Novel Concepts in Directed Biaryl Synthesis, 80[+]

Synthesis of Axially Chiral Biaryls by Atropo-Diastereoselective Cleavage of Configurationally Unstable Biaryl Lactones with Menthol-Derived *O*-Nucleophiles

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Dedicated to Prof. Pierre Potier on the occasion of his 65th birthday

Keywords: Axial chirality / Biaryls / Atropisomerism / Dynamic kinetic resolution / Asymmetric synthesis

Configurationally unstable lactone-bridged biaryls **4** are cleaved atropo-diastereoselectively using chiral menthol-derived alkali metal alkoxides, to give axially chiral biaryl esters of type **5** in high yields and excellent diastereomeric ratios of up to > 99:1. The method permits the optional preparation of each of the two atropisomers from the same lactone precursor ("atropo-divergence"), simply according to the choice of the appropiate mentholate or its enantiomer as the *O*-nucleophile – or by the use of the mentholate in solution or in suspension. Undesired minor atropisomers of **5** possibly formed (if at all) can be recycled ("axially chiral economy") by cyclization back to the lactone **4**. For the preparation of larger amounts of enantiopure biaryl alcohols **9**, an efficient reaction sequence was developed: alcoholysis of **4** → in situ reduction → crystallization. The synthetic value of these alcoholysis reactions for asymmetric biaryl synthesis is illustrated by the transformation of **5** into a broad series of enantiopure biaryls of type **6** with various functional groups *ortho* to the axis.

Introduction

Axially chiral biaryl compounds play an important role as useful ligands or reagents for asymmetric synthesis[1] and as pharmacologically potent natural products.[2][3] A highly efficient strategy for the directed, i.e., regio- and atroposelective synthesis of even complex and highly functionalized biaryls is the "lactone method",[4][5] which is based on the atropisomer-differentiating ring cleavage of configurationally unstable lactone-bridged biaryls with chiral *N*-, *O*- and *H*-nucleophiles or, if additional stereocenters are present in the molecule, also with achiral reagents. The broad applicability of this principle has been demonstrated in the total synthesis of axially chiral catalysts[4][6] and more than 20 naturally occurring biaryls,[2][3] mainly naphthylisoquinoline alkaloids. An early example is ancistrocladisine [(*P*)-**3**, Scheme 1], an alkaloid of *Ancistrocladus heyneanus*,[7] which was obtained in a highly atropo-diastereoselective ring opening (d.r. = 95:5) of the lactone precursor **1** with potassium isopropylate as a cheap, achiral *O*-nucleophile.[8] This goal was not reached by later intermolecular biaryl coupling reactions, which led to (inseparable) mixtures of all four possible stereoisomers of **3**.[9]

As nearly ideal model lactones without stereocenters for (overall) atropo-enantioselective ring-opening reactions,[4][5] benzopyranones of type **4** (Scheme 2) can be easily constructed from their monomeric "halves" by esterification and Pd^{II}-catalyzed intramolecular aryl coupling in excellent yields.[4,10,11] Due to the steric demand of the substituent R *ortho* to the biaryl axis, the lactones **4** are helically distorted, with rapid interconversion of the two enantiomeric forms, (*M*)-**4**[12][13] and (*P*)-**4**.[4][10] With chiral hydride or isopropylate transfer reagents, these configurationally labile lactones **4** can be cleaved atropo-enantioselectively to give stereochemically stable target biaryls with good to excellent enantiomeric ratios (e.r.) of up to 98.5:1.5.[14][15] Likewise possible are atropo-*diastereo*selective ring-cleavage reactions with metal-activated chiral 1-arylethylamines as cheap *N*-nucleophiles, giving d.r.'s (d.r. = diastereomeric ratio) of up to 95:5.[16]

Preliminary investigations revealed the potential of atropo-diastereoselective lactone-cleavage reactions with chiral alkoxides as *O*-nucleophiles.[17] In this paper, we describe highly efficient atropo-enantioselective biaryl syntheses by atropo-diastereoselective ring cleavage of lactones **4** with metal-activated menthol-derived *O*-nucleophiles, leading to biaryl esters of type **5** in high chemical and, in part, excellent optical yields (Scheme 2). The merits of this method are that either atropisomer **5** or *ent*-**5** may be syn-

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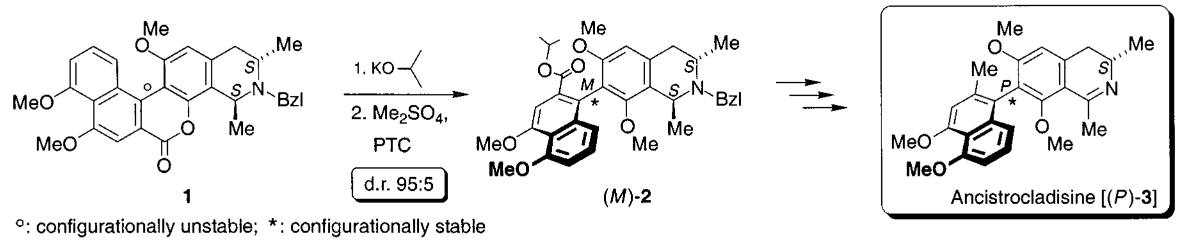
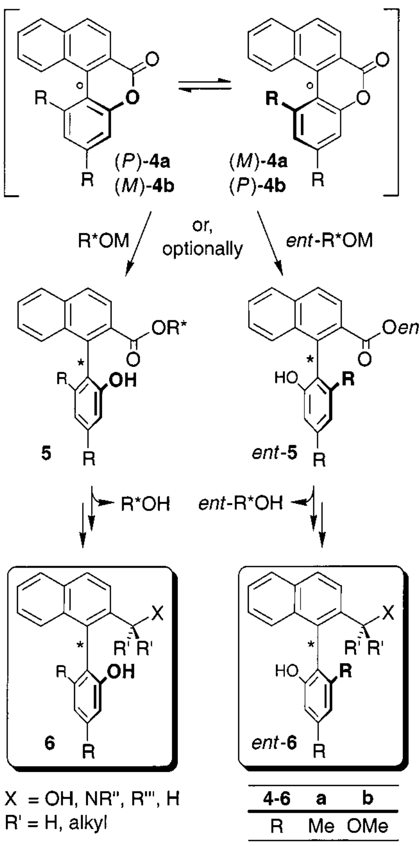


Scheme 1. The stereochemical key step in the synthesis of ancistrocladisine [(*P*)-**3**]: the atropo-diastereoselective ring opening of the biaryl lactone **1** with potassium isopropylate

thesized atropo-diastereo- or -enantiodivergently from the same lactone precursor **4**, by simply using the appropiate mentholate R*OM or its enantiomer *ent*-R*OM; "wrong" stereoisomers can be recycled, and that a broad spectrum of further functionalized enantiopure biaryls **6** or *ent*-**6** are available by subsequent transformations of **5**.

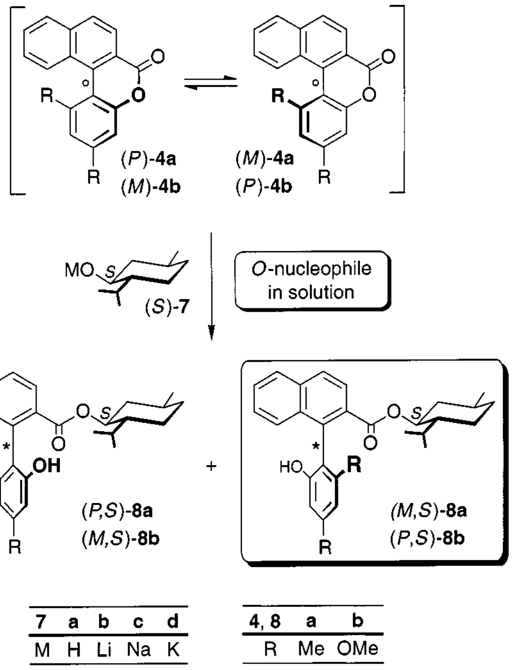


Scheme 2. Enantioselective synthesis of the axially chiral biaryl esters **5** (or, optionally, *ent*-**5**) by ring cleavage of the configurationally unstable lactones **4** with chiral alkoxides R*OM (or *ent*-R*OM) and further derivatization of **5** to the target biaryls **6**

Results and Discussion

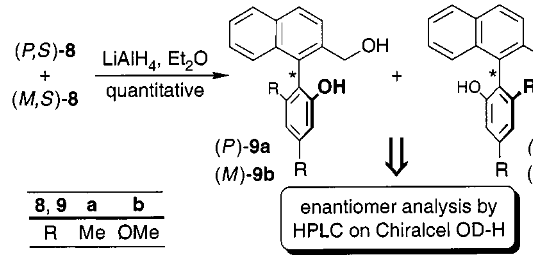
Atropo-Diastereoselective Ring Opening of Biaryl Lactones 4 with Alkali Metal Mentholates

The alcoholysis reactions of **4** were performed with the cheap and simple *O*-nucleophile (*S*)-(+)-menthol [(*S*)-**7a**], which was activated by deprotonation with LDA, NaH, or KH, leading to clear solutions of the alkali metal (1*S*)-mentholates (*S*)-**7b**, **c**, and **d** in the solvents used (THF, CH_2Cl_2, Et_2O, and toluene). With these alkoxides, the ring opening of **4** proceeded cleanly and in good conversions (> 80%), to give the configurationally stable esters **8** (Scheme 3).



Scheme 3. Atropo-diastereoselective ring opening of **4** with solutions of the alkali metal (1*S*)-mentholates (*S*)-**7b**-**d**, to give the configurationally stable biaryl esters **8**

The d.r.'s were measured by (quantitative) reduction of the esters **8** to the corresponding biaryl alcohols **9** and atropo-enantiomer analysis by HPLC on a chiral phase (Scheme 4).



Scheme 4. Stereoanalysis of the esters **8** by reduction to the alcohols **9**

Table 1. Stereoselective cleavage of **4** with solutions of the alkali metal (1*S*)-mentholates (*S*)-**7b**−**d**[a]

Entry	Biaryl lactone	Mentholate	Solvent	*T* [°C]	d.r. (config.)[b]
1	**4a**	(*S*)-**7b** (M = Li)	THF	−78	55:45 (*M*)
2	**4a**	(*S*)-**7b** (M = Li)	CH_2Cl_2	−78	80:20 (*M*)
3	**4a**	(*S*)-**7b** (M = Li)	PE/Et_2O[c]	−78	70:30 (*M*)
4	**4a**	(*S*)-**7b** (M = Li)	Et_2O	−30	66:34 (*M*)
5	**4a**	(*S*)-**7c** (M = Na)	Et_2O	−30	–[d]
6	**4a**	(*S*)-**7d** (M = K)	Et_2O	−30	50:50 (*M*)
7	**4a**	(*S*)-**7b** (M = Li)	toluene	$-78 \rightarrow -40$	81:19 (*M*)
8	**4a**	(*S*)-**7c** (M = Na)[e]	toluene	$-78 \rightarrow -40$	66:34 (*M*)
9	**4a**	(*S*)-**7d** (M = K)	toluene	$-78 \rightarrow -40$	63:37 (*M*)
10	**4b**	(*S*)-**7b** (M = Li)	toluene	$-78 \rightarrow -40$	84:16 (*P*)[f]
11	**4b**	(*S*)-**7c** (M = Na)[e]	toluene	$-78 \rightarrow -40$	81:19 (*P*)[f]
12	**4b**	(*S*)-**7d** (M = K)	toluene	$-78 \rightarrow -40$	79:21 (*P*)[f]

[a] Reaction conditions: 1.8 equiv. of (*S*)-**7b**, **7c**, or **7d**, 1.0 equiv. of **4a** or **4b**, 1−12 h, conversions > 80%. – [b] Determined by HPLC on a Chiralcel OD-H phase after reduction to the alcohol **9** (cf. Scheme 4). – [c] Petroleum ether/Et_2O, 10:1. – [d] No solution of (*S*)-**7c** in Et_2O obtained, but a suspension (see Table 3, entry 2). – [e] The suspension of (*S*)-**7c** in toluene initially attained in the deprotonation reaction, was heated for 16 h to 80−90°C prior to use, resulting in a clear solution. – [f] Note that only for formal reasons (CIP notation[12]), the stereochemically identical esters (*P*,*S*)-**8a**/(*M*,*S*)-**8b** and (*M*,*S*)-**8a**/(*P*,*S*)-**8b** have different descriptors at the biaryl axis.

In a first series of ring-cleavage reactions of **4a**, the solvent was varied and lithium mentholate (*S*)-**7b** was the *O*-nucleophile (Table 1, entries 1−4 and 7). The best (but still only moderate) d.r. of (*M*,*S*)-**8a**/(*P*,*S*)-**8a** = 81:19 was obtained in toluene as the solvent (Table 1, entry 7).

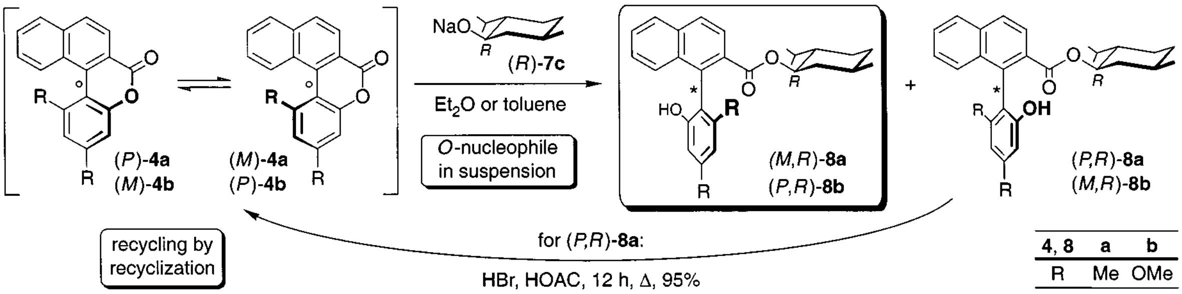
The diastereoselectivities of all ring-opening reactions of **4a** and **4b** in Et_2O and toluene were significantly dependent on which alkali metal of the alkoxide was used (Table 1, entries 4−12): While moderate to good d.r.'s of up to 84:16 (Table 1, entry 10) were obtained with the more covalently bonded lithium (1*S*)-mentholate [(*S*)-**7b**], the stereodifferentiation decreased with the more ionic sodium (1*S*)-mentholate [(*S*)-**7c**], and there was no asymmetric induction at all in the cleavage of **4a** with (*S*)-**7d** (M = K) in Et_2O (Table 1, entry 6). This behavior is in contrast to the related aminolysis reactions of **4** with metalated 1-arylethylamines as *N*-nucleophiles, where the d.r.'s (of up to 95:5) increased in the series Li << Na < K.[16]

The influence of the substitution pattern in the phenolic part of **4** (and thus of the steric hindrance at the biaryl axis) is only low. Slightly increased stereoselectivities were obtained for lactone **4b** (R = OMe), whose ring opening gave the best d.r.: (*P*,*S*)-**8b**/(*M*,*S*)-**8b** = 84:16 with (*S*)-**7b** (M = Li) in toluene (Table 1, entry 10).

Deprotonation of (1*S*)-menthol [(*S*)-**7a**] in toluene or Et_2O with NaH led to the formation only of suspensions of the sodium alkoxide (*S*)-**7c**. With toluene, a clear solution was obtained by heating the reaction mixture for 16 h to 80−90°C prior to use (Table 1, entries 8 and 11). These sodium alkoxide suspensions were found to be very useful for the lactone cleavage, as exemplified by **4a** (Scheme 5 and Table 2). In this case, the enantiomeric sodium (1*R*)-(−)-mentholate [(*R*)-**7c**] was used, which was anticipated to deliver the enantiomeric ester (*P*,*R*)-**8a** as the main product. Unexpectedly, however, the atropo-diastereomeric ester (*M*,*R*)-**8a** was formed preferentially in these slow (1−5 d) but highly stereoselective alcoholysis reactions. When ring-opening reactions of **4a** are carried out with suspensions of (*R*)-**7c**, the asymmetric inductions are reversed relative to when mentholates in solution are used [e.g., solution of (*S*)-**7c** in toluene: (*M*,*S*)-**8a**/(*P*,*S*)-**8a** = 66:34 (cf. Table 1, entry 8); vs suspension of (*R*)-**7c** in toluene: (*P*,*R*)-**8a**/(*M*,*R*)-**8a** = 21:79 (Table 2, entry 2)].

The excellent stereoselectivities achieved (d.r.'s of up to 94:6, cf. Table 2, entry 3) were significantly higher than all of the asymmetric inductions obtained if the alcoholyses were performed with alkali metal mentholate in solution [best d.r. = 81:19 (cf. Table 1, entry 7)].

Under the optimized reaction conditions (solvent: Et_2O, 0°C), both lactones **4a** (R = Me) and **4b** (R = OMe) were cleaved on a preparative scale (> 1 g of **4**), delivering the esters **8a** (d.r. = 93:7, 95% yield) and **8b** (d.r. = 88:12, 97% yield) in high optical and chemical yields (Table 3). For each ester, the diastereomers were separated by column



Scheme 5. Atropo-diastereoselective alcoholysis of **4** with sodium (1*R*)-mentholate [(*R*)-**7c**] as a suspension in Et_2O or toluene

Table 2. Alcoholysis of **4a** with suspensions of sodium (1*R*)-mentholate [(*R*)-**7c**] in Et_2O and toluene[a]

Entry	*T* [°C]	d.r. (config.)[b] (solvent: Et_2O)	d.r. (config.)[b] (solvent: toluene)
1	−78	–[c]	–[c]
2	−30	79:21 (*M*)	89:11 (*M*)
3	0	94:6 (*M*)	89:11 (*M*)
4	20	87:13 (*M*)	[d]

[a] Reaction conditions: 1.8 equiv. of (*R*)-**7c**, 1.0 equiv. of **4a**, 1−5 d, quantitative. – [b] Determined by HPLC on a Chiralcel OD-H phase after reduction to the alcohol **9** (cf. Scheme 4). – [c] No reaction. – [d] Reaction not performed.

chromatography on silica gel, to give the main atropisomers in stereochemically homogeneous form (d.r. > 99:1 in both cases) and in good yields [87% for (*M*,*R*)-**8a** and 82% for (*P*,*R*)-**8b**]. In this procedure, even the minor atropisomer is not lost: For example, for **8a**, (*P*,*R*)-**8a** was quantitatively cyclized back to the lactone **4** (95%) by HBr in HOAc[18] (cf. Scheme 5). This useful recycling of undesired atropisomeric byproducts is another significant advantage of the “lactone concept” over other known stereoselective biaryl coupling methods.[19][20] The alcoholysis of **4** with sodium mentholates (*R*)-**7c** or (*S*)-**7c** in suspension constitutes a most efficient and versatile approach even to larger amounts of enantiopure axially chiral biaryl esters.

Ring Cleavage of 4a with Suspensions of Sodium (1*R*)-8-Phenylmentholate [(*R*)-11c]

Even better asymmetric inductions were expected when a bulkier group than the (probably decisive) isopropyl substituent of (1*R*)-menthol [(*R*)-**7**] is employed, by using the commercially available (1*R*)-8-phenylmenthol [(*R*)-**10a**],[21] with its voluminous dimethylbenzyl group. The methyl-substituted lactone **4a** underwent ring-opening reactions with sodium (1*R*)-8-phenylmentholate [(*R*)-**10c**] under the above optimized (cf. Scheme 5) reaction conditions, to give the ester **11a** in 95% yield as a single product (Scheme 6). For the determination of the d.r., the crude mixture was submitted to an acidic workup and freed from excessive (*R*)-**10a** by distillation. Quantitative reduction with $LiAlH_4$ gave the alcohol **9a** (cf. Scheme 4), whose HPLC analysis on a Chiralcel OD-H phase showed an e.r. of 99:1. This e.r. measured was identical with that of (1*R*)-8-phenylmenthol [(*R*)-**11a**] used for the ring cleavage, thus hinting at a virtually complete asymmetric induction in the stereoselective transformation of **4a** into (*M*,*R*)-**11a** (d.r. > 99:1). These results confirm the anticipated high stereocontrol by the menthol α-alkyl group. The extraordinarily high optical and chemical yields obtained underline the remarkable efficiency of the “lactone method”.[4][5]

In Situ Reduction of the Intermediate Esters: Overall Atropo-Enantioselective Lactone Cleavage

Apart from the use of sodium 8-phenylmetholate as a chiral *O*-nucleophile, another practicable way of obtaining, for example, (*M*)-**9a** in a virtually enantiopure form, is to make use of its excellent crystallizing properties, to avoid the (sometimes time-consuming) diastereomer separations at the level of the intermediate esters (e.g., **8a**). Thus, a reaction sequence was elaborated: ring cleavage of **4a** with (*R*)-**7c** or (*R*)-**10c**, in situ reduction of the resulting esters **8a** or **11a** with $LiAlH_4$ to give the enantiomerically enriched alcohol **9a**, followed by crystallization of **9a** from petroleum ether (PE)/Et_2O to deliver the enantiopure alcohol (*M*)-**9a** (e.r. > 99:1) as white crystals in 81% and 88% yield (Scheme 7). If necessary (e.g., for valuable substrates), the almost racemic mother liquor material can be reused, after oxidative cyclization back to the corresponding lactone, as already demonstrated in the total synthesis of related naphthylisoquinoline alkaloids.[22] With this overall atropo-enantioselective reductive ring-cleavage reaction, an efficient access was found to the biaryl alcohol (*M*)-**9a** or, optionally, to (*P*)-**9a** (mainly by the choice of the enantiomeric mentholate reagent), which is even applicable to the preparation of larger amounts.

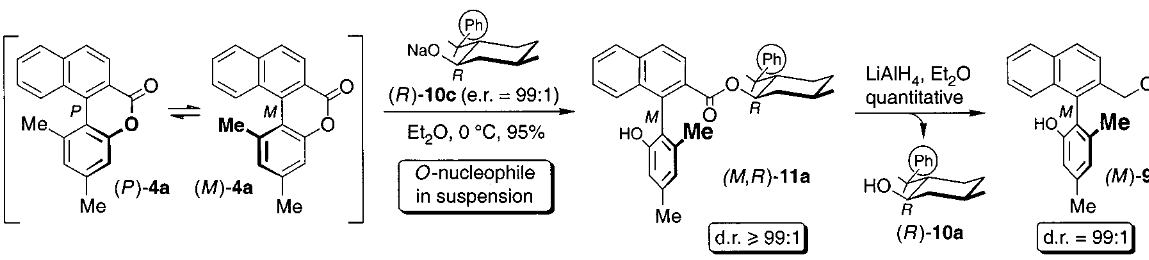
Determination of the Absolute Configuration at the Biaryl Axis

From X-ray structure analyses of the ring-cleavage products (*P*,*S*)-**8a** and (*M*,*S*)-**8b**, the relative configuration at the centers vs axes was established and thus, given the stereochemically known menthol part, as well as the absolute configuration at the axes (Scheme 8). If these two esters were reduced, the axial configuration of the biaryl alcohols (*P*)-**9a** and (*M*)-**9b** could also be established. This in turn made it possible to assign the 8-phenylmenthyl ester **11a**, which can be reduced to *ent*-(*P*)-**9a** = (*M*)-**9a**, to have (*M*) configuration at the axis.

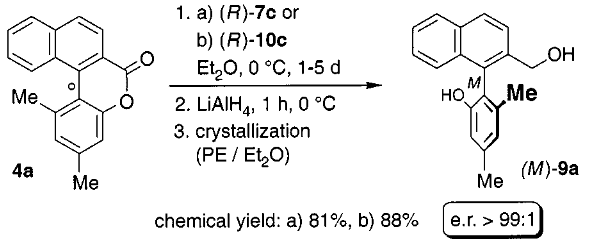
Table 3. Preparative alcoholysis of **4** with a suspension of (*R*)-**7c**[a]

Entry	Biaryl lactone	*t* [d]	Yield [%][b]	d.r. (config.)[c]	Yield of main diastereomer [%][d]
1	**4a**	1	95	93:7 (*M*)	87
2	**4b**	5	97	88:12 (*P*)[e]	82

[a] Reaction conditions: 1.8 equiv. of (*R*)-**7c** as a suspension in Et_2O, 1.0 equiv. **4a** or **4b**, 0°C, 1−5 d, quantitative. – [b] Yield of the crude esters, after acidic workup. – [c] Determined by HPLC on a Chiralcel OD-H phase after reduction to the alcohol **9** (cf. Scheme 4). – [d] Yield after chromatographic separation of diastereomers (d.r. > 99:1). – [e] Note that only for formal reasons (CIP notation[12]), the stereochemically identical esters (*M*,*R*)-**8a**/(*P*,*R*)-**8b** and (*P*,*R*)-**8a**/(*M*,*R*)-**8b** have different descriptors at the biaryl axis.



Scheme 6. Virtually complete stereocontrol in the atroposelelective ring cleavage of **4a** with a suspension of sodium (1*R*)-8-phenylmentholate [(*R*)-**10c**] to give the ester (*M*,*R*)-**11a**; further reduction to (*M*)-**9c**



Scheme 7. An overall atropo-enantioselective reductive pathway to the atropisomerically pure biaryl alcohol (*M*)-**9a**

Biaryl Esters 8 – Valuable Precursors for C_1-Symmetric Axially Chiral Auxiliaries

The axially chiral auxiliary 1,1′-binaphthalene-2,2′-diol (BINOL) is widely used, but the application of its derivatives as catalysts or reagents in asymmetric synthesis is often severely limited by their sometimes problematic preparation, e.g., by the exchange of the phenolic OH groups of BINOL against other functionalities, especially when two different heteroatoms are to be introduced.[1] The ester function of **8**, by contrast, is a C_1 unit that can be easily further modified. This is demonstrated in Scheme 9, which shows some known and new transformations of (*P*)-**8a**, which all proceed without any loss of optical purity. The known reduction of (*P*)-**8a**,[23] which can also be done in situ (see Scheme 6), gives the diol (*P*)-**9a** in 91% yield.[24] Its benzylic OH function can be removed in two steps to deliver (*M*)[25]-**13a**, whose *o*-hydroxy-*o*′-methylbiaryl substitution pattern is present in a broad series of natural products[4][5] (see also Scheme 1). Furthermore, (*M*)-**13a** is a precursor to the monodentate phosphane ligand (*M*)-**14a**.[26]

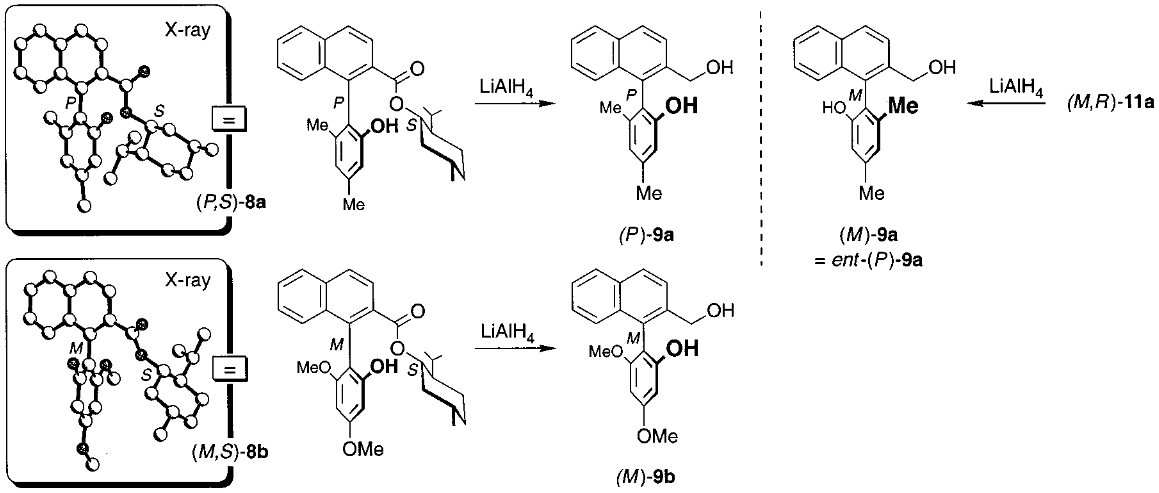
Protection of the phenolic OH function of (*P*)-**9a** and subsequent activation of the C_1 unit by OH/Br exchange resulted in the bromide (*P*)-**15a**, which reacted readily with, for example, diverse amines to give, after deprotection, the amino phenols (*P*)-**16a** which are highly efficient catalysts for enantioselective diethylzinc additions to aldehydes.[23]

New reactions aiming at an enlargement of the *C*-skeleton, e.g., by alkylation of the ester (*P*)-**8** with EtMgBr, led to the tertiary alcohol (*P*)-**12a**, while transformation of the protected bromide (*P*)-**15a** to the corresponding Grignard reagent and its addition to MeCOCMe$_2$OBzl gave the triol (*M*)[25]-**17a** (d.r. = 69:31) after deprotection. The application of the biaryl alcohols (*P*)-**9a**, (*P*)-**12a**, and (*M*)-**17a** as chiral ligands in enantioselective LiAlH$_4$ reductions is currently under investigation.

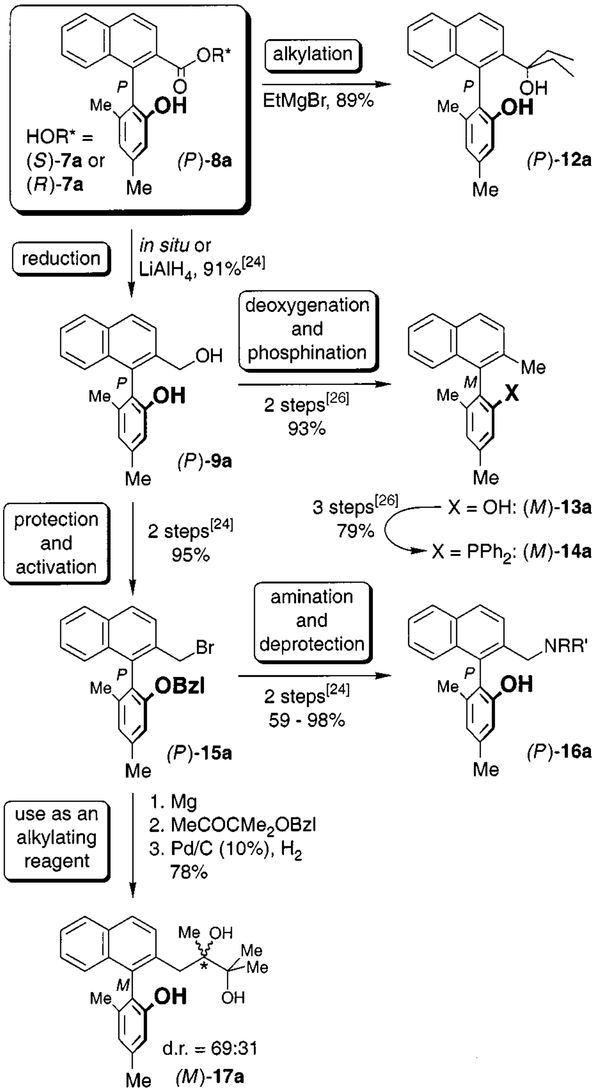
With all these transformations, the easily accessible enantiopure esters **8** constitute versatile precursors for C_1-symmetric axially chiral auxiliaries, whose application in asymmetric synthesis has only just begun.

Conclusion

The atroposelective ring cleavage of configurationally unstable biaryl lactones **4** with chiral mentholate-derived *O*-



Scheme 8. X-ray structure analyses of (*P*,*S*)-**8a** and (*M*,*S*)-**8b** and assignment of the absolute axial configurations of **9a**, **9b**, and **11a**



Scheme 9. New and already described useful further transformations of the biaryl ester (*P*)-**8a**: facile synthetic access to various axially chiral auxiliaries

nucleophiles of type **7** and **10** is a highly efficient and practicable access to axially chiral biaryl esters of type **8** and **11** in d.r.'s of up to > 99:1. The synthetic value of these alcoholysis reactions is enhanced by the preparation of the atropisomeric esters **8** with (*M*) or, optionally, (*P*) configuration by simply starting with either the (*R*)-mentholate or its (*S*)-enantiomer, or, additionally, by performing the ring cleavage either in solution or in suspension ("atropo-divergence"). Furthermore, the smooth, directed recyclization of **8a** back to the lactone **4a** allows the recycling of an undesired minor isomer (chiral economy). Both advantages, which are not present in other biaryl coupling methods,[19][20] underline the high preparative potential of the atroposelective ring opening of **4** with chiral *O*-nucleophiles and, more generally, of the "lactone concept" itself. Subsequent modification of the ester function of (*P*)-**8a** provides an easy access to axially chiral biaryls with two different functional groups *ortho* to the axis, which are currently being applied as chiral catalysts or reagents in asymmetric synthesis.

Experimental Section

General Remarks: Melting points (uncorrected): Kofler hot-stage apparatus. – IR spectra: Perkin–Elmer 1420 infrared spectrophotometer. – Optical rotations: Perkin–Elmer 241 MC polarimeter. – ^1H- and ^{13}C-NMR spectra: Bruker AC 200 or Bruker AC 250 instrument. – Mass spectra: Finnigan MAT 8200 mass spectrometer, measured at 70 eV in the EI mode. – Combustion analyses: LECO CHNS-932 apparatus in the microanalytical laboratory of the University of Würzburg. – HPLC: Waters M 510 HPLC pump, U6K injector, Chiralcel OD-H column (Daicel Chem. Ind., 4.6 mm × 250 mm), ERC-7215 UV-detector, Shimadzu Integrator C-R6A Chromatopac. – Thin layer chromatography (TLC): DC aluminium sheets, silica gel 60 F_{254} (Merck). – Column chromatography: silica gel, 0.063–0.200 mm (Merck). – Short-path distillation: Kugelrohr GKR-50 (Fa. Büchi). – The petroleum ether (PE) used had a boiling range of 40–60°C. – THF was distilled from potassium directly before use, Et_2O and toluene from sodium, and CH_2Cl_2 from P_2O_5. – NaH and KH were washed with dry PE prior to use. – All reactions were carried out under a dry inert gas using the Schlenck-tube technique. – (1*R*)-(–)- and (1*S*)-(+)-menthol [(*R*)-**7a** and (*S*)-**7a**] and (1*R*)-(–)-8-phenylmenthol [(*R*)-**10a**] were purchased from Aldrich, the lactones **4a** and **4b**,[10] the bromine (*P*)-**15a**,[23] and 3-benzyloxy-3-methyl-2-butanone ($MeCOCMe_2OBzl$)[27] were prepared according to literature procedures.

General Procedure for the Ring Cleavage of Lactones 4 with Alkali Metal Mentholates on Analytical Scale: According to the reaction conditions given in Tables 1 and 2, LDA (2.0 M in *n*-heptane/THF/ethylbenzene, 180 μL, 360 μmol), NaH (8.64 mg, 360 μmol), or KH (14.4 mg, 360 μmol) was added at 0°C to a solution of (1*S*)- or (1*R*)-menthol [(*S*)-**7a** or (*R*)-**7a**, 62.5 mg, 400 μmol] in the solvent indicated (5.0 mL). After 30 min of stirring, the reaction mixture was adjusted to the temperature given, the lactone **4** (200 μmol) was added and stirring continued for 16 h–5 d. The mixture was hydrolyzed with water (10 mL), slightly acidified with 0.1 N HCl (5 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo. The crude esters **8** were obtained after column chromatography (PE/Et_2O 5:1). For the determination of the d.r. of **8**, the residue was dissolved at room temp. in anhydrous Et_2O (5 mL) and $LiAlH_4$ (38.0 mg, 1.00 mmol) was added. After 30 min of stirring, the reaction mixture was worked up as described above. Column chromatography or semi-preparative TLC (PE/Et_2O, 1:1) gave the alcohol **9**, the e.r. of which was analyzed by HPLC on chiral phase (Chiralcel OD-H, detection at 280 nm, flow rate: 1 mL/min; **9a**: solvent: *n*-hexane/*i*PrOH, 95:5; retention times t_R: 16 min for (*M*)-**9a** and 22 min for (*P*)-**9a**; **9b**: solvent: *n*-hexane/*i*PrOH, 92:8; t_R: 20 min for (*P*)-**9b** and 23 min for (*M*)-**9b**]. (Note: With the exception of the sodium mentholate suspensions formed in toluene and Et_2O, all other alkali metal mentholates gave clear solutions in the solvents used.)

Ring Cleavage of 4a with (*R*)-7c on Preparative Scale: To a suspension of sodium (1*R*)-mentholate [(*R*)-**7c**], prepared from (1*R*)-menthol [(*R*)-**7a**, 2.53 g, 16.2 mmol] and NaH (350 mg, 14.6 mmol) in Et_2O (100 mL) at 0°C, the lactone **4a** (2.22 g, 8.10 mmol) was added after 30 min of stirring. The cloudy mixture was stirred for 1 d at 0°C, then hydrolyzed with water (100 mL), slightly acidified with 1 N HCl (20 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with $MgSO_4$ and the solvent evaporated in vacuo. Excessive menthol was removed by short-path distillation under reduced pressure and the resulting crude esters **8a** were (3.31 g, 7.69 mmol, 95%, d.r. = 93:7) separated by column chromatography (PE/Et_2O, 30:1 → 3:1) to give, in the order of elution, (*P*,*R*)-**8a** (174 mg, 404 μmol, 5%, d.r. > 99:1) and (*M*,*R*)-**8a** (3.03 g, 7.04 mmol, 87%, d.r. > 99:1) as white solids. The spectroscopic data of both atropo-diastereomeric esters **8a** are fully identical with those of the previously obtained materials.[23]

Ring Cleavage of 4b with (*R*)-7c on Preparative Scale: According to the method for the ring cleavage of **4a** described above, the lactone **4b** (1.00 g, 3.26 mmol) was stirred at 0 °C for 5 d with a suspension of (*R*)-**7c**, prepared from (*R*)-**7a** (1.02 g, 6.52 mmol) and NaH (141 mg, 5.87 mmol) in Et_2O (50 mL). After acidic workup and removal of the excessive menthol, column chromatography of the crude esters **8b** (1.44 g, 3.11 mmol, 97%, d.r. = 88:12) (PE/CH_2Cl_2, 2:1 → 1:1) gave, in the order of elution, (*M*,*R*)-**8b** (156 mg, 337 μmol, 10%, d.r. > 99:1) and (*P*,*R*)-**8b** (1.23 g, 2.66 mmol, 82%, d.r. > 99:1) as white solids.

(*M*,*R*)-**8b**: M.p. 150 °C. − $[\alpha]_D^{20} = -76.6$ (*c* = 0.28, EtOH). − IR (KBr): $\tilde{\nu} = 3380\ cm^{-1}$ (OH), 2940 (CH), 1660 (C=O). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.62−2.00 (m, 9 H, menthyl-H), 0.67 (d, *J* = 6.9 Hz, 3 H, menthyl-CH_3), 0.82, 0.88 [d, d, *J* = 6.8 Hz each, 3 H each, $CH(CH_3)_2$], 3.55 (s, 3 H, 6′-OCH_3), 3.86 (s, 3 H, 4′-OCH_3), 4.96 (dt, *J* = 10.7 Hz, *J* = 4.3 Hz, 1 H, 1′′-H), 6.20, 6.30 (d, d, *J* = 2.2 Hz each, 1 H each, 3′-H and 5′-H), 7.38−7.66 (m, 3 H, Ar−H), 7.85−8.00 (m, 3 H, Ar−H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.19, 20.83, 22.07, 23.28, 26.04, 31.32, 34.26, 40.35, 46.84 (menthyl-C), 55.36, 55.60 (4′-OCH_3 and 6′-OCH_3), 75.07 (C-1′′), 107.0, 125.7, 126.7, 127.1, 127.6, 128.1, 128.6, 131.0, 131.9, 133.1, 135.0, 154.9, 158.6, 161.5 (Ar−C), 167.9 (C=O). − MS; *m*/*z* (%): 462 (30) [M^+], 324 (66) [$M^+ - C_{10}H_{18}$], 306 (100) [$M^+ - C_{10}H_{20}O$]. − $C_{29}H_{34}O_5$ (462. 59): calcd. C 75.30, H 7.41; found C 75.56, H 7.50.

(*P*,*R*)-**8b**: M.p. 159 °C. − $[\alpha]_D^{20} = -29.7$ (*c* = 0.22, EtOH). − IR (KBr): $\tilde{\nu} = 3350\ cm^{-1}$ (OH), 2940 (CH), 1660 (C=O). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.65−2.00 (m, 9 H, menthyl-H), 0.72 (d, *J* = 6.9 Hz, 3 H, menthyl-CH_3), 0.83, 0.87 [d, d, *J* = 6.6 Hz each, 3 H each, $CH(CH_3)_2$], 3.56 (s, 3 H, 6′-OCH_3), 3.86 (s, 3 H, 4′-OCH_3), 4.80 (dt, *J* = 10.6 Hz, *J* = 4.3 Hz, 1H, 1′′-H), 6.21, 6.28 (d, d, *J* = 2.3 Hz each, 1 H each, 3′-H and 5′-H), 7.38−7.65 (m, 3 H, Ar−H), 7.85−8.05 (m, 3 H, Ar−H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.88, 21.04, 22.01, 22.98, 25.77, 31.32, 34.23, 40.38, 46.90 (menthyl-C), 55.30, 55.60 (4′-OCH_3 and 6′-OCH_3), 75.01 (C-1′′), 107.0, 126.0, 126.9, 127.0, 127.7, 128.1, 128.6, 131.3, 131.5, 133.2, 135.0, 154.7, 158.7, 161.4 (Ar−C), 167.8 (C=O). − MS; *m*/*z* (%): 462 (29) [M^+], 324 (64) [$M^+ - C_{10}H_{18}$], 306 (100) [$M^+ - C_{10}H_{20}O$]. − $C_{29}H_{34}O_5$ (462. 59): calcd. C 75.30, H 7.41; found C 75.63, H 7.43.

Cyclization of the Ester (*P,R*)-8a Back to the Lactone 4a: A solution of the ester (*P*,*R*)-**8a** (22.0 mg, 51.1 μmol) in acetic acid (0.7 mL) and hydrobromic acid (48%, 0.7 mL) was refluxed at 120 °C for 12 h. After cautious addition of a saturated Na_2CO_3 solution (3 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried with $MgSO_4$ and the solvent evaporated in vacuo. Purification of the residue by column chromatography (PE/Et_2O 10:1) afforded the lactone **4b** (13.3 mg, 48.5 μmol, 95%) as a pale yellow solid. The spectroscopic data of **4b** are identical to those of the material used for the ring-opening reactions described above.

Ring Cleavage of 4a with (*R*)-10c: A suspension of sodium (1*R*)-8-phenylmentholate [(*R*)-**10c**], prepared from (1*R*)-8-phenylmenthol [(*R*)-**10a** (e.r. = 99:1), 117 μL, 116 mg, 500 μmol] and NaH (10.8 mg, 450 μmol) in Et_2O (5 mL), was stirred for 30 min at 0 °C. The lactone **4a** (68.6 mg, 250 μmol) was added and the cloudy suspension was furthermore stirred for 5 d at 0 °C. The reaction mixture was hydrolyzed with water (10 mL), slightly acidified with 0.1 N HCl (5 mL), and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. The resulting crude ester (*M*,*R*)-**11a** [d.r. = 99:1, determined after reduction to the alcohol (*M*)-**9a**, see general procedure] was purified by column chromatography (PE/Et_2O, 1:1) to give (*M*,*R*)-**11a** (120 mg, 237 μmol, 95%, d.r. = 99:1) as a white solid. − M.p. 156 °C. − $[\alpha]_D^{20} = -47.9$ (*c* = 0.20, $CHCl_3$). − IR (KBr): $\tilde{\nu} = 3400\ cm^{-1}$ (OH), 2920 (CH), 1660 (C=O). − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.50−1.99 (m, 8 H, menthyl-H), 0.79 (d, *J* = 6.7 Hz, 3 H, menthyl-CH_3), 1.23, 1.29 [s, s, 3 H each, $CPh(CH_3)_2$], 1.77 (s, 3 H, 6′-CH_3), 2.33 (s, 3 H, 4′-CH_3), 4.30 (br. s, 1 H, OH), 4.96 (dt, *J* = 10.7 Hz, *J* = 4.3 Hz, 1H, 1′′-H), 6.70, 6.76 (s, s, 1 H each, 3′-H and 5′-H), 7.06 (m_c, 1 H, Ar−H), 7.12−7.28 (m, 4 H, Ar−H), 7.37−7.48 (m, 3 H, Ar−H), 7.56 (m_c, 1 H, Ar−H), 7.83 (d, *J* = 8.5 Hz, 1 H, Ar−H), 7.90 (d, *J* = 8.2 Hz, 1 H, Ar−H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.95, 21.35, 21.71, 26.49 (CH and CH_3), 26.82 (CH_2), 26.94, 31.08 (CH and CH_3), 34.43, 40.00, 40.86 (CH_2), 50.25 (CH or CH_3), 75.34 (C-1′′), 113.7, 121.7, 122.9, 125.2, 125.5, 125.6, 126.5, 127.2, 127.7, 128.0, 128.1, 128.4, 130.7, 132.3, 133.8, 134.9, 138.0, 138.8, 151.2, 152.9 (Ar−C), 167.0 (C=O). − MS; *m*/*z* (%): 506 (8) [M^+], 292 (39) [$C_{19}H_{14}O_3^+$], 274 (100) [$C_{19}H_{14}O_2^+$], 232 (11) [$C_{16}H_{24}O^+$ (8-phenylmenthol)], 231 (14) [$C_{16}H_{23}O^+$]. − $C_{35}H_{38}O_3$ (506. 68): calcd. C 82.97, H 7.56; found C 83.38, H 7.72.

“Reductive” Ring Cleavage of 4a with (*R*)-7c and $LiAlH_4$: According to the method for the ring cleavage of **4a** with (*R*)-**7c** described above, the lactone **4a** (400 mg, 1.46 mmol) was stirred at 0 °C with a suspension of (*R*)-**7c**, prepared from (*R*)-**7a** (456 mg, 2.92 mmol) and NaH (63.1 mg, 2.63 mmol) in Et_2O (20 mL). After quantitative conversion into the esters **8a** (1 d, detected by TLC), $LiAlH_4$ (556 mg, 14.6 mmol) was added at 20 °C and stirring was continued for 30 min. The reaction mixture was cautiously hydrolyzed with water (20 mL), slightly acidified with 1 N HCl (20 mL), and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. Excessive menthol was removed by short-path distillation under reduced pressure to yield the crude alcohol (*M*)-**9a** (385 mg, 1.38 mmol, 95%, e.r. = 94:6) as a pale yellow oil, which gave colorless crystals of (*M*)-**9a** (328 mg, 1.18 mmol, 81%, e.r. > 99:1) from PE/Et_2O. The spectroscopic data of (*M*)-**9a** are fully identical with those of material obtained previously.[23]

“Reductive” Ring Cleavage of 4a with (*R*)-10c and $LiAlH_4$: According to the method for the reductive ring cleavage of **4a** with (*R*)-**7c** described above, the lactone **4a** (200 mg, 730 μmol) was stirred at 0 °C with a suspension of (*R*)-**10c**, prepared from (*R*)-**10a** (343 μL, 339 mg, 1.46 mmol) and NaH (31.6 mg, 1.31 mmol) in Et_2O (10 mL). After quantitative conversion into the esters **11a** (5 d, detected by TLC), $LiAlH_4$ (139 mg, 3.65 mmol) was added at 20 °C and stirring was continued for 30 min. The reaction mixture was cautiously hydrolyzed with water (10 mL), slightly acidified with 1 N HCl (10 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. The excess of (*R*)-**10a** was removed by short-path distillation under reduced pressure to yield the crude alcohol (*M*)-**9a** (193 mg, 694 μmol, 95%, e.r. = 98:2) as a pale yellow oil, which gave colorless crystals of (*M*)-**9a** (179 mg, 642 μmol, 88%, e.r. > 99:1) from PE/Et_2O.

Ethylation of the Menthyl Ester (*P,R*)-8a: To a solution of the ester (*P*,*R*)-**8a** (1.65 g, 3.83 mmol, d.r. > 99:1) in Et_2O (15 mL), EtMgBr

Table 4. Crystallographic data

	(*P*,*S*)-**8a**	(*M*,*S*)-**8b**
Empirical formula	$C_{29}H_{34}O_3$	$C_{29}H_{34}O_5$
Molecular mass	430.59	462.59
Crystal system	orthorombic	orthorombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a [Å]	11.793(3)	14.413(6)
b [Å]	20.851(6)	17.917(8)
c [Å]	10.452(4)	9.976(5)
V [Å^3]	2571(1)	2576(2)
Z	4	4
d(calcd.) [g cm^{-3}]	1.112	1.193
Crystal size [mm]	0.65 × 0.65 × 0.2	0.7 × 0.7 × 0.5
Scan mode	Wyckoff scan	Wyckoff scan
Θ range [°]	1.75−27.5	1.75−27.5
hkl range	0/15, 0/27, 0/13	0/18, 0/23, 0/12
Reflections collected	3375	3369
Unique reflections	3347	3344
Refl. observed [$F > 3\sigma(F)$]	2735	2873
Lin. absorpt. coeff. [$^{-1}$]	0.7	0.8
Absorption correction	ψ scan	ψ scan
Ratio F_{obs}/parameters	9.40	9.36
R, R_w	0.052/0.047	0.066/0.060
Largest diff. peak/hole [eÅ^{-3}]	0.14/0.16	0.41/0.38

(1.0 M in Et_2O, 15.3 mL, 15.3 mmol) was added dropwise at room temp. and the solution was stirred for 6 h. The reaction mixture was cautiously hydrolyzed with water (20 mL), slightly acidified with 1 N HCl (20 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. The menthol formed was removed by short-path distillation under reduced pressure. Column chromatography (PE/Et_2O, 3:1) gave the tertiary alcohol (*P*)-**12a** (1.14 g, 3.41 mmol, 89%) as colorless crystals with an e.r. of 99.5:0.5, as determined by HPLC on a chiral phase [Chiralcel OD-H, detection at 280 nm, flow rate: 1 mL/min, solvent: *n*-hexane/*i*PrOH, 98:2; retention times t_R: 11 min for (*M*)-**12a** and 13 min for (*P*)-**12a**]. − M.p. 47−48°C. − $[\alpha]_D^{20} = +53.4$ (c = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3340, 3230 cm^{-1} (OH), 2960 (CH). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.84, 0.86 [t, t, J = 7.4 Hz each, 3 H each, $C(CH_2CH_3)_2$], 1.70−2.10 [m, 4 H, $C(CH_2CH_3)_2$], 1.85 (s, 3 H, 6′-CH_3), 2.15 [s, 0.8 H, $C(CH_2CH_3)_2OH$], 2.38 (s, 3 H, 4′-CH_3), 4.54 (s, 0.8 H, 2′-OH), 6.75, 6.78 (s, s, 1 H each, 3′-H and 5′-H), 7.16 (d, J = 8.6 Hz, 1 H, 5-H), 7.33 (dt, J = 6.9 Hz, J = 1.4 Hz, 1 H, 6-H or 7-H), 7.47 (dt, J = 6.7 Hz, J = 1.3 Hz, 1 H, 6-H or 7-H), 7.52 (d, J = 8.9 Hz, 1 H, 8-H), 7.82−7.95 (m, 2 H, 3-H and 4-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.49, 8.73 [$C(CH_2CH_3)_2$], 20.17, 21.41 (4′-CH_3 and 6′-CH_3), 34.38, 34.89 [$C(CH_2CH_3)_2$], 80.09 [$C(CH_2CH_3)_2OH$], 114.0, 122.6, 123.5, 125.0, 126.2, 127.0, 127.8, 128.4, 132.6, 133.6, 138.5, 139.5, 143.6, 153.3 (Ar−C). − MS; *m/z* (%): 334 (2) [M^+], 316 (18) [$M^+ - H_2O$], 287 (100) [$M^+ - C_2H_7O$], 259 (61) [$C_{19}H_{15}O^+$]. − $C_{23}H_{26}O_2$ (334.46): calcd. C 82.60, H 7.84; found C 82.56, H 8.03.

Synthesis of the Diastereomeric Triols (*M*)-17a: A solution of the protected bromide (*P*)-**15a** (1.14 g, 2.64 mmol) in Et_2O (10 mL) was added dropwise to Mg (69.8 mg, 2.91 mmol) in Et_2O (10 mL) at room temp. Traces of $(CH_2Br)_2$ were added and the reaction mixture was refluxed for 5 h until complete conversion into the Grignard compound had occurred (detected by TLC after quenching with HCl). The yellow solution was cooled to 0°C and MeCOCMe$_2$OBzl (846 μL, 761 mg, 3.96 mmol) was added. After warming up to room temp. within 2 h, the reaction mixture was hydrolyzed with water (20 mL), slightly acidified with 1 N HCl (5 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. Column chromatography (PE/Et_2O, 8:1 → 3:1) gave a (chromatographically inseparable) mixture of the diastereomeric addition products (1.21 g, 2.22 mmol, 84%). For debenzylation to the triols (*M*)-**17a**, Pd/C (10%, 100 mg) was added to a solution of 1.10 g of this mixture (2.02 mmol) in CH_2Cl_2 (20 mL). After 12 h of hydrogenation (H_2 pressure: 1 bar) at room temp., the catalyst was removed by filtration through Celite with CH_2Cl_2 (20 mL) and the solvent was evaporated in vacuo. The resulting triols (*M*)[25]-**17a** were separated by column chromatography (PE/acetone, 9:1 → 3:1) to give the diastereomers (*M*)-**17a-A** (471 mg, 1.29 mmol, 64%, more rapidly eluting, d.r. > 99:1) and (*M*)-**17a-B** (214 mg, 587 μmol, 29%, more slowly eluting, d.r. > 99:1) as slightly yellow oils. From PE/Et_2O, (*M*)-**17a-A** (408 mg, 1.12 mmol, 55%) and (*M*)-**17a-B** (188 mg, 516 μmol, 26%) were obtained as colorless crystals each.

(*M*)-**17a-A**: M.p. 66−67°C. − $[\alpha]_D^{20} = -29.7$ (c = 0.96, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3600−2500 cm^{-1} (OH), 2960 (CH). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.01, 1.12, 1.24 (s, s, s, 3 H each, 3 × CCH_3), 1.70 (s, 3 H, 6′-CH_3), 2.35 (s, 3 H, 4′-CH_3), 2.64, 3.00 (d, d, J = 13.3 Hz each, 1 H each, 2-CH_2), 6.71, 6.75 (s, s, 1 H each, 3′-H and 5′-H), 7.23−7.39 (m, 2H, Ar−H), 7.44 (tm, J = 7.2 Hz, 1 H, Ar−H), 7.55, 7.81 (d, d, J = 8.4 Hz each, 1 H each, 3-H and 4-H), 7.84 (d, J = 7.5 Hz, 1 H, 8-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.79, 21.25, 22.16, 24.04, 24.68 (CH_3), 38.59 (C-1′′), 75.59, 77.56 (C-2′′ and C-3′′), 114.9, 123.4, 123.6, 125.5, 125.7, 126.4, 127.4, 127.9, 129.3, 132.6, 132.8, 134.2, 135.1, 137.7, 138.7, 153.6 (Ar−C). − MS; *m/z* (%): 364 (3) [M^+], 346 (1) [$M^+ - H_2O$], 305 (24) [$M^+ - C_3H_7O$], 287 (14) [$M^+ - C_3H_9O_2$], 262 (100) [$C_{19}H_{18}O^+$]. − $C_{24}H_{28}O_3$ (364.48): calcd. C 79.09, H 7.74; found C 78.30, H 7.80.

(*M*)-**17a-B**: M.p. 66−68°C. − $[\alpha]_D^{20} = -31.7$ (c = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3600−2700 cm^{-1} (OH), 2960 (CH). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95, 1.07, 1.10 (s, s, s, 3 H each, 3 × CCH_3), 1.82 (s, 3 H, 6′-CH_3), 2.37 (s, 3 H, 4′-CH_3), 2.66, 2.97 (d, d, J = 13.9 Hz each, 1 H each, 2-CH_2), 6.72, 6.76 (s, s, 1 H each, 3′-H and 5′-H), 7.36−7.41 (m, 2 H, Ar−H), 7.46 (m_c, 1 H, Ar−H), 7.75, 7.86 (d, d, J = 8.6 Hz each, 1 H each, 3-H and 4-H), 7.88 (d, J = 7.8 Hz, 1 H, 8-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.89, 21.34, 24.37, 24.65 (CH_3), 38.62 (C-1′′), 75.68, 77.65 (C-2′′ and C-3′′), 113.6, 121.7, 123.3, 125.6, 125.8, 126.7, 128.0, 128.1, 129.8, 132.1, 132.5, 132.7, 136.8, 138.2, 139.1, 153.1 (Ar−C). − MS; *m/z* (%): 364 (2) [M^+], 346 (2) [$M^+ - H_2O$], 305 (26) [$M^+ - C_3H_7O$], 287 (14) [$M^+ - C_3H_9O_2$], 262 (100) [$C_{19}H_{18}O^+$]. − $C_{24}H_{28}O_3$ (364.48): calcd. C 79.09, H 7.74; found C 78.68, H 7.75.

X-ray Crystallographic Study:[28] The single crystals of (*P*,*S*)-**8a** and (*M*,*S*)-**8b** that were measured were obtained from PE/Et_2O. The cell parameters were determined on the basis of 70 reflections. The number of measured reflections reported in Table 4 were obtained with Mo-K_α radiation (0.71073 Å) and $2\theta_{max}$ = 55° (graphite monochromator). All data were collected at room temp. with a Siemens P4 diffractometer. The SHELXTL-PLUS program package[29] was employed. The structures were solved by direct methods and refined anisotropically by the least-squares method. The weighting scheme for R_w is $1/\sigma^2$. The positions of the hydrogen atoms were calculated by the riding model and included with isotropic descriptions.

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[1] [1a] C. Rosini, L. Franzini, A. Raffaelli, P. Salvadori, *Synthesis* **1992**, 503−517. − [1b] L. Pu, *Chem. Rev.* **1998**, *98*, 2405−2494.

[2] Reviews: [2a] G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler in *Prog. Chem. Org. Nat. Prod.* (Eds.: W. Herz, H. Falk, G. W. Kirby, R. E. Moore, C. Tamm), submitted. − [2b] G. Bringmann, F. Pokorny in *The Alkaloids*, vol. 46 (Ed.: G. A. Cordell), Academic Press, New York, **1995**, pp. 127−271. − [2c] G. Bringmann, G. François, L. Aké Assi, J. Schlauer, *Chimia* **1998**, *52*, 18−28. − [2d] G. Bringmann, *Bull. Soc. Chim. Belg.* **1996**, *105*, 601−613.

[3] Reviews: [3a] K. B. G. Torssell, *Natural Product Chemistry*, Taylor and Francis, New York, **1997**. − [3b] T. Okuda, T. Yoshida, T. Hatano in *Prog. Chem. Org. Nat. Prod.*, vol. 66 (Eds.: W. Herz, G. W. Kirby, R. E. Moore, W. Steglich, C. Tamm), Springer, Vienna, **1995**, pp. 1−117. − [3c] M. A. Rizzacasa in *Studies in Natural Product Chemistry*, vol. 20, Part F (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1998**, pp. 407−455.

[4] G. Bringmann, M. Breuning, S. Tasler, *Synthesis* **1999**, 525−558.

[5] [5a] G. Bringmann, S. Tasler in *Current Trends in Organic Synthesis* (Eds.: C. Scolastico, F. Nicotra), Plenum Publishing Corporation, New York, **1999**, pp. 105−116. − [5b] G. Bringmann, O. Schupp, *S. Afr. J. Chem.* **1994**, *47*, 83−102.

[6] G. Bringmann, M. Breuning, *Tetrahedron: Asymmetry* **1998**, *9*, 667−679.

[7] [7a] T. R. Govindachari, P. C. Parthasarathy, *Tetrahedron* **1971**, *27*, 1013−1026. − [7b] T. R. Govindachari, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, K. S. Ramachandran, E. Lee, *J. Chem. Soc., Perkin Trans. 1* **1975**, 2134−2136.

[8] [8a] G. Bringmann, H. Reuscher, *Tetrahedron Lett.* **1989**, *30*, 5249−5252. − [8b] G. Bringmann, H. Reuscher, *Angew. Chem.* **1989**, *101*, 1725−1726; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1672−1673.

[9] [9a] M. A. Rizzacasa, M. V. Sargent, *J. Chem. Soc., Chem. Commun.* **1989**, 301−302. − [9b] M. A. Rizzacasa, M. V. Sargent, *J. Chem. Soc, Perkin Trans. 1* **1991**, 845−854.

[10] G. Bringmann, T. Hartung, L. Göbel, O. Schupp, C. L. J. Ewers, B. Schöner, R. Zagst, K. Peters, H. G. von Schnering, C. Burschka, *Liebigs Ann. Chem.* **1992**, 225−232.

[11] For further syntheses of related (albeit sterically less hindered) biaryl lactones, see ref.[18] and: [11a] D. I. Davies, C. Waring, *J. Chem. Soc. C* **1967**, 1639−1642. − [11b] O. deFrutos, A. M. Echavarren, *Tetrahedron Lett.* **1996**, *37*, 8953−8956.

[12] For the now recommended (*M*)/(*P*) notation for axial chirality, see: G. Helmchen in *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed., vol. E21a (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 11−13.

[13] Note that, for formal reasons within the CIP notation,[12] the stereochemically analogous biaryls with R = Me ("**a** series") and R = OMe ("**b** series") have different stereodescriptors at the biaryl axis.

[14] [14a] G. Bringmann, T. Hartung, *Synthesis* **1992**, 433−435. − [14b] G. Bringmann, T. Hartung, *Angew. Chem.* **1992**, *104*, 782−783; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 761−762. − [14c] G. Bringmann, T. Hartung, *Tetrahedron* **1993**, *49*, 7891−7902. − [14d] G. Bringmann, M. Breuning, *Tetrahedron: Asymmetry* **1999**, 10, 385−390.

[15] [15a] D. Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, R. Formisano, D. A. Chaplin, M. Breuning, G. Bringmann, *Tetrahedron* **1997**, *53*, 7539−7556. − [15b] G. Bringmann, T. Pabst, S. Busemann, K. Peters, E.-M. Peters, *Tetrahedron* **1998**, *54*, 1425−1438.

[16] G. Bringmann, M. Breuning, S. Tasler, H. Endress, C. L. J. Ewers, L. Göbel, K. Peters, E.-M. Peters, *Chem. Eur. J.*, **1999**, in press.

[17] G. Bringmann, R. Walter, C. L. J. Ewers, *Synlett* **1991**, 581−583.

[18] W. Wang, V. Snieckus, *J. Org. Chem.* **1992**, *57*, 424−426.

[19] Reviews: [19a] S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263−303. − [19b] G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990**, *102,* 1006−1019; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977−991. − [19c] G. Bringmann, R. Walter, R. Weirich in *Methods of Organic Chemistry (Houben Weyl)*, 4th ed., vol. E21a (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 567−587.

[20] [20a] T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297−2360. − [20b] K. S. Feldman, R. S. Smith, *J. Org. Chem.* **1996**, *61*, 2606−2612. − [20c] K. Kamikawa, T. Watanabe, M. Uemura, *J. Org. Chem.* **1996**, 1375−1384. − [20d] B. H. Lipshutz, F. Kayser, Z.-P. Liu, *Angew. Chem.* **1994**, *106*, 1962−1964; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1842−1844. − [20e] G.-Q. Lin, M. Zhong, *Tetrahedron: Asymmetry* **1997**, *8*, 1369−1372. − [20f] T. Sugimura, H. Yamada, S. Inoue, A. Tai, *Tetrahedron: Asymmetry* **1997**, *8*, 649−655. − [20g] S. Miyano, H. Fukushima, S. Handa, H. Ito, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249−3254. − [20h] V. H. Rawal, A. S. Florjancic, S. P. Singh, *Tetrahedron Lett.* **1994**, *35*, 8985−8988.

[21] E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908−6909.

[22] G. Bringmann, W. Saeb, M. Rübenacker, *Tetrahedron* **1999**, *55*, 423−432.

[23] G. Bringmann, M. Breuning, *Tetrahedron: Asymmetry* **1998**, *9*, 667−679.

[24] For other approaches to the enantiopure alcohols (*P*)-**9a** or (*M*)-**9a**, see. ref.[14]

[25] For formal reasons within the CIP notation,[12] the stereodescriptor at the biaryl axis changes from (*P*) to (*M*).

[26] G. Bringmann, A. Wuzik, M. Breuning, P. Henschel, E.-M. Peters, K. Peters, *Tetrahedron Asymmetry*, **1999**, *10*, 3025−3031.

[27] V. P. Fedulov, E. M. Glazunova, V. I. Nicitin, *Khim. Tadzh.* **1973**, 35−40 [*Chem. Abstr.* **1976**, *84*, 73791c].

[28] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-117637 and -116638. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[29] G. M. Sheldrick, *Program Package SHELXTL-PLUS, Release 4.1*, Siemens Analytical Instruments Inc., Madison, WI 53719, USA, **1990**.

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