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2-(2-Hydroxyaryl)cinnamic amides: a new class of axially chiral molecules

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Abstract—The syntheses of several differently substituted amides formally derived from a chiral amine, either *E*-2-(2-hydroxyphenyl)-cinnamic acid or both *E*- and *Z*-2-(2-hydroxynaphthyl)cinnamic acid, are reported. These molecules display a restricted rotation about the C_2–C_{aryl} bond. The barriers to rotation about the C_2–C_{aryl} bond were measured by the dynamic ^{1}H NMR and were found to vary between 11.8 and 24.5 kcal mol^{-1}, depending on the substitution. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides, displayed a high barrier to rotation ($\Delta G_c^{\ddagger}$=24.4 kcal mol^{-1}) and could be isolated in both diastereomerically pure forms at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, was resolved, enabling for the determination of the absolute configuration of the chiral axis (a*R*).

1. Introduction

Axial chirality represents one of the most interesting stereochemical features of modern synthetic chemistry. Axially chiral molecules are often used as versatile auxiliaries or as ligands in transition-metal promoted asymmetric synthesis,[1] and nature offers a large number of representatives of this class of compounds, with, in many cases, interesting pharmacological activities.[2] Axial chirality is often associated with atropisomerism and atropisomers, i.e., with the stereoisomers resulting from hindered rotation about single bonds, where the barrier to rotation is high enough to allow for the isolation of the conformers. The condition for the existence of atropisomerism has been defined as one where stereoisomers can be isolated and have a half-life of at least 1000 s.[3] The most extensively studied class of atropisomers is biaryls,[4] especially with respect to the substitution required for restricted rotation. Reported examples of other classes of atropisomeric molecules include: substituted styrenes,[5] axially chiral amides (e.g., anilides,[6] benzamides[7] and 1-naphthamides[8]), *o*-substituted arylcarbinols of the Ar–C(OH)R_2 type,[9] 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones,[10] *o*-substituted *N*-aryl-4-alkyl-thiazoline-2-thiones[11] and substituted *N*-(2-hydroxynaphthalen-1yl)-*N*,*N*′-diacyl-hydrazines.[12]

As a part of the project aimed at synthesizing new chiral structures to be used as ligands in catalytic asymmetric applications, we decided to investigate the chiral 2-(2-hydroxyaryl)cinnamic amides **1** (Fig. 1), obtained from the coupling of the corresponding 2-(2-hydroxyaryl) cinnamic acids and a chiral primary amine. These molecules were chosen since they possess several potential sites of diversity (R^1, R^2, R^3 and Ar), which allow for the fine-tuning of their steric, electronic and conformational properties. In addition, we were also intrigued by the fact that they were structurally reminiscent of biaryl compounds and might display restricted rotation about the C_2–C_{aryl} bond and, depending on the energetic barrier to rotation, be resolved into two diastereomeric atropisomeric forms.

Herein we report the syntheses of several differently substituted amides of general type **1** (Fig. 1) derived from 2-(2-hydroxyphenyl)cinnamic and 2-(2-hydroxynaphthyl)-cinnamic acid. The barriers to rotation about the C_2–C_{aryl} bond were experimentally determined for both the phenyl and naphthyl derivatives by dynamic ^{1}H NMR methods

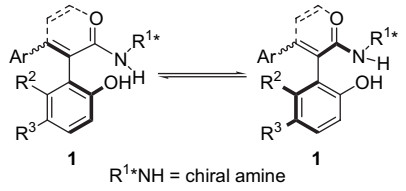

Figure 1. General structure and atropisomeric behaviour of amides **1**, and their similarity to biaryl compounds (dashed lines).

Keywords: Axial chirality; Cinnamic acid; Atropisomerism.
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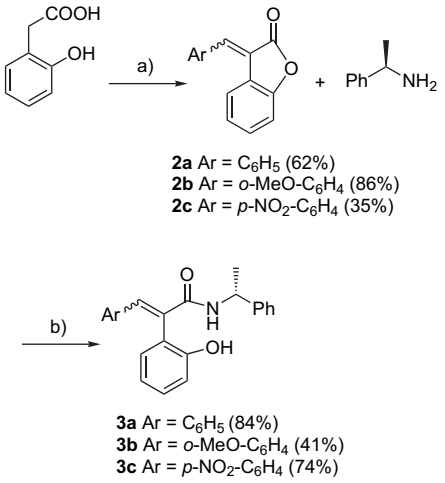
and were found to be significantly lower than those observed in biaryls bearing similar substitution pattern. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides, displayed a high barrier to rotation ($\Delta G_c^{\ddagger}$>24.4 kcal mol^{-1}) and both diastereomerically pure forms could be isolated at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, was determined and the absolute configuration of the chiral axis assigned.

2. Results and discussion

The syntheses of 2-(2-hydroxyphenyl)cinnamic amides **3** were performed using 2-hydroxyphenylacetic acid, as a starting material, which was converted into lactones **2a–c** (Scheme 1 and Table 1), through a Perkin condensation with different aromatic aldehydes.[13]



Scheme 1. (a) AcONa (1 equiv), ArCHO (1 equiv), Ac_2O, reflux, 6 h and (b) (*R*)-1-phenylethylamine (2 equiv), 2-hydroxypyridine (0.2 equiv), THF, rt, 72 h.

Single-crystals of lactone *E*-**2a** (Ar=Ph) suitable for an X-ray data collection were obtained from a saturated solution of AcOEt/hexane. In the solid state, the fused rings of lactone *E*-**2a** show a very limited deviation from coplanarity, with a τ_1 torsional angle (Fig. 2) of less than 5°. A more pronounced deviation from planarity is observed at torsion τ_2 (Fig. 2), reaching a value of about 12°.

The opening of lactones **2** was then performed, using (*R*)-1-phenylethylamine. Simple aminolysis of lactone **2a** in several solvents (DCM, toluene, THF) almost led to the exclusive formation of 2-hydroxy phenylacetamide **4** [R=(*R*)-1-phenylethylamine], probably through a tandem Michael retro–Mannich sequence (Scheme 2).

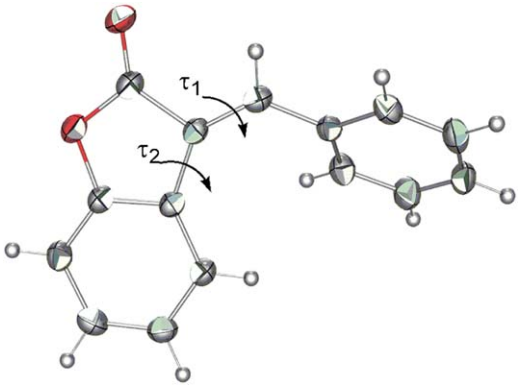
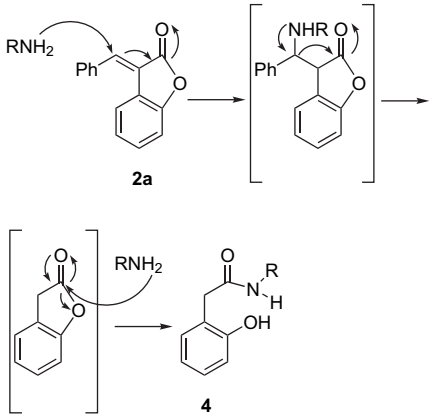


Figure 2. Ortep representation (30% probability level) of the X-ray molecular structure of lactone *E*-**2a**. Carbon, grey; hydrogen, light grey; oxygen, red.



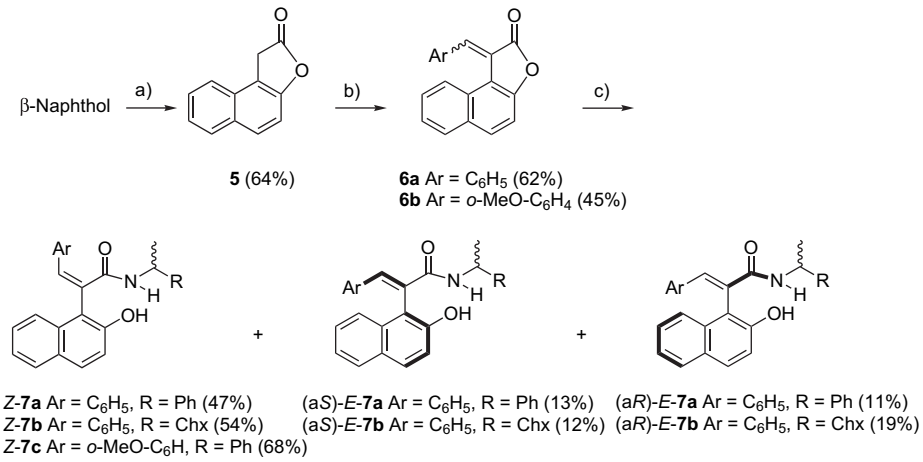
Scheme 2. Proposed mechanism for the reaction of lactone **2** with amines.

In order to favour the opening of lactone **2** with respect to the Michael addition, which is the first step of the tandem conjugate addition retro-Mannich sequence, 2-hydroxypyridine was employed as a proton transfer catalyst.[14] Under these conditions, good yields of amides **3** were obtained as separable mixtures of *E* and *Z* isomers (Table 1).

2-(2-Hydroxynaphthyl)cinnamic amides **7** were prepared starting from β-naphthol (Scheme 3), which was transformed into lactone **5**,[15] and then subjected to Perkin condensation using several aromatic aldehydes. Lactones **6** were obtained as mixtures of *E* and *Z* isomers (Table 1). X-ray quality crystals of lactone *E*-**6a** (Ar=Ph) were obtained from a saturated solution of AcOEt/hexane. The solid state molecular structure of lactone *E*-**6a** is substantially similar to that of *E*-**2a**, with the notable exception of an enhanced deviation from co-planarity, the τ_1 between the naphtholic aromatic ring and the exocyclic double bond being

Table 1. Synthesis of lactones **2** and **5**, and amides **3** and **7**

Entry	Ar	Lactone	Yield (%)	*E*/*Z*	R	*R*/*S*	Amide	Yield (%)	*E*/*Z*	a*S*/a*R*
1	C_6H_5	**2a**	62	85/15	Ph	*R*	**3a**	84	75/25	—
2	*o*-MeO–C_6H_4	**2b**	86	100/0	Ph	*R*	**3b**	41	100/0	—
3	*p*-NO_2–C_6H_4	**2c**	35	100/0	Ph	*R*	**3c**	74	76/24	—
4	C_6H_5	**6a**	62	25/75	Ph	*R*	**7a**	71	34/66	1.2/1
5	C_6H_5	**6a**	62	25/75	Chx	*S*	**7b**	88	39/61	1/1.3
6	*o*-MeO–C_6H_4	**6b**	45	0/100	Ph	*R*	**7c**	68	0/100	—



Scheme 3. (a) Glyoxal (7 equiv), KOH (1 equiv), H_2O, 30 °C, 4.5 h; (b) AcONa (1 equiv), RCHO (1 equiv), Ac_2O, reflux, 6 h and (c) *n*BuLi (3 equiv), $RCH(CH_3)NH_2$ (2.5 equiv), THF, rt, 1 h, −40 °C, **6** (1 equiv), 2 h.

about 26°. At variance, the τ_2 dihedral angle is only marginally lowered to ca. 10°. Attempts to open lactones **6** by reaction with amines in various solvents and in the presence of 2-hydroxypyridine met with limited success and the major isolated products were the 2-hydroxynaphthylacetamides derived from the conjugate addition retro-Mannich mechanism described above. To overcome this problem, we reasoned that the hardness of the amine nucleophile had to be increased, in order to favour the attack to the carbonyl of the lactone with respect to the Michael addition.

This was achieved by first deprotonating the amines, (*R*)-1-phenylethylamine or (*S*)-1-ethylcyclohexylamine, with *n*BuLi and then adding the lithium amide solution to a cold solution of the lactone (Scheme 3). In this way, no 2-hydroxynaphthylacetamide was detected, and good yields of amides **7** were obtained as separable mixtures of one *Z* isomer and two atropisomeric *E* isomers (Table 1 and Scheme 3). X-ray quality crystals of amide a*R*-*E*-**7a** (Ar=Ph and R=Ph) were obtained from a saturated solution of AcOEt/hexane. The solid state structure of amide a*R*-*E*-**7a** shows that, in the crystal, the molecule adopts a staggered conformation with a dihedral angle of ca. 89° between the naphtholic ring and the unsaturated amide plane (Fig. 3). The absolute configuration of the chiral axis, based on the fixed stereocenter of (*R*)-1-phenylethylamine, resulted to be a*R*.

Circular dichroism (CD) curves were measured for compounds a*R*-*E*-**7a** and a*S*-*E*-**7b** (Fig. 4): two nearly mirror image curves were obtained for the two compounds. In the case of a*R*-*E*-**7a**, an intense positive band at 228 nm ($\Delta\varepsilon$ +14), a negative band at 264 mn ($\Delta\varepsilon$ −8) and a weak positive band at 333 nm ($\Delta\varepsilon$ +1.7), were observed. In particular the exciton band at about 228 nm has been attributed to the long axis polarized ^1B_b transition of naphthalene,[16] while the band at 264 nm is probably due to the absorption of the cinnamic moiety.[17] These two chromophores are oriented perpendicularly to each other and can be described as two interacting orthogonal dipoles. The strong positive–negative exciton is in agreement with a positive helicity[18] and with the a*R* absolute configuration of the chiral axis, as shown also by the X-ray molecular structure. A negative band at 228 nm ($\Delta\varepsilon$ −6), a positive band at 262 mn ($\Delta\varepsilon$ +3) and a weak negative band at 335 nm ($\Delta\varepsilon$ −0.6), were observed for a*S*-*E*-**7b**. In this case a negative–positive exciton is indicative of a negative helicity and of the a*S* configuration of the chiral axis.

A study of the barrier to rotation about the C_2–C_{aryl} bond was then undertaken for all the amides synthesized. Kinetic data

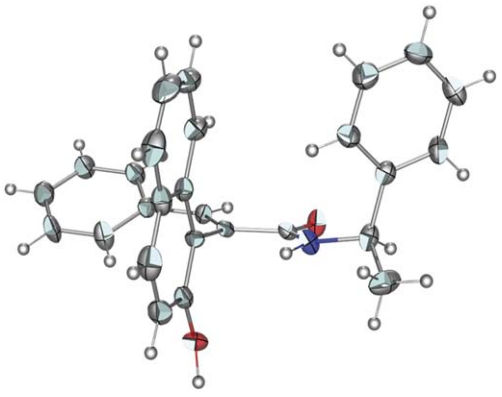


Figure 3. Ortep representation (30% probability level) of the X-ray molecular structure in amide a*R*-*E*-**7a**. Carbon, grey; hydrogen, light grey; nitrogen, blue; oxygen, red.

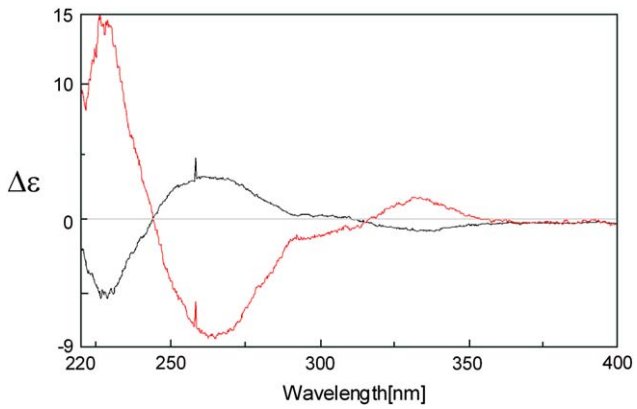


Figure 4. CD spectra of a*R*-*E*-**7a** (red curve) and a*S*-*E*-**7b** (black curve) showing nearly enantiomeric behaviour.

Table 2. Coalescence temperature and activation parameters of the configurationally unstable amides **3a–c** and *Z*-**7a–c**

Entry	Amide	T_c (K)	k_c (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	**3a**	243	120.6	11.8
2	**3b**	245	72.5	12.2
3	**3c**	248	96.7	12.2
4	*Z*-**7a**	298	88.4	14.8
5	*Z*-**7b**	303	48.3	15.3
6	*Z*-**7c**	303	193.6	14.6

and energy barriers of interconversion of configurationally labile compounds have been conveniently investigated, among others, by means of dynamic NMR.[19] The free energy barriers to internal rotation in the phenol-substituted amides **3a–c** and *Z*-**7a–c** were estimated from their variable temperature ^{1}H NMR spectra by measuring the coalescence temperature of the N–H signal (Table 2). The rate constants k_c were calculated from the relationship $k_c=\pi\Delta\nu/\sqrt{2}$, and the free energies of activation ($\Delta G_c^{\ddagger}$) were derived by substituting k_c into the Eyring equation.[19]

For amides **3a–c**, the NMR experiments were run in CD_2Cl_2 and, as a general trend, the signals are well resolved at 298 K, broaden in the 253–233 K range and split below 233 K yielding two sets of signals (Fig. 5). The values for $\Delta G_c^{\ddagger}$ are less than 12.2 kcal mol^{-1} (Table 2, entries 1–3) and are in agreement with the free rotation of the two substituents about the chiral axis at room temperature. For amides *Z*-**7a–c**, the NMR experiments were performed in $CDCl_3$ and the coalescence is observed near room temperature, with a single set of well resolved signals above 313 K and two completely resolved sets of signals below 243 K (Fig. 4). The $\Delta G_c^{\ddagger}$ are comprised between 14.6 and 15.3 kcal mol^{-1} (Table 2, entries 4–6).

The barriers to rotation for amides *E*-**7a–b** were also investigated. In this case, in variable temperature ^{1}H NMR studies, the coalescence temperature was not reached even upon heating a DMSO-d_6 sample to 413 K. The atropisomers are stable enough to be isolated at room temperature, although it was noticed that both diastereomerically pure atropisomers slowly equilibrated to a 1/1 mixture of the a*R* and a*S* atropisomers, upon standing in solution (24 h in $CDCl_3$) at room temperature. The transformation

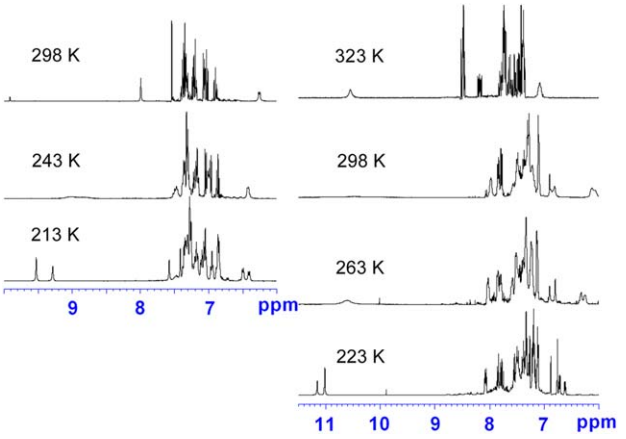


Figure 5. Variable temperature ^{1}H NMR spectra of amides **3a** (left) and *Z*-**7a**.

Table 3. Activation parameters of amides (a*R*)-*E*-**7a–b** in $CDCl_3$ at 298 K

Entry	Compound	k_c (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	(a*R*)-*E*-**7a**	6.40×10^6	24.4
2	(a*R*)-*E*-**7b**	7.85×10^6	24.5

rates of (a*R*)-*E*-**7a** and (a*R*)-*E*-**7b** were followed at 298 K, by monitoring the time-dependent first-order variation of the relative intensities of the ^{1}H NMR spectra in $CDCl_3$. The Eyring equation was used to derive the $\Delta G_c^{\ddagger}$ values from the rate constants k_c (Table 3).

When comparing the values of the barrier to rotation for compounds **3a–c** and *Z*-**7a–c** to those observed for 2,2′,6 trisubstituted biphenyls[20] and 1,1′,10 trisubstituted-2,2′-binaphthyls[21] (actually, both amides **3a–c** and *Z*-**7a–c** are reminiscent of a trisubstituted biaryl chiral axis, see Fig. 1), it can be noted that the former are significantly lower. A similar behaviour is found in amides *E*-**7a–b** with respect to tetrasubstituted biaryl moieties. In fact, slowly interconverting atropisomeric biaryls have been observed, particularly, when associated to 2,2′,6 trisubstituted biphenyls, and 1,1′,10 trisubstituted-2,2′-binaphthyls, depending on the size of the substituents, but in general tetrasubstituted biarlys are configurationally stable compounds. In the case of our 2-(2-hydroxyaryl)cinnamic amides, the rather low barrier to rotation and the relatively fast atropisomerization process can be explained assuming that, in the lower energy transition state for rotation, the carboxamide moiety is not coplanar with the double bond, thus facilitating the rotation about the C_2–C_{aryl} bond.[22]

3. Conclusions

The syntheses of several differently substituted chiral amides formally derived from a chiral amine, either *E*-2-(2-hydroxyphenyl)cinnamic acid (**3a–c**) or both *E*- and *Z*-2-(2-hydroxynaphthyl)cinnamic acid (**7a–c**), are reported. These molecules display a restricted rotation about the C_2–C_{aryl} bond and, depending on their barrier to rotation, can be isolated in two atropisomeric forms. The barriers to rotation about the C_2–C_{aryl} were measured by dynamic ^{1}H NMR and were found to vary between 11.8 and 24.5 kcal mol^{-1}, depending on the substitution. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides **7** displayed a high barrier to rotation ($\Delta G_c^{\ddagger}>24.4$ kcal mol^{-1}) and could be isolated in both diastereomerically pure forms at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, (a*R*)-*E*-**7a**, was resolved, allowing the determination of the absolute configuration of the chiral axis. The application of these new chiral structures as chiral organic catalysts and ligands for enantioselective metal catalyzed reactions is now actively being investigated in our laboratories.

4. Experimental

4.1. General

All manipulations requiring anhydrous conditions were carried out in flame-dried glassware, with magnetic stirring, and

under an atmosphere of purified nitrogen. All aldehydes were distilled before use. All other commercially available reagents were used as received. Anhydrous solvents were purchased from commercial sources and withdrawn from the container by syringe, under a slightly positive pressure of nitrogen. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a permanganate solution. Flash column chromatography was performed using silica gel 60 A, particle size 40–64 μm, following the procedure by Still and co-workers.[23] Melting points are uncorrected. Proton NMR spectra were recorded on a 400 MHz spectrometer. Proton chemical shifts are reported in parts per million (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as an internal standard ($CDCl_3$ δ 7.26 ppm). Carbon NMR spectra were recorded on a 400 spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) with the solvent reference relative to (TMS) employed as an internal standard ($CDCl_3$ δ 77.0 ppm). Infrared spectra were recorded on a standard Infrared spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter with 1-dm cell at the sodium D line. CHN-analyses were performed using a Perkin Elmer 2400 Series II CHNS/O Analyzer. CD spectra were recorded at 298 K on a Jasco J-500C spectropolarimeter, in acetonitrile, in a 0.01-cm cell in the range 220–400 nm.

4.1.1. 3-[1-Phenyl-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one (2a). $NaHCO_3$ (1 equiv, 32.9 mmol, 2.80 g) was dissolved in 50 mL of water. 2-Hydroxyphenylacetic acid (1 equiv, 32.9 mmol, 5 g) was added to the mixture to obtain a yellow solution. The system was stirred vigorously and warmed at 50 °C for 2 h. The solvent was evaporated under reduced pressure affording a white solid and the last traces of water were azeotropically removed by evaporation with toluene (2×30 mL) and drying under vacuum. Sodium 2-hydroxyphenylacetate (5.60 g, 32.0 mmol) was treated with benzaldehyde (3.4 mL, 33.6 mmol) and acetic anhydride (13 mL) at reflux temperature for 6 h. The hot mixture was then added to water and stirred vigorously overnight. HCl concentrated was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and successively precipitated with petroleum ether at −15 °C affording the lactone **2a** as an orange solid (2.14 g, 62% yield), mp=88 °C. IR (nujol): ν_{max}=1782, 1769, 1629, 1607, 1293, 1240, 1148, 1121, 1082, 1080, 1022, 967, 932, 877, 757, 754, 732, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90 (s, 1H, C*H*), 7.75 (d, J=7.7 Hz, 1H, Ar*H*), 7.69–7.72 (m, 2H, Ar*H*), 7.48–7.54 (m, 3H, Ar*H*), 7.37 (dddd, J_1=8.1 Hz, J_2=7.3 Hz, J_3=1.2 Hz, J_4=1.2 Hz, 1H, Ar*H*), 7.16 (d, J=8.1 Hz, 1H, Ar*H*), 7.06 (dd, J_1=7.8 Hz, J_2=7.5 Hz, 1H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ=169.2, 154.9, 141.3, 134.4, 131.4, 131.0, 129.8, 129.3, 124.1, 123.2, 122.6, 122.2, 111.6; $C_{15}H_{10}O_2$ calcd. C 81.07, H 4.54; found: C 79.96, H 4.46.

X-ray crystallographic data of ***2a***. Orthorhombic, space group *Pcab*, a=9.855(1), b=12.208(2), c=18.268(3) Å, V=2197.8(6) Å^3, Z=8, ρ=1.343 g/cm^3, μ(Mo Kα)=0.09 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final R and wR values of 0.047 for 1171 reflections with $I>2\sigma I$, and 0.111 for 1928 reflections, respectively. All the crystallographic data presented in the manuscript (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 602856. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

4.1.2. 3-[1-(2-Methoxy-phenyl)-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one (2b). 2-Hydroxyphenylacetic acid (1 equiv, 9.85 mmol, 1.50 g) was treated with sodium acetate (1 equiv, 9.85 mmol, 1.35 g), 2-methoxy-benzaldehyde (1 equiv, 9.85 mmol, 1.35 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. Water (70 mL) was then added to the hot mixture followed by vigorous stirring overnight. Concentrated HCl (10 mL) was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and the organic phase was successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was then purified by flash chromatography on silica gel (CH_2Cl_2/hexane=75/25) affording the desired product as a yellow solid (2.13 g, 86% yield), mp=123 °C. IR (Nujol): ν_{max}=1782, 1723, 1634, 1594, 1316, 1295, 1255, 1165, 1126, 1075, 1021, 967, 876, 773, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, 1H, C*H*), 7.76 (d, J=7.6 Hz, 1H, Ar*H*), 7.65 (d, J=7.7 Hz, 1H, Ar*H*), 7.49 (dd, J_1=7.8 Hz, J_2=7.9 Hz, 1H, Ar*H*), 7.33 (dd, J_1=7.8 Hz, J_2=7.8 Hz, 1H, Ar*H*), 7.13 (d, J=8.1 Hz, 1H, Ar*H*), 7.01–7.09 (m, 3H, Ar*H*), 3.91 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=169.4, 158.7, 154.7, 137.8, 132.9, 130.9, 130.0, 123.9, 123.5, 123.1, 122.7, 122.1, 120.6, 111.5, 111.4, 56.0; $C_{16}H_{12}O_3$ calcd. C 76.19, H 4.76; found: C 76.07, H 4.57.

4.1.3. 3-[1-(4-Nitro-phenyl)-meth-(*E*)-ylidene]-3*H*-benzofuran-2-one (2c). 2-Hydroxyphenylacetic acid (1 equiv, 9.85 mmol, 1.5 g) was treated with sodium acetate (1 equiv, 9.85 mmol, 1.35 g), 4-nitro-benzaldehyde (1 equiv, 9.85 mmol, 1.50 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. The hot mixture was then poured into water (70 mL) and stirred vigorously overnight. Concentrated HCl (10 mL) was added and the mixture was warmed at 60 °C for 5 h. The product was then extracted with toluene and the organic phase was successively washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was then purified by flash chromatography on silica gel (hexane/AcOEt=70/30) affording the desired product as a yellow solid (0.92 g, 35% yield), mp=189 °C. IR (Nujol): ν_{max}=1780, 1613, 1588, 1524, 1515, 1343, 1319, 1239, 1145, 1123, 1079, 880, 774, 751, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.38 (d, J=8.5 Hz, 2H, Ar*H*), 7.86 (s, 1H, C*H*), 7.85 (d, J=8.2 Hz, 2H, Ar*H*), 7.57 (d, J=7.7 Hz, 1H, Ar*H*), 7.43 (dd, J_1=8.0 Hz, J_2=7.7 Hz, 1H, Ar*H*), 7.19 (d, J=8.0 Hz, 1H, Ar*H*), 7.08 (dd, J_1=7.7 Hz, J_2=7.7 Hz, 1H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ=168.3, 155.5, 148.8, 140.9, 137.2, 132.6, 131.8, 130.4, 124.6, 124.4, 123.3, 121.4, 112.1;

$C_{15}H_9NO_4$ calcd C 67.41, H 3.37, N 5.24; found: C 67.23, H 3.25, N 5.14.

4.2. General procedure for the synthesis of 2-(2-hydroxyphenyl)cinnamic amides

A solution of lactone (1 equiv, 1.35 mmol), (*R*)-1-phenylethylamine (2 equiv, 2.70 mmol, 350 μL) and 2-hydroxypyridine (0.2 equiv, 0.27 mmol, 28 mg) in THF (24 mL) was stirred at room temperature for 3 d. The reaction mixture was then hydrolyzed with HCl 1 M and extracted with AcOEt (12×3 mL). The combined organic layers were washed with brine and then dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography on silica gel.

4.2.1. (*E*)-2-(2-Hydroxy-phenyl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (3a). Pale orange solid (0.29 g, 63% yield). IR (Nujol): ν_{max}=3397, 1644, 1612, 1595, 1514, 1293, 1247, 1234, 1015, 937, 750, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (s, 1H, C*H*), 7.31–7.35 (m, 3H, Ar*H*), 7.24–7.27 (m, 3H, Ar*H*), 7.13–7.21 (m, 3H, Ar*H*), 7.03–7.10 (m, 4H, Ar*H*), 6.90–6.95 (m, 1H, Ar*H*), 6.20 (d, *J*=7.9 Hz, 1H, N*H*), 5.18 (m, 1H, C*H*), 1.44 (d, *J*=6.9 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=168.2, 154.9, 143.2, 139.0, 134.7, 131.3, 131.1, 130.5, 129.4, 129.1, 128.7, 127.9, 127.8, 126.3, 122.3, 121.6, 117.9, 49.8, 22.3; $[\alpha]_D$ −25.6 (*c* 0.50, $CHCl_3$); $C_{23}H_{21}NO_2$ calcd C 80.19, H 7.01, N 3.90; found: C 79.80, H 6.87, N 3.96.

4.2.2. (*E*)-2-(2-Hydroxy-phenyl)-3-(2-methoxy-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (3b). Yellow solid (0.06 g, 41% yield), mp=125 °C. IR (Nujol): ν_{max}=3410, 3402, 3125, 1653, 1600, 1522, 1292, 1252, 1163, 1105, 1024, 759, 750, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88 (s, 1H, C*H*), 7.23–7.37 (m, 6H, Ar*H*), 7.18 (dd, J_1=7.8 Hz, J_2=7.8 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.2 Hz, 1H, Ar*H*), 6.96 (d, *J*=7.6 Hz, 1H, Ar*H*), 6.84–6.75 (m, 3H, Ar*H*), 6.62 (dd, J_1=7.5 Hz, J_2=7.5 Hz, 1H, Ar*H*), 6.28 (d, *J*=7.8 Hz, 1H, N*H*), 5.26–5.19 (m, 1H, C*H*), 1.51 (d, *J*=6.9 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=169.3, 158.2, 155.2, 143.2, 133.7, 132.8, 131.2, 130.8, 130.5, 130.3, 129.1, 127.8, 126.5, 123.8, 122.7, 121.0, 120.7, 117.9, 110.8, 55.8, 49.8, 22.2; $[\alpha]_D$ −10.1 (*c* 0.11, $CHCl_3$); $C_{24}H_{23}NO_3$ calcd C 77.21, H 6.17, N 3.75; found: C 76.87, H 6.16, N 3.65.

4.2.3. (*E*)-2-(2-Hydroxy-phenyl)-3-(4-nitro-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (3c). Yellow solid (0.07 g, 56% yield), mp=70 °C. IR (Nujol): ν_{max}=3404, 3240, 1651, 1614, 1599, 1518, 1343, 1289, 1109, 1043, 1014, 852, 833, 758, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (br s, 1H, O*H*), 7.96 (d, *J*=8.4 Hz, 2H, Ar*H*), 7.65 (s, 1H, C*H*), 7.25–7.35 (m, 6H, Ar*H*), 7.14 (d, *J*=8.3 Hz, 2H, Ar*H*), 7.06 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.86–6.94 (m, 2H, Ar*H*), 6.28 (d, *J*=7.9 Hz, 1H, N*H*), 5.14–5.21 (m, 1H, C*H*), 1.46 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=167.8, 155.0, 147.6, 142.8, 141.6, 136.3, 135.6, 131.7, 130.9, 130.8, 130.0, 129.2, 127.9, 126.3, 123.8, 121.7, 121.4, 118.2, 50.0, 22.1; $[\alpha]_D$ −15.5 (*c* 0.15, $CHCl_3$); $C_{23}H_{20}N_2O_4$ calcd C 71.13, H 5.15, N 7.22; found: C 70.84, H 5.06, N 7.03.

4.3. 1*H*-Naphtho[2,1-*b*]furan-2-one (5)

The compound was prepared following a literature procedure.[14] The analytical data were in agreement with those reported.

4.4. 1-[1-Phenyl-meth-(*E*)-ylidene]-1*H*-naphtho[2,1-*b*]-furan-2-one + 1-[1-phenyl-meth-(*Z*)-ylidene]-1*H*-naphtho[2,1-*b*]furan-2-one (6a)

1*H*-Naphtho[2,1-*b*]furan-2-one (1 equiv, 10.15 mmol, 1.87 g) was treated with sodium acetate (1 equiv, 10.15 mmol, 1.38 g), benzaldehyde (1 equiv, 10.15 mmol, 1.03 mL) and acetic anhydride (7 mL) at reflux temperature for 6 h. The hot mixture was added to water (120 mL) and stirred vigorously overnight. The mixture was then acidified with concentrated HCl (15 mL) keeping the system under magnetic stirring at 60 °C for 5 h. The reaction mixture was cooled and the product was extracted in toluene, drying the organic phase over Na_2SO_4. Evaporation of toluene gave the crude product, which was purified by flash chromatography on silica gel (hexane/AcOEt=8/2) affording the desired product as a yellow solid (1.68 g, 62% yield) and as a 1/3 mixture of *E* and *Z* diastereomers.

IR (Nujol): ν_{max}=1771, 1610, 1573, 1523, 1262, 1139, 1106, 987, 889, 853, 801, 765, 740, 688; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.37 (d, *J*=8.6 Hz, 1H, Ar*H*), 8.30 (s, 1H, C*H*), 8.09 (s, 1H, C*H*), 8.04–8.07 (m, 2H, Ar*H*), 7.95 (d, *J*=8.7 Hz, 2H, Ar*H*), 7.89 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.86 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.69 (ddd, J_1=7.6 Hz, J_2=7.1 Hz, J_3=1.3 Hz, 1H, Ar*H*), 7.35–7.53 (m, 12H, Ar*H*), 7.16 (ddd, J_1=7.8 Hz, J_2=7.7 Hz, J_3=1.1 Hz, 1H, Ar*H*), 6.99 (d, *J*=8.5 Hz, 1H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$): 170.2, 155.0, 153.1, 143.1, 140.7, 135.7, 134.0, 133.6, 132.4, 131.9, 131.6, 131.5, 131.1, 130.7, 130.6, 129.8, 129.1, 128.7, 127.5, 127.2, 125.2, 125.1, 123.7, 123.1, 122.5, 112.1, 112.0; $C_{19}H_{12}O_2$ calcd C 83.82, H 4.41; found: C 83.46, H 4.34.

X-ray crystallographic data of ***6a***. Orthorhombic, space group *Pcab*, *a*=7.932(4), *b*=13.908(10), *c*=24.500(17) Å, *V*=2703(3) Å^3, *Z*=8, ρ=1.338 g/cm^3, μ(Mo Kα)=0.09 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.068 for 971 reflections with $I>2\sigma I$, and 0.145 for 2458 reflections, respectively. CCDC No. 602857.

4.5. 1-[1-(2-Methoxy-phenyl)-meth-(*E*)-ylidene]-1*H*-naphtho[2,1-*b*]furan-2-one (6b)

1*H*-Naphtho[2,1-*b*]furan-2-one (1 equiv, 4.54 mmol, 0.83 g) was treated with sodium acetate (1 equiv, 4.54 mmol, 0.37 g), 2-methoxy-benzaldehyde (1 equiv, 4.54 mmol, 0.62 g) and acetic anhydride (6 mL) at reflux temperature for 6 h. The hot mixture was added to water (120 mL) and stirred vigorously overnight. The mixture was then acidified with HCl (15 mL) keeping the system under magnetic stirring at 60 °C for 5 h. A brown precipitate was formed. The reaction mixture was cooled and the product was extracted in toluene, drying the organic phase over Na_2SO_4. Evaporation of toluene gave the crude product, which was purified by flash chromatography on silica gel (hexane/AcOEt=75/25)

affording the desired product as an orange solid (1.47 g, 45% yield).

Mp=157 °C. IR (Nujol): ν_{max}=1775, 1599, 1524, 1292, 1254, 1112, 1001, 1020, 973, 807, 780, 744; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.58 (s, 1H, Ar*H*), 8.38 (d, *J*=8.5 Hz, 1H, Ar*H*), 8.19 (d, *J*=7.7 Hz, 1H, Ar*H*), 7.92 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.86 (d, *J*=8.7 Hz, 1H, Ar*H*), 7.67 (dd, J_1=7.4 Hz, J_2=7.9 Hz, 1H, Ar*H*), 7.52–7.45 (m, 2H, Ar*H*), 7.34 (d, *J*=8.7 Hz, 1H, Ar*H*), 7.08 (dd, J_1=7.6 Hz, J_2=7.6 Hz, 1H, Ar*H*), 6.99 (d, *J*=8.3 Hz, 1H, Ar*H*), 3.96 (s, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.7, 158.6, 152.8, 141.5, 138.7, 132.9, 132.4, 131.9, 131.5, 130.5, 128.9, 128.7, 125.1, 123.0, 122.8, 120.5, 117.4, 112.0, 110.8, 56.1; $C_{20}H_{14}O_3$ calcd C 79.47, H 4.63; found: C 79.44, H 4.50.

4.6. 2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (7a)

*n*BuLi (1.6 M in hexanes 4.31 mL, 6.90 mmol) was slowly added to a solution of (*R*)-1-phenylethylamine (0.742 mL, 5.75 mmol) in anhydrous tetrahydrofuran (14 mL), in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to −40 °C and lactone **6a** (626 mg, 2.30 mmol) was added. The reaction mixture was stirred at −40 °C for 2 h, quenched with 1 M HCl (42 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography giving three pale yellow solids.

4.6.1. (*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide [(a*R*)-*E*-7a]. 0.10 g, 11% yield, mp=180 °C. IR (Nujol): ν_{max}=3403, 3397, 3115, 1650, 1600, 1582, 1342, 1276, 1247, 1211, 1158, 1079, 992, 955, 821, 775, 751, 699, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.85–7.88 (m, 1H, Ar*H*), 7.60–7.63 (m, 1H, Ar*H*), 7.39–7.41 (m, 2H, Ar*H*), 7.29 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.16–7.21 (m, 4H, Ar*H*), 6.97–7.10 (m, 6H, Ar*H*), 5.82 (d, *J*=7.8 Hz, 1H, N*H*), 5.15–5.20 (m, 1H, C*H*), 1.31 (d, *J*=6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.5, 151.8, 143.3, 142.4, 134.4, 132.8, 131.6, 130.2, 130.0, 129.6, 129.0, 128.9, 128.8, 128.0, 127.5, 126.8, 126.1, 124.6, 124.4, 118.6, 114.0, 49.6, 22.3; $[\alpha]_D$ −200.4 (*c* 0.15, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd C 82.44, H 5.85, N 3.56; found: C 80.71, H 6.17, N 3.32.

*X-ray crystallographic data of (aR)-E-**7a***. Monoclinic, space group $P2_1$, *a*=10.014(6), *b*=10.129(3), *c*=21.348(15) Å, β=99.30(6)°, *V*=2137(2) Å^3, *Z*=4, ρ=1.223 g/cm^3, μ(Mo Kα)=0.08 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares, with final *R* and *wR* values of 0.063 for 2160 reflections with $I>2\sigma I$, and 0.117 for 4114 reflections, respectively. CCDC No. 602858.

4.6.2. (*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide [(a*S*)-*E*-7a]. 0.12 g, 13% yield, mp=181 °C. IR (Nujol): ν_{max}=3399, 3150, 1651, 1593, 1576, 1537, 1516, 1504, 1342, 1285, 1246, 1209, 1141, 1080, 923, 955, 822, 766, 754, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.32 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.88 (d, *J*=7.7 Hz, 1H, Ar*H*), 7.69 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.39–7.48 (m, 2H, Ar*H*), 7.00–7.29 (m, 11H, Ar*H*), 5.84 (d, *J*=7.8 Hz, 1H, N*H*), 5.13–5.21 (m, 1H, C*H*), 1.24 (d, *J*=6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.3, 151.8, 143.3, 142.5, 134.4, 132.8, 131.6, 130.3, 130.0, 129.7, 129.0, 128.9, 128.0, 127.6, 126.7, 126.2, 124.6, 124.2, 118.6, 114.0, 49.6, 22.1; $[\alpha]_D$ +93.2 (*c* 0.19, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd C 82.44, H 5.85, N 3.56; found: C 80.71, H 6.17, N 3.32.

4.6.3. (*Z*)-2-(2-Hydroxy-naphthalen-1-yl)-3-phenyl-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (*Z*-7a). 0.43 g, 47% yield, mp=81 °C. IR (Nujol): ν_{max}=3320, 3056, 1618, 1512, 1510, 1260, 1232, 1225, 975, 950, 819, 751, 698; ^{1}H NMR (400 MHz, $CDCl_3$, 313 K): δ=7.99 (d, *J*=8.5 Hz, 1H, Ar*H*), 7.84 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.78 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.25–7.51 (m, 11H, Ar*H*), 7.09–7.11 (m, 2H, Ar*H*), 6.85 (s, 1H, C*H*), 6.05 (d, *J*=7.3 Hz, 1H, N*H*), 5.13–5.20 (m, 1H, C*H*), 1.39 (d, *J*=6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$, 313 K): δ=171.2, 153.9, 141.9, 138.1, 135.2, 133.4, 130.7, 129.8, 129.2, 129.1, 129.0, 128.9, 128.7, 128.0, 127.0, 123.7, 123.3, 120.4, 118.1, 50.0, 21.1; $[\alpha]_D$ −26.1 (*c* 0.15, $CHCl_3$); $C_{27}H_{23}NO_2$ calcd C 82.44, H 5.85, N 3.56; found: C 80.99, H 5.88, N 3.34.

4.7. *N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide (7b)

*n*BuLi (1.6 M in hexanes 3.80 mL, 5.94 mmol) was slowly added to a solution of (*S*)-1-cyclohexyl-ethylamine (0.74 mL, 4.95 mmol) in anhydrous tetrahydrofuran, in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to −40 °C and lactone **6a** (540 mg, 1.98 mmol) was added. The reaction mixture was stirred at −40 °C for 2 h, quenched with HCl 1 M (42 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The product obtained was purified by flash chromatography giving three different pale yellow solids.

4.7.1. (*E*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide [(a*R*)-*E*-7b]. 0.09 g, 15% yield, mp=70 °C. IR (Nujol): ν_{max}=3410, 3171, 1652, 1600, 1506, 1344, 1282, 1206, 958, 820, 749, 690, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.86 (d, *J*=7.6 Hz, 1H, Ar*H*), 7.64 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.37–7.43 (m, 2H, Ar*H*), 7.29 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.02–7.15 (m, 5H, Ar*H*), 5.44 (d, *J*=8.9 Hz, 1H, N*H*), 3.85–3.95 (m, 1H, C*H*), 1.47–1.65 (m, 5H, Cy*H*), 1.01–1.16 (m, 4H, Cy*H*), 0.85–0.89 (m, 4H, C*H*$_3$), 0.62–0.71 (m, 1H, C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.5, 151.8, 141.9, 134.6, 132.8, 131.5, 130.2, 129.8, 129.6, 128.9, 128.8, 128.0, 127.1, 124.5, 124.2, 118.5, 114.3, 50.5, 43.1, 29.5, 28.9, 26.7, 26.4, 18.0; $[\alpha]_D$ −57.9 (*c* 0.39, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

4.7.2. (*E*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide [(a*S*)-*E*-7b]. 0.07 g, 19% yield, mp=179 °C. IR (Nujol): ν_{max}=3399, 3227, 1652, 1605, 1595, 1511, 1351, 1246, 1205, 1143,

827, 749, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.31 (s, 1H, C*H*), 7.90 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.86 (d, *J*=7.9 Hz, 1H, Ar*H*), 7.67 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.37–7.46 (m, 2H, Ar*H*), 7.27 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.16–7.21 (m, 1H, Ar*H*), 7.05–7.12 (m, 4H, Ar*H*), 6.04 (br s, 1H, O*H*), 5.36 (d, *J*=9.0 Hz, 1H, N*H*), 3.88–3.97 (m, 1H, C*H*), 1.48–1.60 (m, 3H, Cy*H*), 1.23–1.38 (m, 3H, Cy*H*), 0.68–1.10 (m, 7H, Cy*H*), 0.33–0.42 (m, 1H, Cy*H*); ^{13}C NMR (400 MHz, $CDCl_3$): δ=166.3, 151.5, 141.9, 134.5, 132.8, 131.5, 130.2, 129.9, 129.6, 129.0, 128.8, 127.9, 127.1, 124.6, 118.4, 114.2, 50.2, 43.3, 29.4, 28.3, 26.6, 26.4, 26.3, 18.2; $[\alpha]_D$ +154.8 (*c* 0.12, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

4.7.3. (*Z*)-*N*-((*S*)-1-Cyclohexyl-ethyl)-2-(2-hydroxy-naphthalen-1-yl)-3-phenyl-acrylamide (*Z*-7b). 0.41 g, 54% yield, mp=168 °C. IR (Nujol): ν_{max}=3333, 3150, 1602, 1555, 1305, 1258, 1218, 1204, 1169, 1146, 1107, 1000, 919, 885, 819, 818, 753, 699, 639, 635; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.62 (br s, 1H, O*H*), 7.97 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.84 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.78 (d, *J*=8.9 Hz, 1H, Ar*H*), 7.50–7.56 (m, 3H, Ar*H*), 7.35–7.45 (m, 4H, Ar*H*), 7.29 (d, *J*=8.9 Hz, 1H, Ar*H*), 6.84 (s, 1H, C*H*), 5.60 (br s, 1H, N*H*), 3.78–3.90 (m, 1H, C*H*), 1.60–0.73 (m, 11H, Cy*H*), 0.93 (d, *J*=6.5 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ=171.6, 153.9, 137.7, 133.2, 130.3, 129.7, 129.2, 129.0, 128.9, 127.1, 125.0, 123.6, 123.3, 120.5, 117.5, 50.9, 43.0, 29.3, 29.2, 26.6, 26.4, 16.8; $[\alpha]_D$ +36.5 (*c* 0.20, $CHCl_3$); $C_{27}H_{29}NO_2$ calcd C 81.40, H 7.04, N 3.52; found: C 78.43, H 7.56, N 3.15.

4.8. (*E*)-2-(2-Hydroxy-naphthalen-1-yl)-3-(2-methoxy-phenyl)-*N*-((*R*)-1-phenyl-ethyl)-acrylamide (*Z*-7c)

*n*BuLi (1.6 M in hexanes 0.62 mL, 0.99 mmol) was slowly added to a solution of (*R*)-1-phenylethylamine (0.107 mL, 0.83 mmol) in anhydrous tetrahydrofuran, in a Schlenk tube, under nitrogen, at 0 °C. After stirring for 1 h the mixture was cooled to −40 °C and lactone **6b** (100 mg, 0.33 mmol) was added. The reaction mixture was stirred at −40 °C for 2 h, quenched with HCl 1 M (7 mL) and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography giving a greenish-yellow solid (0.10 g, 68% yield), mp=65 °C. IR (Nujol): ν_{max}=3406, 3292, 3061, 3031, 2974, 2931, 1665, 1617, 1602, 1538, 1510, 1463, 1336, 1250, 1114, 1026, 821, 753, 700, 623; ^{1}H NMR (400 MHz, $CDCl_3$, 313 K): δ=10.50 (br s, 1H, O*H*), 8.18 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.81 (d, *J*=8.0 Hz, 1H, Ar*H*), 7.77 (d, *J*=8.9 Hz, 1H, Ar*H*), 6.85–7.61 (m, 13H, Ar*H*), 6.18 (br s, 1H, N*H*), 5.00–5.07 (m, 1H, C*H*), 3.83–3.90 (m, 3H, CH_3), 1.35–1.27 (m, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$, 313 K): δ=171.1, 157.3, 153.9, 135.2, 133.6, 130.2, 130.0, 129.7, 129.0, 128.7, 127.7, 126.8, 126.5, 124.2, 123.1, 121.5, 120.4, 111.2; $[\alpha]_D$ −31.7 (*c* 0.28, $CHCl_3$); $C_{28}H_{25}NO_3$ calcd C 79.43, H 5.91, N 3.31; found: C 78.51, H 5.95, N 3.16.

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