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Atropodiastereoselective Cleavage of Configurationally Unstable Biaryl Lactones with Amino Acid Esters[‡]

Gerhard Bringmann,*[a] Heiko Scharl,[a] Katja Maksimenka,[a] Krzysztof Radacki,[b] Holger Braunschweig,[b] Peter Wich,[a] and Carsten Schmuck[a]

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An improved procedure for the stereoselective synthesis of axially chiral biaryl systems is described, by atroposelective ring cleavage of configurationally unstable lactone-bridged biaryls with amino acid esters as inexpensive and efficient chiral N-nucleophiles. Starting with configurationally unstable lactones of type **2**, which are readily accessible by intramolecular Heck reaction of the respective bromo esters **1**, the atroposelective ring cleavage succeeds by using a broad variety of amino acid esters of type **5**, leading to configuratively stable axially chiral biaryl amides **3** in good chemical yields and excellent diastereomeric ratios of up to > 99.5:0.5. The axial configurations of the products were assigned by quantum chemical CD calculations and by X-ray structure analysis. From the diastereomerically pure ring cleavage products, the chiral auxiliary can be eliminated, e.g., by treatment with sodium nitrite to give the respective nitrogen-free biaryl enantiomers of type **9**, with merely axial chirality. By using a standard solid-phase Fmoc strategy, this approach allows to incorporate the biaryl fragment into peptide strands.

Introduction

The atroposelective construction of rotationally hindered biaryl molecules – among them, axially chiral bioactive natural products[2] or catalysts and reagents for asymmetric synthesis[3] – is an attractive goal in organic chemistry.[1,4] Besides the direct, "classical" approach to achieve the biaryl bond formation with immediate asymmetric induction, novel strategies have emerged more recently in which these two formal goals are achieved consecutively: In a first step the axis is built up non-stereoselectively, to give a biaryl that is either rotationally hindered, but achiral (since symmetric), or chiral, but configurationally unstable, and then, in a second step, it is atroposelectively converted into a configurationally stable, stereochemically homogeneous axis.[1] Among these novel strategies, the "lactone method",[5] as developed by our group, has proven to be particularly successful.[6,7] Key intermediates in this concept are configurationally unstable biaryl lactones of type **2** (Scheme 1), which can be obtained by intramolecular Heck coupling of esters of type **1**, in which the two aryl portions (here a bromonaphthoic acid and a phenol) are prefixed to each other. These lactones **2** are not flat, but, depending on the size of the residue R next to the biaryl axis, more or less helically distorted and thus chiral, so that they exist in two enantiomeric forms, (*P*)-**2** and (*M*)-**2**,[8] which interconvert at room temperature more or less rapidly. Out of this enantiomeric equilibrium, lactone **2** can be cleaved atropodiastereoselectively by using chiral N- or O-nucleophiles,[9–11] or atropo-enantioselectively, by reduction with chiral hydride transfer reagents,[12] to give configurationally stable biaryls of type **3** or **4**. Because many of these ring-cleavage nucleophiles are available in both enantiomeric forms, the "lactone concept" permits the directed, atropodivergent synthesis of either of the two possible atropoenantio- or -diastereomers, with *M*- or *P*-configuration, from the same "late" precursor, i.e., the configuratively unstable lactone-bridged compound **2**. The method even includes the possibility of re-using undesired atropisomeric by-products by recyclization back to the lactone **2**,[6,10,11] and has shown its applicability in the total synthesis of numerous axially chiral natural products[13] and reagents.[14]

Among the chiral reagents for the atroposelective lactone cleavage, only two types of N-nucleophiles have so far been used: On the one hand, a series of alkali-metal-activated primary 1-arylethylamines as introduced by our group,[10] like 1-phenylethyl or 1-naphthylethylamine, and, on the other hand, D-valinol, i.e., a chiral α-amino alcohol, by Suzuki et al., as applied in the total synthesis of benanomycin B.[15] In this paper, we report on the use of easily available α-amino acid esters as chiral N-nucleophiles in the atropodiastereoselective opening of configurationally unstable lactones to generate configuratively stable biaryls in high

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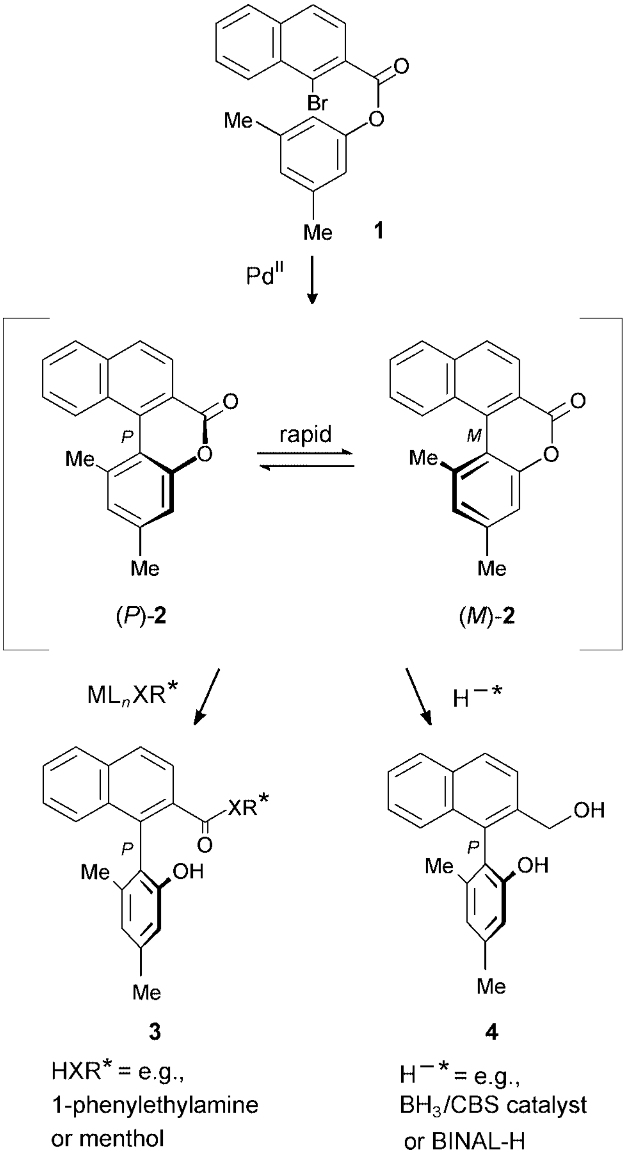
[a] Institut für Organische Chemie, Universität Würzburg,
Am Hubland, 97074 Würzburg, Germany
Fax: +49-931-888-4755
E-mail: bringman@chemie.uni-wuerzburg.de
[b] Institut für Anorganische Chemie, Universität Würzburg,
Am Hubland, 97074 Würzburg, Germany



Scheme 1. Basic principle of the "lactone concept" for the atroposelective synthesis of axially chiral biaryls.

yields and excellent asymmetric inductions. Exemplarily for L-valine methyl ester (**5a**), the influence of the activating base on the atropodiastereoselective cleavage of lactone **2** has been investigated, followed by an exploration of the influence of the side chain and the ester group of the amino acid esters on the diastereomeric ratios and optimal conditions for the atropodiastereoselective ring-opening reaction are described, as well as the amidolysis of amide **3** to give the enantiopure biaryl **9**. The method also opens the way to incorporate the biaryl unit into a peptide strand using solid phase synthesis, thus introducing a chiral turn into an otherwise linear peptide strand giving rise to tweezer-type structures. Similar peptide tweezers, yet derived from nonchiral turn elements, have been proven useful as efficient peptide receptors in the past.[16] An axially biaryl unit might improve the binding features of tweezer receptors both, in terms of affinity (due to its hydrophobic shielding) and stereoselectivity (due to its stereogenic nature).

Results and Discussion

Aminolysis of Lactone 2 with L-Valine Methyl Ester (5a)

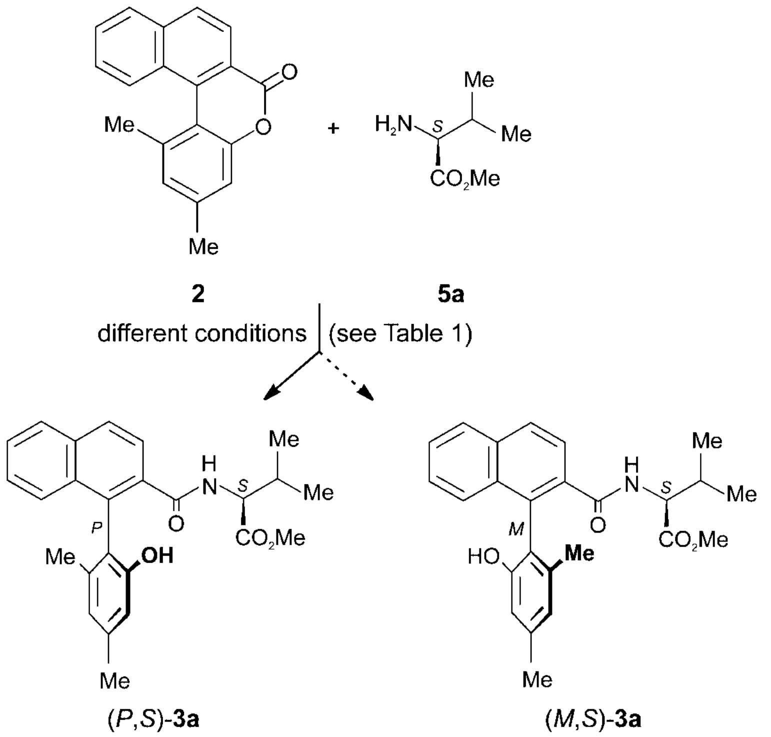
In previous investigations, the lactone **2**[17] had proven to be a useful model compound for atroposelective cleavage reactions.[10–12] For first exploratory investigations on this bridged biaryl, L-valine methyl ester (**5a**) was chosen as the N-nucleophile, activated by a series of different bases, such as Cs_2CO_3, K_2CO_3, Na_2CO_3, or $(NH_4)_2CO_3$ (data for the latter three not shown). For L-valine methyl ester (**5a**), Cs_2CO_3 proved to be a good activating reagent to convert **2** into the desired amide **3a** (Table 1, Entries 1 and 2). By stirring **2** and **5a** at room temperature with Cs_2CO_3 in ethyl acetate (EtOAc), a 86:14 mixture of two atropodiastereomers, (*P*,*S*)- and (*M*,*S*)-**3a**, was isolated, yet only in 27% yield. In toluene as the solvent, a higher chemical yield (80%) was obtained, but with a significant decrease of the diastereomeric ratio (*dr*) to 70:30 (Scheme 2).

Table 1. Conditions for the aminolysis of **2** with **5a**.

Entry	Conditions	Yield [%]	*dr* (*P*,*S*):(*M*,*S*)
1	5 equiv. Cs_2CO_3, EtOAc, 23 °C, 72 h	27	86:14
2	5 equiv. Cs_2CO_3, toluene, 23 °C, 72 h	80	70:30
3	1 equiv. *n*BuLi, THF, 0 °C, 14 h	–	–
4	1 equiv. LDA, THF, 0 °C, 14 h	–	–
5	4 equiv. LiH, THF, 0 °C, 14 h	24	84:16
6	2 equiv. NaH, THF, 0 °C, 3 h	80	94:6
7	2 equiv. KH, THF, 0 °C, 3 h	76	>99.5:0.5[a]

[a] Only one diastereomer detectable by NMR measurement.

In order to improve the diastereomeric ratio and to reduce the reaction time, we investigated the use of stronger bases for the activation of L-valine methyl ester (**5a**), see Table 1, Entries 3–7. Treatment of **5a** with *n*BuLi or LDA with subsequent addition of the lactone **2**, however, did not lead to the desired product **3a** (Entries 3 and 4). The use of alkali metal hydrides such as LiH, NaH, or KH (Entries 5–7), by contrast, did permit to obtain compound **3a**. In an attempt to change the above standard procedure of first activating the nucleophile before adding the lactone by doing the activation in situ, a solution of lactone **2** and the amino acid ester **5a** in THF was treated with small portions of the alkali metal hydrides until complete conversion was detected (controlled by TLC). Under these conditions, the amino acid ester **5a** was apparently deprotonated by the metal hydrides to generate the corresponding metal amides, which then immediately attacked the lactone **2** in situ to generate amide **3a**. While the reaction with LiH as the activating base led to results similar to that with Cs_2CO_3 in EtOAc (24% yield, 84:16 *dr*), the higher homologs, NaH and KH, effected an increase of the diastereomeric ratio. Thus, in-situ treatment of **5a** with NaH gave the desired product with a high yield of 80% and a very good diastereomeric ratio of 94:6 (Entry 6). With KH as the activating base, the *P*,*S*-product **3a** was even obtained as the only diastereomer (Entry 7) in 76% yield, revealing a

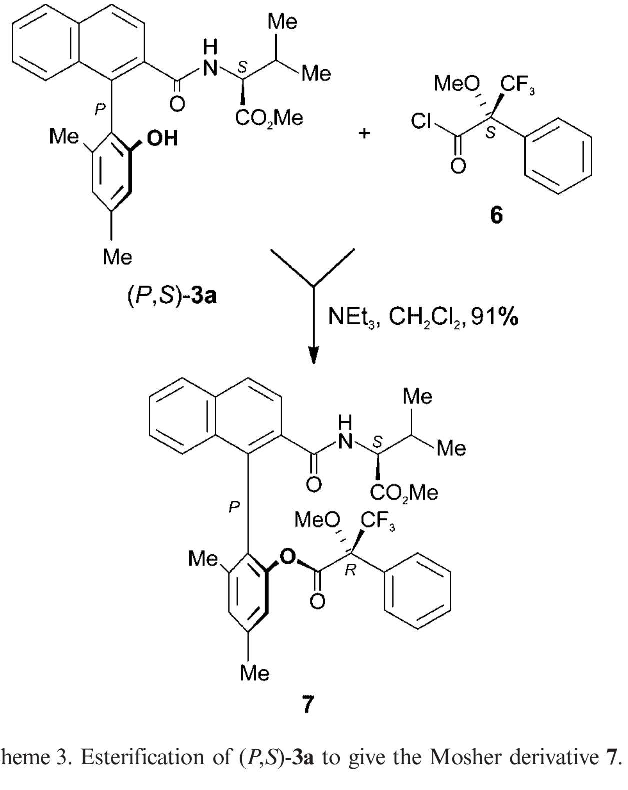


Scheme 2. Aminolysis of **2** with L-valine methyl ester (**5a**).

significant dependence of the diastereomeric ratio (*P*,*S*)-**3a**:(*M*,*S*)-**3a** from the activating metal. The diastereomeric ratios were determined by ^{1}H NMR after workup.

Enantiomeric Purity of the Ring Cleavage Products

Due to the in part very basic reaction conditions, a stereochemical analysis was required to test whether the amino acid derivatives **5** had remained stereochemically intact or whether partial or total racemization and thus loss of stereochemical information had taken place. This would – regardless of possibly even high observed diastereoselectivities – have led to racemic or partially racemic ring cleavage products. Thus, exemplarily for the main product (*P*,*S*)-**3a**, obtained by the cleavage reaction of **2** with **5a** and KH as the activating agent, an esterification with (*S*)-Mosher acid chloride (MTPA chloride, **6**)[18] was performed, leading to the (*R*)-Mosher ester **7** in 91 % yield. The fact that **7** showed only one set of signals both, in the ^{1}H and ^{13}C NMR spectra, indicated that (*P*,*S*)-**3a** was enantiomerically pure and thus no racemization had taken place during the ring cleavage process (Scheme 3).



Scheme 3. Esterification of (*P*,*S*)-**3a** to give the Mosher derivative **7**.

Assignment of the Absolute Axial Configurations

The attribution of the absolute axial configuration to the respective atropisomer of **3a** succeeded by means of quantum chemical CD calculations, by X-ray crystallographic methods, and by chemical transformations.

a) By Quantum Chemical CD Calculations: As expected from previous cases,[19] the measured CD spectra of the two atropodiastereomers of **3a** showed an almost opposite, nearly enantiomer-like behavior, indicating a dominating influence of the axial chirality on the CD spectrum in comparison to the stereogenic center. For a stereochemical assignment, quantum chemical CD calculations were carried out for both atropodiastereomers, (*P*,*S*)-**3a** and (*M*,*S*)-**3a**, independently. Such theoretical CD investigations constitute a valuable tool in the stereochemical analysis of novel

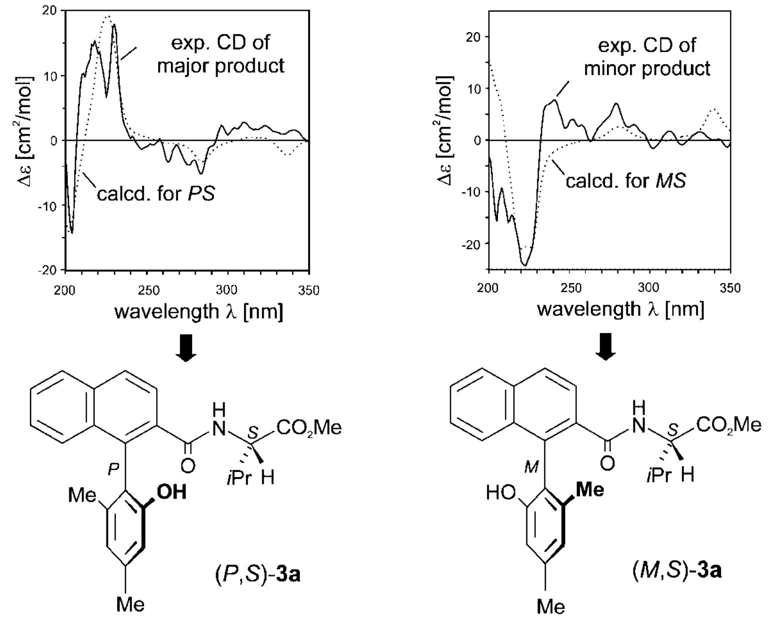


Figure 1. Assignment of the absolute axial configuration of the major and minor ring cleavage products of **2**, by comparison of the measured CD spectra with the ones theoretically predicted for the two atropodiastereomers, (*P*,*S*)-**3a** and (*M*,*S*)-**3a**.

chiral compounds.[20] In the case of the *P*-atropisomer of **3a**, the AM1[21] based conformational analysis resulted in seven minimum conformers within an energetic range of 3 kcal/mol above the global minimum, while for the *M*-diastereomer of **3a** only five geometries besides the global minimum were found. The single CD and UV spectra for these structures were semiempirically calculated using the CNDO/S-CI[22] approach and then added up according to the Boltzmann statistic to give the overall CD and UV curves. The comparison of the measured UV spectrum with the predicted ones revealed that the calculated transition energies were underestimated, and thus for reasons of com-

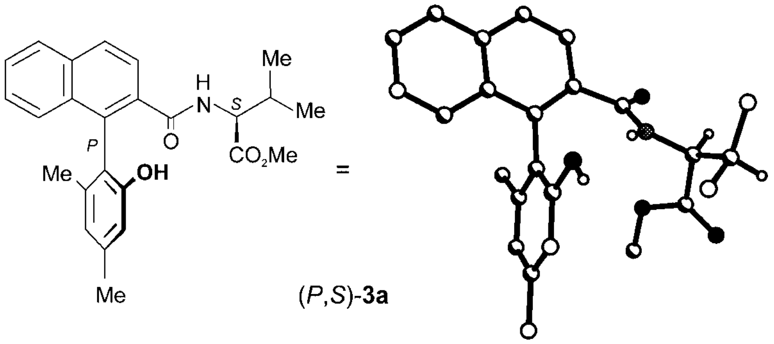
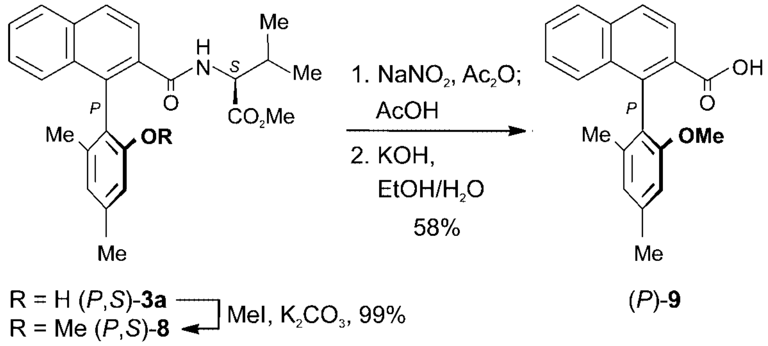


Figure 2. Crystal structure of (*P*,*S*)-**3a**.



Scheme 4. Exemplarily for (*P*,*S*)-**3a**: Elimination of the chiral auxiliary; simultaneously further, chemical proof of axial configuration, by transformation into the stereochemically known[10] phenylnaphthoic acid (*P*)-**9**.

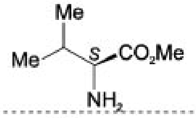
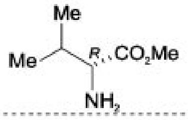
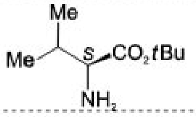
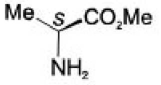
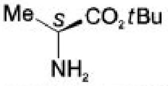
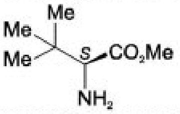
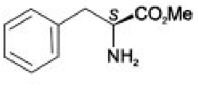
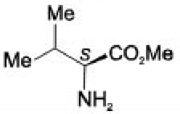
paring the theoretical UV and CD spectra were blue-shifted by 10 nm. As seen in Figure 1, the overall CD spectrum thus predicted for (*P*,*S*)-**3a** matched very well with the CD curve measured for the main product, while the experimental CD spectrum for the minor product showed a good agreement with the curve calculated for (*M*,*S*)-**3a**.

b) By X-ray Structure Analysis: The axial configuration was further investigated by an X-ray diffraction analysis of crystals obtained from the chromatographically more rapid atropisomer, i.e., the main product (*P*,*S*)-**3a** from the cleavage of **2** with L-valine methyl ester. The X-ray structure analysis (see Figure 2) fully confirmed the constitution and the relative configuration and thus, given the known absolute L-configuration in the amino acid part, also the absolute axial configuration, again fully corroborating the previous *P*,*S*-configurational assignment above. The crystallographic data are given in Table 3 in the Exp. Sect.

Preparation of N-Free Biaryls by Cleavage of the Chiral Auxiliary

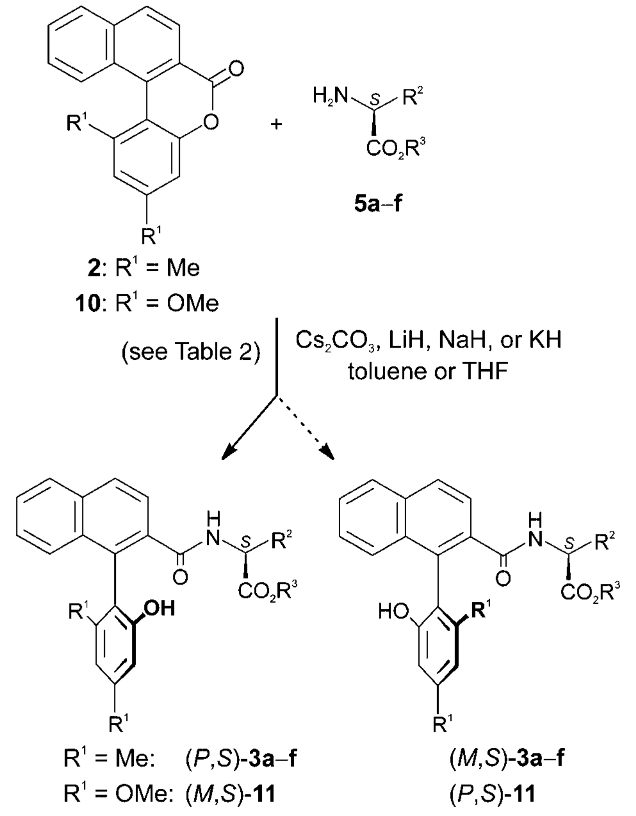
For a more general applicability of the method, beyond the possibility of synthesizing axially chiral amino acid derivatives, the chiral auxiliary was split off, based on a procedure published earlier by our group.[10] Thus, after protection of the phenolic oxygen function of (*P*,*S*)-**3a** to give (*P*,*S*)-**8** (to prevent re-cyclization back to the lactone) ni-

Table 2. Aminolysis of **2** with amino acid esters **5**.

Entry	Lactone	Amino acid ester **5**		Amide **3**	Base[a] Cs_2CO_3[b]	 LiH[c]	 NaH[c]	 KH[c]
					dr [*P*:*M*][d] (yield [%])[e]			
1	**2**		**5a**	**3a**	70:30 (80)[f]	84:16 (24)	94:6 (80)	>99.5:0.5 (92)
2	**2**		*ent*-**5a**	*ent*-**3a**	–	18:82 (58)	7:93 (56)	–
3	**2**		**5b**	**3b**	74:26 (98)[g]	>99.5:0.5 (41)	>99.5:0.5 (58)	>99.5:0.5 (77)
4	**2**		**5c**	**3c**	60:40 (18)[f]	77:23 (36)	95:5 (57)	>99.5:0.5 (16)
5	**2**		**5d**	**3d**	>99.5:0.5 (45)[g]	>99.5:0.5 (99)	>99.5:0.5 (84)	>99.5:0.5 (91)
6	**2**		**5e**	**3e**	73:27 (31)[g]	70:30 (22)	>99.5:0.5 (24)	>99.5:0.5 (46)
7	**2**		**5f**	**3f**	41:59 (30)[f]	82:18 (81)	63:37 (39)	78:22 (13)
8	**10**		**5a**	**11**	25:75[h] (45)[f]	33:67[h] (16)	1:99[h] (17)	14:86[h] (39)

[a] Bases used for activation of the amino acid esters. [b] 5 Equiv. of Cs_2CO_3. [c] 2–4 Equiv. of the respective metal hydrides. [d] Determined by ^1H NMR; assignment of the axial configurations by CD comparison with (*P*,*S*)-**3a**, (*M*,*S*)-**3a**, and (*P*,*S*)-**3d**. [e] Yields of the isolated diastereomeric mixtures after workup. [f] Reaction at room temperature. [g] Reaction at 50 °C. [h] Configuration assigned by analogy to the ring cleavage of **2** with **5a** and by CD comparison with previous ring cleavage products using other N-nucleophiles;[10] mind that, despite the same stereo-orientation of the main product in the cleavage of **2** with **5a**, the descriptors are opposite for reasons of the Cahn–Ingold–Prelog formalism (OMe > Me).

trite-induced cleavage of the amide function in acetic anhydride, with subsequent hydrolysis with KOH, furnished the naphthoic acid (*P*)-**9** in 58% yield (Scheme 4). This product was found to be fully identical, in particular with respect to its chiroptical data, with material synthesized earlier from stereochemically known precursors,[10] thus confirming, once again, the above stereochemical assignment of (*P*,*S*)-**3a** at the axis.



Scheme 5. Lactone cleavage of **2** with different amino acid esters **5**.

Variation of the N-Nucleophile

On the basis of the promising results of the lactone cleavage with L-valine methyl ester presented above, the diastereoselective ring opening of **2** was performed with a whole series of other amino acid derivatives, **5b–h**, to investigate the influence of the size of the ester group and the side chain on the chemical yields and asymmetric inductions (Table 2, Scheme 5). In most cases again excellent results were obtained; in particular with KH as the base and mostly even with NaH. The virtually exclusive formation of only one of the atropodiastereomers even made it necessary to prepare the other one by intentionally reducing the selectivity, to provide it as a reference. For this purpose, all of the reactions were also performed with Cs_2CO_3, because this base had given atropisomeric mixtures in the above described investigations.

For a first exploration of the size of the ester group, **5a** was replaced by its bulky *tert*-butyl analog, **5b** (Entry 3). Using Cs_2CO_3 as the activating base, only a slight increase of the diastereomeric ratio (up to 74:26) was observed. A significantly larger effect of the ester group was obtained with alkali metal hydrides as the base. With Na and K as the bulkier counter-cations, i.e., with NaH or KH, only one diastereomer was obtained, viz. (*P*,*S*)-**3b**, when using **5b** as the N-nucleophile. In this case, even the smaller lithium ion permitted complete asymmetric induction, delivering (*P*,*S*)-**3b** as the only diastereomer, albeit in a lower yield.

Decreasing the size of the side chain from the isopropyl group in L-valine down to the methyl group in the L-alanine derivative **5c** (Entry 4) gave results similar to those obtained for the valine derivative **5a**. Like for **5a** the best results for **5c** were obtained with KH as the base, again giving only one single diastereomeric product, yet here with a very low yield of only 16%. The use of the *tert*-butyl ester **5d** of alanine (Entry 5), however, resulted in perfect asymmetric inductions with any of the bases employed, even for Cs_2CO_3, the best chemical results being obtained with LiH, giving the *P*-configured biaryl as the only product in a quantitative yield.

Like in the case of (*P*,*S*)-**3a** (see above), compound (*P*,*S*)-**3d** gave crystals suited for an X-ray structure analysis (see Figure 3). The crystal structure, as given in Figure 3, unambiguously confirmed the *P*,*S*-configuration assigned. The crystallographic data of (*P*,*S*)-**3d** are given in Table 3 in the Exp. Sect.

Likewise excellent results were obtained by using L-*tert*-leucine in the form of its methyl ester **5e**, again giving complete asymmetric inductions in the case of NaH and KH as

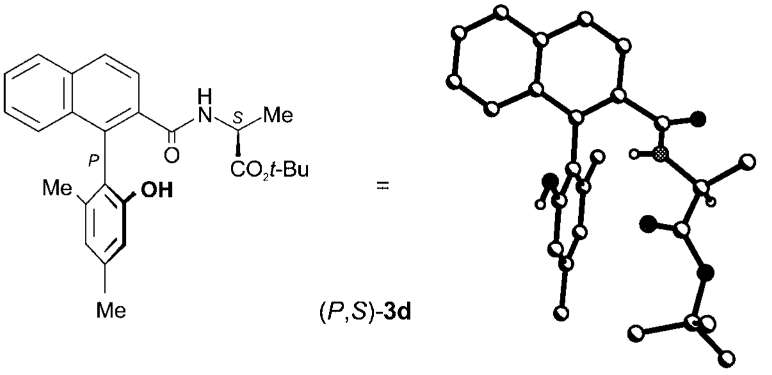


Figure 3. Crystal structure of (*P*,*S*)-**3d**.

the base, yet with low chemical yields, the best one being attained with KH (Entry 6).

Replacing the aliphatic amino acids alanine, valine, or *tert*-leucine used above, by an aromatic one, viz. L-phenylalanine as its methyl ester **5f**, gave **3f**, with results inferior to those obtained for the other amino acid derivatives (Entry 7).

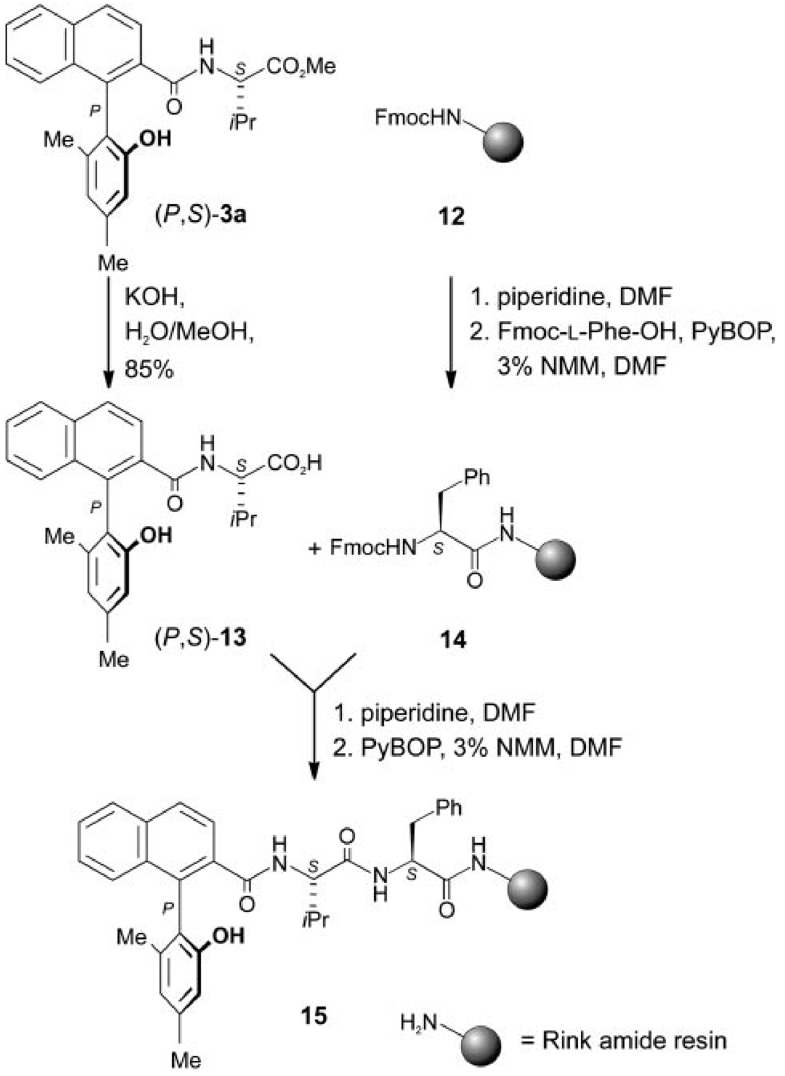
Exemplarily for the valine methyl ester, the D-configured analog, *ent*-**5a**, was used (Entry 2), expectedly leading to the other enantiomer, i.e., with *M*,*R* instead for the usual *P*,*S*-configuration, showing the possibility of atropodivergently attaining any desired configuration at the biaryl axis, as previously also demonstrated for other N-,[10] but also O-[9,11] and H-nucleophiles.[12]

Likewise exemplarily for the 'standard' valine-derived N-nucleophile **5a**, a related, but bismethoxy-substituted biaryl lactone, **2b**, was used as the substrate, giving similar results as compared to those obtained for **2a** under the same conditions (Entry 8).

The above lactone opening reactions with L-alanine *tert*-butyl ester **5d** (Entry 5) vs. L-*tert*-leucine methyl ester **5e** (Entry 6), clearly showed that formal L- or D-configuration of the amino acid esters **5a**–**f** is responsible for the direction of the asymmetric induction at the biaryl axis of **3a**–**f**. Thus, even by exchanging the sizes of the groups of the side chain and the ester function from methyl to *tert*-butyl or vice versa, and thereby reversing the steric demand, only a slight difference in the stereoselectivity occurred, but no change of the axial conformation (see Entries 5 vs. 6). This can be explained by the close proximity of the amino acid residue R^2 to the nucleophilic nitrogen atom (and thus to the stereocenter) and hence its effect on the formation of the axial configuration, while the (more remote) alkyl portion R^3 of the ester group had no major influence on the formation of the new axial stereocenter (Entries 1 vs. 3).

Incorporation of the Biaryl into a Solid-Phase Peptide Synthesis

The successful ring-opening of lactone **2** with amino acid based N-nucleophiles provides a most promising chiral



Scheme 6. Incorporation of the biaryl (*P*,*S*)-**3a** into a polymer-supported peptide strand.

building block (*P*,*S*)-**3a**, which might prove useful for the synthesis of chiral tweezer receptors for the stereoselective binding of peptides in aqueous solvents. A similar biaryl unit is for example a key feature of the antibiotic vancomycin, which selectively binds the L-Lys-D-Ala-D-Ala fragment of a bacterial peptidoglycan.[23] We therefore tested the applicability of the free acid (*P*,*S*)-**13**, as derived from methyl ester (*P*,*S*)-**3a** by basic cleavage (0.4 N KOH in MeOH/H_2O, 1:6) for classical Fmoc solid-phase peptide synthesis. For this purpose, Fmoc-protected L-phenylalanine (Fmoc-L-Phe-OH) was coupled to Rink amide resin using PyBOP [(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate] as the coupling reagent (Scheme 6). After deprotection of the Fmoc group (20% piperidine in DMF), the chiral biaryl acid (*P*,*S*)-**13** was coupled to the free amino group on the solid support using the same protocol as before but with only 1.5 equiv. of (*P*,*S*)-**13** instead of the 2.5 equiv. of acid normally used. The coupling was again performed with PyBOP in DMF containing 3% NMM (reaction time 20 h). A negative Kaiser test showed complete reaction under these conditions, no remaining, unreacted free amino groups could be detected. Hence, the biaryl unit can be incorporated into a peptide strand using a standard Fmoc protocol.

Using this approach, we are currently preparing tweezer receptors. Their syntheses and binding features will be reported in the near future.

Conclusions

In this paper, we have shown that configuratively unstable biaryl lactones can be ring-cleaved most efficiently with respect to asymmetric inductions and, in most cases, also chemical yields, by using simple, easily available amino acid esters as the N-nucleophiles. The best results were obtained with the *tert*-butyl ester **5d** of alanine, giving extremely high asymmetric inductions for all bases used, and, in the case of LiH as the base, in a quantitative yield. If required, the chiral N-nucleophile can subsequently be split off, giving nitrogen-free atropoenantiomerically pure biaryls, which, due to the commercial availability of both amino acid enantiomers, can thus be synthesized in either atropoenantiomeric form. The method is a valuable complementation of previously described ring cleavage reactions using H-, O-, or other N-nucleophiles. The application of this methodology for the directed construction of naturally occurring biaryl compounds or synthetic tools is in progress. As an example, we could show that the amino acid part in (*P*,*S*)-**3a** now allows to incorporate the biaryl fragment into a growing peptide strand using a standard Fmoc solid phase synthesis on Rink amide resin. By this strategy, new tweezer receptors for peptides with the biaryl as a stereogenic turn element are currently synthesized and will be reported in due course.

Experimental Section

General Section: Melting points were measured with a Reichert–Jung Thermovar and are uncorrected. IR spectra were taken with a Jasco FT-IR 460 and are reported in wave numbers (cm^{-1}). Optical rotation were measured with a Perkin–Elmer P 1024 polarimeter. CD spectra were recorded at room temperature in MeOH with a Jasco J-715 spectropolarimeter. NMR spectra were taken either with a Bruker AC 250 or a Bruker AV 400 at room temperature in $CDCl_3$. The chemical shifts δ are given on the ppm scale with the proton signal of the deuterated solvent as the internal reference for ^1H and ^{13}C NMR spectroscopy. The coupling constants are given in Hertz (Hz). Mass spectra were determined with a Finnigan MAT 8200 at 70 eV in the EI mode and with a micrOTOF focus of Bruker Daltonik GMbH in the ESI mode. For TLC, precoated silica gel 60 F254 plates (5 × 10 cm, Merck) were used. HPLC analyses were performed on a Chromolith Performance RP 18e column using a Jasco MD 1510 detector and an ELSD Sedex 75 light-scattering detector with UV detection at 254 nm. Method (A: water + 0.05% TFA; B: MeCN + 0.05% TFA): 0.5 min 10% B with 3 mL min^{-1} flow; 5 min 50% B with 5 mL min^{-1} flow; 9 min 100% B with 5 mL min^{-1} flow; 13 min 100% with 6 mL min^{-1} flow. The spots were detected under UV light. THF was distilled from potassium directly prior to use. Petroleum ether (PE) and EtOAc were distilled before being used for chromatography.

Synthesis Section: General Procedure for the Aminolysis of Lactone 2 with Amino Acid Esters 5 with Cs_2CO_3: Cs_2CO_3 (910 µmol) was added to a solution of lactone **2** (182 µmol) and **5** (273 µmol) in toluene (5 mL), and the mixture was stirred for 16 h at 50 °C or 40 h at room temperature. The solution was concentrated and chromatographed (SiO_2, PE/EtOAc as the eluent) to give the desired product **3**.

General Procedure for the Aminolysis of Lactone 2 with Alkali Metal Activated Amino Acid Esters 5: LiH, NaH, or KH (2–4 equiv.) was added at 0 °C in small portions to a solution of lactone **2** (73 µmol) and amino acid ester **5** (109 µmol) in THF (1 mL) until the initial compound was fully converted (3–16 h, TLC control). Then an aqueous saturated solution of NH_4Cl (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2, PE/EtOAc) to give the desired product **3**.

Methyl (*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-methylbutanoate [(*P*,*S*)-3a]: Colorless solid. R_t (HPLC) = 4.82 min. M.p. 79 °C. CD (MeOH): λ_{max} ($\Delta\varepsilon$) = 204 (–14), 218 (+15), 230 (+18), 283 (–5.1) nm. $[\alpha]_D^{20}$ = +37 (*c* = 0.12, MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.64 (d, ^3J = 6.8 Hz, 3 H, CH_3), 0.73 (d, ^3J = 6.8 Hz, 3 H, CH_3), 1.87 (s, 3 H, CH_3), 1.94–2.03 (m, 1 H, CH), 2.35 (s, 3 H, CH_3), 3.68 (s, 3 H, OCH_3), 4.58 (dd, ^3J = 8.6 Hz, ^3J = 4.8 Hz, 1 H, CH), 6.45 (d, ^3J = 8.5 Hz, 1 H, NH), 6.77 (d, ^4J = 0.5 Hz, 1 H, Ar-H), 6.82 (d, ^4J = 0.8 Hz, 1 H, Ar-H), 7.38 (dt, ^3J = 8.4 Hz, ^4J = 0.7 Hz, 1 H, Ar-H), 7.42 (ddd, ^3J = 8.5 Hz, ^3J = 6.4 Hz, ^4J = 1.3 Hz, 1 H, Ar-H), 7.55 (ddd, ^3J = 8.2 Hz, ^3J = 6.5 Hz, ^4J = 1.5 Hz, 1 H, Ar-H), 7.91 (d, ^3J = 8.1 Hz, 1 H, Ar-H), 7.96 (d, ^3J = 9.1 Hz, 1 H, Ar-H), 7.99 (d, ^3J = 8.6 Hz, 1 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 17.21 (CH_3), 18.58 (CH_3), 19.75 (CH_3), 21.24 (CH_3), 31.11 (CH), 52.00 (OCH_3), 57.65 (CH), 115.20 (CH), 121.44 (C), 123.88 (CH), 125.41 (CH), 126.23 (CH), 127.34 (CH), 127.50 (CH), 128.26 (CH), 128.95 (CH), 131.31 (C), 132.23 (C), 133.28 (C), 134.66 (C), 138.15 (C), 139.87 (C), 153.38 (C), 168.54 (C), 172.06 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3326(m), 3062 (w), 2965 (m), 2923 (m), 1740 (s), 1626 (s), 1613 (s) 1542 (s), 1316 (s), 1264 (m), 1030 (s) cm^{-1}. MS (EI = 70 eV): *m*/*z* (%) = 405.2 (15) [M^+], 274 (100), 231 (12), 202 (12), 72 (11). $C_{25}H_{27}NO_4$ (405.49): calcd. C 74.05, H 6.71, N 3.45; found C 74.17, H 6.97, N 3.40.

Methyl (*M*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-methylbutanoate [(*M*,*S*)-3a]: Colorless solid. R_t (HPLC) = 5.22 min. M.p. 84 °C. CD (MeOH): λ_{max} ($\Delta\varepsilon$) = 205 (–16), 223 (–24), 241 (+7.7), 279 (+7.1) nm. $[\alpha]_D^{20}$ = +55 (*c* = 0.30, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.64 (d, ^3J = 6.8 Hz, 3 H, CH$_3$), 0.70 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 1.82 (s, 3 H, CH$_3$), 1.95–2.01 (m, 1 H, CH), 2.39 (s, 3 H, CH$_3$), 3.67 (s, 3 H, OCH$_3$), 4.59 (dd, ^3J = 8.6 Hz, ^4J = 4.8 Hz, 1 H, CH), 6.53 (d, ^3J = 8.5 Hz, 1 H, NH), 6.75 (d, ^4J = 0.5 Hz, 1 H, Ar-H), 6.79 (d, ^4J = 0.6 Hz, 1 H, Ar-H), 7.36 (dt, ^3J = 8.5 Hz, ^4J = 0.6 Hz, 1 H, Ar-H), 7.41 (ddd, ^3J = 8.5 Hz, ^3J = 6.6 Hz, ^4J = 1.3 Hz, 1 H, Ar-H), 7.54 (ddd, ^3J = 8.2 Hz, ^3J = 6.6 Hz, ^4J = 1.4 Hz, 1 H, Ar-H), 7.91 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.92 (d, ^3J = 8.7 Hz, 1 H, Ar-H), 7.96 (d, ^3J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 17.24 (CH$_3$), 18.53 (CH$_3$), 19.73 (CH$_3$), 21.22 (CH$_3$), 31.12 (CH), 52.08 (OCH$_3$), 57.67 (CH), 114.62 (CH), 121.61 (C), 124.00 (CH), 125.64 (CH), 126.13 (CH), 127.26 (CH), 127.40 (CH), 128.25 (CH), 128.81 (CH), 131.28 (C), 132.09 (C), 133.78 (C), 134.54 (C), 138.45 (C), 139.73 (C), 153.30 (C), 169.27 (C), 172.21 (C) ppm. IR (KBr): ṽ = 3399 (br), 2956 (m), 1743 (s), 1638 (s), 1529 (s), 1314 (s), 1025 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 428 (100) [M$^+$+Na]. C$_{25}$H$_{27}$NO$_4$ (405.49): calcd. C 74.05, H 6.71, N 3.45; found C 74.23, H 6.81, N 3.31.

***tert*-Butyl (*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-methylbutanoate [(*P*,*S*)-3b]:** Colorless solid. R_t (HPLC) = 6.27 min. M.p. 72 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 199 (–23), 210 (+20), 225 (+21), 281 (–5.0) nm. $[\alpha]_D^{20}$ = +37 (*c* = 0.10, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.67 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 0.71 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 1.44 (s, 9 H, 3×CH$_3$), 1.85 (s, 3 H, CH$_3$), 1.95–2.03 (m, 1 H, CH), 2.33 (s, 3 H, CH$_3$), 4.48 (dd, ^3J = 8.7 Hz, ^4J = 4.4 Hz, 1 H, CH), 6.44 (d, ^3J = 8.7 Hz, 1 H, NH), 6.74 (d, ^4J = 0.6 Hz, 1 H, Ar-H), 6.78 (d, ^4J = 0.6 Hz, 1 H, Ar-H), 7.37–7.44 (m, 2 H, 2×Ar-H), 7.54 (ddd, ^3J = 8.2 Hz, ^3J = 6.2 Hz, ^4J = 1.9 Hz, 1 H, Ar-H), 7.86 (d, ^3J = 8.6 Hz, 1 H, Ar-H), 7.91 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.95 (d, ^3J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 17.12 (CH$_3$), 18.46 (CH$_3$), 19.82 (CH$_3$), 21.20 (CH$_3$), 27.99 (CH$_3$), 31.44 (CH), 57.77 (CH), 81.90 (C), 115.47 (CH), 121.75 (C), 123.69 (CH), 124.87 (CH), 126.23 (CH), 127.22 (CH), 127.25 (CH), 128.20 (CH), 128.75 (CH), 131.43 (C), 132.22 (C), 133.98 (C), 134.38 (C), 137.98 (C), 139.33 (C), 153.47 (C), 169.14 (C), 170.72 (C) ppm. IR (KBr): ṽ = 3441 (br), 3283 (br), 2962 (m), 2928 (m), 1731 (s), 1631 (s), 1533 (s), 1371 (m), 1155 (s), 1029 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 470 (100) [M$^+$+Na]. HRMS (ESI): calcd. for C$_{28}$H$_{33}$NNaO$_4$ [M$^+$ + Na]: 470.23018; found 470.22922.

***tert*-Butyl (*M*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-methylbutanoate [(*M*,*S*)-3b]:** Colorless solid. R_t (HPLC) = 5.92 min. M.p. 156 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 222 (–18), 238 (+8.8), 253 (+1.7), 278 (+6.9) nm. $[\alpha]_D^{20}$ = +53 (*c* = 0.24, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.66 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 0.70 (d, ^3J = 6.9 Hz, 3 H, CH$_3$), 1.43 (s, 9 H, 3×CH$_3$), 1.81 (s, 3 H, CH$_3$), 1.93–2.01 (m, 1 H, CH), 2.34 (s, 3 H, CH$_3$), 4.48 (dd, ^3J = 8.6 Hz, ^4J = 4.6 Hz, 1 H), 6.52 (d, ^3J = 8.5 Hz, 1 H, NH), 6.74 (s, 1 H, Ar-H), 6.77 (s, 1 H, Ar-H), 7.36 (ddd, ^3J = 8.5 Hz, ^3J = 7.5 Hz, ^4J = 6.4 Hz, 1 H, Ar-H), 7.41 (ddd, ^3J = 8.3 Hz, ^4J = 6.9 Hz, ^5J = 1.3 Hz, 1 H, Ar-H), 7.54 (ddd, ^3J = 8.2 Hz, ^4J = 6.5 Hz, ^5J = 1.5 Hz, 1 H, Ar-H), 7.86 (d, ^3J = 8.6 Hz, 1 H, Ar-H), 7.91 (d, ^3J = 8.1 Hz, 1 H, Ar-H), 7.95 (d, ^3J = 8.5 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 17.21 (CH$_3$), 18.47 (CH$_3$), 19.75 (CH$_3$), 21.10 (CH$_3$), 27.98 (CH$_3$), 31.44 (CH), 58.00 (CH), 81.91 (C), 114.95 (CH), 121.82 (C), 123.96 (CH), 125.44 (CH), 126.13 (CH), 127.22 (CH), 127.28 (CH), 128.23 (CH), 128.75 (CH), 131.27 (C), 132.10 (C), 134.33 (C), 134.42 (C), 138.50 (C), 139.53 (C), 153.30 (C), 170.84 (C), 173.40 (C) ppm. IR (KBr): ṽ = 3458 (br), 2959 (m), 2926 (m), 1734 (s), 1636 (s), 1529 (s), 1369 (m), 1023 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 470 (100) [M$^+$+Na]. C$_{28}$H$_{33}$NO$_4$ (447.57): calcd. C 75.14, H 7.43, N 3.13; found C 75.18, H 7.47, N 3.08.

Methyl (*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]propanoate [(*P*,*S*)-3c]: Colorless solid. R_t (HPLC) = 4.53 min. M.p. 176 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 205 (+2.9), 210 (+19), 223 (+26), 244 (–4.7), 280 (–4.6) nm. $[\alpha]_D^{20}$ = +18 (*c* = 0.0033, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.16 (d, ^3J = 7.1 Hz, 3 H, CH$_3$), 1.86 (s, 3 H, CH$_3$), 2.37 (s, 3 H, CH$_3$), 3.69 (s, 3 H, CH$_3$), 4.57 (quint., ^3J = 7.2 Hz, 1 H, CH), 6.36 (d, ^3J = 7.2 Hz, NH), 6.76 (s, 1 H, Ar-H), 6.81 (d, ^4J = 0.6 Hz, Ar-H), 7.43 (d, ^3J = 4.8 Hz, 1 H, Ar-H), 7.44 (d, ^3J = 4.8 Hz, 1 H, Ar-H), 7.56 (ddd, ^3J = 8.0 Hz, ^3J = 4.7 Hz, ^4J = 3.1 Hz, 1 H, Ar-H), 7.92 (d, ^3J = 8.1 Hz, 1 H, Ar-H), 7.93 (d, ^3J = 8.6 Hz, 1 H, Ar-H), 7.98 (d, ^3J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 17.93 (CH$_3$), 19.76 (CH$_3$), 21.29 (CH$_3$), 48.30 (CH), 52.35 (OCH$_3$), 114.83 (CH), 121.34 (C), 123.70 (CH), 125.23 (CH), 126.25 (CH), 127.34 (CH), 127.49 (CH), 128.28 (CH) 128.95 (CH), 131.45 (C), 132.16 (C), 133.36 (C), 134.60 (C), 138.04 (C), 139.77 (C), 153.31 (C), 168.13 (C), 173.03 (C) ppm. IR (KBr): ṽ = 3386 (br), 2954 (m), 2925 (m), 1743 (s), 1638 (s), 1534 (m), 1451 (m), 1314 (m), 1027 (m) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 400 (100) [M$^+$ + Na]. HRMS (ESI): calcd. for C$_{23}$H$_{23}$NNaO$_4$ [M$^+$ + Na]: 400.15193; found 400.15230. No full separation of the obtained diastereomeric mixtures to give pure or enriched compound (*M*,*S*)-**3c** was possible.

***tert*-Butyl (*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]propanoate [(*P*,*S*)-3d]:** Colorless solid. R_t (HPLC) = 5.51 min. M.p. 184 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 196 (–18), 210 (+16), 223 (+22), 245 (–3.7), 280 (–4.1) nm. $[\alpha]_D^{20}$ = +37 (*c* = 0.027, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.13 (d, ^3J = 7.1 Hz, 3 H), 1.43 (s, 9 H, 3×CH$_3$), 1.83 (s, 3 H, CH$_3$), 2.34 (s, 3 H, CH$_3$), 4.42 (quint., ^3J = 7.3 Hz, 1 H, CH), 6.45 (d, ^3J = 7.3 Hz, 1 H, NH), 6.73 (d, ^4J = 0.5 Hz, 1 H, Ar-H), 6.76 (d, ^4J = 0.3 Hz, 1 H, Ar-H), 7.41–7.44 (m, 2 H, Ar-H), 7.53 (ddd, ^3J = 8.2 Hz, ^4J = 5.7 Hz, J = 2.5 Hz, 1 H, Ar-H), 7.83 (d, ^3J = 8.6 Hz, 1 H, Ar-H), 7.90 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.94 (d, ^3J = 8.5 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 18.22 (CH$_3$), 19.79 (CH$_3$), 21.22 (CH$_3$), 27.90 (CH$_3$), 48.94 (CH), 81.86 (C), 115.11 (CH), 121.66 (C), 123.55 (CH), 124.90 (CH), 126.31 (CH), 127.19 (CH), 127.24 (CH), 128.22 (CH), 128.72 (CH), 131.73 (C), 132.24 (C), 133.93 (C), 134.43 (C), 137.94 (C), 139.37 (C), 153.48 (C), 168.56 (C), 171.86 (C) ppm. IR (KBr): ṽ = 3465 (br), 1979 (m), 2927 (m), 1739 (s), 1631 (s), 1533 (s), 1318 (s), 1155 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 442 (100) [M$^+$+Na]. HRMS (ESI): calcd. for C$_{26}$H$_{29}$NNaO$_4$ [M$^+$+Na]: 442.19888; found 442.19984. C$_{26}$H$_{29}$NO$_4$ (419.51): calcd. C 74.44, H 6.97, N 3.34; found C 74.61, H 7.51, N 3.03.

Methyl (*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3,3-dimethylbutanoate [(*P*,*S*)-3e]: Colorless solid. R_t (HPLC) = 5.21 min. M.p. 86 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 197 (–19), 210 (+17), 222 (+20), 279 (–6.9) nm. $[\alpha]_D^{20}$ = +23 (*c* = 0.06, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.77 (s, 9 H, 3×CH$_3$), 1.87 (s, 3 H, CH$_3$), 2.35 (s, 3 H, CH$_3$), 3.68 (s, 3 H, OCH$_3$), 4.64 (d, ^3J = 9.1 Hz, 1 H, CH), 6.57 (d, ^3J = 9.0 Hz, 1 Hz, 1 H, NH), 6.77 (d, ^4J = 0.6 Hz, 1 H, Ar-H), 6.83 (d, ^4J = 0.6 Hz, 1 H, Ar-H), 7.36 (d, ^3J = 8.5 Hz, 1 H, Ar-H), 7.42 (ddd, ^3J = 8.5 Hz, ^4J = 6.6 Hz, ^5J = 1.3 Hz, 1 H, Ar-H), 7.55 (ddd, ^3J = 8.2 Hz, ^4J = 6.7 Hz, ^5J = 1.3 Hz, 1 H, Ar-H), 7.91 (ddd, ^3J = 8.2 Hz,^4J = 1.2 Hz, ^5J = 0.8 Hz, 1 H, Ar-H), 7.97 (s, 2 H, 2×Ar-

H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 19.75 (CH$_3$), 21.25 (CH$_3$), 26.19 (CH$_3$), 34.37 (C), 51.69 (OCH$_3$), 60.81 (CH), 115.27 (CH), 121.41 (C), 123.97 (CH), 125.37 (CH), 126.17 (CH), 127.34 (CH), 127.49 (CH), 128.25 (CH), 128.95 (CH), 131.18 (C), 132.19 (C), 133.25 (C), 134.62 (C), 138 ppm. 20 (C), 139.90 (C), 153.34 (C), 168.40 (C), 171.66 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3421 (br), 3315 (br), 2960 (m), 2923 (m), 1740 (s), 1627 (s), 1543 (s), 1314 (m), 1266 (m), 1027 (m) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 442.2 (100) [M$^+$ + Na]. C$_{26}$H$_{29}$NO$_4$ (419.51): calcd. C 74.44, H 6.97, N 3.34; found C 74.42, H 7.02, N 3.26.

Methyl (*M*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3,3-dimethylbutanoate [(*M*,*S*)-3e]: Colorless solid. *R*$_\text{t}$ (HPLC) = 5.34 min. M.p. 188 °C. CD (MeOH): $\Delta\lambda_\text{max}$ ($\Delta\varepsilon$) = 218 (–40), 239 (+18), 256 (+5.0), 281 (+17) nm. $[\alpha]_\text{D}^{20}$ = +62 (*c* = 0.28, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.75 (s, 9 H, 3×CH$_3$), 1.82 (s, 3 H, CH$_3$), 2.35 (s, 3 H, CH$_3$), 3.67 (s, 3 H, OCH$_3$), 4.49 (d, ^3J = 9.0 Hz, 1 H, CH), 6.59 (d, ^3J = 8.9 Hz, 1 H, NH), 6.77 (d, ^4J = 0.5 Hz, 1 H, Ar-H), 6.79 (d, ^4J = 0.5 Hz, 1 H, Ar-H), 7.35 (dt, ^3J = 8.6 Hz, ^4J = 0.6 Hz, 1 H, Ar-H), 7.41 (ddd, ^3J = 8.2 Hz, ^4J = 6.7 Hz, ^5J = 1.3 Hz, 1 H, Ar-H), 7.91 (d, ^3J = 8.4 Hz, 1 H, Ar-H), 7.93 (d, ^3J = 8.7 Hz, 1 H, Ar-H), 7.96 (d, *J* = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 19.75 (CH$_3$), 21.20 (CH$_3$), 26.24 (CH$_3$), 34.39 (C), 51.74 (OCH$_3$), 60.97 (CH), 114.76 (CH), 121.49 (C), 124.08 (CH), 125.72 (CH), 126.10 (CH), 127.29 (CH), 127.45 (CH), 128.25 (CH), 128.86 (CH), 131.16 (C), 132.07 (C), 133.65 (C), 134.57 (C), 138 ppm. 47 (C), 139.82 (C), 153.27 (C), 168.73 (C), 171.74 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3424 (br), 2953 (m), 1741 (m), 1637 (s), 1525 (m), 1219 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 442 (100) [M$^+$ + Na]. HRMS (ESI): calcd. for C$_{26}$H$_{29}$NNaO$_4$ [M$^+$ + Na]: 442.19888; found 442.19890. C$_{26}$H$_{29}$NO$_4$ (419.51): calcd. C 74.44, H 6.97, N 3.34; found C 74.03, H 7.22, N 3.14.

Methyl (*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-phenylpropanoate [(*P*,*S*)-3f]: Colorless oil. *R*$_\text{t}$ (HPLC) = 5.27 min. CD (MeOH): $\Delta\lambda_\text{max}$ ($\Delta\varepsilon$) = 193 (+5.7), 200 (–11), 215 (+20), 240 (–8.2) nm. $[\alpha]_\text{D}^{20}$ = –28 (*c* = 0.14, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.78 (s, 3 H, CH$_3$), 2.36 (s, 3 H, CH$_3$), 2.94 (dd, ^2J = 14.0 Hz, ^3J = 6.1 Hz, 1 H, CH*H*), 3.01 (dd, ^2J = 14.0 Hz, ^3J = 5.9 Hz, 1 H, C*H*H), 3.66 (s, 3 H, CH$_3$), 4.88 (dt, ^3J = 8.5 Hz, ^3J = 6.1 Hz, 1 H, CH), 6.46 (d, ^3J = 7.4 Hz, 1 H, NH), 6.69 (s, 1 H, Ar-H), 6.80 (d, ^4J = 0.8 Hz, 1 H, Ar-H), 6.96 (d, ^3J = 7.1 Hz, 1 H, Ar-H), 6.97 (d, ^3J = 7.7 Hz, 1 H, Ar-H), 7.20–7.24 (m, 3 H), 7.36 (dt, ^3J = 8.5 Hz, ^4J = 0.8 Hz, 1 H, Ar-H), 7.41 (ddd, ^3J = 8.6 Hz, ^3J = 6.6 Hz, ^4J = 1.3 Hz, 1 H, Ar-H), 7.53 (ddd, ^3J = 8.2 Hz, ^3J = 6.6 Hz, ^4J = 1.5 Hz, 1 H, Ar-H), 7.78 (d, ^3J = 8.6 Hz, 1 H, Ar-H), 7.89 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.93 (d, ^3J = 8.5 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 19.87 (CH$_3$), 21.31 (CH$_3$), 37.74 (CH), 52.24 (OCH$_3$), 53.73 (CH), 115.32 (CH), 121.79 (C), 123.79 (CH), 124.73 (CH), 126.26 (CH), 126.96 (CH), 127.30 (CH), 127.37 (CH), 128.21 (CH), 128.47 (CH), 128 ppm. 74 (CH), 129.16 (CH), 132.07 (C), 132.24 (C), 133.32 (C), 134.47 (C), 135.75 (C), 138.32 (C), 139.46 (C), 153.36 (C), 168.98 (C), 171.64 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3411 (br), 2951 (m), 2923 (m), 1738 (s), 1639 (s), 1526 (m), 1454 (m), 1026 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 476 (100) [M$^+$ + Na]. HRMS (ESI): calcd. for C$_{29}$H$_{27}$NNaO$_4$ [M$^+$ + Na]: 476.18323; found 476.18407.

Methyl (*M*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-phenylpropanoate [(*M*,*S*)-3f]: Colorless oil. *R*$_\text{t}$ (HPLC) = 5.43 min. CD (MeOH): $\Delta\lambda_\text{max}$ ($\Delta\varepsilon$) = 194 (–7.7), 197 (–13), 224 (+13) nm. $[\alpha]_\text{D}^{20}$ = –3.8 (*c* = 0.11, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.74 (s, 3 H, CH$_3$), 2.37 (s, 3 H, CH$_3$), 2.84 (dd, ^2J = 14.0 Hz, ^3J = 6.7 Hz, 1 H, CH*H*), 2.95 (dd, ^2J = 14.0 Hz, ^3J = 6.2 Hz, 1 H, C*H*H), 3.63 (s, 3 H, CH$_3$), 4.84 (dt, ^3J = 7.3 Hz, ^3J = 6.6 Hz, 1 H, CH), 6.42 (d, ^3J = 7.0 Hz, 1 H, NH), 6.74 (d, ^4J = 0.8 Hz, 1 H, Ar-H), 6.74 (s, 1 H, Ar-H), 7.05 (d, ^3J = 7.7 Hz, 1 H, Ar-H), 7.06 (d, ^3J = 8.1 Hz, 1 H, Ar-H), 7.21–7.30 (m, 3 H), 7.36 (dt, ^3J = 8.5 Hz, ^4J = 0.8 Hz, 1 H, Ar-H), 7.41 (ddd, ^3J = 8.6 Hz, ^3J = 6.4 Hz, ^4J = 1.2 Hz, 1 H, Ar-H), 7.54 (ddd, ^3J = 8.2 Hz, ^3J = 6.6 Hz, ^4J = 1.5 Hz, 1 H, Ar-H), 7.79 (d, ^3J = 8.6 Hz, 1 H, Ar-H), 7.90 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.94 (d, ^3J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 19.73 (CH$_3$), 21.32 (CH$_3$), 37.81 (CH), 52.22 (OCH$_3$), 53.85 (CH), 114.95 (CH), 121.71 (C), 123.88 (CH), 124.94 (CH), 126.23 (CH), 126.99 (CH), 127.30 (CH), 127.42 (CH), 128.21 (CH), 128.51 (CH), 128 ppm. 79 (CH), 129.06 (CH), 132.01 (C), 132.21 (C), 133.24 (C), 134.53 (C), 135.99 (C), 138.22 (C), 139.54 (C), 153.41 (C), 168.67 (C), 171.81 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3406 (br), 2952 (m), 1742 (m), 1639 (s), 1525 (m), 1024 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 476 (100) [M$^+$ + Na]. HRMS (ESI): calcd. for C$_{29}$H$_{27}$NNaO$_4$ [M$^+$ + Na]: 476.18323; found 476.18324.

Methyl (*M*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethoxyphenyl)naphthalene-2′-carboxamido]-3-methylbutanoate [(*M*,*S*)-11]: Colorless solid. *R*$_\text{t}$ (HPLC) = 4.47 min. M.p. 97 °C. CD (MeOH): $\Delta\lambda_\text{max}$ ($\Delta\varepsilon$) = 205 (+10), 225 (–9.0), 245 (+3.6), 283 (+1.8) nm. $[\alpha]_\text{D}^{20}$ = +33 (*c* = 0.78, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.64 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 0.68 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 1.95 (dq, ^3J = 6.8 Hz, ^3J = 1.8 Hz, 1 H, CH), 3.66 (s, 3 H, CH$_3$), 3.7161 (s, 3 H, CH$_3$), 3.85 (s, 3 H, CH$_3$), 4.63 (dd, ^3J = 9.0 Hz, ^3J = 5.1 Hz, 1 H, CH), 6.26 (d, ^4J = 2.3 Hz, 1 H, Ar-H), 6.32 (d, ^4J = 2.3 Hz, 1 H, Ar-H), 6.69 (d, ^3J = 8.8 Hz, 1 H, NH), 7.42–7.44 (m, 2 H, Ar-H), 7.51–7.55 (m, 1 H, Ar-H), 7.78 (d, ^3J = 8.5 Hz, 1 H, Ar-H), 7.90 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.96 (d, ^3J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 63 MHz): δ = 17.41 (CH$_3$), 18.44 (CH$_3$), 31.59 (CH), 52.09 (OCH$_3$), 55.50 (OCH$_3$), 55.77 (OCH$_3$), 57.59 (CH), 92.06 (CH), 94.36 (CH), 106.05 (C), 124.96 (CH), 126.32 (CH), 127.11 (CH), 127.17 (CH), 127.75 (C), 128.14 (CH), 129.14 (CH), 132.91 (C), 134.36 (C), 135.59 (C), 158.62 (C), 161.85 (C), 169.61 (C), 172.16 (C), 172.62 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3360 (br), 3273 (br), 2964 (m), 1738 (s), 1635 (s), 1519 (m), 1358 (m), 1203 (s), 1153 (s), 1103 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 460 (100) [M$^+$ + Na]. HRMS (ESI): calcd. for C$_{25}$H$_{27}$NNaO$_6$ [M$^+$ + Na]: 460.17306; found 460.17358. No full separation of the obtained diastereomeric mixtures to give pure or enriched compound (*P*,*S*)-**11** was possible.

Methyl (*P*,2*S*,2′′′*R*)-2-{1′-[2′′-(3′′′,3′′′,3′′′-Trifluoro-2′′′-methoxy-2′′′-phenylpropanoyloxy)-4′′,6′′-dimethylphenyl]naphthalene-2′-carboxamido}-3-methylbutanoate [(*P*,*S*,*R*)-7]: (*S*)-Mosher acid chloride **6** (18.7 mg, 73.98 µmol), NEt$_3$ (87.5 mg, 73.98 µmol), and a catalytic amount of DMAP were added to a solution of **3a** (20.0 mg, 49.32 µmol) in 1 mL CH$_2$Cl$_2$ and stirred for 16 h at room temperature. A saturated solution of NH$_4$Cl (3 mL) and CH$_2$Cl$_2$ (3 mL) were then added, and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 3 mL). The combined organic layers were dried (MgSO$_4$) and concentrated. The residue was chromatographed (SiO$_2$, PE/EA, 2:1) to give the Mosher ester **7** (23 mg, 37.0 µmol, 75%) as a colorless oil. *R*$_\text{t}$ (HPLC) = 7.19 min. CD (MeOH): $\Delta\lambda_\text{max}$ ($\Delta\varepsilon$) = 208 (–22), 233 (+5.6), 248 (–12), 291 (+0.1) nm. $[\alpha]_\text{D}^{20}$ = –31 (*c* = 0.085, MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.68 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 0.75 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 1.93–1.97 (m, 1 H, CH), 1.97 (s, 3 H, CH$_3$), 2.45 (s, 3 H, CH$_3$), 2.86 (s, 3 H, OCH$_3$), 3.59 (s, 3 H, OCH$_3$), 4.44 (dd, ^3J = 7.7 Hz, ^3J = 5.3 Hz, 1 H, CH), 6.56 (d, ^3J = 7.6 Hz, 1 H, NH), 6.90 (s, 1 H), 6.92 (s, 1 H), 6.95 (s, 1 H), 7.11 (d, ^3J = 7.4 Hz, 1 H, Ar-H), 7.13 (d, ^3J = 8.2 Hz, 1 H, Ar-H), 7.19 (t, ^3J = 0.8 Hz, 1 H, Ar-H), 7.26 (tt, ^3J = 7.4 Hz, ^3J = 1.3 Hz, 1 H, Ar-H), 7.37 (d, ^{3}J = 4.3 Hz, 1 H, Ar-H), 7.38 (d, ^{3}J = 4.6 Hz, 1 H, Ar-H), 7.49 (ddd, ^{3}J = 8.0 Hz, ^{4}J = 4.8 Hz, ^{4}J = 3.0 Hz, 1 H, Ar-H), 7.83 (dt, ^{3}J = 8.1 Hz, ^{4}J = 1.0 Hz, 1 H, Ar-H), 7.89 (d, ^{3}J = 8.6 Hz, 1 H, Ar-H), 7.92 (d, ^{3}J = 8.6 Hz, 1 H, Ar-H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ = 17.63 (CH_3), 18.46 (CH_3), 19.85 (CH_3), 21.19 (CH_3), 30.65 (CH), 51.61 (CH_3), 54.71 (CH_3), 58.29 (CH), 119.99 (CH), 126.07 (CH), 126.59 (CH), 126.91 (CH), 126.92 (CH), 126.95 (CH), 127.10 (C), 127.26 (CH), 127.88 (CH), 128.26 (CH), 128.68 (CH), 129.36 (CH), 129.97 (CH), 130.73 (C), 130.99 (C), 131.65 (C), 133 ppm. 12 (C), 134.32 (C), 139.78 (C), 140.18 (C), 148.33 (C), 165.59 (C), 168.16 (C), 171.39 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3426 (br), 2955 (m), 2927 (m), 1745 (s), 1655 (s), 1506 (m), 1172 (s), 1030 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 644 (100) [M^+ + Na]. HRMS (ESI): calcd. For $C_{35}H_{34}F_3NNaO_6$ [M^+ + Na]: 644.22304; found 644.22130.

Methyl (*P*,2*S*)-2-[1′-(2′′-Methoxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-methylbutanoate [(*P*,*S*)-8]: MeI (47.7 mg, 336 µmol) and K_2CO_3 (45 mg, 326 µmol) were added to a solution of **5a** (20.0 mg, 49.3 µmol) in 4 mL 2-butanone and stirred at 80 °C for 20 h. A 2 N NH_3 solution was added and stirred for 1 h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated in vacuo to give 20.5 mg (48.87 µmol, 99 %) (*P*,*S*)-**8** as colorless crystals. R_t (HPLC) = 5.93 min. M.p. 116 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 199 (–39), 225 (+52), 239 (–17), 257 (–2.2), 277 (–6.9) nm. $[\alpha]_D^{20}$ = +14 (*c* = 0.335 MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.68 (d, ^{3}J = 7.0 Hz, 3 H, CH_3), 0.80 (d, ^{3}J = 7.0 Hz, 3 H, CH_3), 1.84 (s, 3 H, CH_3), 1.84–2.02 (m, 1 H, CH), 2.42 (s, 3 H, CH_3), 3.60 (s, 3 H, CH_3), 3.64 (s, 3 H, CH_3), 4.54 (dd, ^{3}J = 8.6 Hz, ^{3}J = 5.3 Hz, 1 H, CH), 6.53 (d, *J* = 8.3 Hz, 1 H, NH), 6.73 (s, 1 H, Ar-H), 6.84 (s, 1 H, Ar-H), 7.26 (dt, ^{3}J = 8.6 Hz, ^{4}J = 0.6 Hz, 1 H, Ar-H), 7.35 (ddd, ^{3}J = 8.5 Hz, ^{3}J = 6.8 Hz, ^{4}J = 1.3 Hz, 1 H, Ar-H), 7.50 (ddd, ^{3}J = 8.0 Hz, ^{3}J = 6.8 Hz, ^{4}J = 1.3 Hz, 1 H, Ar-H), 7.88 (d, ^{3}J = 8.2 Hz, 1 H, Ar-H), 7.91 (d, ^{3}J = 9.1 Hz, 1 H, Ar-H), 7.99 (d, ^{3}J = 8.6 Hz, 1 H, Ar-H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ = 17.40 (CH_3), 18.68 (CH_3), 19.61 (CH_3), 21.68 (CH_3), 31.06 (CH), 51.74 (OCH_3), 55.49 (OCH_3), 57.65 (CH), 109.59 (CH), 123.11 (C), 123.77 (CH), 125.89 (CH), 126.33 (CH), 126.52 (CH), 126.86 (CH), 127.29 (CH), 128.05 (CH), 132.18 (C), 132.48 (C), 133 ppm. 33 (C), 134.45 (C), 138.72 (C), 139.20 (C), 156.94 (C), 168.63 (C), 171.80 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3399 (br), 2955 (m), 2961 (s), 1741 (s), 1654 (s), 1518 (s), 1463 (m), 1313 (m), 1095 (m), 1026 (m) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 442 (100) [M^+ + Na]. HRMS (ESI): calcd. for $C_{26}H_{29}NNaO_4$ [M^+ + Na]: 422.19888; found 422.19847.

(*P*)-1-(2′-Methoxy-4′,6′-dimethylphenyl)naphthalene-2-carboxylic Acid [(*P*)-9]:[10] $NaNO_2$ (225 mg, 3.26 mmol) was added to a solution of (*P*,*S*)-**8** (19 mg, 45.3 µmol) in 5 mL Ac_2O. After stirring the mixture at room temperature for 15 h, three drops of acetic acid were added, and the mixture was stirred for 4 h at 40 °C. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed in vacuo. The residue was treated with KOH (300 mg), EtOH (5 mL) and H_2O (2 drops) and heated for 5 h at 80 °C. Water (10 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 10 mL). The aqueous solution was acidified with concd. HCl and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with $MgSO_4$ and the solvent removed under vacuo to give 8.0 mg (26.1 µmol, 58 %) (*P*,*S*)-**9** as a colorless oil. CD (EtOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 223 (+38), 240 (–15), 254 (–0.31), 281 (–4.7) nm. $[\alpha]_D^{20}$ = +10 (*c* = 0.20, EtOH) {ref.[10] $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 223 (+130), 238 (–78), 251 (–5.1), 276 (–17) nm. $[\alpha]_D^{20}$ = +14 (*c* = 0.29, EtOH)}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.79 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 3.59 (s, 3 H, CH_3), 6.71 (s, 1 H, Ar-H), 6.80 (s, 1 H, Ar-H), 7.38–7.40 (m, 2 H, Ar-H), 7.53–7.57 (ddd, ^{3}J = 8.1 Hz, ^{3}J = 6.0 Hz, ^{4}J = 2.3 Hz, 1 H, Ar-H), 7.90 (d, ^{3}J = 8.2 Hz, 1 H, Ar-H), 7.91 (d, ^{3}J = 8.7 Hz, 1 H, Ar-H), 8.09 (d, ^{3}J = 8.7 Hz, 1 H, Ar-H) ppm.

(*P*,2*S*)-2-[1′-(2′′-Hydroxy-4′′,6′′-dimethylphenyl)naphthalene-2′-carboxamido]-3-methylbutanoic Acid [(*P*,*S*)-13]: Aqueous KOH (3 mL, 0.4 N) was added to a solution of (*P*,*S*)-**3a** (150 mg, 0.37 mmol) in 0.5 mL MeOH, and the solution was stirred for 2 h. Concd. HCl was added until a colorless solid precipitated. Filtration and drying of the filter cake gave 123 mg (0.31 mmol, 85 %) (*P*,*S*)-**13** as a colorless solid. R_t (HPLC) = 4.37 min. M.p. 267 °C. CD (MeOH): $\Delta\lambda_{max}$ ($\Delta\varepsilon$) = 198 (–24), 211 (+24), 243 (–3.2), 280 (–5.2) nm. $[\alpha]_D^{20}$ = +67 (*c* = 0.14, MeOH). ^{1}H NMR (MeOH, 400 MHz): δ = 0.77 (d, ^{3}J = 7.0 Hz, 3 H, CH_3), 0.89 (d, ^{3}J = 6.8 Hz, 3 H, CH_3), 1.84 (s, 3 H, CH_3), 2.03–2.11 (m, 1 H, CH), 2.37 (s, 3 H, CH_3), 4.40 (d, ^{3}J = 5.1 Hz, 1 H, CH), 6.72 (s, 1 H, CH, Ar-H), 6.78 (d, ^{4}J = 0.6 Hz, 1 H, Ar-H), 7.36 (d, ^{3}J = 8.1 Hz, 1 H, Ar-H), 7.43 (ddd, ^{3}J = 8.5 Hz, ^{3}J = 8.1 Hz, ^{4}J = 1.3 Hz, 1 H, Ar-H), 7.57 (ddd, ^{3}J = 8.1 Hz, ^{3}J = 8.0 Hz, ^{4}J = 1.3 Hz, 1 H, Ar-H), 7.92 (d, ^{3}J = 8.6 Hz, 1 H, Ar-H), 7.98 (d, ^{3}J = 8.7 Hz, 1 H, Ar-H), 8.00 (d, ^{3}J = 9.0 Hz, 1 H, Ar-H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 63 MHz): δ = 18.14 (CH_3), 19.67 (CH_3), 20.25 (CH_3), 21.73 (CH_3), 32.32 (CH), 59.70 (CH), 115.67 (CH), 122.93 (C), 124.10 (CH), 126.69 (CH), 127.81 (CH), 128.04 (C), 128.49 (CH), 129.16 (CH), 129.45 (CH), 130.18 (C), 133.82 (C), 134.00 (C), 135.64 (C), 136.40 (C), 139.73 (C), 140.96 (C), 156.24 (C), 171.59 (C), 174.41 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3456 (br), 3392 (br), 2964 (m), 2503 (m), 1712 (s), 1600 (s), 1533 (s), 1259 (s), 1167 (s) cm^{-1}. MS (ESI-pos): *m*/*z* (%) = 414 (100) [M^+ + Na]. HRMS (ESI): calcd. for $C_{24}H_{25}NNaO_4$ [M^+ + Na]: 414.16758; found 414.16758. $C_{24}H_{25}NO_4$ (391.46): calcd. C 73.64, H 6.50, N 3.58; found C 73.33, H 6.50, N 3.48.

Solid-Phase Reactions: Rink amide resin (100 mg, 0.74 mmol g^{-1}, 0.0074 mmol) was swollen in DMF for 1.5 h. The Fmoc protecting group was removed by agitation with piperidine in DMF (20 %) for 20 min. For the coupling of the first amino acid, the resin was treated with Fmoc-L-Phe-OH (69.73 mg, 0.18 mmol, 2.5 equiv.) and PyBOP (93.67 mg, 0.18 mmol, 2.5 equiv.) in DMF containing 3 % NMM (10 mL). The mixture was shaken for 20 h to ensure quantitative coupling. The complete coupling was confirmed by a negative Kaiser test indicating the absence of any unreacted free amino function on the solid support. For the next coupling, the Fmoc protecting group on the phenylalanine was removed by agitation with piperidine (20 %) in DMF. The attachment of the biaryl acid (*P*,*S*)-**13** (42.24 mg, 0.108 mmol, 1.5 equiv.) was then performed under similar conditions as before using PyBOP (2.5 equiv.) in DMF containing 3 % NMM (reaction time 20 h). The complete coupling was again confirmed by a negative Kaiser test.

Computational Methods: The conformational analyses of (*P*,*S*)-**3a** and (*M*,*S*)-**3a** were carried out using the semiempirical AM1[21] method as implemented in the program package Gaussian 98.[24]

The wave functions of the ground and excited states required for the calculations of oscillator and rotatory strengths were obtained by semiempirical CNDO/S-CI[22] computations with a CI expansion including 576 occupied configurations and the ground state determinant. The oscillator and rotatory strengths were then computed using the dipole-velocity formalism.[25] These calculations were performed by means of the BDZDO/MCDSPD[26] program package.

The rotatory and oscillator strengths calculated for the single geometries of (*P*,*S*)-**3a** and (*M*,*S*)-**3a** were added up according to the Boltzmann statistic. The overall spectra were then simulated as

Table 3. Crystallographic data of (*P*,*S*)-**3a** and (*P*,*S*)-**3d**.

Data	(*P*,*S*)-**3a**	(*P*,*S*)-**3d**
Empirical formula	$C_{25}H_{27}NO_4$	$C_{26}H_{29}NO_4$
Formula weight	405.48	419.50
Temperature [K]	100(2)	100(2)
Radiation, λ [Å]	Mo-K_α 0.71073	Mo-K_α 0.71073
Crystal system	triclinic	monoclinic
Space group	*P*1	*P*2(1)
a [Å]	7.04820(10)	10.0818(2)
b [Å]	15.2156(2)	7.20650(10)
c [Å]	20.6724(3)	16.2259(3)
α [°]	86.9530(10)	90.00
β [°]	86.4510(10)	96.4360(10)
γ [°]	88.5940(10)	90.00
V [Å^3]	2209.08(5)	1171.45(4)
Z	4	2
Calculated density [g cm^{-3}]	1.219	1.189
Absorption coefficient [mm^{-1}]	0.082	0.080
F(000)	864	448
Theta range for collection	1.34–31.54°	2.03–33.27°
Reflections collected	54847	49269
Independent reflections	12973	4801
Minimum/maximum transmission	0.97/0.99	0.9827/0.9933
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data/parameters/restraints	12973/1101/3	4801/281/1
Goodness-of-fit on F^2	1.020	1.091
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0429, wR_2 = 0.1060	R_1 = 0.0360, wR_2 = 0.1025
R indices (all data)	R_1 = 0.0535, wR_2 = 0.1140	R_1 = 0.0369, wR_2 = 0.1037
Maximum/minimum residual electron density [e·Å^{-3}]	0.569/–0.489	0.479/–0.261

sums of Gaussian functions centered at the wavelengths of the corresponding electronic transitions and multiplied by the respective overall rotatory or oscillator strengths. For both, UV and CD spectra empirically chosen exponential half widths of 5.06 nm in the wavelength interval 180–235 nm and 6.40 nm in the range of 235–350 nm were used.

Crystal Structure Determination: The crystal data of (*P*,*S*)-**3a** and (*P*,*S*)-**3d** were collected at Bruker X8Apex diffractometer with CCD area detector and multi-layer mirror monochromated Mo-K_α radiation (see Table 3). The structure was solved by direct methods, refine with Shelx software package (G. Sheldrick, University of Göttingen, 1997) and expanded using Fourier techniques. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned idealized positions and were included in structure factor calculations. As flack parameter esd values for both structures were larger than 0.4, the Friedel pairs were merged (MERG 4), and refinement was repeated.

CCDC-602177 and -602178 contain the crystallographic data of (*P*,*S*)-**3a** and (*P*,*S*)-**3d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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