1) gave **30** (36.8 mg, 66.8 µmol, 53%, $dr_{M:P}$ = 54:46) as a colorless solid, along with (1′*S*)-3,4-dimethoxy-5-(1′,2′,2′-trimethylcyclopentyl)benzaldehyde[28] (19.6 mg, 70.9 µmol, 28%). The atropisomers (*M*)-**30** and (*P*)-**30** could not be separated at this point and were thus characterized as a diastereomeric mixture.[48]

IR (KBr): ν = 3090 (Ar-H), 2930, 2835, 2805 (C-H), 1675 (C=O), 1570 (C=C), 1285 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) [(*M*)-**30**]: δ = 0.71, 1.18, 1.44 (3 × s, each 6H, each CH_3), 1.51−1.90 (m, 10H, 3″-H, 4″-H, 5″-C*H*H), 2.63−2.72 (m, 2H, 5″-CH*H*), 3.46, 3.89 (2 × s, each 6H, each OCH_3), 7.91 (s, 2H, 3-H, 3′-H), 9.67 (s, 2H, CHO).

^{1}H NMR (400 MHz, $CDCl_3$) [(*P*)-**30**]: δ = 0.74, 1.18, 1.45 (3 × s, each 6H, each CH_3), 1.49−1.92 (m, 10H, 3″-H, 4″-H, 5″-C*H*H), 2.61−2.74 (m, 2H, 5″-CH*H*), 3.55, 3.90 (2 × s, each 6H, each OCH_3), 7.87 (s, 2H, 3-H, 3′-H), 9.60 (s, 2H, CHO).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.41/20.43 (CH_2), 23.49/23.82, 25.26/25.38, 27.00/27.02 (CH_3), 39.21/39.36, 41.06/41.20 (CH_2), 44.91/44.94, 51.95/51.96 (C-1″, C-2″), 59.34/59.70, 60.27/60.31 (OCH_3), 124.3/124.7, 128.9/129.2, 129.2/129.9, 142.0/142.2, 151.2/151.5, 158.2/158.4, 190.5/190.8 (C=O).

MS (70 eV): *m/z* (%) = 550 (100) [M^+], 535 (6) [M^+-CH_3], 521 (18) [M^+−CHO], 520 (18) [M^+-CH_2O], 519 (44) [M^+-CH_3O], 492 (29), 480 (9) [$M^+-C_5H_{10}$], 468 (4) [$M^+-C_6H_{10}$].

HRMS: *m/z* calcd for $C_{34}H_{46}O_6$: 550.3294. Found: 550.3291.

(1′*S*)-3,9-Bis(1′,2′,2′-trimethylcyclopentyl)-1,2,10,11-tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one (31)

A solution of dialdehyde **30** (35.3 mg, 64.1 µmol) in EtOH (3 mL) was treated with KOH (119 mg, 2.12 mmol) at reflux for 1.5 h. The solvent was removed in vacuo, H_2O (10 mL) was added, and the mixture was acidified with 2 N HCl. Extraction with CH_2Cl_2 (drying with Na_2SO_4) gave the corresponding hydroxy acid as a colorless solid, which was used without purification for the next step: It was dissolved in CH_2Cl_2 (8 mL), together with DCC (19.8 mg, 96.0 µmol) and DMAP (3.92 mg, 32.1 µmol), and stirred for 8 h at r.t. under Ar. Then the solution was washed with H_2O (20 mL) and brine (20 mL), the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography (petroleum ether/Et_2O, 3:1) to yield lactone **31** (17.9 mg, 32.5 µmol, 51% over two steps, $dr_{M:P}$ = 58:42) as a slightly yellow oil. The inseparable atropisomers (*M*)-**31** and (*P*)-**31** were characterized as a diastereomeric mixture.[49]

IR (KBr): ν = 3080 (Ar-H), 2930, 2845 (C-H), 1705 (C=O), 1570 (C=C), 1380, 1360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) [(*M*)-**31**]: δ = 0.74, 0.74, 1.16, 1.18, 1.41, 1.42 (6 × s, each 3H, each CH_3), 1.50−1.94 (m, 10H, 3′-H, 4′-H, 5′-C*H*H), 2.54−2.71 (m, 2H, 5′-CH*H*), 3.51, 3.52, 3.86, 3.91 (4 × s, each 3H, each OCH_3), 4.80 and 4.96 (AB system, 2H, ^2J = 11.9 Hz, OCH_2), 7.15 (s, 1H, 8-H), 7.65 (s, 1H, 4-H).

^{1}H NMR (400 MHz, $CDCl_3$) [(*P*)-**31**]: δ = 0.72, 0.74, 1.15, 1.17, 1.39, 1.43 (6 × s, each 3H, each CH_3), 1.48−1.92 (m, 10H, 3′-H, 4′-H, 5′-C*H*H), 2.53−2.74 (m, 2H, 5′-CH*H*), 3.55, 3.63, 3.85, 3.87 (4 × s, each 3H, each OCH_3), 4.78 and 4.96 (AB system, 2H, ^2J = 11.9 Hz, OCH_2), 7.15 (s, 1H, 8-H), 7.64 (s, 1H, 4-H).

^{13}C NMR (101 MHz, $CDCl_3$) [(*M*)-**31**]: δ = 20.36, 20.44 (CH_2), 23.97, 24.13, 25.26, 25.32, 26.83, 26.96 (CH_3), 39.05, 39.30, 40.95, 41.09 (CH_2), 45.14, 45.15, 51.76, 51.88 (C-1′, C-2′), 60.12, 60.23, 60.30, 60.35 (OCH_3), 70.18 (OCH_2), 123.6, 125.8, 126.1, 126.3, 126.4, 126.5, 130.2, 141.8, 142.1, 153.2, 154.0, 156.2, 170.6 (C=O).

^{13}C NMR (101 MHz, $CDCl_3$) [(*P*)-**31**]: δ = 20.29, 20.78 (CH_2), 23.82, 23.95, 25.10, 25.29, 27.09, 27.12 (CH_3), 39.10, 39.26, 40.86,

41.12 (CH_2), 44.84, 44.92, 51.90, 51.97 (C-1′, C-2′), 60.11, 60.14, 60.21, 60.39 (OCH_3), 70.15 (OCH_2), 123.8, 125.5, 125.8, 126.1, 126.3, 126.4, 130.3, 141.2, 141.7, 153.1, 154.0, 156.2, 170.6 (C=O).

MS (70 eV): *m/z* (%) = 550 (100) [M^+], 535 (7) [M^+-CH_3], 532 (18), 519 (20) [M^+-CH_3O], 501 (20), 480 (9) [$M^+-C_5H_{10}$], 468 (8) [$M^+-C_6H_{10}$], 467 (6) [$M^+-C_6H_{11}$], 419 (13).

HRMS: *m/z* calcd for $C_{34}H_{46}O_6$: 550.3294. Found: 550.3296.

Kinetic Resolution of (1′*S*)-3,9-Bis(1′,2′,2′-trimethylcyclopentyl)-1,2,10,11-tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one (31)

To a solution of oxazaborolidine (*R*)-**12** (23.9 mg, 86.2 µmol) in THF (2 mL), BH_3•THF (1 M in THF, 115 µL, 115 µmol) was added at 0 °C under Ar. After stirring for 30 min at r.t., the solution was cooled to −20 °C and added dropwise during 5 min to a solution of the above prepared diastereomeric mixture of lactone **31** (15.8 mg, 28.7 µmol) in THF (2 mL) at −20 °C. After 2 h, the mixture was hydrolyzed by careful addition of H_2O (4 mL) and acidified with 2 N HCl (4 mL). This mixture was extracted with CH_2Cl_2, the organic phase was dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was chromatographed over silica gel (petroleum ether/Et_2O, 3:1 → 1:2), leading to alcohol (*P*)-**33** (colorless oil, 6.92 mg, 12.5 µmol, 43%, dr = 65:35) and lactone (*M*)-**31** (colorless oil, 8.10 mg, 14.7 µmol, 51%, dr = 81:19). The atropisomers (*M*)-**33** and (*P*)-**33** could not be separated and were thus characterized as a diastereomeric mixture.[50]

(*M*,1′*S*)-3,9-Bis(1′,2′,2′-trimethylcyclopentyl)-1,2,10,11-tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one [(*M*)-**31**]
dr = 81:19; $[\alpha]^{23}_D$ −19.1° (*c* 0.76, $CHCl_3$).

CD (EtOH): $\Delta\varepsilon_{192}$ −7.5, $\Delta\varepsilon_{212}$ +4.7, $\Delta\varepsilon_{236}$ −3.3, $\Delta\varepsilon_{269}$ +5.8, $\Delta\varepsilon_{308}$ −1.7.

(*P*,1″*S*)-6,6'-Dihydroxymethyl-2,2′,3,3′-tetramethoxy-4,4′-bis-(1″,2″,2″-trimethylcyclopentyl)-1,1′-biphenyl [(*P*)-**33**]

dr = 65: 35

IR (KBr): ν = 3370 (OH), 3075 (Ar-H), 2920, 2895, 2835 (C-H), 1580 (C=C), 1445, 1375, 1285 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) [(*M*)-**33**]: δ = 0.74, 1.15, 1.42 (3 × s, each 6H, each CH_3), 1.51−1.91 (m, 10H, 3″-H, 4″-H, 5″-C*H*H), 2.74−2.85 (m, 2H, 5″-CH*H*), 3.57, 3.80 (2 × s, each 6H, each OCH_3), 4.18 and 4.22 (AB system, 4H, ^2J = 11.5 Hz, CH_2OH), 7.29 (s, 2H, 5-H, 5′-H).

^{1}H NMR (400 MHz, $CDCl_3$) [(*P*)-**33**]: δ = 0.70, 1.17, 1.45 (3 × s, each 6H, each CH_3), 1.52−1.89 (m, 10H, 3″-H, 4″-H, 5″-C*H*H), 2.55−2.67 (m, 2H, 5″-CH*H*), 3.57, 3.82 (2 × s, each 6H, each OCH_3), 4.17 and 4.23 (AB system, 4H, ^2J = 11.4 Hz, CH_2OH), 7.29 (s, 2H, 5-H, 5′-H).

^{13}C NMR (101 MHz, $CDCl_3$) [(*M*)-**33**]: δ = 20.39 (CH_2), 24.40, 25.06, 26.96 (CH_3), 38.75, 40.70 (CH_2), 44.99, 51.75 (C-1″, C-2″), 59.82, 60.28 (OCH_3), 63.81 (CH_2OH), 126.0, 128.0, 133.7, 140.7, 150.8, 152.7.

^{13}C NMR (101 MHz, $CDCl_3$) [(*P*)-**33**]: δ = 20.42 (CH_2), 23.54, 25.43, 26.99 (CH_3), 39.21, 41.07 (CH_2), 44.99, 51.74 (C-1″, C-2″), 59.82, 60.05 (OCH_3), 64.22 (CH_2OH), 126.1, 127.7, 134.2, 141.1, 150.5, 152.7.

MS (70 eV): *m/z* (%) = 554 (38) [M^+], 537 (37) [555−H_2O], 536 (100) [M^+-H_2O], 505 (5) [536−CH_3O], 466 (7) [536−C_5H_{10}], 454 (10) [536−C_6H_{10}], 453 (10) [536−C_6H_{11}].

HRMS: *m/z* calcd for $C_{34}H_{50}O_6$: 554.3607. Found: 554.3599.

(*M*,1″*S*)-6,6′-Dihydroxymethyl-2,2′,3,3′-tetramethoxy-4,4′-bis(1″,2″,2″-trimethylcyclopentyl)-1,1′-biphenyl [(*M*)-33]

$LiAlH_4$ (1.03 mg, 27.1 µmol) was added to a solution of (*M*)-**31** (7.50 mg, 13.6 µmol, dr = 81:19) in THF (2 mL) under an Ar atm. After stirring for 2 h at r.t., the mixture was acidified by addition of 2 N HCl (1 mL), H_2O (5 mL) was added, and this mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 2:1). Crystallization from EtOAc/cyclohexane gave (*M*)-**33** (6.41 mg, 11.6 µmol, 85%, dr = 78:22) as colorless crystals, mp 192−193 °C.

$[\alpha]^{23}_D$ −60.7° (*c* 0.25, $CHCl_3$).

CD (EtOH): $\Delta\varepsilon_{202}$ +6.1, $\Delta\varepsilon_{221}$ −13.0.

Mastigophorene B (6b)

Under an atm of dry Ar, 1,2-dibromotetrachloroethane [$(CBrCl_2)_2$, 8.05 mg, 24.7 µmol] and PPh_3 (6.48 mg, 24.7 µmol) were added to (*M*)-**33** (4.90 mg, 8.83 µmol, dr = 78:22) in CH_2Cl_2 (2 mL). After stirring for 4 h at r.t., Et_2O (2 mL) and $LiAlH_4$ (1.41 mg, 37.2 µmol) were added, and the reaction was stirred at r.t. for 4 h. After addition of H_2O (4 mL) and 2 N HCl (2 mL), extraction (CH_2Cl_2, drying over Na_2SO_4) and removal of the solvent in vacuo gave a colorless residue, which was dissolved in CH_2Cl_2 (3 mL) and treated with BBr_3 (5.85 µL, 61.9 µmol) at 0 °C under an Ar atm. After stirring for 1 h at r.t., excess BBr_3 was destroyed by addition of MeOH (1 mL), the solvent was removed in vacuo, and the residue purified by preparative TLC [1 mm plates (Merck), hexane/CH_2Cl_2, 1:1], to yield enantio- and diastereomerically pure mastigophorene B (**6b**) (2.43 mg, 5.21 µmol, 59% over three steps) as a colorless oil, fully identical spectroscopically with the natural product,[11] $[\alpha]^{23}_D$ −38.8° (*c* 0.11, $CHCl_3$) [Lit.[11]: $[\alpha]^{19}_D$ −39.1° (*c* 0.35, $CHCl_3$)].

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Crystal data for **21**: $C_{26}H_{34}O_6$, monoclinic, space group $P2_1/c$; unit cell parameters: a = 829.7(1), b = 1176.9(2), c = 2561.9(4) pm; ß = 94.05(1)°; V = 2495.2(7)·10^6 pm^3.
Crystal data for **22**: $C_{26}H_{34}O_6$, monoclinic, space group $P2_1/c$; unit cell parameters: a = 1175.9(3), b = 1054.9(3), c = 2017.5(8) pm; ß = 101.10(1)°; V = 2455.6(1)·10^6 pm^3.
Further details of the structure investigations are available on request from the Cambridge Crystallographic Data Centre, on quoting the depository numbers CCDC-147219 (for **19**), CCDC-147220 (for **21**) or CCDC-147221 (for **22**), the names of the authors and the journal citation.
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(48) Due to the prevalence of (*M*)-**30**, the ^{1}H NMR signals could be attributed to each diastereomer.
(49) Due to the prevalence of (*M*)-**31** in the next step (kinetic resolution), the NMR signals could be attributed to each diastereomer.
(50) Due to the prevalence of (*M*)-**33** in the next step, the NMR signals could be attributed to the two diastereomers.

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