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PAPER

Synthesis and configuration determination of all enantiopure stereoisomers of the melatonin receptor ligand 4-phenyl-2-propionamidotetralin using an expedient optical resolution of 4-phenyl-2-tetralone†

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An efficient and practical approach for the synthesis of all four stereoisomers of the MT_2 melatonin receptor ligand 4-phenyl-2-propionamidotetralin (4-P-PDOT), each in enantiomerically pure form (ee > 99.9%), was developed. The strategy involved an optical resolution procedure of the key precursor (±)-4-phenyl-2-tetralone with the unusual resolving agent (*S*)-mandelamide, through the formation of four dihydronaphtalene-spiro-oxazolidin-4-one diastereomers. Interestingly, NMR experimental observations in combination with geometric calculations, provided unambiguous configuration assignments of all stereocenters of the key spiro stereoisomers. Cleavage of each single spiro diastereomer under acidic conditions gave enantiopure (*R*)- or (*S*)-4-phenyl-2-tetralone, which were then converted to each 4-P-PDOT single enantiomer by using stereoselective reactions.

Introduction

Among the countless motifs reported in the literature, there are some scaffolds that are more likely to provide, through suitable functional group modifications, potent and specific therapeutic agents or candidates toward different therapeutic targets. The aminotetraline core can be regarded as one of these privileged structures, as it is found in several biologically active molecules, whose functions range from central nervous system agents to antibiotics, immunoregulatory and antitumor agents.

Examples of active pharmaceutical ingredients (API) which are currently marketed or under development and have an aminotetraline structural element with chiral substituents include the antidepressants sertraline[1] and (*S*)-8-OH-DPAT,[2] the anti-Parkinson agent Naxagolide,[3] and the antiplatelet agent Terutroban[4] (Fig. 1). These examples illustrate, in particular, the interest towards 1- or 2-aminotetraline scaffolds characterized by the presence of one or more stereogenic centers. Considering the chiral nature of living systems, stereochemistry has evident implications on biologically active compounds, and in most cases the enantiomers of chiral drugs show remarkable differences in their activities, pharmacokinetics, pharmacodynamics and potential adverse reactions.

Only a few efficient asymmetric transformations, such as hydrogenation processes[5] or the Rh(I)-catalyzed asymmetric ring-opening reaction of strained oxabicyclic alkenes with heteroatom nucleophiles,[6] have proven suitable for achieving enantiopure β-aminotetralines. However, most of these elegant approaches are not applicable to the synthesis of enantiomerically pure 4-substituted-2-aminotetralines. Considering the interesting biological activities reported for several 4-phenyl-β-aminotetraline derivatives,[7] the development of a convenient approach to suitably functionalized enantiopure aminotetralines is highly desirable.

In the course of our studies on both the discovery of new melatonin receptor ligands and the definition of pharmacophore elements for MT_1/MT_2 subtype selectivity,[8] we recently focused

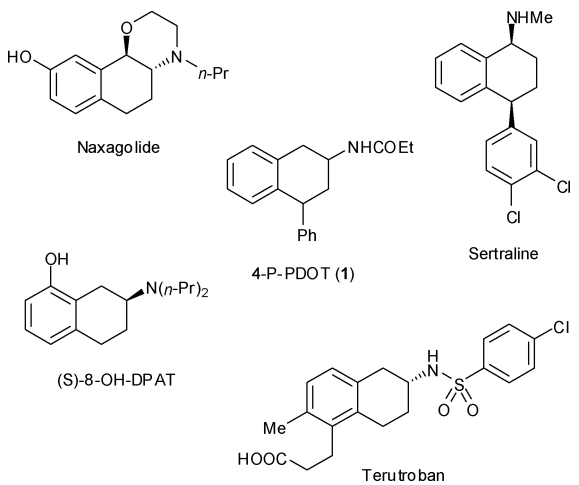

Fig. 1 4-P-PDOT and examples of API containing the aminotetralin core.

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† Electronic supplementary information (ESI) available: NOESY spectra of compounds **6a–d** and chiral chromatograms of the *cis*/*trans* racemic mixture **1** and of each stereoisomer **1a–d** are available. See DOI: 10.1039/c1ob06369c

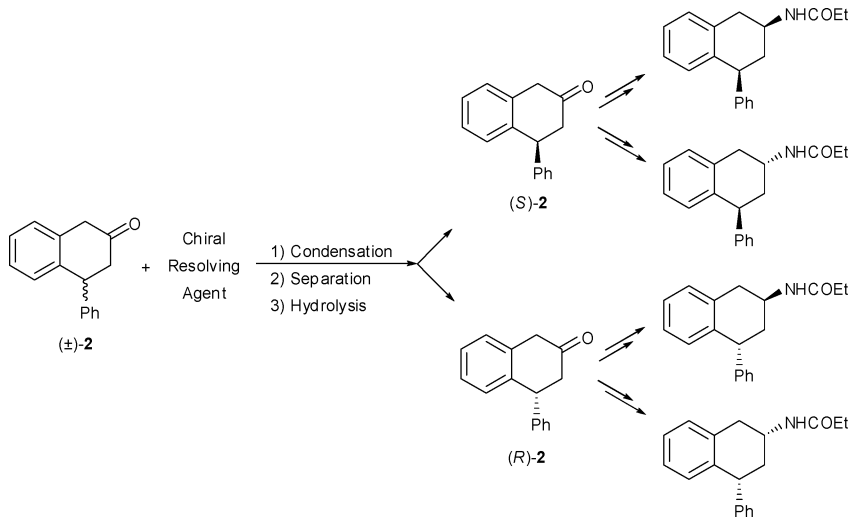
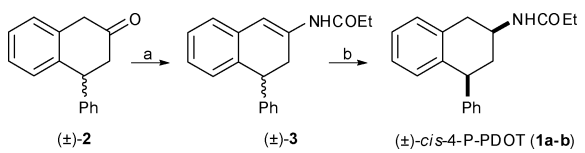


Fig. 2 Rational scheme for the chiral resolution of ketone (±)-**2**, a key intermediate for the synthesis of 4-P-PDOT.

our attention on the structural requirements of the MT_2-selective ligand 4-phenyl-2-propionamidotetralin (4-P-PDOT, **1**) (Fig. 1).[9] This pharmacological tool has been employed in several tests to discriminate the role of MT_1 and MT_2 melatonin receptors in melatonin mediated effects,[10] but there is no available information regarding the stereochemistry of the mixture employed. Therefore, we investigated possible approaches to obtain all enantiomerically pure 4-P-PDOT stereoisomers in order to assess their individual pharmacological properties.

Recently, we reported a convenient protocol for the gram-scale synthesis of (±)-*cis*-4-P-PDOT,[11] involving the condensation of 4-phenyl-2-tetralone (**2**) with propionamide and the diastereoselective reduction of the cyclic enamide (**3**) (Scheme 1).



Scheme 1 Reagents and conditions: (a) propionamide, cat. PTSA, toluene, reflux, 4 h; (b) TES, TFA, –10 °C, 10 min or H_2 (4 atm), 10% Pd/C, rt, 10 min.

We also tried catalytic asymmetric hydrogenation of enamide **3** with different combinations of transition metals and chiral ligands.[12] Unfortunately, the trisubstituted endocyclic chiral enamide **3** proved to be a very challenging substrate,[13] and only limited enantioselectivity (64% and 76% ee for the *cis* and *trans* 4-P-PDOT isomers, respectively) was achieved. Therefore, it seemed worthwhile to develop and optimize an alternative method for the isolation of each 4-P-PDOT enantiomers.

Although enormous advances have been made in asymmetric synthesis,[14] resolution still remains the most inexpensive and operationally simplest method for producing pure enantiomers.[15] In a far greater number of cases, it is still much easier and less expensive to access racemates. As a result, despite what one may lack in "elegance", resolution strategies must always be carefully evaluated against any asymmetric process, in particular in those cases in which all stereoisomers are necessary.

The absence of an easily derivatizable functional group in the 4-P-PDOT molecule, prompted us to explore the chiral resolution of a synthetic precursor of 4-P-PDOT, such as the racemic tetralone (**2**).

Herein we report a practical resolution procedure to access both 4-phenyl-2-tetralone enantiomers and their stereoselective conversion into all four single enantiomerically pure 4-P-PDOT stereoisomers (Fig. 2).

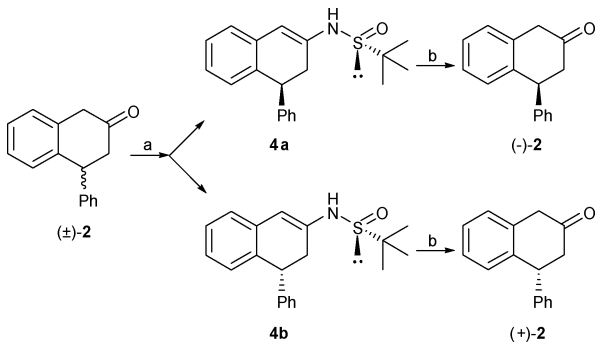
Moreover, we present the combination of NMR spectroscopy and geometric calculations for the configuration determination of the key synthetic intermediates.

Results and discussion

Optical resolution of tetralone (±)-2

The racemic ketone **2** was synthesized in multigram quantities by the condensation of β-naphthol with benzene in the presence of aluminum chloride as previously described,[16] and attention quickly turned to its optical resolution and configurational assignment.

Our initial approach to resolve the racemic tetralone (±)-**2** (Scheme 2) was inspired by previous work disclosing the chiral resolution of a racemic 4-aryl-α-tetralone derivative.[17] The reported procedure involved the condensation of



Scheme 2 Reagents and conditions: (a) (*R*)-(+)-2-methyl-2-propanesulfinamide, $Ti(OEt)_4$, THF, reflux, 20 h; (b) HCl/MeOH, rt, 1 h.

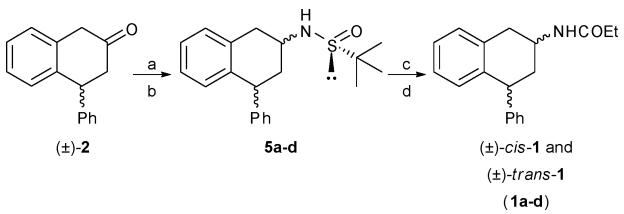
(±)-4-aryl-α-tetralone with enantiopure *tert*-butansulfinamide (TBSA), chromatographic separation of the corresponding sulfinyl ketimine diastereomers, and subsequent imine hydrolysis.

Therefore, we condensed our racemic β-tetralone (±)-**2** with (*R*)-TBSA, in the presence of titanium ethoxide. However, only low yields of both sulfinyl enamide diastereomers **4a** and **4b** were obtained after chromatographic purification (Scheme 2).[18]

The low recovery yields were probably due to chromatographic instability of unusual sulfinyl enamides **4a–b** on silica gel. Equally unsatisfactory (20–30%) were the yields of the hydrolysis of **4a–b** to give the desired enantiopure tetralones (+)-**2** and (−)-**2** and, therefore, this resolution strategy was abandoned.

The Ellman group has recently reported a one-pot diastereoselective reductive amination protocol for the asymmetric synthesis of α-substituted amines.[19] Furthermore, a series of investigations has shown that the *tert*-butanesulfinyl group induces high levels of stereoselectivity (96 : 4 dr) also in the reduction of *tert*-butanesulfinyl-ketimines bearing an α-stereocenter, independently of the configuration of this α-stereocenter.[20]

Taking into account these interesting results, we explored the use of the powerful chiral directing *tert*-butanesulfinyl group to control the formation of the new C_2–N stereogenic center in the reductive amination of (±)-4-phenyl-3,4-dihydronaphthalen-2-one, avoiding the isolation of unstable intermediates **4**. Nevertheless, by condensation of (±)-4-phenyl-3,4-dihydronaphtalen-2-one with (*R*)-TBSA in the presence of $Ti(OEt)_4$, and subsequent reduction *in situ* with $NaBH_4$ (Scheme 3) we obtained all four tetrahydronaphthalen-2-sulfinamides **5** (Scheme 3).[21] These results indicate that, in this case, the directing capacity of the chiral auxiliary (*R*)-TBSA is not strong enough to overcome the intrinsic substrate bias of the tetralone 4-stereogenic center.



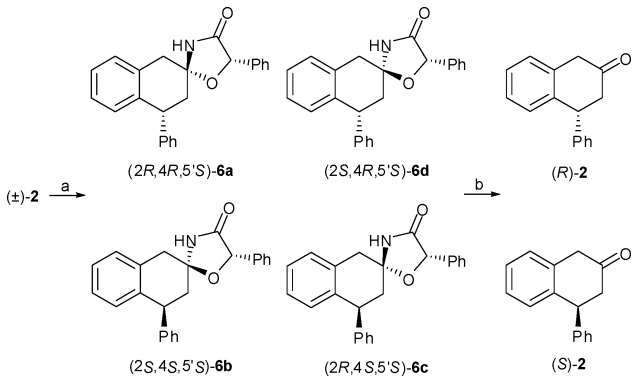
Scheme 3 Reagents and conditions: (a) (*R*)-(+)-2-methyl-2-propanesulfinamide, $Ti(OEt)_4$, THF reflux, 20 h; (b) $NaBH_4$, THF, −15 °C to rt, 4 h; (c) HCl/MeOH, rt, 1 h; (d) $(EtCO)_2O$, TEA, THF, rt, 1 h.

Given the instability of the sulfinyl enamides **4**, the problems encountered in their separation, and the low diastereoselectivity observed in the direct reductive amination (Scheme 3), we decided to use a new resolving agent.

Choosing the best resolving agent and the optimum conditions is not always straightforward. Polyfunctional compounds are generally preferred over monofunctional ones and aromatic compounds over aliphatic ones.[22] Multiple interaction sites in covalent diastereomers are often responsible for their selective "anchoring" to chromatographic adsorbents or for dissolving them in chromatographic eluents in such a manner as to allow differential elution. The conformational rigidity of diastereomeric molecules might also play a role in their separation.[23]

(*S*)-(+)-Mandelamide could be a good resolving agent for our purpose, considering its commercial availability at low prices and that it is a multifunctional compound with an aromatic ring. Furthermore, it can add rigidity to the resulting diastereomers, seeing that the acid catalyzed reaction of (*S*)-α-hydroxy acid amides with ketones has been reported to give 4-oxazolidinones.[24]

Gratifyingly, condensation of commercial (*S*)-mandelamide with racemic 4-phenyl-2-tetralone (**2**) gave a mixture of four stable spiro-diastereomers **6a–d** in nearly quantitative yield, which were fully separated by column chromatography (Scheme 4). The isolated yield of each pure spiro stereoisomers **6a–d** was reproducibly around 20–25%. Cleavage of each single spiro diastereomer under acidic conditions gave enantiopure (+)-**2** or (−)-**2**.



Scheme 4 Reagents and conditions: (a) (*S*)-(+)-mandelamide, cat. PTSA, toluene, reflux, 4 h; (b) HCl/dioxane, 100 °C, 16 h.

Configuration determination of spiro compounds 6a–d

In order to ascertain the configuration of the four spiro-diastereomers **6a–d** a combination of NMR experimental observations together with geometric computations was used, according to the following scheme. First, inspection of the ^{1}H-NMR 1D spectra showed that the two interproton vicinal coupling constants of the fragment –CH_2–CH(Ph)– in three of the isomers **6a–d** are around 12.5 and 5.5 Hz. Regrettably, in the case of one isomer, due to the degeneracy of the CH_2 chemical shifts, one can obtain from the resulting deceptively simple spectrum just their sum, which nevertheless amounts to 18 Hz. These observations suggest that the cyclohexene ring of tetraline is preferentially locked in the conformation with the phenyl substituent arranged in the pseudoequatorial orientation (Fig. 3).

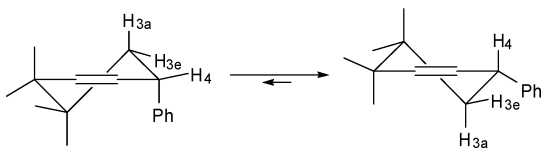


Fig. 3 Possible half-chair conformations of compounds **6a–d**.

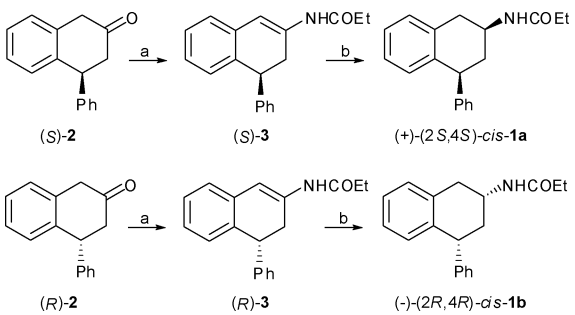
To confirm this hypothesis, the molecular geometry was optimized by energy minimization with the help of computational chemistry techniques, in the beginning at the level of molecular mechanics and then at the *ab initio* level. The results showed that indeed for all the four stereoisomers the most populated conformation (over 95%) is the one with the phenyl group in the equatorial arrangement.

Moreover, from the optimized geometry it appears that some critical interproton distances, such as NH–H_4, NH–H_{3a}, $H_{5'}$–H_{3e} and $H_{5'}$–H_{1e}, are strongly dependent on the relative configurations of the three stereocenters at C_2, C_4 and $C_{5'}$. For example, the NH–H_4 distance is small (<300 pm) when the relative configurations of C_2 and C_4 are *like* but it is large (>400 pm) when they are *unlike*. On the other hand, the $H_{5'}$–H_{3e} distance is small when the relative configurations of C_2 and $C_{5'}$ are *like* but it is large when they are *unlike*. In summary, each relative configuration is described by a unique set of the above mentioned four distances. At this point, the configuration of the isomers can be unequivocally assigned simply by inspection of the relative magnitudes of these distances obtained from the volumes of the cross peaks in the 2D-NMR-NOESY spectrum. However, since the configuration of $C_{5'}$ is known, this means that this procedure allows for the absolute configuration to be determined. The four pertinent interproton distances, calculated from computed models and measured by 2D-NMR-NOESY spectroscopy are shown in Table 1, together with the configuration of stereocenters 2 and 4 assigned relatively to that of 5′. The obtained agreement between the observed and predicted sizes of the distances is, in our opinion, a good test of the reliability of the proposed assignment.

Synthesis of the all enantiopure isomers of 4-P-PDOT

The enantiopure tetralone enantiomers, (*R*)-**2** or (*S*)-**2**, were then easily transformed into either the two pure *cis*-4-P-PDOT enantiomers (**1a** or **1b**) and the two *trans*-4-P-PDOT ones (**1c** or **1d**).

For the *cis* isomers (**1a** and **1b**), the procedures which had been previously established for racemic *cis*-4-P-PDOT were reproduced successfully (Scheme 5). The enantiomeric purity (ee > 99.9%) of each *cis*-4-P-PDOT enantiomers **1a** and **1b** was verified by chiral HPLC (see electronic supplementary information†) and measuring their optical rotation, [(2*S*,4*S*)-**1a**: $[\alpha]_D^{20}$ = +58.2 and (2*R*,4*R*)-**1b**: $[\alpha]_D^{20}$ −58.2].



Scheme 5 Reagents and conditions: (a) propionamide, cat. PTSA, toluene, reflux, 4 h; (b) H_2 (4 atm), 10% Pd/C, rt, 10 min.

Starting from the two pure tetralones (*R*)-**2** and (*S*)-**2**, we were also able to prepare the two enantiopure *trans*-4-P-PDOT stereoisomers **1c–d**, using an already reported synthetic procedure for similar compounds.[25]

In particular, each tetralone (*S*)-**2** or (*R*)-**2** was separately reduced with sodium borohydride to a 85 : 15 *cis*/*trans* mixture of the corresponding tetralols, from which the enantiomerically pure *cis*-tetralol (2*S*,4*S*)-**7a** or (2*R*,4*R*)-**7b** was obtained by chromatographic purification and subsequent crystallization. Each *cis*-tetralol **7a** or **7b** was converted to the *trans*-4-phenyl-2-azidotetralin **9a** or **9b** by mesylation, followed by reaction of the *cis*-mesylate **8a** or **8b** with sodium azide. The two *trans*-4-P-PDOT pure enantiomers **1c–d** were finally obtained by catalytic reduction of the *trans*-azides **9a** or **9b** with hydrogen over 10% Pd/C in the presence of propionic anhydride (Scheme 6).

Enantiomeric purity (ee> 99.9%) of each *trans*-4-P-PDOT was evaluated by chiral HPLC analysis (see electronic supplementary information†) and optical rotation determination [(2*R*,4*S*)-**1c**: $[\alpha]_D^{20}$ = +49.5; and (2*S*,4*R*)-**1d**: $[\alpha]_D^{20}$ −51.3].

Conclusions

In summary, a convenient protocol was established to allow easy access to all four enantiopure stereoisomers of 4-P-PDOT (ee > 99.9%). The key step involves the efficient optical resolution of the readily available racemic 4-phenyltetralin-2-one, using (*S*)-mandelamide as an unprecedented and practical resolving agent. Enantiopure 4-aryl-2-tetralones are versatile intermediates, capable of undergoing a variety of chemical transformations, especially for the stereoselective synthesis of biologically active tetralines, including β-aminotetralines. Finally, it was possible to assign the configuration of each single enantiomer without using X-ray crystallography, but simply by comparing computed interproton distances with those observed in the NMR-NOESY spectrum.

Experimental section

General experimental procedures

Melting points were determined on a Buchi B-540 capillary melting point apparatus and are uncorrected. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker AVANCE 200 spectrometer, using $CDCl_3$ as solvent unless stated otherwise. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in hertz (Hz). The 2D NOESY experiment was performed using the pulse program noesygpph[26] using a mixing time of 0.5 s. The interproton distances were obtained using the relation $v_x/v_{ref} = (x/x_{ref})^{-6}$, where the v_x and v_{ref} are the off-diagonal volumes and x_{ref} is the reference distance H–H of the CH_2 group, taken as 180 pm.

Molecular geometry of the four spiro compounds **6a–d** was optimized with the Hyperchem 8 computer program, using the MM2 molecular mechanics force field[27] and the algorithm of conjugated gradient of Polak-Ribiere, reaching convergence to a final slope of 0.01 kcal Å^{-1} mol^{-1}.

ESI-MS spectra were taken on a Waters Micromass Zq instrument; only molecular ions (M+1) are given. Infrared spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer; absorbances are reported in cm^{-1}.

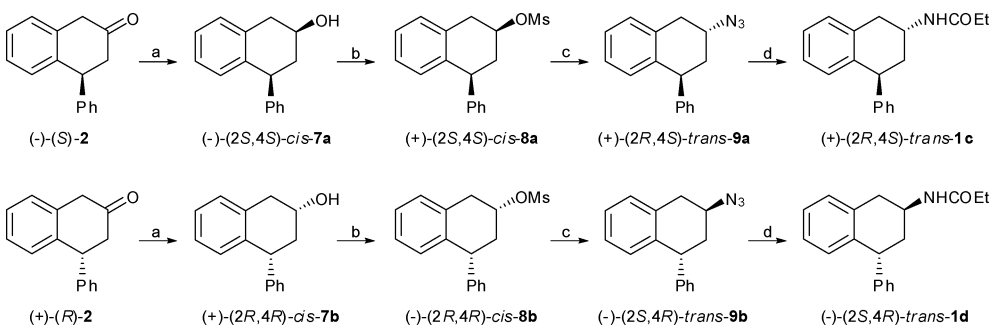
Elemental analyses for C, H and N were performed on a Carlo Erba analyzer, and the results are within 0.3% of the calculated values. Purity of new compounds was greater than 95%.

Optical rotation analysis was performed using a Perkin–Elmer 241 polarimeter using a sodium lamp (λ 589 nm, D-line) and mercury lamp (λ 436 nm, Hg-line); $[\alpha]_D^{20}$ and $[\alpha]_{Hg}^{20}$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (*c*) is in g per 100 mL.

Table 1 Interprotonic distances (in picometres) of the four spiro-diastereomers **6a–d**

Cpd	Configuration	NH–H_4		NH–H_{3a}		$H_{5'}$–H_{3e}		$H_{5'}$–H_{1e}	
		calc.	exp.[a]	calc.	exp.[a]	calc.	exp.[a]	calc.	exp.[a]
6a	2*R*,4*R*,5′*S*	235	228	394	>400	282	247	450	>400
6b	2*S*,4*S*,5′*S*	226	227	391	>400	446	>400	283	291
6c	2*R*,4*S*,5′*S*	485	>400	282	283	281	280	445	>400
6d	2*S*,4*R*,5′*S*	481	>400	276	275	450	>400	280	280

[a] The interproton distances were obtained using the relation $v_x/v_{ref} = (x/x_{ref})^{-6}$, where v_x and v_{ref} are the off-diagonal volumes and x_{ref} is the reference distance H–H of the CH_2 group, taken as 180 pm.



Scheme 6 Reagents and conditions: (a) $NaBH_4$, MeOH, reflux, 4 h; (b) MsCl, Py, rt, 2 h; (c) NaN_3, DMF, 110 °C, 1 h; (d) H_2 (4 atm), 10% Pd/C, *i*-PrOH, $(EtCO)_2O$, rt, 16 h.

Enantiomeric excesses were determined by HPLC on the following apparatus: Shimadzu LC-10AT (liquid chromatograph), Shimadzu SPD-10A (UV detector), Shimadzu C-R6A Chromatopac, using chiracel AD-H as a column.

Column chromatography purifications were performed under "flash" conditions using Merck 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F254 plates.

2-Methyl-*N*-(4-phenyl-3,4-dihydronaphthalen-2-yl)propane-2-sulfinamide (4a and 4b)

Titanium ethoxide (20 wt% solution in ethanol, 1.38 ml, 6.6 mmol) was added to a solution of (±)-4-phenyl-2-tetralone (**2**) (0.58 g, 2.63 mmol) and (*R*)-(+)-2-methyl-2-propanesulfinamide (0.36 g, 3.02 mmol) in dry THF (6 ml) and the resulting mixture was heated to reflux for 20 h under a N_2 atmosphere. After cooling to room temperature, the mixture was poured into an equal volume of brine while rapidly stirring. The resulting suspension was filtered through a plug of Celite and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel, the brine layer was extracted with EtOAc, the combined organic phases were washed with brine, and dried (Na_2SO_4). The solvent was removed by distillation under reduced pressure and the crude residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 7 : 3 as eluent). We were not able to completely separate the diastereoisomeric mixture, that also resulted quite instable.

2-Methyl-*N*-(4-phenyl-3,4-dihydronaphthalen-2-yl)propane-2-sulfinamide (4a). NMR δ_H (200 MHz, $CDCl_3$) 1.26 (s, 9H), 2.72–2.81 (m, 2H), 4.22 (dd, 1H, J_{H4H3a} = 7.5, J_{H4H3b} = 10.0), 5.18 (1H, brs), 6.06 (s, 1H), 6.74 (d, 1H, J = 7.5), 6.94–7.49 (m, 8H); δ_C (50 MHz, $CDCl_3$) 22.4, 35.4, 44.7, 56.6, 105.9, 125.0, 125.38, 126.8, 126.0, 127.2, 128.5, 128.60, 128.60, 134.9, 139.4, 143.4; ESI-MS (*m*/*z*): 326 (M+1).

2-Methyl-*N*-(4-phenyl-3,4-dihydronaphthalen-2-yl)propane-2-sulfinamide (4b). NMR δ_H (200 MHz, $CDCl_3$) 1.27 (s, 9H), 2.76 (app. t, 2H, J = 9.0), 4.23 (dd, 1H, J_{H4H3a} = 7.5, J_{H4H3b} = 10), 5.02 (brs, 1H), 6.09 (s, 1H), 6.75–7.51 (m, 9H, ArH); δ_C (50 MHz, $CDCl_3$) 22.3, 35.9, 44.7, 56.4, 105.6, 125.2, 125.5, 126.8, 127.0, 127.1, 128.3, 128.6, 128.8, 134.8, 138.9, 143.5; ESI MS (*m*/*z*): 326 (M+1).

Cleavage of the *tert*-butanesulfinyl group by treatment with acid: synthesis of (+)- or (–)-4-phenyl-3,4-dihydronaphthalen-2(1*H*)-one

Concentrated HCl (0.13 ml) was added to a solution of **4a** or **4b** (0.08 g, 0.24 mmol) in MeOH (0.65 ml), and the resulting mixture was stirred at room temperature for 1 h. After cooling to 0 °C an aqueous saturated solution of $NaHCO_3$ was added and the resulting aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a crude residue which was purified by flash chromatography (silica gel, cyclohexane/EtOAc 9 : 1, as eluent), yield 15%. HPLC-MS and ^{1}H-NMR spectra were identical with those previously reported for racemic **2**.[16]

General procedure for the synthesis of the spiro-compounds 6a–d

A solution of tetralone (±)-**2** (0.9 g, 4.05 mmol), (*S*)-(+)-mandelamide (1.5 g, 10.12 mmol) and *p*-toluenesulfonic acid (0.08 g, 0.46 mmol) in toluene (25 ml), was heated under reflux with azeotropic removal of water for 4 h. After cooling, the excess mandelamide was removed by filtration, the filtrate was washed with a saturated aqueous solution of $NaHCO_3$ and then with brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude residue that was purified by flash chromatography (silica gel, cyclohexane/EtOAc 6 : 4, as eluent).

All four single diastereomers **6** were isolated after further chromatography and subsequent crystallization from Et_2O/petroleum ether or CH_2Cl_2/petroleum ether.

(2*R*,4*R*,5′*S*)-4,5′-Diphenyl-3,4-dihydro-1*H*-spiro(naphthalene-2,2′-oxazolidin)-4′-one (6a). Yield 21%; m.p. 211–212 °C; $[\alpha]_D^{20}$ –53.7 (*c* 0.097 in $CHCl_3$); Found: C 80.98; H 5.93; N 3.77%. Calc. for $C_{24}H_{21}NO_2$: C 81.10; H 5.96; N 3.94%; IR (film) ν_{max}/cm^{-1} 3400 (NH), 1710 (CO);

NMR δ_H (200 MHz, $CDCl_3$) 2.19 (1H, dd, $J_{H3aH4} \approx J_{H3aH3b}$ = 12.0 Hz, *H*3a), 2.37 (1H, ddd, J_{H3bH1b} = 2.0 Hz, J_{H3bH4} = 6.0 Hz, J_{H3bH3a} = 12.0 Hz, *H*3b), 3.01 (1H, dd, J_{H1bH3b} = 2.0 Hz, J_{H1bH1a} = 16.0 Hz, *H*1b), 3.47 (1H, d, J_{H1aH1b} = 16.0 Hz, *H*1a), 4.11 (1H, dd, J_{H4H3b} = 6.0 Hz, J_{H4H3a} = 12.0 Hz, *H*4), 5.24 (1H, s, *H*5′), 6.75 (1H, d, J = 7.5 Hz, Ar*H*), 6.93–7.43 (14H, m, Ar*H*, N*H*); δ_C (50 MHz, $CDCl_3$) 42.9, 44.6, 45.3, 78.0, 91.0, 126.4, 126.8, 126.8, 127.0, 128.5, 128.5, 128.6, 128.7, 129.4, 129.6, 133.2, 136.2, 137.4, 144.9, 172.3; ESI-MS: *m*/*z* 356 (M+1).

(2*S*,4*S*,5′*S*)-4,5′-diphenyl-3,4-dihydro-1*H*-spiro(naphthalene-2,2′-oxazolidin)-4′-one (6b). Yield 23%; m.p. 187–188 °C; $[\alpha]_D^{20}$ +108.3 (*c* 0.067 in $CHCl_3$); Found: C 81.22; H 5.98; N 3.78%. Calc. for $C_{24}H_{21}NO_2$: C 81.10; H 5.96; N 3.94%; IR (film) ν_{max}/cm^{-1} 3423 (NH), 1708 (CO);

NMR δ_H (200 MHz, $CDCl_3$) 2.30 (2H, dd, J = 9.0 Hz), 3.04 (1H, d, J = 16.0 Hz, *H*1b), 3.42 (1H, d, J = 16.0 Hz, *H*1a), 4.11 (1H, app. t, J = 9.0 Hz), 5.28 (1H, s), 6.74 (1H, d, J = 8 Hz, Ar*H*), 6.97–7.36 (13H, m, Ar*H*), 7.95 (1H, s, N*H*); δ_C (50 MHz, $CDCl_3$) 43.1, 45.1, 45.3, 78.2, 91.6, 125.9, 126.7, 126.8, 126.9, 128.2, 128.4, 128.6, 128.7, 129.4, 129.7, 133.2, 136.5, 137.5, 145.1, 172.8; ESI-MS: *m*/*z* 356 (M+1).

(2*R*,4*S*,5′*S*)-4,5′-diphenyl-3,4-dihydro-1*H*-spiro(naphthalene-2,2′-oxazolidin)-4′-one (6c). Yield 24%; m.p. 205–206° C; $[\alpha]_D^{20}$ + 170° (*c* 0.049 in $CHCl_3$); Found: C 80.90; H 5.94; N 4.01%. Calc. for $C_{24}H_{21}NO_2$: C 81.10; H 5.96; N 3.94%; IR (film) ν_{max}/cm^{-1} 3197, 1712;

NMR δ_H (200 MHz, $CDCl_3$) 2.09 (1H, dd, J_{H3bH4} = 5.5 Hz J_{H3bH3a} = 12.0 Hz, J_{H3bH1b} = 1.5 Hz, *H*3b), 2.29 (1H, ddd, J_{H3aH4} = 12.0 Hz, J_{H3aH3b} = 12.0 Hz, *H*3a), 3.08 (1H, dd, J_{H1bH1a} = 17.0 Hz, J_{H1bH3b} = 1.5 Hz, *H*1b), 3.28 (1 H, d, J_{H1aH1b} = 17.0 Hz, *H*1a), 4.38 (1H, dd, J_{H4H3b} = 5.5, J_{H4H3a} = 12.0 Hz, *H*4), 5.3 (1 H, s, *H*5′), 6.69 (1 H, d, J = 7.5 Hz, Ar*H*), 6.91–7.38 (13 H, m, Ar*H*), 8.55 (1 H, s, N*H*); δ_C (50 MHz, $CDCl_3$) 42.3, 44.1, 44.1, 79.1, 91.0, 126.5, 126.7, 126.7, 126.7, 128.6, 128.6, 128.7, 128.9, 129.0, 129.2, 133.0, 136.3, 138.1, 144.9, 173.3; ESI-MS: *m*/*z* 356 (M+1).

(2*S*,4*R*,5′*S*)-4,5′-diphenyl-3,4-dihydro-1*H*-spiro(naphthalene-2,2′-oxazolidin)-4′-one (6d). Yield 25%; m.p. 188–189° C; $[\alpha]_D^{20}$

–20.1 (*c* 0.055 in $CHCl_3$); Found: C 81.01; H 5.90; N 4.07%. Calc. for $C_{24}H_{21}NO_2$: C 81.10; H 5.96; N 3.94%; IR (film) ν_{max}/cm^{-1} 3215, 1713;

NMR δ_H (200 MHz, $CDCl_3$) 2.16 (1H, dd, $J_{H3aH4} \approx J_{H3aH3b}$ = 11.0 Hz, *H*3a), 2.25 (1H, dd, J_{H3bH4} = 6.5 Hz, J_{H3bH3a} = 11.0 Hz, *H*3b), 3.16 (1H, d, J_{H1bH1a} = 17.0 Hz, *H*1b), 3.26 (1H, d, J_{H1aH1b} = 17.0 Hz, *H*1a), 4.44 (1H, dd, J_{H4H3b} = 6.5 Hz, J_{H4H3a} = 11.0 Hz, *H*4), 5.30 (1H, s, *H*5′), 6.70 (1H, d, *J* = 7.5, Ar*H*), 6.92–7.38 (13 H, m), 8.67 (1H, s, N*H*); δ_C (50 MHz, $CDCl_3$) 41.9, 44.0, 45.0, 79.2, 91.1, 126.8, 126.9, 127.0, 127.05, 128.92, 128.9, 129.0, 129.2, 129.4, 129.6, 133.5, 136.7, 138.4, 145.3, 173.9; ESI-MS: *m*/*z* 356 (M+1).

General procedure for hydrolysis of the spiro-oxazolidin-4′-one derivatives 6a–d

Concentrated HCl (3.4 ml) was added to a solution of **6** (233 mg, 0.65 mmol) in dioxane (14 ml) and the resulting mixture was heated at 100 °C for 16 h. After removing the solvent by distillation under reduced pressure, the residue was neutralized with a saturated aqueous solution of $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a crude residue which was purified by flash chromatography (silica gel, cyclohexane/EtOAc 9 : 1, as eluent).

(–)-(*S*)-4-Phenyl-3,4-dihydronaphthalen-2(1*H*)-one [(*S*)-2]. Hydrolysis of compounds **6b** and/or **6c**; Yield 95%; $[\alpha]_D^{20}$ –11.7 (*c* 0.13 in $CHCl_3$). Chemical physical data were identical to those already reported for racemic mixture.[16]

(–)-(*R*)-4-Phenyl-3,4-dihydronaphthalen-2(1*H*)-one [(*R*)-2]. Hydrolysis of compounds **6a** and/or **6d**; yield 86%; $[\alpha]_D^{20}$ +7.5 (*c* 0.12 in $CHCl_3$). Chemical physical data were identical to those already reported for racemic mixture.[16]

(*S*)-*N*-(4-Phenyl-3,4-dihydronaphthalen-2-yl) propionamide [(*S*)-3]. A solution of tetralone (–)-(*S*)-**2** (0.14 g, 0.63 mmol), propionamide (0.11 mg, 1.57 mmol) and *p*-toluenesulfonic acid (0.02 g, 0.063 mmol) in toluene (3 ml), was heated under reflux with azeotropic removal of water for 4 h. After cooling, the excess propionamide was removed by filtration, the filtrate was washed with a saturated aqueous solution of $NaHCO_3$ and then with brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude residue that was purified by flash chromatography (silica gel, cyclohexane/EtOAc 7 : 3, as eluent) and subsequent crystallization from Et_2O/petroleum ether. Yield 84%; $[\alpha]_D^{20}$ –3.2 (*c* 0.21 in $CHCl_3$); $[\alpha]_{Hg}^{20}$ + 25.2° (*c* 0.21 in $CHCl_3$). m.p. 105–106 °C. Chemical-physical data are identical to those previously reported for racemic mixture.[11]

(*R*)-*N*-(4-Phenyl-3,4-dihydronaphthalen-2-yl) propionamide [(*R*)-3]. Compound (4*R*)-**3** was obtained using the above described procedure, starting from (+)-(*R*)-**2** instead of (–)-(*S*)-**2**. Yield 78%; $[\alpha]_D^{20}$ + 1.65° (*c* 0.17 in $CHCl_3$); $[\alpha]_{Hg}^{20}$ – 23.61° (*c* 0.17 in $CHCl_3$). m.p. 102–103 °C. Chemical-physical data are identical to those previously reported for racemic mixture.[11]

(+)-(2*S*,4*S*)-*cis*-*N*-(4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propanamide (1a). A solution of the enamide (*S*)-**3** (0.12 g, 0.42 mmol) in MeOH (10 ml) was hydrogenated over 10% Pd/C (0.014 g) at 4 atm of H_2 for 5–10 min at room temperature. The catalyst was filtered off over a Celite plug and washed with methanol. The filtrate was concentrated under reduced pressure to afford the crude desired product which was purified by chromatography and crystallization from acetone/n-hexane. Yield 91%; m.p. 187–188 °C; $[\alpha]_D^{20}$ + 58.2° (*c* 0.33 in $CHCl_3$).

Enantiomeric excess was determined by HPLC on a Chiralcel (Chiralpak) AD-H column, with hexane/iPrOH, 19 : 1 as eluent, flux 1.0 mL min^{-1}, λ 262 nm; retention time = 17.8 min; ee >99.9%. The physical-chemical properties were identical with those previously reported for racemic mixture.[11]

(–)-(2*R*,4*R*)-*cis*-*N*-(4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propanamide (1b). **1b** was prepared according to the above procedure starting from the enamide (*R*)-**3** instead of the enamide (*S*)-**3**. Yield: 85%; $[\alpha]_D^{20}$ –58.2 (*c* 0.19 in $CHCl_3$). Chiral HPLC retention time = 21.4 min; ee >99.9%. m.p. 186–187 °C. The physical-chemical properties were identical with those previously reported for racemic mixture.[11]

General procedure for the synthesis of the *cis*-alcohols 7a–b

$NaBH_4$ (0.13 g; 3.5 mmol) was added portionwise to a stirred ice-cooled solution of tetralone **2** (0.22 g; 1 mmol) in dry methanol (7.5 ml), and the resulting mixture was heated under reflux for 4 h. After cooling to room temperature, water was added and the aqueous solution was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated by distillation under reduced pressure. The crude desired alcohol was purified by flash-chromatography (cyclohexane/EtOAc, 8 : 2 as eluent) and crystallization from Et_2O/petroleum ether.

(–)-(2*S*,4*S*)-4-Phenyl-1,2,3,4-tetrahydronaphthalene-2-ol (7a). **7a** was prepared according to the above procedure starting from tetralone (–)-(*S*)-**2**. Yield 47%; white solid, mp 130–132 °C; $[\alpha]_D^{20}$ –17.9 (*c* 0.046 in $CHCl_3$); $[\alpha]_{Hg}^{20}$ –33.6° (*c* 0.046 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3623, 3057, 2966, 1613;

NMR δ_H (200 MHz, $CDCl_3$) 1.80 (1H, brs, O*H*), 1.94 (1H, ddd, $J_{H3aH4} = J_{H3aH2} = J_{H3aH3b}$ = 12.0 Hz, *H*3a), 2.43 (1H, ddd, J_{H3bH4} = 5.5 Hz, J = $_{H3bH2}$ = 3.0 Hz, J_{H3bH3a} = 12.0 Hz, *H*3b), 2.95 (1H, dd, J_{H1aH2} = 10.5 Hz, J_{H1aH1b} = 15.5 Hz, *H*1a), 3.23 (1H, dd, J_{H1bH2} = 5.5 Hz, J_{H1bH1a} = 15.5 Hz, *H*1b), 4.18 (1H, dd, J_{H4H3b} = 5.5 Hz, J_{H4H3a} = 12.0 Hz, *H*4), 4.26 (1H, dddd, J_{H2H3b} = 3.0 Hz, J_{H2H1b} = 5.5 Hz, J_{H2H1a} = 10.5 Hz, J_{H2H3a} = 12.0 Hz, *H*2), 6.78 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.17 (8*H*, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 39.6, 43.2, 46.3, 67.7, 126.2, 126.3, 126.5, 128.6, 128.8, 129.2, 129.3, 135.0, 138.9, 146.0; ESI-MS: *m*/*z* 225 (M+1).

(+)-(2*R*,4*R*)-4-Phenyl-1,2,3,4-tetrahydronaphthalene-2-ol (7b). **7b** was prepared according to the above procedure starting from the tetralone (+)-(*R*)-**2**. Yield 51%; white solid, mp 129–131 °C; $[\alpha]_D^{20}$ +13.24 (*c* 0.06 in $CHCl_3$); $[\alpha]_{Hg}^{20}$ +33.1° (*c* 0.06 in $CHCl_3$).

General procedure for the synthesis of methanesulfonates 8a and 8b

Methanesulfonyl chloride (0.24 g; 2.1 mmol) was added dropwise to an ice-cooled solution of the alcohol **7** (1 mmol) in dry pyridine (1.5 ml), and the resulting mixture was stirred for 2 h at room temperature under a N_2 atmosphere. The mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with 0.3 N HCl and then with brine. After drying (Na_2SO_4) the solvent was removed by distillation under reduced pressure to give a crude residue that was purified by

flash chromatography on silica gel (cyclohexane/EtOAC 8 : 2, as eluent).

(+)-(2*S*,4*S*)-4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl methanesulfonate (8a). **8a** was prepared according to the above procedure starting from the alcohol (–)-(2*S*,4*S*)-**7a**. Yield 80%; oil; $[\alpha]_D^{20}$ = +11.1 (*c* 0.099 in $CHCl_3$); $[\alpha]_{Hg}^{20}$ = +22.2° (*c* 0.099 in $CHCl_3$). Found: C 67.36; H 5.97%. Calc. for $C_{17}H_{18}O_3S$: C 67.52; H 6.00%.

NMR δ_H (200 MHz, $CDCl_3$) 2.19 (1H, ddd, $J_{H3aH4} = J_{H3aH2} = J_{H3aH3b}$ = 11.5 Hz, *H*3a), 2.64 (1H, ddd, J_{H3bH2} = 3.0 Hz, J_{H3bH3a} = 11.5 Hz, *H*3b), 3.04 (3H, s, OSO_2CH_3), 3.24 (1H, dd, J_{H1aH2} = 10.0 Hz, J_{H1aH1b} = 15.5 Hz, *H*1a), 3.40 (1H, dd, J_{H1bH2} = 5.0 Hz, J_{H1bH1a} = 15.5 Hz, *H*1b), 4.24 (1H, dd, J_{H4H3b} = 5.5 Hz, J_{H4H3a} = 11.5 Hz, *H*4), 5.18 (1H, dddd, J_{H2H1b} = 5.0 Hz, J_{H2H1a} = 10.0 Hz, J_{H2H3a} = 11.5 Hz, J_{H2H3b} = 3.0 Hz, *H*2), 6.78 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.23 (8H, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 36.8, 38.8, 39.8, 45.6, 77.4, 126.7, 126.74, 126.8, 128.67, 128.7, 129.1, 129.3, 133.1, 138.0, 144.9; ESI-MS: *m*/*z* 303 (M+1).

(–)-(2*R*,4*R*)-4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl methanesulfonate (8b). **8b** was prepared according to the above procedure starting from the alcohol (+)-(2*R*,4*R*)-**7b**. Yield 89%; oil; $[\alpha]_D^{20}$ –10.1 (*c* 0.089 in $CHCl_3$); $[\alpha]_{Hg}^{20}$ = –20.2° (*c* 0.089 in $CHCl_3$). Found: C 67.31; H 5.96%. Calc. for $C_{17}H_{18}O_3S$: C 67.52; H 6.00%.

(+)-(2*R*,4*S*)-2-azido-4-Phenyl-1,2,3,4-tetrahydronaphthalene (9a). Sodium azide (0.10 g; 1.6 mmol) was added to a solution of (+)-(2*S*,4*S*)-**8a** (0.25 g; 1 mmol) in dry DMF (3.5 ml) and the resulting mixture was stirred at 110 °C for 1 h, under a N_2 atmosphere. After cooling to room temperature, the mixture was poured into water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated by distillation under reduced pressure to give the desired crude azido derivative, that was used for the next step without further purification.

(–)-(2*S*,4*R*)-2-azido-4-Phenyl-1,2,3,4-tetrahydronaphthalene (9b). **9b** was prepared as described above for **9a**, starting from (–)-(2*R*,4*R*)-**8b**.

General procedure for the synthesis of *trans*-4-P-PDOT 1c and 1d

A solution of the above crude azide **9** in isopropanol (25 ml) and propionic anhydride (1.85 ml; 14 mmol) was hydrogenated over 10% Pd/C (0.018 g) at 4 atm of H_2 for 16 h at room temperature. The catalyst was filtered off over a Celite plug and the filtrate was concentrated by distillation under reduced pressure. The crude residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 7 : 3, as eluent) and crystallization from acetone/n-hexane.

(+)-*N*-(2*R*,4*S*)-*trans*-(4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (1c). **1c** was prepared according to the above procedure starting from the azide (2*R*,4*S*)-**9a**. Yield 70%; white solid, m.p. 151–152 °C; $[\alpha]_D^{20}$ = +49.5 (*c* 0.13, $CHCl_3$); $[\alpha]_{Hg}^{20}$ = +106.5° (*c* 0.13, $CHCl_3$).

Enantiomeric excess was determined by HPLC on a Chiralcel (Chiralpak) AD-H column, with hexane/iPrOH, 19 : 1 as eluent, flux 1.0 mL min^{-1}, λ 262 nm; retention time = 13.6 min; ee >99%. The physical-chemical properties were identical with those previously reported for racemic mixture.[25]

(–)-*N*-(2*S*,4*R*)-*trans*-(4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (1d). **1d** was prepared according to the above procedure starting from the azide (2*S*,4*R*)-**9b**. Yield 74%; white solid, m.p. 149–150 °C; $[\alpha]_D^{20}$ –51.3 (*c* 0.13, $CHCl_3$); $[\alpha]_{Hg}^{20}$ = –106.5° (*c* 0.13, $CHCl_3$).

Enantiomeric excess was determined by HPLC on a Chiralcel (Chiralpak) AD-H column, with hexane/iPrOH, 19 : 1 as eluent, flux 1.0 mL min^{-1}, λ 262 nm; retention time = 10.1 min; ee >99%. The physical-chemical properties were identical with those previously reported for racemic mixture.[25]

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