Novel Concepts in Directed Biaryl Synthesis, Part 79[+]

Atropo-Diastereoselective Cleavage of Configurationally Unstable Biaryl Lactones with Alkali Metal Activated Primary 1-Arylethylamines

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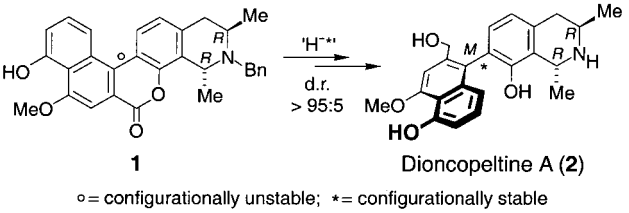
Abstract: The atropo-diastereoselective cleavage of lactone-bridged and thus configurationally unstable biaryls with chiral metal-activated 1-arylethylamines gives axially chiral biaryl amides in good yields and high atropo-diastereomeric ratios of up to 95:5. In this methodology, even the minor not desired rotational isomer can be recycled literally by recyclization back to the configurationally unstable lactone, and renewed stereoselective cleavage. Furthermore, by the use of the corresponding enantiomer of the N-nucleophile, the enantiomeric biaryl product is also attainable from the same lactone precursor ("atropo-divergence"). In addition, several methods have been developed to transform the amide function into a methyl or an aminomethylene group. All these options further enlarge the scope and the utility of the method elaborated.

Keywords: asymmetric synthesis · atropisomerism · axial chirality · biaryls · dynamic kinetic resolution

Introduction

The directed, that is regio- and stereoselective construction of axially chiral biaryl target molecules—bioactive natural products[1] and useful ligands or reagents for asymmetric synthesis[2, 3]—is a rewarding goal in organic synthesis. Key molecules of our "lactone methodology"[4, 5] are lactone-bridged biaryls, which, if embedded into a chiral molecule such as **1** (Scheme 1),[6] can be atropo-diastereodivergently ring cleaved by appropriate achiral or chiral H- or O-nucleophiles with high (internal) asymmetric inductions. This principle has led to the total synthesis of a broad series of naturally occurring biaryls,[4, 7] mainly naphthylisoquinoline alkaloids such as dioncopeltine A (**2**).[6]

As useful model biaryl lactones devoid of stereocenters and thus substrates for (at least overall) atropo-*enantioselective* cleavage reactions, we have established benzonaphthopyranones of type **4**.[4, 5] They are easily accessible by Pd^{II}-catalyzed aryl coupling of bromoesters **3** in excellent yields even with highest steric hindrance.[8, 9] Depending on the size of the residue R next to the biaryl axis, the lactones **4** (Scheme 2) are not flat, but rather helically distorted and thus exist in their two enantiomeric forms, (*P*)-**4** and (*M*)-**4**,[10] which, because of the bridging lactone function, rapidly interconvert at room temperature.[8] From this enantiomeric equilibrium, **4** can be ring-opened highly atropo-diastereoselectively or -enantioselectively with chiral O-[11, 12] or H-nucleophiles.[13] In preliminary investigations, several chiral N-nucleophiles were tested which led to the corresponding biaryl amides **5** in good diastereomeric ratios.[14]



Scheme 1. The atropo-selective reduction of biaryl lactone **1**—the stereochemically decisive step in the synthesis of dioncopeltine A (**2**).

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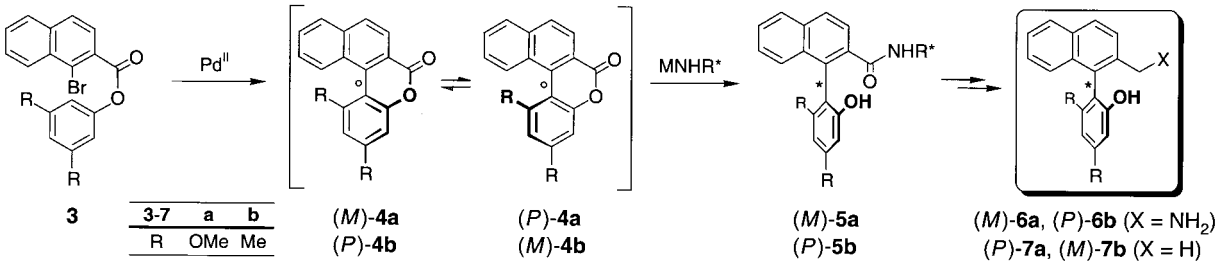
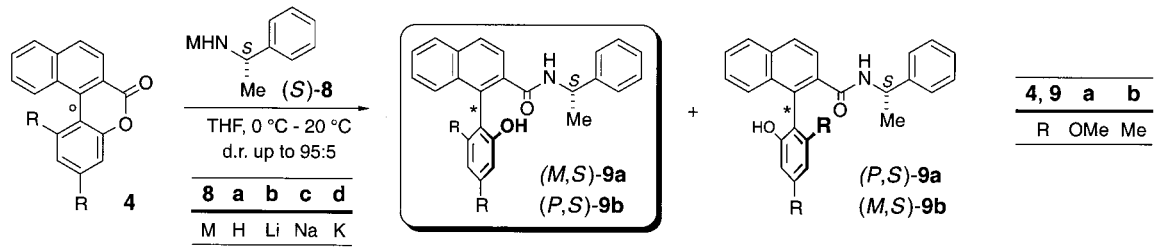


Scheme 2. Synthesis and atropo-selective aminolysis of the model lactones **4** and further derivatization of the resulting amides **5**.[15]



Scheme 3. Atropo-diastereoselective ring-opening of the lactones **4** with (*S*)-1-phenylethylamides (*S*)-**8b**–**d** to give the amides **9**.

inductions. In contrast to most other methods for stereoselective biaryl coupling,[16, 17] the "lactone concept" includes the possibility of atropo-divergently preparing *M*- or, optionally, *P*-configured products starting from the same lactone precursor **4**, and, if required, to recycle an undesired minor atropisomer by its recyclization back to **4**. This lactone can then, once again, be ring-opened stereoselectively (chiral economy). Furthermore, we describe subsequent transformation reactions of the resulting biaryl amide functionality of **5** into aminomethylene and methyl groups as in **6** and **7**, respectively.

Results and Discussion

Atropo-diastereoselective ring opening of 4 with (*S*)-1-arylethylamides: Based on the results of earlier investigations,[14] the aminolyses of **4** were mainly performed with the cheap and simple N-nucleophile (*S*)-phenylethylamine [(*S*)-**8a**] (Scheme 3), which was first activated by deprotonation, ideally with *n*BuLi, NaH, or KH. For an efficient cleavage of the lactone bridge the resulting alkali metal amides (*S*)-**8b**–**d** were added at 0 °C to a solution of **4** in THF and the mixture was then allowed to warm to 20 °C.

In all cases, the isolated yields of amides **9** were higher than 90% for the Li and Na amides (*S*)-**8b** and **c**, and about 80% for the K derivative (*S*)-**8d** (Table 1). For lactones **4a** and **4b**, the same significant dependence of the diastereomeric ratios (*P*,*S*)-**9**:(*M*,*S*)-**9** on the activating metal was observed: With (*S*)-**8b**, that is with Li as the counter metal, ring cleavage of **4** proceeded with only low stereodifferentiation (diastereomeric ratios of up to 59:41). By contrast, good to excellent diastereomeric ratios of up to 95:5 were obtained if (*S*)-**8c** or (*S*)-**8d** were used with the higher homologues Na and, in particular, K. This behavior is in contrast to the ring cleavage of the lactones **4** with O-nucleophiles such as menthol, which gave the highest asymmetric induction with Li as the counter metal.[11]

Table 1. Aminolysis of **4** with the (*S*)-1-phenylethylamides (*S*)-**8b**, **c**, and **d**.[a]

Entry	Lactone	Amide	d.r.[b,c] (yield [%])[d] (*S*)-**8a** (M = H)	(*S*)-**8b** (M = Li)	(*S*)-**8c** (M = Na)	(*S*)-**8d** (M = K)
1	**4a**	**9a**	–[e]	51:49 (93)	89:11 (98)	91:9 (70)
2	**4b**	**9b**	–[e]	59:41 (95)	92:8 (99)[f]	95:5 (85)

[a] Lactone **4** (200 μmol), amide (*S*)-**8** (360 μmol), THF, 0 → 20 °C, 3–5 h. [b] For **9a**: d.r. = *(M,S)*-**9a**:*(P,S)*-**9a**, for **9b**: d.r. = *(P,S)*-**9b**:*(M,S)*-**9b**; note that the stereochemically identical amides *(M,S)*-**9a**/*(P,S)*-**9b** and *(P,S)*-**9a**/*(M,S)*-**9b** have different descriptors at the biaryl axis only for formal reasons (CIP-denotion[10]). [c] Determined by ^{1}H NMR and, for **9b**, additionally confirmed by HPLC (μPorasil). [d] Yields of the diastereomeric mixtures after workup. [e] No reaction. [f] After crystallization from petroleum ether/Et_2O: d.r. > 99.5:0.5 (68% yield).

The steric hindrance at the biaryl axis has no major effect on the diastereomeric ratio; only slightly better asymmetric inductions were obtained for the lactone **4b** compared to **4a** (Table 1, entry 1 vs. 2). Thus the best atropo-differentiation (d.r. 95:5) was achieved in the ring opening of **4b** with (*S*)-**8d** (M = K).

Analogously two further related enantiopure (*S*)-1-arylethylamines were tested, namely the sterically more demanding and also commercially available (*S*)-1-naphthylethylamine [(*S*)-**11a**] and the trimethoxy derivative of (*S*)-1-phenylethylamine, (*S*)-**12a**,[18] whose *ortho*-methoxy group might allow an additional prefixation of the activating metal and thus create even more differentiated diastereomorphous transition states (Scheme 4).

As already determined for the atropo-selective cleavage with (*S*)-**8b**, **c**, and **d**, the ring-opening reactions of **4b** with the amides (*S*)-**11b**–**d** and (*S*)-**12b**–**d** similarly gave the *P*-configured diastereomers of **10** and **13** as the main products (Table 2). Again, the same strong dependence of the d.r. on the activating alkali metal was observed. The asymmetric inductions, however, did not exceed those obtained with (*S*)-**8**; the best diastereomeric ratios were again attained with the kaliated amines (*S*)-**11d** (d.r. 90:10) and (*S*)-**12d** (d.r. 93:7),

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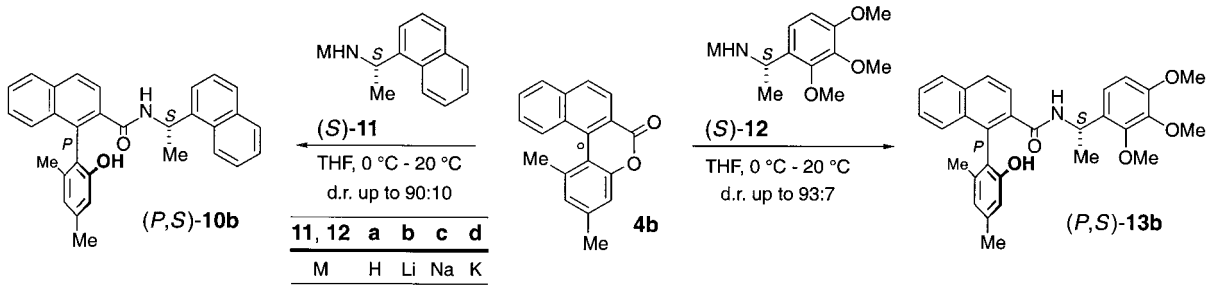
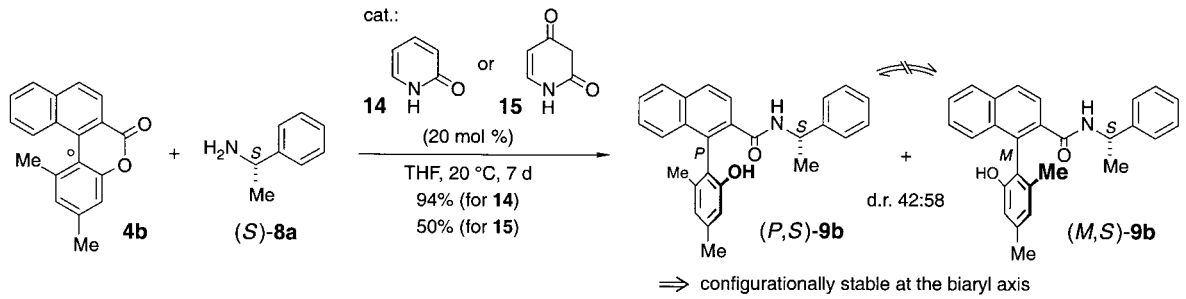


Scheme 4. Aminolyses of the lactone **4b** with (*S*)-**11** and (*S*)-**12**.



Scheme 5. Acid-catalyzed aminolysis of **4b** with (*S*)-1-phenylethylamine [(*S*)-**8a**] and configurational stability of **9b** under the reaction conditions.

Table 2. Diastereomeric ratios and yields obtained in the ring opening of **4b** with the (*S*)-1-arylethylamides (*S*)-**11** and (*S*)-**12**.[a]

Entry	Amine	Amide	d.r. *P*:*M* [b] (yields [%])[c] M = Li	M = Na	M = K
1	(*S*)-**11**	**10b**	44:56[d] (76)	76:24 (83)	90:10 (78)
2	(*S*)-**12**	**13b**	63:37 (94)	90:10 (88)	93:7 (79)

[a] Lactone **4b** (200 μmol), amide M-(*S*)-**11** or M-(*S*)-**12** (360 μmol each), THF, 0 → 20 °C, 3–5 h. [b] Determined by ^{1}H NMR and, for **10b**, additionally confirmed by HPLC (μPorasil). [c] Yields of the diastereomeric mixtures after workup. [d] This reproducible inversed asymmetric induction was found only in this particular case.

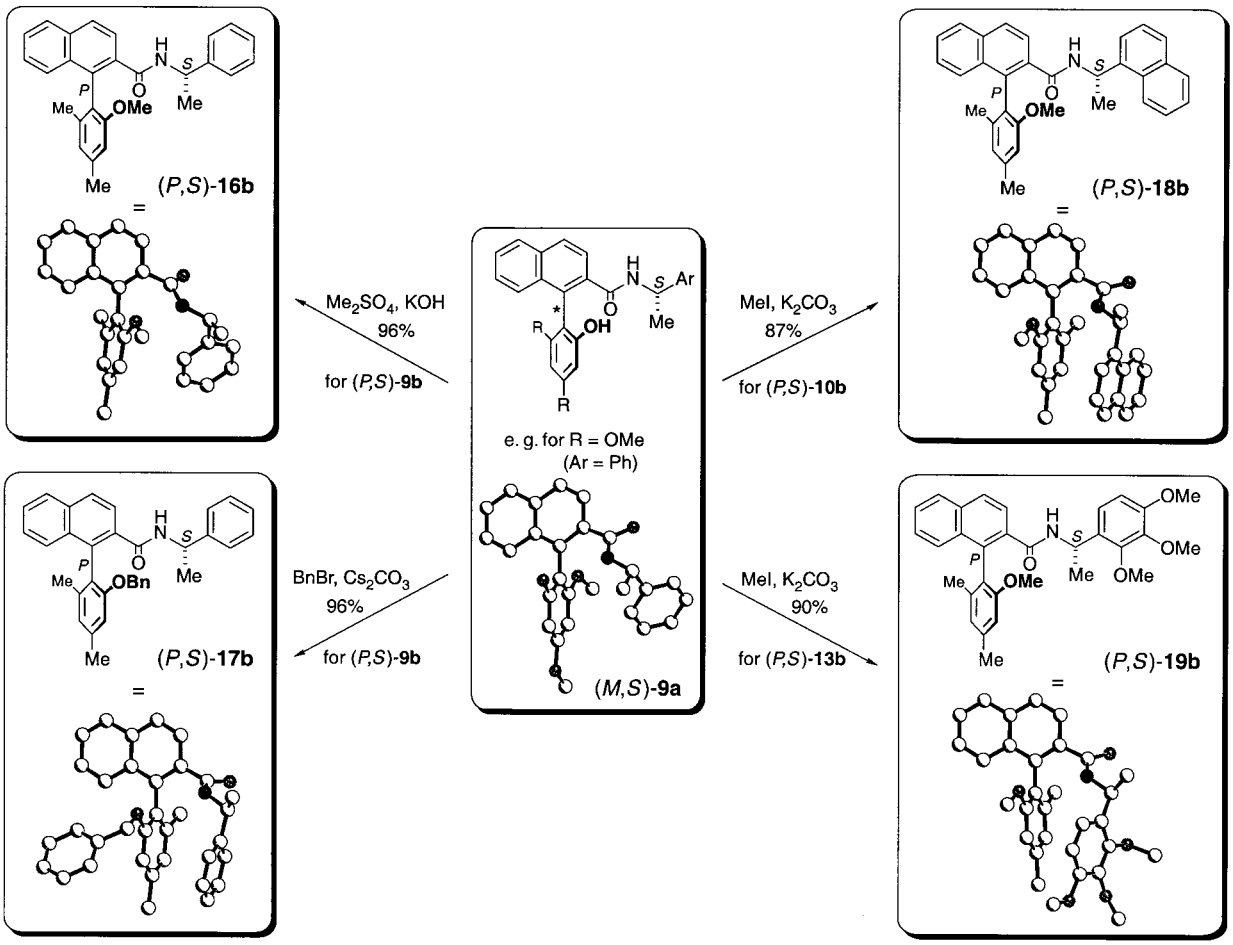
ranging slightly below the one obtained with (*S*)-**8d** (d.r. 95:5, cf. Table 1, entry 2).

Resolution of the diastereomeric amides **9b** and **10b** was achieved by column chromatography on silica gel and subsequent crystallization of the separated atropisomers. For **9a** and **13b**, only the main isomers (*M*,*S*)-**9a** and (*P*,*S*)-**13a** were obtained as diastereomerically pure compounds. The remaining diastereomerically enriched minor diastereomers, however, were purified by preparative HPLC on a Waters Nova-Pak HR silica phase for characterization. The stereochemically pure main atropisomers can be obtained by direct crystallization from diastereomerically enriched crude reaction products without chromatographic separation. As an example, the 92:8 mixture of (*P*,*S*)-**9b**:(*M*,*S*)-**9b** resulting from the aminolysis of **4b** with (*S*)-**8c** (Table 1, entry 2) gave (*P*,*S*)-**9b** in a d.r. > 99.5:0.5 in 68 % yield.

Acid-catalyzed aminolyses of the lactone 4b: As a possible alternative to the metal-activated ring-cleaving reactions acid-catalyzed aminolysis reactions of **4b** with the amine (*S*)-**8a** were investigated (Scheme 5) with 20 mol % of 2-pyridone (**14**) or thymine (**15**) as simultaneously efficient[19] proton donors and acceptors.[20] These ring-opening reactions of **4b** proceeded only very slowly (7 d) and with low diastereomeric ratios of 42:58 for both catalysts, but now, in contrast to the aminolyses with the metalated amines (compare Tables 1 and 2) with the other atropo-diastereomer (*M*,*S*)-**9b** as the main product. These "reversed" (and for both catalysts identical) stereoselectivities might in principle reflect the thermodynamically controlled equilibrium mixture as the result of a subsequent atropisomerization: The stereogenic biaryl axis might be configurationally unstable under the reaction conditions as a result of a catalyzed cyclization–helimerization–ring-opening sequence known for the related biaryl hydroxy aldehydes.[21] This possibility, however, was excluded by stirring an 80:20 enriched mixture of (*P*,*S*)-**9b** with 20 mol % of the catalyst **14** for 10 days, which did not lead to any noticeable change of this ratio towards the above-mentioned ratio; this shows that the amides are configurationally stable at the biaryl axis also under these conditions.

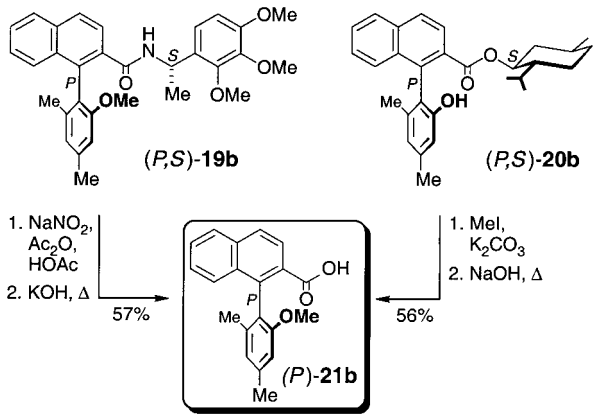
Determination of the absolute configuration at the biaryl axis: As a result of the presence of a stereocenter of known absolute configuration in the amine part, the elucidation of the axial configuration is reduced to the determination of the stereoarray of the axis relative to the stereocenter. The good crystallization properties of (*M*,*S*)-**9a** and of the *O*-protected derivatives of the methyl substituted compounds (*P*,*S*)-**16b**, (*P*,*S*)-**17b**, (*P*,*S*)-**18b**, and (*P*,*S*)-**19b** allowed us to perform X-ray structure analyses of the main atropo-diastereomers of all amides prepared (Scheme 6) and thus permitted a reliable assignment of the absolute configuration at the axis.

A more general pathway to determine the absolute configuration at the axis, independent of the N-nucleophiles used for ring opening and the (in this case indeed good) crystallizing properties of the resulting products, is based on the conversion of the amides into the (stereochemically known) cor-



Scheme 6. Determination of the relative (to the centers) and thus absolute configuration at the biaryl axes of the amides by X-ray structure analyses.

responding carboxylic acids. As exemplified for the *O*-methyl protected trimethoxybenzamide (*P*,*S*)-**19b** (Scheme 7), this



Scheme 7. General pathway for the elucidation of the absolute configuration at the biaryl axis: Transformation of the *O*-methyl protected amide (*P*,*S*)-**19b** into the stereochemically known biaryl carboxylic acid (*P*)-**21b**.

was achieved by nitrosylation with sodium nitrite[22] and subsequent base-induced hydrolysis to give (*P*)-**21b**. This product was fully identical (including its CD-spectrum) with the one obtained by saponification of the stereochemically known[11] menthyl ester (*P*,*S*)-**20b**.

Chiral economy and atropo-divergent biaryl synthesis: The basic principle of the lactone concept, the dynamic kinetic resolution of configurationally unstable lactone precursors with chiral nucleophiles,[4, 5] allows to fulfil two crucial requirements for a highly efficient stereoselective biaryl synthesis: First, the optional preparation of both atropisomers from the same precursor (atropo-divergence) by using enantiomeric reagents and, second, possible recycling of the undesired minor isomer by recyclization to the lactone and its renewed ring cleavage (chiral economy). In the following, these two advantages are demonstrated for the aminolysis of **4b** (Scheme 8).

For atropo-divergent ring-opening reactions, the phenylethylamines (*S*)-**8a** and (*R*)-**8a**, which are cheap and commercially available in both enantiomeric forms, constitute an ideal pair of enantiomeric N-nucleophiles. As already expected from the aminolysis of **4b** with (*S*)-**8c** (M = Na, Scheme 3 and Table 1), which led to (*P*,*S*)-**9 b** as the main diastereomer (d.r. 92:8), the lactone cleavage with the enantiomeric reagent (*R*)-**8c** afforded the enantiomeric amide (*M*,*R*)-**9b** with the same diastereomeric ratio of 92:8 under identical conditions. An upscaling of the latter reaction of up to 2 g of lactone **4b** was also successful: The diastereopure amides (*P*,*R*)-**9b** (5%) and (*M*,*R*)-**9b** (86%) were obtained in good yields after chromatographic separation of the crude product mixture and subsequent crystalli-

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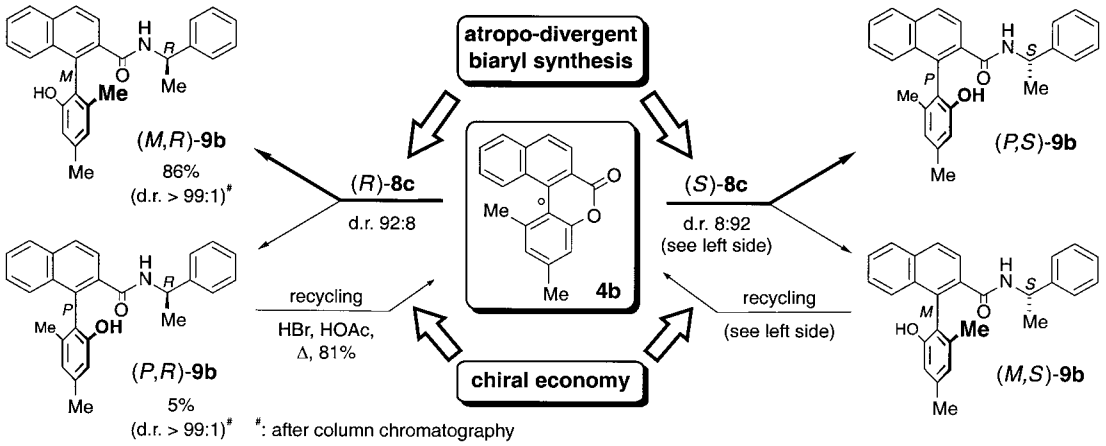
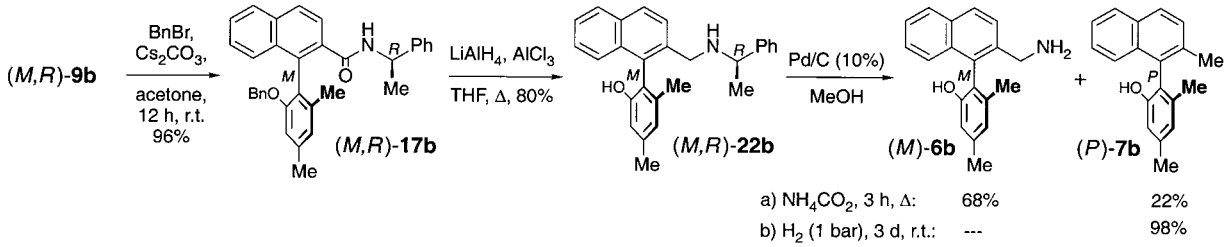


Scheme 8. Advantages of the "lactone concept": atropo-divergent biaryl synthesis and chiral economy.



Scheme 9. Optional preparation of target biaryls with or without nitrogen.

zation of each diastereomer from PE/Et_2O. Moreover, a recycling of the minor isomer (*P*,*R*)-**9b** was achieved in 81% yield by its recyclization to the lactone **4b** in refluxing HBr (48%) in acetic acid.[23] With these advantages, the aminolysis represents an easy and practical access even to larger amounts of stereochemically homogenous biaryl amides.

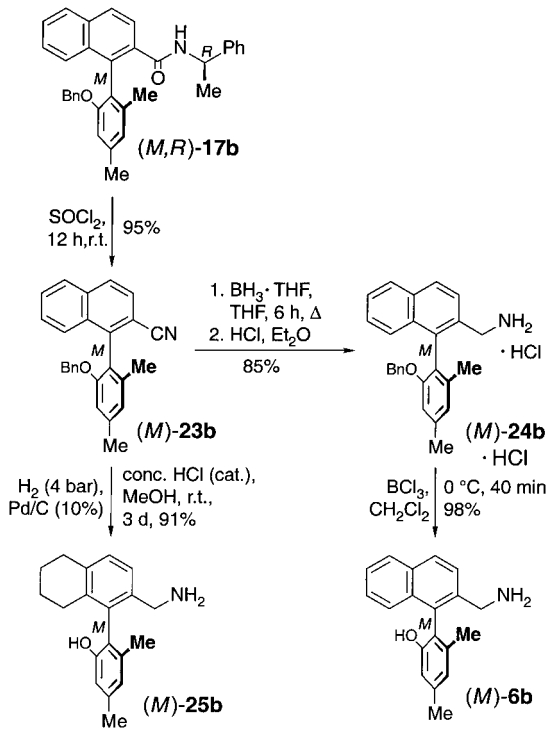
Further transformation reactions on the amide function: For even more diversified applications of the ring-opening reactions with metalated phenylethylamine (**8**) to the enantioselective synthesis of various axially chiral biaryl target molecules, efficient routes for the removal of the centrochiral amine substituent are required, either with conservation or cleavage of the (aryl-C*HMe)–N bond and thus retention or loss of the nitrogen introduced. The saponification of these amides to give the corresponding carboxylic acids has already been shown in Scheme 7. Particularly interesting are transformations of the amide function into a methyl group, as needed for the atropo-selective preparation of biologically active naturally occurring biaryls, and into an aminomethylene group, which may provide a novel access to the class of enantiopure N,O-bidentate auxiliaries of type **6**[3] (see Scheme 2).

First investigations focused on the hydrogenolysis of the amine (*M*,*R*)-**22b** (Scheme 9), which was accessible from (*M*,*R*)-**9b** by benzylation of the phenolic hydroxy group (96%)[24] and reduction of the resulting amide (*M*,*R*)-**17b** with $LiAlH_4/AlCl_3$ in refluxing THF with simultaneous cleavage of the benzyl ether function (80%). Despite the harsh reaction conditions no loss of optical purity occurred.[25] In contrast to previous highly specific cleavage reactions on *N*-(1-arylethyl)-*N*-(1-phenylethyl)amines,[18, 26] the hydrogenolysis of (*M*,*R*)-**22b** on Pd/C (1 bar) gave the primary amine (*M*)-**6b** (68%) as the main product, along with the methyl analogue (*P*)-**7b**[27] (22%). With ammonium formiate as the hydrogen source, however, the nitrogen-free target biaryl (*P*)-**7b** was obtained highly selectively in 98% yield.

A more directed, convenient pathway to the amine (*M*)-**6b** was found through nitrile (*M*)-**23b**, which was obtained in 95% yield by dehydration of amide (*M*,*R*)-**17b** with thionyl chloride (Scheme 10). Reduction of (*M*)-**23b** with borane in refluxing THF and precipitation from PE/Et_2O led to the hydrochloride of the primary amine, (*M*)-**24b**·HCl, which was deprotected with boron trichloride to obtain the desired amino alcohol (*M*)-**6b** in a virtually quantitative yield. Hydrogenolysis of (*M*)-**23b** took place only under more drastic conditions and did not lead to the expected formation of (*M*)-**6b**, but resulted in an over-reduction to the phenylaminomethyltetralin (*M*)-**25b** with the distal naphthalene ring hydrogenated—an interesting additional modification reaction.

Conclusion

A most efficient access to enantiopure axially chiral biaryls has been found in the atropo-diastereoselective ring-opening (d.r. of up to 95:5) of the configurationally unstable lactones with sodium or potassium 1-arylethylamides. The advantages of this method are the atropo-divergent preparation of biaryl amides with any configuration at the axis and the option of recycling undesired atropo-diastereomeric by-products possibly formed. With the presented further transformations of the amide function into methyl or aminomethylene groups, these



Scheme 10. Derivatization of amide (*M*,*R*)-**17b** through nitrile (*M*)-**23b**.

ring-opening reactions have a high potential in the synthesis of both natural and unnatural axially chiral target molecules.

Experimental Section

Melting points were measured on a Kofler hot-stage apparatus and are corrected. IR spectra were taken on a Perkin–Elmer 1420 infrared spectrophotometer and were reported in wave numbers (cm^{-1}). Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. CD-spectra were recorded at room temperature in EtOH on a Jobin–Yvon Model CD6 spectrograph. NMR spectra were recorded with either a Bruker AC 200 or a Bruker AC 250 spectrometer at room temperature in $CDCl_3$ or CD_3OD. The chemical shifts δ are given on the ppm scale with the proton signal of the deuterated solvent as internal reference for ^1H and ^{13}C NMR. The coupling constants *J* are given in Hertz. Mass spectra were obtained on a Finnigan MAT 8200 mass spectrometer at 70 eV in the EI mode. Combustion analyses were performed in the microanalytical laboratory of the University of Würzburg on a LECO CHNS-932 apparatus. HPLC was carried out with a Waters M 510 HPLC pump, an U6 K injector, an ERC-7215 UV-detector, and a Shimadzu Integrator C-R6A Chromatopac. Reactions were monitored by thin-layer chromatography (TLC) on TLC aluminum sheets silica gel 60 F_{254} (Merck). Silica gel (0.063–0.200 mm, Merck) was used for column chromatography. The petroleum ether (PE) used had a boiling point range of 40–60 °C. THF was distilled from potassium directly before use, and toluene was distilled from sodium. NaH and KH were washed with dry PE prior to use. All reactions were carried out under an atmosphere of dry inert gas with the Schlenck-tube technique. (*S*)- and (*R*)-1-phenylethylamine [(*R*)-**8a** and (*S*)-**8a**] and (*S*)-1-(1′-naphthyl)ethylamine [(*S*)-**11a**] were purchased from Aldrich, (*S*)-1-(2′,3′,4′-trimethoxyphenyl)ethylamine [(*S*)-**12a**][18] and the lactones **4a** and **4b**[8] were prepared according to literature procedures.

General procedure for the aminolysis of the lactones 4 with alkali metal activated 1-arylethylamines: *n*BuLi (1.6 M in hexane), NaH, or KH (360 μmol each) was added at 0 °C to a solution of the amine [(*S*)-**8a**, (*S*)-**11a**, or (*S*)-**12a**, 400 μmol each] in THF (5.0 mL). After the reation mixture was stirred for 30 min, lactone **4** (200 μmol) was added, the reaction mixture warmed up to 20 °C within 2 h and stirred for further 2–3 h at 20 °C, until complete conversion into the amides **9**, **10**, or **13** was detected by TLC (PE/Et_2O 1:1). The mixture was hydrolyzed with water (20 mL), slightly acidified with HCl (0.1 N, 3 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. The d.r. was determined by ^1H NMR spectroscopy (6′-OCH_3 or 6′-CH_3 resonances) and for **9b** and **13b** additionally confirmed by HPLC on a Waters μPorasil phase [125 Å, 10 μm, 30 cm × 3.9 mm; flow rate 0.8 mL min^{-1}; UV detection at 280 nm; eluent ratio: CH_2Cl_2/MeOH/HCO_2H 100:0.2:0.05; retention times t_R: 16.4 min for (*M*,*S*)-**9b** and 22.8 min for (*P*,*S*)-**9b**; 16.1 min for (*M*,*S*)-**13b** and 24.0 min for (*P*,*S*)-**13b**] (for diastereomeric ratios and yields, see Tables 1–3). Separation of the diastereomeric amides **9b**, **10b**, and **13b** was achieved by column chromatography on silica gel (PE/Et_2O 3:1 → 1:3) and crystallization of the resulting oils from PE/Et_2O to give the diastereo- and enantiomerically pure compounds as white solids. By this way, the minor diastereomers (*P*,*S*)-**9a** and (*M*,*S*)-**13a** were only obtained as diastereomerically enriched mixtures, which were transformed into the pure diastereomers by preparative HPLC on a Waters preparative Nova-Pak HR silica phase [6–8 μm, 30 cm × 19 mm; flow rate 6.0 mL min^{-1}; UV detection at 280 nm; eluent ratio: CH_2Cl_2/MeOH/HCO_2H 100:0.1:0.05; retention times t_R: 29.9 min for (*M*,*S*)-**9a** and 35.3 min for (*P*,*S*)-**9a**; 31.1 min for (*P*,*S*)-**13b** and 43.5 min for (*M*,*S*)-**13b**]. Crystallization of a 92:8 diastereomeric mixture of (*M*,*S*)-**9b** and (*P*,*S*)-**9b** without any chromatographic separation of the isomers gave the diastereopure amide (*P*,*S*)-**9b** (d.r. > 99.5:0.5) in 68% yield. With nonactivated (*S*)-1-phenylethylamine [(*S*)-**8a**], no ring-opening reaction of **4a** or **4b** occurred under the same conditions.

(*P*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethoxyphenyl)-2-naphthoic acid 1″-phenylethylamide [(*P*,*S*)-9a]: M.p. 232 °C; $[\alpha]_D^{22} = +70.9$ ($c = 1.0$ in EtOH); CD: $\Delta\varepsilon_{282}$ +4.1, $\Delta\varepsilon_{210}$ −11.8; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.33$ (d, J = 6.9 Hz, 3H; NCHCH_3), 3.38 (s, 3H; 6′-OCH_3), 3.78 (s, 3H; 4′-OCH_3), 5.02 (quint, $J = 6.9$ Hz, 1H, NC*H*CH_3), 6.01/6.23 (2d, $J = 2.2$ Hz each, 1H each; 3′-, 5′-H), 6.54 (d, $J = 7.2$ Hz, 1H; NH), 6.91–6.96 (m, 1H; ArH), 7.11–7.26 (m, 4H; ArH), 7.36–7.51 (m, 3H; ArH), 7.71 (d, $J = 8.5$ Hz, 1H; 4-H), 7.82–7.88 (m, 2H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 21.41$ (C-2″), 49.14 (C-1″), 55.43, 55.48 (4′-OCH_3, 6′-OCH_3), 92.01 94.21, 105.8, 125.1, 126.1, 126.3, 127.1, 127.7, 128.1, 128.5, 129.0, 132.8, 134.3, 135.9, 142.6, 155.5, 158.3, 161.8 (ArC), 168.9 (C=O); IR (film): $\tilde{\nu} = 3150$ cm^{-1} (NH, OH), 1610 (C=O); MS (70 eV, EI): *m/z* (%): 427 (26) $[M]^+$, 307 (30) $[M - C_8H_{10}N]^+$, 306 (100) $[M - C_8H_{11}N]^+$, 120 (29); $C_{27}H_{25}NO_4$ (427.5): calcd C 75.86, H 5.89, N 3.28; found C 75.92, H 5.94, N 3.21.

(*M*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethoxyphenyl)-2-naphthoic acid 1″-phenylethylamide [(*M*,*S*)-9a]: M.p. 181 °C; $[\alpha]_D^{22} = +83.2$ ($c = 0.9$ in EtOH); CD: $\Delta\varepsilon_{230}$ +223, $\Delta\varepsilon_{213}$ −68; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.17$ (d, $J = 6.8$ Hz, 3H; NCHCH_3), 3.49 (s, 3H; 6′-OCH_3), 3.85 (s, 3H; 4′-OCH_3), 5.09 (quint, $J = 7.2$ Hz, 1H; NC*H*CH_3), 6.20/6.31 (2d, $J = 2.3$ Hz each, 1H each; 3′-, 5′-H), 6.33 (d, $J = 7.3$ Hz, 1H; NH), 7.14–7.30 (m, 5H; ArH), 7.39–7.55 (m, 4H; ArH), 7.79 (d, $J = 8.5$ Hz, 1H, 3-H or 4-H), 7.87 (d, $J = 8.1$ Hz, 1H; ArH), 7.94 (d, $J = 8.5$ Hz, 1H; 3-H or 4-H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 21.14$ (C-2″), 49.07 (C-1″), 55.51, 55.62 (4′-OCH_3, 6′-OCH_3), 91.96, 94.15, 105.8, 125.2, 126.1, 126.3, 127.1, 127.2, 127.3, 127.7, 128.2, 128.6, 129.0, 132.9, 134.3, 135.9, 142.8, 155.6, 158.4, 161.9 (ArC), 168.5 (C=O); IR (KBr): $\tilde{\nu} = 3350$ cm^{-1} (NH, OH), 1615 (C=O); MS (70 eV, EI): *m/z* (%): 427 (30) $[M]^+$, 307 (31) $[M - C_8H_{10}N]^+$, 306 (100) $[M - C_8H_{11}N]^+$, 120 (20); $C_{27}H_{25}NO_4$ (427.5): calcd C 75.86, H 5.89, N 3.28; found C 76.03, H 6.07, N 3.10.

(*M*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-phenylethylamide [(*M*,*S*)-9b]: M.p. 199 °C; $[\alpha]_D^{22} = +96.0$ ($c = 0.5$ in EtOH); CD: $\Delta\varepsilon_{236}$ +113, $\Delta\varepsilon_{211}$ −162; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.16$ (d, J = 6.8 Hz, 3H; NCHCH_3), 1.81 (s, 3H; 6′-CH_3), 2.37 (s, 3H; 4′-CH_3), 5.06 (quint, $J = 7.0$ Hz, 1H; NC*H*CH_3), 6.15 (br d, $J = 7.1$ Hz, 1H; NH), 6.72/6.79 (2s, 1H each; 3′-H, 5′-H), 7.04–7.08 (m, 2H; ArH), 7.19–7.24 (m, 3H; ArH), 7.39–7.41 (m, 2H; ArH), 7.49–7.57 (m, 1H; ArH), 7.87–7.94 (m, 3H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.65, 21.23, 21.25$ (4′-CH_3, 6′-CH_3, C-2″), 49.19 (C-1″), 114.2, 121.5, 123.4, 125.3, 126.0, 126.2, 126.9, 127.1, 128.1, 128.4, 131.7, 132.0, 134.0, 134.3, 138.5, 139.4, 142.7, 153.6 (ArC), 168.5 (C=O); IR (KBr): $\tilde{\nu} = 3300$ cm^{-1} (NH, OH), 1615 (C=O); MS (70 eV, EI): *m/z* (%): 395 (32) $[M]^+$, 275 (28) $[M - C_8H_{10}N]^+$, 274 (100) $[M - C_8H_{11}N]^+$, 105 (14); $C_{27}H_{25}NO_2$ (395.5): calcd C 82.00, H 6.37, N 3.54; found C 82.30, H 6.51, N 3.68.

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(*P*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-phenylethylamide [(*P*,*S*)-9b]: M.p. 191 °C; $[\alpha]_D^{20} = +119.5$ ($c = 0.5$ in EtOH); CD: $\Delta\varepsilon_{280} -16$, $\Delta\varepsilon_{227} +116$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.26$ (d, $J =$ 7.0 Hz, 3H; NCHCH_3), 1.74 (s, 3H; 6′-CH_3), 2.36 (s, 3H; 4′-CH_3), 5.06 (quint, $J = 7.0$ Hz, 1H; NCHCH$_3$), 6.27 (d, $J = 7.0$ Hz, 1H; NH), 6.67/6.74 (2 brs, 1H each; 3′-H/5′-H), 6.94–6.99 (m, 2H; ArH), 7.20–7.26 (m, 3H; ArH), 7.35–7.45 (m, 2H; ArH), 7.50–7.58 (m, 1H; ArH), 7.89 (d, $J =$ 7.9 Hz, 1H; ArH), 7.96 (s, 2H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta =$ 19.48, 21.20, 21.88 (4′-CH_3, 6′-CH_3, C-2″), 49.55 (C-1″), 114.2, 121.5, 123.0, 125.4, 125.7, 126.3, 126.6, 126.7, 126.9, 128.0, 128.1, 132.1, 132.4, 133.4, 134.3, 138.4, 139.2, 142.9, 153.8 (ArC), 168.9 (C=O); IR (KBr): $\tilde{\nu} = 3280$ cm^{-1} (NH, OH), 1615 (C=O); MS (70 eV, EI): *m/z* (%): 395 (33) $[M]^+$, 275 (28) $[M - C_8H_{10}N]^+$, 274 (100) $[M - C_8H_{11}N]^+$, 105 (14); $C_{27}H_{25}NO_2$ (395.5): calcd C 82.00, H 6.37, N 3.54; found C 82.31, H 6.41, N 3.78.

(*M*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-(1‴-naphthyl)ethylamide [(*M*,*S*)-10b]: M.p. 224–226 °C; $[\alpha]_D^{20} = +122.4$ ($c =$ 1.04 in DMSO); CD: $\Delta\varepsilon_{286} +12.1$, $\Delta\varepsilon_{236} +49.6$, $\Delta\varepsilon_{222} -92.1$, $\Delta\varepsilon_{196} +27.5$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.36$ (d, $J = 6.7$ Hz, 3H; NCHCH_3), 1.76 (s, 3H; 6′-CH_3), 2.29 (s, 3H; 4′-CH_3), 5.04 (brs, 1H; OH), 5.88 (quint, $J =$ 7.0 Hz, 1H; NCHCH$_3$), 6.26 (d, $J = 8.9$ Hz, 1H; NH), 6.47/6.71 (2 s, 1H each; 3′-H, 5′-H), 7.23 (d, $J = 7.5$ Hz, 1H; ArH), 7.32–7.42 (m, 3H; ArH), 7.43–7.56 (m, 3H; ArH), 7.74 (d, $J = 7.9$ Hz, 1H; ArH), 7.79–7.93 (m, 4H; ArH), 8.01 (m, 1H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.71$, 20.14, 21.27 (4′-CH_3, 6′-CH_3, C-2″), 44.88 (C-1″), 114.4, 121.4, 122.3, 123.4, 123.7, 125.1, 125.5, 125.7, 126.1, 126.4, 127.2, 127.3, 128.2, 128.3, 128.6, 128.8, 131.0, 131.2, 132.0, 133.8, 133.9, 134.4, 138.0, 138.1, 139.7, 153.2 (ArC), 167.7 (C=O); IR (KBr): $\tilde{\nu} = 3400$ cm^{-1}, 3290 (NH, OH), 1610 (C=O); MS (70 eV, EI): *m/z* (%): 445 (25) $[M]^+$, 291 (12) $[M - C_{12}H_{11}]^+$, 274 (92) $[M - C_{12}H_{13}N]^+$, 155 (100) $[C_{12}H_{11}]^+$; $C_{31}H_{27}NO_2$ (445.6): calcd C 83.57, H 6.11, N 3.14; found C 82.74, H 6.16, N 3.21.

(*P*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-(1‴-naphthyl)ethylamide [(*P*,*S*)-10b]: M.p. 241–242 °C; $[\alpha]_D^{20} = +318.4$ ($c =$ 1.02 in DMSO); CD: $\Delta\varepsilon_{235} +54.0$, $\Delta\varepsilon_{222} -30.6$, $\Delta\varepsilon_{212} +2.1$, $\Delta\varepsilon_{197} -37.9$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.48$ (d, $J = 7.0$ Hz, 3H; NCHCH_3), 1.57 (s, 3H; 6′-CH_3), 2.16 (s, 3H; 4′-CH_3), 4.14 (brs, 1H; OH), 5.94 (quint, $J =$ 7.0 Hz, 1H; NCHCH$_3$), 6.27 (s, 2H; NH, 3′-H or 5′-H), 6.43 (s, 1H; 3′-H or 5′-H), 7.11 (d, $J = 6.7$ Hz, 1H; ArH), 7.29–7.42 (m, 3H; ArH), 7.44–7.56 (m, 3H; ArH), 7.75 (d, $J = 8.5$ Hz, 1H; ArH), 7.81–7.98 (m, 3H; ArH), 8.00–8.09 (m, 2H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.64$, 20.47, 21.26 (4′-CH_3, 6′-CH_3, C-2″), 44.76 (C-1″), 114.0, 121.0, 122.2, 123.4, 123.7, 125.0, 125.7, 126.0, 126.1, 126.3, 127.2, 127.4, 128.1, 128.3, 128.6, 128.9, 130.9, 131.1, 132.0, 133.8, 134.3, 134.6, 138.0, 138.1, 139.5, 152.6 (ArC), 167.2 (C=O); IR (KBr): $\tilde{\nu} = 3400$ cm^{-1}, 3250 (NH, OH), 1610 (C=O); MS (70 eV, EI): *m/z* (%): 445 (26) $[M]^+$, 291 (14) $[M - C_{12}H_{11}]^+$, 274 (100) $[M - C_{12}H_{13}N]^+$, 155 (32) $[C_{12}H_{11}]^+$; $C_{31}H_{27}NO_2$ (445.6): calcd C 83.57, H 6.11, N 3.14; found C 83.26, H 5.93, N 3.15.

(*M*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-(2‴,3‴,4‴-trimethoxyphenyl)ethylamide [(*M*,*S*)-13b]: M.p. 205–207 °C; $[\alpha]_D^{20} = +55.7$ ($c = 1.3$ in EtOH); CD: $\Delta\varepsilon_{282} +6.6$, $\Delta\varepsilon_{235} +18.7$, $\Delta\varepsilon_{207} -22.0$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.05$ (d, $J = 7.0$ Hz, 3H; NCHCH_3), 1.82 (s, 3H; 6′-CH_3), 2.36 (s, 3H; 4′-CH_3), 3.81 (s, 3H; OCH_3), 3.82 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3), 5.22 (quint, $J = 7.0$ Hz, 1H; NCHCH$_3$), 6.05 (brs, 1H; OH), 6.55 (brs, 1H; NH), 6.58/6.68 (2 d, $J = 8.5$ Hz, 1H each; 5″-H, 6″-H), 6.76/6.85 (2 s, 1H each; 3′-H, 5′-H), 7.36–7.44 (m, 2H; ArH), 7.52 (m, 1H; ArH), 7.85–7.93 (m, 3H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta =$ 19.76, 21.30, 21.71 (4′-CH_3, 6′-CH_3, C-2″), 45.38 (C-1″), 55.95, 60.67, 61.11 (2″-OCH_3, 3″-OCH_3, 4″-OCH_3), 107.2, 114.4, 121.2, 121.5, 123.6, 125.7, 126.2, 127.1, 127.2, 128.2, 128.5, 129.0, 131.4, 132.1, 134.3, 134.5, 138.4, 139.6, 142.1, 151.2, 152.9, 153.5 (ArC), 167.6 (C=O); IR (film): $\tilde{\nu} = 3350$ cm^{-1}, 3130 (NH, OH), 1620 (C=O); MS (70 eV, EI): *m/z* (%): 485 (12) $[M]^+$, 275 (11) $[M - C_{11}H_{16}NO_3]^+$, 274 (12) $[M - C_{11}H_{17}NO_3]^+$, 210 (5) $[C_{11}H_{16}NO_3]^+$, 195 (100) $[C_{10}H_{13}NO_3]^+$; $C_{30}H_{31}NO_5$ (485.6): calcd C 74.21, H 6.43, N 2.88; found C 73.94, H 6.51, N 2.92.

(*P*,1″*S*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-(2‴,3‴,4‴-trimethoxyphenyl)ethylamide [(*P*,*S*)-13b]: M.p. 209 °C; $[\alpha]_D^{20} =$ +71.8 ($c = 1.2$ in EtOH); CD: $\Delta\varepsilon_{228} +18.3$, $\Delta\varepsilon_{198} -14.7$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.16$ (d, $J = 7.0$ Hz, 3H; NCHCH_3), 1.77 (s, 3H; 6′-CH_3), 2.34 (s, 3H; 4′-CH_3), 3.84 (s, 6H; 2 OCH_3), 3.85 (s, 3H; OCH_3), 5.22 (quint, $J = 7.3$ Hz, 1H; NCHCH$_3$), 6.46/6.52 (2 d, $J = 8.5$ Hz, 1H each; 5″-H, 6″-H), 6.62 (br d, $J = 7.0$ Hz, 1H; NH), 6.74/6.80 (2 s, 1H each; 3′-H, 5′-H), 7.37–7.41 (m, 2H; ArH), 7.51 (m, 1H; ArH), 7.85–7.92 (m, 3H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.74$, 21.26, 21.93 (4′-CH_3, 6′-CH_3, C-2″), 45.44 (C-1″), 55.95, 60.65, 61.08 (2″-OCH_3, 3″-OCH_3, 4″-OCH_3), 107.1, 114.8, 121.1, 121.5, 123.3, 125.7, 126.4, 127.0, 127.1, 128.1, 128.4, 129.0, 131.8, 132.2, 134.1, 134.3, 138.0, 139.6, 142.0, 151.1, 152.8, 153.8 (ArC), 167.7 (C=O); IR (film): $\tilde{\nu} = 3310$ cm^{-1} (NH, OH), 1620 (C=O); MS (70 eV, EI): *m/z* (%): 485 (12) $[M]^+$, 275 (11) $[M - C_{11}H_{16}NO_3]^+$, 274 (11) $[M - C_{11}H_{17}NO_3]^+$, 210 (5) $[C_{11}H_{16}NO_3]^+$, 195 (10) $[C_{10}H_{13}NO_3]^+$; $C_{30}H_{31}NO_5$ (485.6): calcd C 74.21, H 6.43, N 2.88; found C 74.21, H 6.38, N 3.01.

Aminolysis of 4b with (*R*)-8c in large scale: According to the general procedure, the lactone ring of **4b** (2.03 g, 7.40 mmol) was opened with (*R*)-**8c**, prepared from (*R*)-**8a** (1.91 mL, 1.80 g, 14.8 mmol) and NaH (320 mg, 13.3 mmol) in THF (175 mL). The resulting diastereomeric amides (96%, d.r. 92:8) were resolved by column chromatography. Crystallization afforded the diastereomerically pure amides (*P*,*R*)-**9b** [146 mg, 370 μmol, 5%, $[\alpha]_D^{20} = -103.0$ ($c = 1.1$ in EtOH)] and (*M*,*R*)-**9b** [2.51 g, 6.36 mmol, 86%, $[\alpha]_D^{20} = -127.9$ ($c = 1.1$ in EtOH)] as white solids (d.r. > 99:1 each). The spectroscopic data of (*P*,*R*)-**9b** (*M*,*R*)-**9b** were identical to those of their enantiomers (*M*,*S*)-**9b** and (*P*,*S*)-**9b**.

Acid-catalyzed aminolysis of 4b with (*S*)-8a: A solution of lactone **4b** (54.9 mg, 200 μmol), (*S*)-**8a** (51.6 μL, 48.5 mg, 400 μmol), and 2-pyridone (**14**, 5.71 mg, 60 μmol) in THF (5 mL) was stirred at room temperature for 7 d. The reaction mixture was hydrolyzed with water (10 mL), slightly acidified with HCl (0.1N), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel (PE/Et_2O 3:1 → 1:1) to give a mixture of the atropisomeric amides (*P*,*S*)-**9b** and (*M*,*S*)-**9b** (74.4 mg, 188 μmol, 94%) with a diastereomeric ratio of 58:42. The analogous reaction with thymine (**15**, 7.57 mg, 60 μmol) as the catalyst afforded (*P*,*S*)-**9b** and (*M*,*S*)-**9b** (39.6 mg, 100 μmol, 50%) with the same diastereomeric ratio of 58:42.

Proof of the configurational stability of the biaryl axis under the acid-catalyzed reaction conditions: A mixture of the amides (*P*,*S*)-**9b** and (*M*,*S*)-**9b** (50.0 mg, 126 μmol, d.r. 80:20) was stirred with 2-pyridone (**14**, 3.60 mg, 37.9 μmol) in THF (5 mL) at room temperature for 10 d. The reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. The amides (*P*,*S*)-**9b** and (*M*,*S*)-**9b** (45.0 mg, 113 μmol, 90%) were recovered with the initial diastereomeric ratio of 80:20 (determined by ^{1}H NMR).

(*P*,1″*S*)-1-(2′-Methoxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-phenylethylamide [(*P*,*S*)-16b]: Me_2SO_4 (48.0 μL, 64.0 mg, 506 μmol) and $BnNMe_3Cl$ (28.7 mg, 126 μmol) were added to a solution of the amide (*P*,*S*)-**9b** (50.0 mg, 126 μmol) and 3N aqueous KOH (100 μL) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 15 min. The solvent was removed in vacuo and the residue filtered over silica gel (CH_2Cl_2). (*P*,*S*)-**16b** × ½MTB (51.0 mg, 112 μmol, 89%) was obtained as colorless crystals from PE/methyl *tert*-butyl ether (MTB). M.p. 59 °C; $[\alpha]_D^{22} = +54.2$ ($c = 0.96$ in MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.33$ (d, $J = 6.9$ Hz, 3H; NCHCH_3), 1.69 (s, 3H; 6′-CH_3), 2.40 (s, 3H; 4′-CH_3), 3.45 (s, 3H; 2′-OCH_3), 4.99 (quint, $J = 6.9$ Hz, 1H; NCHCH$_3$), 6.43 (br d, $J = 7.1$ Hz, 1H; NH), 6.48 (s, 1H; ArH), 6.77–6.82 (m, 3H; ArH), 7.14–7.24 (m, 4H; ArH), 7.31 (m, 1H; ArH), 7.47 (m, 1H; ArH), 7.83 (m, 1H; ArH), 7.88 (s, 2H; ArH); IR (KBr): $\tilde{\nu} = 3380$ cm^{-1} (NH), 1655 (C=O); MS (70 eV, EI): *m/z* (%): 409 (76) $[M]^+$, 289 (100) $[C_{20}H_{17}O_2]^+$, 288 (43) $[C_{20}H_{16}O_2]^+$, 274 (37) $[C_{19}H_{14}O_2]^+$, 120 (25) $[C_8H_{10}N]^+$; $C_{28}H_{27}NO_2 \times ½C_5H_{12}O$ (453.6): calcd C 80.76, H 7.33, N 3.09; found C 80.45, H 7.22, N 3.00.

(*M*,1″*R*)-1-(2′-Benzyloxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-phenylethylamide [(*M*,*R*)-17b]: A suspension of the amide (*M*,*R*)-**9b** (2.40 g, 6.07 mmol), benzyl bromide (1.44 mL, 2.07 g, 12.1 mmol), and Cs_2CO_3 (3.96 g, 12.1 mmol) in distilled acetone (120 mL) was stirred for 12 h and the solvent removed in vacuo. Water (100 mL) was added to the residue and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated in vacuo. Column chromatography on silica gel (PE/Et_2O 5:1 → 1:2) afforded the benzylated product (*M*,*R*)-**17b** (2.92 g, 6.01 mmol, 99%) as a yellow oil. For characterization, the amide (100 mg, 206 μmol) was crystallized from PE/Et_2O to yield (*M*,*R*)-**17b** (95.9 mg, 197 μmol, 96%) as a colorless solid. M.p. 92 °C; $[\alpha]_D^{22} = -17.3$ ($c = 1.2$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.27$ (d, $J = 6.9$ Hz, 3H; NCHCH_3), 1.76 (s, 3H; 6′-CH_3), 2.39 (s, 3H; 4′-CH_3), 4.74 (m, 2H; OCH_2), 5.00 (sept, $J =$

7.0 Hz, 1H; NC*H*CH_3), 6.47 (br d, J = 6.7 Hz, 1H; NH), 6.54 (s, 1H; ArH), 6.82 (m, 5H; ArH), 7.08–7.22 (m, 6H; ArH), 7.24–7.39 (m, 2H; ArH), 7.51 (dm, J = 7.2 Hz, 1H; ArH), 7.91 (m, 3H; ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.64, 21.43, 21.73 (4′-CH_3, 6′-CH_3, C-2″), 49.05 (C-1″), 69.79 (OCH_2), 111.21, 124.2, 124.3, 125.6, 126.2, 126.3, 126.5, 126.6, 126.9, 127.5, 127.9, 128.1, 128.3, 132.2, 132.7, 133.9, 134.2, 136.7, 139.1, 143.0, 155.7 (ArC), 168.4 (C=O); IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (NH), 1640 (C=O); MS (70 eV, EI): *m/z* (%): 485 (34) $[M]^+$, 290 (31) $[C_{20}H_{16}NO_2]^+$, 275 (46) $[C_{19}H_{15}O_2]^+$, 105 (100) $[C_8H_9]^+$, 91 (79) $[C_7H_7]^+$; $C_{34}H_{31}NO_2$ (485.6): calcd C 84.09, H 6.43, N 2.88; found C 83.89, H 6.38, N 2.88. *(P,S)*-**17b** prepared analogously from (*P,S*)-**9b**, showed identical NMR spectroscopic data.

(*P*,1″*S*)-1-(2′-Methoxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-(1‴-naphthyl)ethylamide [(*P,S*)-18b]: A suspension of the amide (*P,S*)-**10b** (125 mg, 280 μmol), MeI (19.8 μL, 45.0 mg, 312 μmol), and K_2CO_3 (170 mg, 1.23 mmol) in 2-butanone (5 mL) was refluxed for 4 h. Aqueous NH_3 (2N, 5 mL) was added at room temperature and stirred for 30 min. The reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated in vacuo. (*P,S*)-**18b** (112 mg, 244 μmol, 87%) gave colorless crystals from PE/CH_2Cl_2. M.p. 173 °C; $[\alpha]_D^{22}$ = +190.2 (c = 0.53 in CH_2Cl_2); CD: $\Delta\varepsilon_{226}$ −340, $\Delta\varepsilon_{277}$ +470; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56 (d, J = 6.7 Hz, 3H; NCHCH_3), 1.58 (s, 3H; 6′-CH_3), 2.11 (s, 3H; 4′-CH_3), 3.32 (s, 3H; 6′-OCH_3), 5.89 (quint, J = 7.3 Hz, 1H; NC*H*CH_3), 6.00/6.25 (2s, 1H each; 3′-H, 5′-H), 6.62 (br d, J = 7.6 Hz, 1H; NH), 7.05 (m, 2H; ArH), 7.22–7.50 (m, 5H; ArH), 7.70–8.00 (m, 6H; ArH); IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (NH), 1640 (C=O); MS (70 eV, EI): *m/z* (%): 459 (51) $[M]^+$, 289 (100) $[C_{20}H_{17}O_2]^+$, 274 (34) $[C_{19}H_{14}O_2]^+$, 155 (38) $[C_{12}H_{11}]^+$; $C_{32}H_{29}NO_2$ (459.6): calcd C 83.63, H 6.36, N 3.05; found C 84.01, H 6.44, N 2.93.

(*P*,1″*S*)-1-(2′-Methoxy-4′,6′-dimethylphenyl)-2-naphthoic acid 1″-(2‴,3‴,4‴-trimethoxyphenyl)ethylamide [(*P,S*)-19b]: According to the preparation for (*P,S*)-**18b** (see above) a suspension of amide (*P,S*)-**13b** (100 mg, 206 μmol) was *O*-methylated with MeI (19.8 μL, 45.0 mg, 312 μmol), and K_2CO_3 (170 mg, 1.23 mmol) in 2-butanone (5 mL). After work-up of the reaction mixture, (*P,S*)-**19b** (93.0 mg, 186 μmol, 90%) was crystallized from PE/CH_2Cl_2 as a colorless solid. M.p. 158 °C; $[\alpha]_D^{22}$ = +123.6 (c = 0.37 in CH_2Cl_2); CD: $\Delta\varepsilon_{226}$ +356, $\Delta\varepsilon_{277}$ −55.2; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (d, J = 6.9 Hz, 3H; NCHCH_3), 1.73 (s, 3H; 6′-CH_3), 2.42 (s, 3H; 4′-CH_3), 3.61, 3.83, 3.84, 3.85 (4s, 3H each; 4OCH_3), 5.22 (quint, J = 7.0 Hz, 1H; NC*H*CH_3), 6.13/6.43 (2d, J = 8.6 Hz each, 1H each; 5″-H, 6″-H), 6.51 (br d, J = 7.6 Hz, 1H; NH), 6.63/6.82 (2s, 1H each; 3′-H, 5′-H), 7.22–7.56 (m, 3H; ArH), 7.80–7.95 (m, 3H; ArH); IR (KBr): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 1670 (C=O); MS (70 eV, EI): *m/z* (%): 499 (25) $[M]^+$, 289 (100) $[C_{20}H_{17}O_2]^+$, 274 (18) $[C_{19}H_{14}O_2]^+$, 210 (44), 195 (48) $[C_{11}H_{16}NO_3]^+$; $C_{31}H_{33}NO_5$ (499.6): calcd C 74.53, H 6.66, N 2.80; found C 74.42, H 6.75, N 2.78.

Crystal-structure determinations: The single crystals were obtained from the following solvent mixtures: (*P,S*)-**16b** from PE/MTB, (*P,S*)-**17b** from PE/Et_2O, (*M,S*)-**9 b**, (*P,S*)-**18b**, and (*P,S*)-**19b** from PE/CH_2Cl_2. The cell parameters were determined on the basis of 70 reflections. The number of measured reflections reported in Table 3 were obtained with $Mo_{K\alpha}$ radiation (0.71073 Å) and $2\Theta_{max}$ = 55° (graphite monochromator). All data were collected at room temperature with a Siemens P4 diffractometer. The SHELXTL-PLUS program package[28] 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. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-116953–116957. Copies of the data can be obtained free of charge on application to CCDC, 12 Union road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

(*P*)-1-(2′-Methoxy-4′,6′-dimethylphenyl)-naphthoic acid [(*P*)-21b]: A solution of the amide (*P,S*)-**19b** (20.0 mg, 40.0 μmol) and $NaNO_2$ (200 mg, 2.89 mmol) in acetic anhydride (5 mL) was stirred at room temperature for 20 h. Acetic acid (three drops) was added and the reaction mixture stirred at 40 °C for 4 h. The reaction mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the solvent removed in vacuo. The residue was treated with KOH (300 mg), water (100 μL), and EtOH (3 mL) and heated for 5 h under reflux. Water (10 mL) was added, the reaction mixture slightly acidified with 2N HCl, and extracted with CH_2Cl_2 (3 × 10 mL). After removal of the solvent in vacuo preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH/HCO_2H 20:1:0.01) gave the acid (*P*)-**21b** (7.00 mg, 22.8 μmol, 57%) as a colorless solid. The spectroscopic data and the CD-spectrum of (*P*)-**21b** were identical to the reference material as synthesized below.

Preparation of (*P*)-21b from the menthyl ester (*P,S*)-20b: According to the preparation of (*P,S*)-**18b** (see above), a suspension of the menthyl ester (*P,S*)-**20b**[11] (90 mg, 209 μmol) was *O*-methylated with MeI (31.7 μL, 72.0 mg, 500 μmol), and K_2CO_3 (170 mg, 1.23 mmol) in 2-butanone (10 mL). After work-up of the reaction mixture, *O*-methyl protected menthyl ester (90 mg, 202 μmol, 97%) was crystallized from PE/Et_2O as a colorless solid. M.p. 115 °C; $[\alpha]_D^{20}$ = −41.2 (c = 0.35 in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.60–1.85 (m, 18H; menthyl-H), 1.76 (s, 3H; 6′-CH_3), 2.42 (s, 3H; 4′-CH_3), 3.56 (s, 3H; OCH_3), 4.89 (ddd, J = 10.7 Hz, J = 10.7 Hz, J = 4.5 Hz, 1H; CO_2CH), 6.65/6.75 (2s, 1H each; 3′-H, 5′-H),

Table 3. Crystallographic data.

	(*M,S*)-**9a**	(*P,S*)-**16b**	(*P,S*)-**17b**	(*P,S*)-**18b**	(*P,S*)-**19b**
chemical formula	$C_{27}H_{25}NO_4$	$C_{28}H_{27}NO_2 \times {}^1/_2C_5H_{12}O$	$C_{34}H_{31}NO_2$	$C_{32}H_{29}NO_2$	$C_{31}H_{33}NO_5$
molecular weight	427.4	409.5 + 44.1	485.6	459.6	499.6
crystal system	monoclinic	orthorombic	orthorhombic	orthorhombic	monoclinic
space group	$P2_1$	$P2_12_12$	$P2_12_12_1$	$P2_12_12_1$	*P21*
a [Å]	12.955(8)	15.910(1)	9.928(1)	13.342(4)	9.133(1)
b [Å]	12.437(4)	16.175(1)	10.553(2)	15.003(6)	36.673(2)
c [Å]	7.355(4)	10.376(1)	26.704(3)	12.824(6)	9.374(1)
β [°]	98.91(5)				118.29(1)
V [Å^3]	1171(1)	2670.2(1)	2797.9(3)	2567(2)	2764.7(1)
Z	2	4	4	4	4
ρ(calcd) [g cm^{-3}]	1.212	1.127	1.153	1.189	1.200
crystal size [mm]	0.35 × 0.9 × 0.15	0.55 × 0.85 × 0.2	2.3 × 1.5 × 0.7	0.45 × 0.75 × 0.3	0.6 × 0.6 × 0.05
scan mode	Wyckoff scan	ω scan	ω scan	Wyckoff scan	ω scan
Θ range [°]	1.75–27.5	1.75–30.0	1.75–27.5	1.75–30.0	1.75–30.0
hkl range	0/16, 0/16, −9/9	−20/20, −1/20, −1/13	−1/12, −1/13, −34/34	0/18, 0/21, 0/18	−11/1, −47/47, −11/12
reflections collected	2951	7811	8726	4195	15036
unique reflections	2837	6088	6422	4168	12656
refl. observed [$F > 3\sigma(F)$]	2145	3159	5216	2904	7600
lin. absorpt. coeff. [cm^{-1}]	0.8	0.7	0.7	0.7	0.8
absorption correction	ψ scan	ψ scan	ψ scan	ψ scan	ψ scan
ratio F_{obs}/parameters	7.03	12.50	15.39	9.05	10.72
R, R_W	0.049/0.038	0.076/0.065	0.063/0.071	0.064/0.050	0.068/0.043
largest diff. peak/hole [e Å^{-3}]	0.15/0.16	0.23/0.19	0.28/0.32	0.34/0.18	0.20/0.19

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7.30–7.55 (m, 3H; ArH), 7.85–7.89 (m, 2H; ArH), 8.01 (d, $J = 8.8$ Hz, 1H; ArH); IR (KBr): $\tilde{\nu} = 2940$ cm^{-1}, 2900, 2850 (CH), 1685 (C=O); MS (70 eV, EI): *m/z* (%): 444 (27) $[M]^+$, 306 (100) $[C_{20}H_{18}O_3]^+$, 288 (44) $[C_{20}H_{16}O_2]^+$, 273 (34) $[C_{19}H_{13}O_2]^+$, 185 (25); $C_{30}H_{36}O_3$ (444.60): calcd C 81.05, H 8.16; found C 80.71, H 8.28.

The *O*-methyl protected menthyl ester (35 mg, 78.8 μmol) was heated under reflux in aqueous NaOH (30%, 10 mL) and EtOH (5 mL) for 2 d. The reaction mixture was slightly acidified with 2N HCl and extracted with Et_2O (3 × 25 mL). After removal of the solvent in vacuo, preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH/HCO_2H 20:1:0.01) gave, along with unreacted starting material (13.0 mg, 29.2 μmol, 37%), the desired acid (*P*)-**21b** (14.0 mg, 45.7 μmol, 58%) as a colorless solid. M.p. 237 °C; $[\alpha]_D^{20} = +14.4$ ($c = 0.29$ in EtOH); CD (EtOH): $\Delta\varepsilon_{223} +129.5$, $\Delta\varepsilon_{238} -78.1$, $\Delta\varepsilon_{251} -5.1$, $\Delta\varepsilon_{276} -16.7$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.78$ (s, 3H; 6′-CH_3), 2.44 (s, 3H; 4′-CH_3), 3.58 (s, 3H; OCH_3), 6.70/6.80 (2s, 1H each; 3′-H, 5′-H), 7.37–7.40 (m, 2H; ArH), 7.51–7.59 (m, 1H; ArH), 7.89 (m, 2H; ArH), 8.09 (d, $J = 8.7$ Hz, 1H; ArH); IR (KBr): $\tilde{\nu} = 3200$–2300 cm^{-1} (OH), 1670 (C=O); MS (70 eV, EI): *m/z* (%): 306 (100) $[M]^+$, 288 (49) $[M - H_2O]^+$, 273 (67) $[M - CH_3O]^+$, 185 (30); $C_{20}H_{18}O_3$ (306.36): calcd C 78.41, H 5.92; found C 77.95, H 5.79.

Cyclization of the amide (*P*,*R*)-9b back to the lactone 4b: A solution of the amide (*P*,*R*)-**9b** (100 mg, 253 μmol) in acetic acid (10 mL) and hydrobromic acid (48%, 10 mL) was refluxed at 120 °C for 12 h. After cautious addition of water (25 mL), the reaction mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (3 × 25 mL), dried over $MgSO_4$, and the solvent was evaporated in vacuo. Purification of the brown residue by column chromatography on silica gel (PE/Et_2O 5:1) and crystallization from PE/Et_2O afforded the lactone **4b** (56.3 mg, 205 μmol, 81%) as a slightly yellow solid. The spectroscopic data of **4b** were identical to those of the material used for the ring-opening reactions described above.

(*M*,1″*R*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-(*N*-(1″-phenylethyl)aminomethyl)naphthalene [(*M*,*R*)-22b]: $AlCl_3$ (2.72 g, 20.4 mmol) and $LiAlH_4$ (774 mg, 20.4 mmol) were added successively at 0 °C (*Caution*: Upon addition of $LiAlH_4$ a highly exothermic reaction occurs!) to a solution of the amide (*M*,*R*)-**17b** (990 mg, 2.04 mmol) in THF (30 mL) and the reaction mixture was refluxed for 3 d. After cautious addition of water (30 mL), the reaction mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Column chromatography on deactivated silica gel (7.5 Vol-% conc. NH_3, PE/Et_2O 10:1 →3:1) afforded the amine (*M*,*R*)-**22b** (677 mg, 1.77 mmol, 87%) as a yellow oil. (*M*,*R*)-**22b** was crystallized from PE/Et_2O as a white solid (623 mg, 1.63 mmol, 80%). M.p. 129–130 °C; $[\alpha]_D^{20} = +12.1$ ($c = 1.0$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.31$ (d, $J = 6.7$ Hz, 3H; NCHC*H*$_3$), 1.59 (s, 3H; 6′-CH_3), 2.37 (s, 3H; 4′-CH_3), 3.47, 3.48 (2d, $J = 12.8$ Hz each, 2H each; CH_2N), 3.83 (q, $J = 6.7$ Hz, 1H; NC*H*CH_3), 6.68/6.86 (2s, 1H each; 3′-H, 5′-H), 7.18–7.31 (m, 7H; ArH), 7.32–7.45 (m, 1H; ArH), 7.38 (d, $J = 8.2$ Hz, 1H; ArH), 7.82 (d, $J = 8.2$ Hz, 2H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.98$, 21.27, 23.83 (4′-CH_3, 6′-CH_3, C-2″), 50.57/57.39 (NCH, CH_2N), 118.1, 123.5, 124.8, 125.8, 126.0, 126.5, 126.9, 127.2, 127.6, 127.9, 128.0, 128.6, 133.1, 133.4, 134.9, 135.2, 137.8, 138.5, 154.9 (ArC); IR (KBr): $\tilde{\nu} = 3300$ cm^{-1} (OH), 3300–2000 (NH); MS (70 eV, EI): *m/z* (%): 381 (62) $[M]^+$, 366 (36) $[M - CH_3]^+$, 276 (44) $[C_{19}H_{18}NO]^+$, 261 (100) $[C_{19}H_{17}O]^+$, 260 (64) $[C_{19}H_{16}O]^+$, 259 (58) $[C_{19}H_{15}O]^+$, 105 (44) $[C_8H_9]^+$; $C_{27}H_{27}NO$ (381.52): calcd C 85.00, H 7.13, N 3.67; found C 84.73, H 7.43, N 3.55.

(*P*)-1-(2′-Hydroxy-4′,6′-dimethylphenyl)-2-methylnaphthalene [(*P*)-7b]: A mixture of the amine (*M*,*R*)-**22b** (50 mg, 131 mmol), Pd/C (10%, 13.4 mg), and NH_4CO_2H (33mg, 524 mmol) in MeOH (10 mL) was refluxed for 3 h. After evaporation of the solvent in vacuo and column chromatography on silica gel (PE/Et_2O 10:1) the alcohol (*P*)-**7b**[27] (33.6 mg, 128 μmol, 98%) was obtained as a yellowish solid. (*P*)-**7b** (29.1 mg, 111 μmol, 85%) was obtained from PE/Et_2O as colorless crystals. M.p. 88 °C; $[\alpha]_D^{20} = -58.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.82$ (s, 3H; 6′-CH_3), 2.22/2.39 (2s, 3H each; 4′-CH_3, 2-CH_3), 4.36 (brs, 1H; OH), 6.76/6.79 (2s, 1H each; 3′-H, 5′-H), 7.35–7.48 (m, 3H; ArH), 7.48/7.85 (2d, $J = 8.2$ Hz each, 1H each; 3-H, 4-H), 7.87 (d, $J = 7.9$ Hz, 1H; 8-H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.56$, 20.00, 21.36 (2-CH_3, 4′-CH_3, 6′-CH_3), 113.3, 121.7, 123.0, 125.0, 125.4, 126.7, 128.1, 128.5, 128.8, 130.2, 132.5, 132.8, 136.0, 136.1, 137.7, 138.8, 152.9 (ArC); IR (film): $\tilde{\nu} = 3450$ cm^{-1} (OH), 2930, 2890 (CH); MS (70 eV, EI): *m/z* (%): 262 (100) $[M]^+$, 247 (46) $[M - CH_3]^+$, 232 (16) $[M - C_2H_6]^+$, 202 (13); $C_{19}H_{18}O$ (262.4): calcd C 86.49, H 6.92; found C 86.53, H 6.85.

(*M*)-2-Aminomethyl-1-(2′-hydroxy-4′,6′-dimethylphenyl)naphthalene [(*M*)-6b]: A catalytic amount of Pd/C (10%) was added to amine (*M*,*R*)-**22b** (50 mg, 131 mmol) in MeOH (5 mL) and CH_2Cl_2 (5 mL), and the reaction mixture was hydrogenated at room temperature for 3 d with H_2 (1 bar). The catalyst was removed by filtration over Celite with CH_2Cl_2 as the solvent. Column chromatography on deactivated silica gel (7.5 vol-% conc. NH_3) gave, in the order of elution: (*P*)-**7b** (7.56 mg, 28.8 μmol, 22%, eluent: PE/Et_2O 20:1) as a slightly yellow oil and (*M*)-**6b** (24.7 mg, 89.1 μmol, 68%, eluent: Et_2O/MeOH 5:1) as a gray-white powder. (*M*)-**6b**: m.p. 120 °C (decomp.); $[\alpha]_D^{20} = +48.2$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.72$ (s, 3H; 6′-CH_3), 2.37 (s, 3H; 4′-CH_3), 3.63, 3.78 (2d, $J = 12.2$ Hz each, 1H each; CH_2N), 4.06 (brs, 3H; OH, NH_2), 6.77, 6.79 (2s, 1H each; 3′-H, 5′-H), 7.28–7.39 (m, 2H; ArH), 7.40–7.49 (m, 2H; ArH), 7.84 (d, $J = 8.6$ Hz, 1H; ArH); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.98$, 21.26 (4′-CH_3, 6′-CH_3), 45.12 (CH_2N), 116.9, 123.2, 123.7, 125.8, 125.9, 126.6, 126.7, 128.0, 128.5, 133.0, 133.3, 133.9, 136.8, 138.0, 138.8, 154.8 (ArC); IR (KBr): $\tilde{\nu} = 3600$–2100 cm^{-1} (OH), 3310, 3250 (NH), 2930, 2890 (CH); MS (70 eV, EI): *m/z* (%): 277 (38) $[M]^+$, 261 (20) $[M - NH_2]^+$, 259 (100) $[C_{19}H_{15}O]^+$, 245 (28); HRMS calcd for $C_{19}H_{19}NO$: 277.147; found 277.146.

(*M*)-1-(2′-Benzyloxy-4′,6′-dimethylphenyl)-2-naphthoic acid nitrile [(*M*)-23b]: Amide (*M*,*R*)-**17b** (1.00 g, 2.06 mmol) was dissolved in thionyl chloride (25 mL) and stirred at room temperature for 12 h. Excess thionyl chloride was removed in vacuo, the residue dissolved in water (25 mL), and extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated in vacuo. Column chromatography on silica gel (PE/CH_2Cl_2 2:1 →1:3) afforded the nitrile (*M*)-**23b** (711 mg, 1.96 mmol, 95%) as a slightly yellow gummy oil. $[\alpha]_D^{23} = +21.9$ ($c = 0.29$ in chloroform); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.96$ (s, 3H; 6′-CH_3), 2.43 (s, 3H; 4′-CH_3), 4.97, 5.02 (2d, $J = 12.4$ Hz each, 1H each; OCH_2), 6.81/6.88 (2s, 1H each; 3′-H, 5′-H), 6.93–7.00 (m, 2H; ArH), 7.12–7.22 (m, 3H; ArH), 7.41–7.66 (m, 3H; ArH), 7.72 (d, $J = 8.5$ Hz, 1H; 3-H or 4-H), 7.91 (d, $J = 8.1$ Hz, 1H; 8-H), 7.94 (d, $J = 8.5$ Hz, 1H; 3-H or 4-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.55$, 21.76 (4′-CH_3, 6′-CH_3), 70.04 (OCH_2), 110.9, 111.2, 118.8, 122.5, 123.9, 126.5, 126.6, 126.8, 127.3, 127,4, 128.1, 128.3, 128.4, 132.0, 134.8, 137.1, 138.0, 139.8, 143.4, 156.3 (ArC, CN); IR (film): $\tilde{\nu} = 2900$ cm^{-1} (CH), 2210 (CN); MS (70 eV, EI): *m/z* (%): 363 (20) $[M]^+$, 348 (3) $[M - CH_3]^+$, 272 (2) $[M - C_7H_7]^+$, 259 (4) $[C_{19}H_{15}O]^+$, 91 (100) $[C_7H_7]^+$; $C_{26}H_{21}NO$ (363.46): calcd. C 85.92, H 5.82, N 3.85; found C 85.71, H 6.03, N 3.67.

(*M*)-2-Aminomethyl-1-(2′-benzyloxy-4′,6′-dimethylphenyl)naphthalene hydrochloride [(*M*)-24b·HCl]: BH_3·THF (1.0M in THF, 154 μL, 1.54 mmol) was added dropwise to a solution of the nitrile (*M*)-**23b** (56.0 mg, 154 μmol) in THF (10 mL). Water was added (10 mL) after 6 h reflux and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated in vacuo. Column chromatography on deactivated silica gel (7.5 vol% conc. NH_3, PE/Et_2O 1:1 →Et_2O) afforded the aminoalcohol (52.2 mg, 142 μmol, 92%) as a slightly yellow oil. Precipitation from PE/Et_2O 1:1 with gaseous HCl gave the hydrochloride (*M*)-**24b**·HCl (52.6 mg, 132 μmol, 85%) as a white solid. M.p. 188 °C; $[\alpha]_D^{20} = +32.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (200 MHz, CD_3OD): $\delta = 1.81$ (s, 3H; 6′-CH_3), 2.41 (s, 3H; 4′-CH_3), 3.90/4.02 (2d, $J = 14.0$ Hz each, 1H each; CH_2N), 4.87/5.01 (2d, $J = 12.2$ Hz each, 1H each; OCH_2), 6.81 (m, 2H; ArH), 6.95 (m, 2H; ArH), 7.00–7.15 (m, 3H; ArH), 7.28 (d, $J = 8.4$ Hz, 1H; ArH), 7.40 (m, 1H; ArH), 7.54 (m, 1H; ArH), 7.64 (d, $J = 8.6$ Hz, 1H; 3-H or 4-H), 7.97 (d, $J = 8.7$ Hz, 1H; 8-H), 8.03 (d, $J = 8.4$ Hz, 1H; 3-H or 4-H); ^{13}C NMR (63 MHz, CD_3OD): $\delta = 19.83$, 21.73 (4′-CH_3, 6′-CH_3), 42.67 (CH_2N), 71.66 (OCH_2), 113.5, 124.3, 125.5, 125.8, 127.0, 127.8, 128.0, 128.1, 128.7, 129.3, 129.4, 129.7, 130.0, 133.7, 135.1, 136.9, 138.2, 139.5, 141.1, 157.3 (ArC); IR (KBr): $\tilde{\nu} = 3600$–2100 cm^{-1} (NH), 2900, 2830 (CH); MS (70 eV, EI): *m/z* (%): 367 (16) $[M - HCl]^+$, 350 (52) $[M - NH_4Cl]^+$, 276 (100) $[C_{19}H_{18}NO]^+$, 259 (85) $[C_{19}H_{15}O]^+$, 91 (49) $[C_7H_7]^+$; HRMS calcd for $C_{26}H_{25}NO$: 367.194; found 367.194.

Debenzylation of (*M*)-24b·HCl to (*M*)-6b: BCl_3 (1.0M in hexane, 5.20 mL, 5.20 mmol) was added at 0 °C to a solution of the amine hydrochloride (*M*)-**24b**·HCl (700 mg, 1.73 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 40 min and then carefully hydrolyzed with water (30 mL), made alkaline with K_2CO_3, and extracted with CH_2Cl_2 (3 × 30 mL). The

combined organic layers were dried over $MgSO_4$ and the solvent evaporated in vacuo. Column chromatography on deactivated silica gel [7.5 vol% conc. NH_3, 1) PE/Et_2O 1:1 (for removal of some rapidly eluting by-products), 2) acetone] and thorough evaporation of the solvent gave the amino alcohol (*M*)-**6b** (470 mg, 1.69 mmol, 98%) as a slightly yellow solid.

(*M*)-2-Aminomethyl-1-(2′-hydroxy-4′,6′-dimethylphenyl)-5,6,7,8-tetrahydronaphthalene [(*M*)-25b]: A suspension of the nitrile (*M*)-**23b** (400 mg, 1.21 mmol), conc. HCl (100 μL), and Pd/C (10%, 400 mg) in MeOH (30 mL) was hydrogenated with H_2 (4 bar) at room temperature for 3 d. Evaporation of the solvent in vacuo, column chromatography on deactivated silica gel (7.5 vol% conc. NH_3, PE/acetone 5:1), and crystallization from PE/CH_2Cl_2 afforded the phenyl-aminomethyltetralin (*M*)-**25b** (308 mg, 1.10 mmol, 91%) as a white powder. M.p. 113–115 °C; $[\alpha]_D^{20} = -54.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.62-1.78$ (m, 4H; 6-CH_2, 7-CH_2), 1.82 (s, 3H; 6′-CH_3), 2.17 (m, 2H; 5-CH_2 or 8-CH_2), 2.20–2.70 (br s, 3H; NH_2, OH), 2.32 (s, 3H; 4′-CH_3), 2.81 (m, 2H; 5-CH_2 or 8-CH_2), 3.43/3.63 (2 d, $J = 11.9$ Hz each, 1H each; CH_2N), 6.71/6.74 (2 s, 1H each; 3′-H, 5′-H), 7.09, 7.11 (2 d, $J = 7.9$ Hz each, 1H each; 3-H, 4-H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.71$, 21.20 (4′-CH_3, 6′-CH_3), 22.71, 23.20 (C-6, C-7), 27.20, 29.99 (C-5, C-8), 44.70 (CH_2N), 116.6, 123.5, 124.8, 126.1, 126.6, 129.1, 136.4, 136.7, 137.1, 137.8, 138.4, 153.4 (ArC); IR (KBr): $\tilde{\nu} = 3320$ cm^{-1}, 3260, 3500–2200 (NH_2, OH), 2910, 2840 (CH); MS (70 eV, EI): *m/z* (%): 281 (45) $[M]^+$, 264 (100) $[M - NH_3]^+$, 263 (45) $[M - NH_4]^+$, 249 (63) $[M - CH_6N]^+$; $C_{19}H_{23}NO$ (281.40): calcd. C 81.10, H 8.24, N 4.98; found C 80.68, H 8.16, N 4.70. No hydrogenation was obeserved without conc. HCl and 1 bar H_2 pressure.

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