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Induced circular dichroism in chiral *N*-methyl amides possessing an achiral binaphthyl chromophore and its application to absolute configuration determination of aliphatic chiral amines

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ABSTRACT

Induced circular dichroism (ICD) was observed in binaphthyl *N*-methyl amides of chiral primary amines. The CD spectra showed split curves centered at 225 nm. A good correlation was found between the sign of the exciton chirality of the binaphthyl derivative and the absolute configuration of the original amine. Furthermore, the screw sense of the two naphthyl groups in the most stable conformer obtained from molecular mechanics (MM) calculation was in agreement with those expected from the exciton chirality, indicating that the method based on MM calculations can be used to determine unknown absolute configurations of aliphatic chiral amines. The practical use of the present method was demonstrated by the determination of the absolute configurations of the natural products, D- and L-cycloserines.

1. Introduction

The detection and assignment of molecular chirality are of particular importance from the viewpoint of differences in pharmacokinetic and pharmacodynamic activities toward a pair of enantiomeric drugs. Various methods based on NMR spectroscopy and circular dichroism (CD) are utilized as reliable tools, together with the X-ray diffraction method. Exciton-coupled circular dichroism (ECCD), in particular, has been extensively applied to organic molecules, including natural products, as a microscale method to determine their absolute configurations in a non-empirical manner.[1–3] In the past, the application of ECCD was limited to compounds that have two or more chiral functional groups. However, recent studies have clearly indicated that this method can be applied to molecules that have only one chiral site.[4–11]

Over the course of our stereochemical studies on chiral monofunctional molecules by the ECCD method, induced CD (ICD) was observed in dinitrodiphenic[7] and 2,2′-binaphthyl[8] esters of chiral secondary alcohols, indicating that the chirality of the substrates was efficiently transferred to the biaryl chromophores. For 1,1′-binaphthyls, the relationship between the sign of the CD couplet and the dihedral angle between the two naphthalene chromophores was investigated in great detail.[12] In contrast, the chiroptical properties of 2,2′-binaphthyl chromophoric systems remain unexplored. We have shown that the ICD of 2,2′-binaphthyl chromophores could be used to establish the absolute stereochemistry of chiral mono-alcohols,[8] and have reported the successful application of the ICD of binaphthyl chromophores in combination with molecular mechanics (MM) calculations, CONFLEX algorism, for the determination of the absolute configurations of several types of natural products possessing a secondary alcohol.[13] In a previous paper, we reported that the method was applicable to a chiral primary mono-amine, indicating a possible application for the determination of the absolute configurations of *N*-methylated binaphthyl derivatives.[14] Herein, further investigations of its scope and limitations and its application to natural products are described in detail.

2. Results and discussion

2.1. Preparation of binaphthyl amides

First, chromophoric reagent **1**, designed by us, was applied to chiral primary amines. A general procedure of derivatization of chiral secondary alcohols with acyl cyanide **1** failed to proceed in the absence of a base, such as 4-dimethylaminopyridine (DMAP).[8] However, for chiral primary amines, the derivatization proceeded as expected even in the absence of a base due to the larger nucleophilicity. Thus, the condensation of amines **2a**–**j** with reagent **1** in

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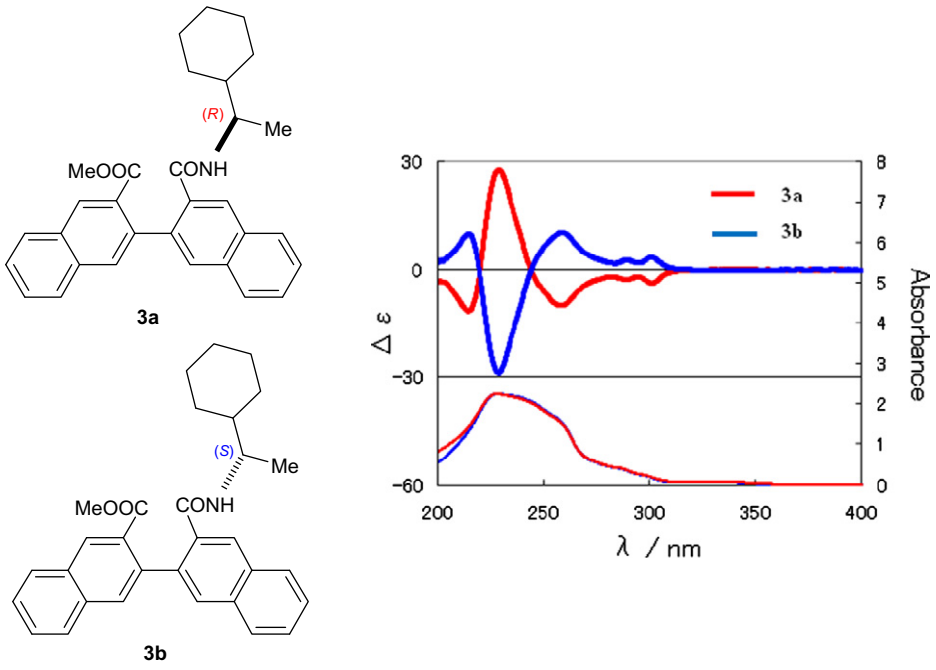


Figure 1. UV and CD spectra of binaphthyl amides **3a** and **3b** in cyclohexane.

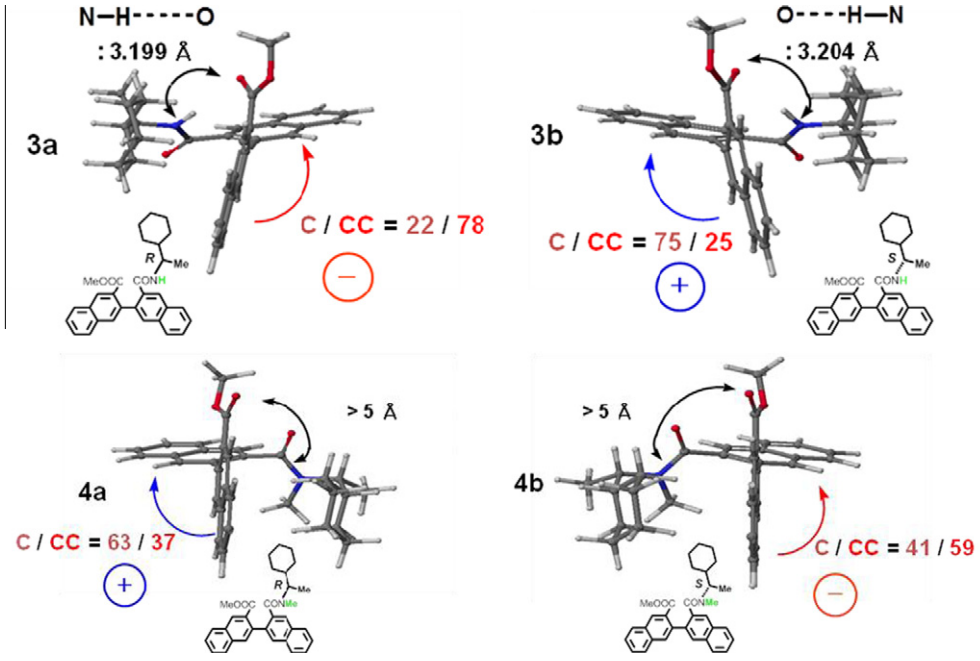


Figure 2. Conformational analysis of binaphthyl derivatives **3a**, **3b** and *N*-methyl derivatives **4a**, **4b**.

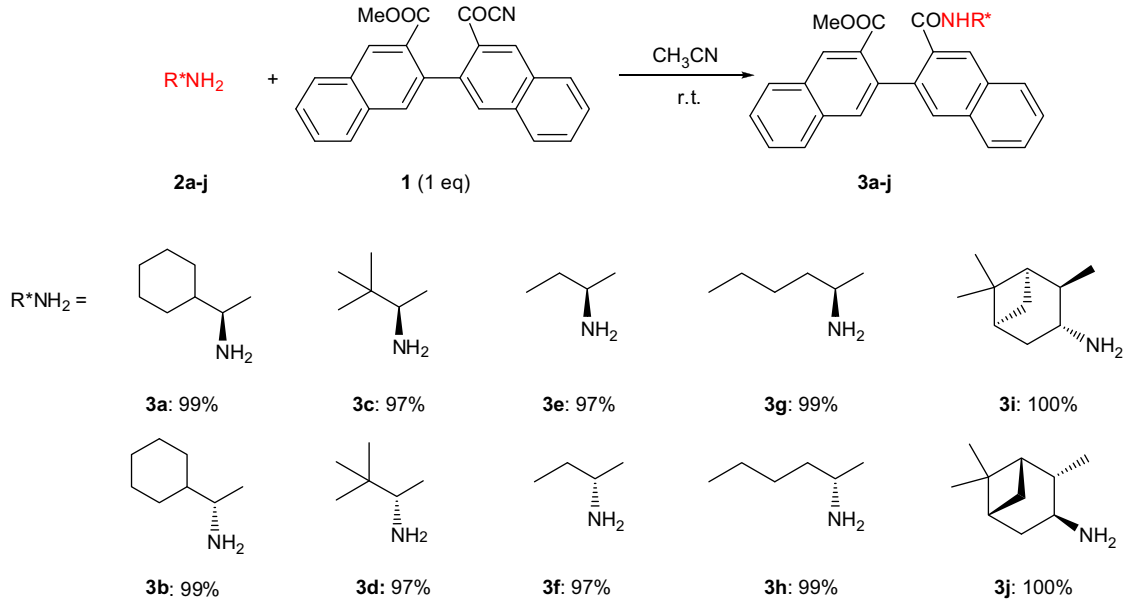
CH_3CN gave the corresponding amides **3a–j** almost quantitatively (Scheme 1).

2.2. UV and CD spectra of binaphthyl amides

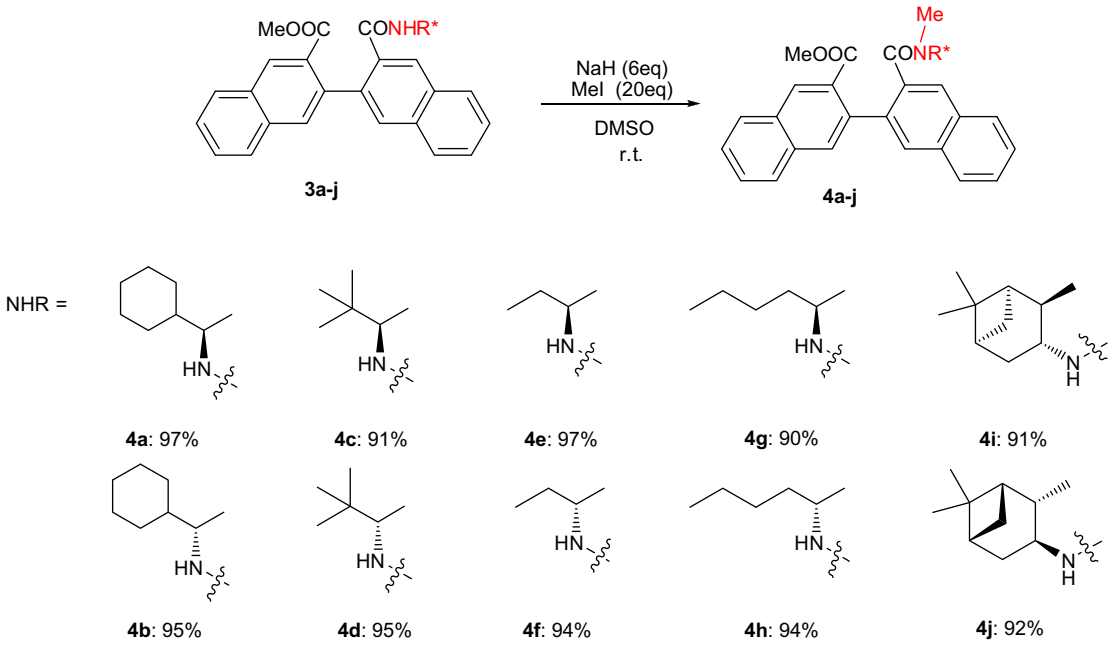
The UV spectra of the derived compounds showed absorption maxima at ca. 227 and 333 nm. The ^1H NMR spectra of the amides derived from an antipodal pair of chiral primary amines (e.g., **2a** and **2b**) in $CDCl_3$ were identical. The CD spectra of the derivatives in cyclohexane exhibited the following features (Table 1 and Fig. 1): (1) for all of the antipodal pairs, the CD spectra were symmetrical to the *x*-axis, indicating that the two isomers are enantiomeric to each other in solution; (2) the CD spectra showed bisignate curves at around 240 nm and the spectroscopic pattern was basically identical for all of the compounds examined, except for their signs of the Cotton effect. However, the curves obtained here do not show a diagnostic split, which is clearly obtained for chiral secondary alcohols.[8] In an empirical manner, we could guess the absolute configuration of the compounds as listed in Table 1 by referring to the exciton chirality at around 240 nm, but this estimation is not proper in terms of the basic idea of the ECCD method. Thus, we needed the assistance of computational chemistry.

Table 1
UV and CD spectra of binaphthyl amides **3a–j** in cyclohexane

Compound	UV	λ_{max} (ε) nm	CD	λ_{ext} (Δε) nm	Absolute configuration
			258.6	(−10.0)	(*R*)
3a	333.0	(670)	244.1	(0)	
	228.2	(22,400)	228.8	(−27.9)	
			219.5	(0)	
			258.8	(10.3)	(*S*)
3b	333.0	(801)	244.1	(0)	
	227.6	(22,400)	228.8	(−28.9)	
			219.5	(0)	
			233.7	(0)	(*R*)
3c	227.0	(21,200)	223.6	(−19.3)	
			216.9	(0)	
			212.6	(6.9)	
			231.9	(0)	(*S*)
3d	226.8	(21,700)	224	(16.7)	
			217.7	(0)	
			211.2	(−10.3)	
			239.5	(0)	(*R*)
3e	226.8	(22,200)	223.6	(−8.8)	
			217.1	(0)	
			211.6	(3.9)	
			242.1	(0)	(*S*)
3f	226.6	(22,200)	224.4	(9.4)	
			217.1	(0)	
			213.4	(−4.3)	
			255.4	(−6.0)	(*R*)
3g	226.6	(21,900)	240.7	(0)	
			229.0	(13.7)	
			220.1	(0)	
			256.8	(5.0)	.(*S*)
3h	226.8	(22,500)	242.1	(0)	
			228.6	(−16.8)	
			218.3	(0)	
			257.6	(−5.3)	(*R*)
3i	227.8	(21,000)	242.7	(0)	
			225.6	(15.1)	
			217.1	(0)	
			258.8	(5.6)	(*S*)
3j	227.6	(21,800)	242.7	(0)	
			225.4	(−15.8)	
			216.9	(0)	



Scheme 1. Preparation of binaphthyl amide derivatives **3a–j**.



Scheme 2. Preparation of *N*-methyl binaphthyl derivatives **4a**–**j**.

2.3. Conformational analysis of binaphthyl amides

Conformational analysis was performed using molecular mechanics calculations (CONFLEX-MM2[15]) to assess the most stable conformer of the target derivative and to examine the screw senses between the two longitudinal ^1B_b electric transition moments of the 2-naphthoyl groups in the stable conformer.[16] By referring to the calculation result for each compound, we found a clear correlation between the screw sense of the most stable conformer and the sign of the apparent exciton chirality at around 240 nm, that is, the positive exciton chirality is correlated with the clockwise (C) turn and the negative one with the counterclockwise (CC) turn. For each binaphthyl amide examined here, a greater number of conformers are found as a result of MM calculations, in which the screw sense of the conformers is not always uniform. However, the calculation result reveals that the conformers with the same screw sense of the most stable conformer are always the majority as shown in Figure 2.

In order to gain further structural information on the binaphthyl derivatives, semi-empirical molecular orbital calculations (AM1)[15] were performed, in which the geometries for the most stable conformers were used as the initial estimate. The distance between the nitrogen atom of the amide and the carbonyl oxygen atom of the ester was found to be ca. 3.2 Å in the binaphthyl amides **3a**, **3b** (Fig. 2). This distance lies in the range of the hydrogen-bonding distance between C=O and N–H in the α-helical

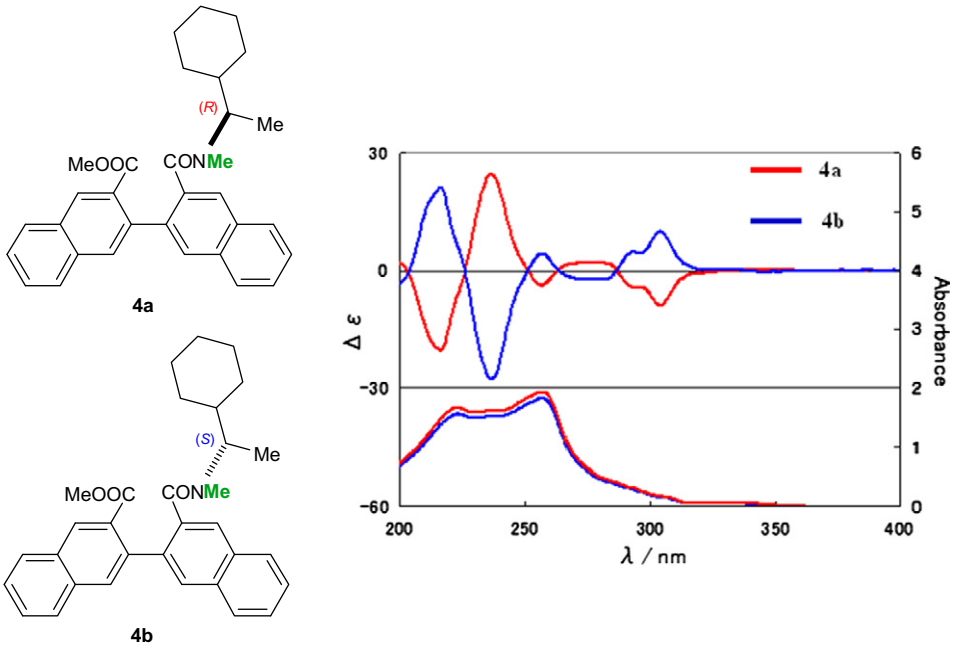


Figure 3. UV and CD spectra of binaphthyl amides **4a** and **4b** in cyclohexane.

Table 2
UV and CD spectra of *N*-methyl derivatives **4a**–**j** in cyclohexane

Compound	UV	λ_{max} (ε) nm	CD	$\lambda_{ex\ t}$ (Δε) nm	Exciton chirality	Absolute configuration
4a	334.4	(500)	251.3	(0)	+	(*R*)
	257.0	(18,300)	236.6	(24.8)		
	223.0	(15,600)	226.1	(0)		
			216.0	(−20.4)		
4b	335.2	(600)	251.3	(0)	−	(*S*)
	257.0	(19,400)	236.8	(−27.8)		
	223.0	(16,600)	225.9	(0)		
			216.2	(21.1)		
4c	257.4	(16,900)	237.0	(21.0)	+	(*R*)
	221.8	(17,200)	227.1	(0)		
			216.6	(−20.9)		
4d	257.4	(17,000)	237.2	(−22.8)	−	(*S*)
	221.6	(17,400)	227.5	(0)		
			216.2	(17.9)		
4e	257.2	(18,700)	236.6	(18.1)	+	(*R*)
	221.8	(18,000)	226.7	(0)		
			216.0	(−16.3)		
4f	257.2	(18,600)	236.4	(−17.7)	−	(*S*)
	221.8	(17,700)	226.7	(0)		
			215.4	(15.3)		
4g	257.2	(18,100)	236.6	(23.4)	+	(*R*)
	221.6	(17,700)	226.5	(0)		
			215.4	(−20.7)		
4h	257.2	(18,200)	236.8	(−24.6)	−	(*S*)
	221.8	(17,800)	225.7	(0)		
			215.4	(18.1)		
4i	256.8	(19,400)	235.4	(13.1)	+	(*R*)
	222.6	(18,200)	222.9	(0)		
			215.2	(−5.6)		
4j	256.8	(18,300)	235.4	(−12.1)	−	(*S*)
	222.6	(17,400)	220.9	(0)		
			215.4	(3.8)		

structure of a protein (2.9 Å to 3.2 Å) based on X-ray crystallographic analysis.[17] Thus, it can be expected that the binaphthyl amides **3a**–**j** form an intramolecular hydrogen-bond, which may play an important role in the conformational stability and in the resulting CD spectrum.

2.4. UV and CD spectra of *N*-methyl derivatives

In order to investigate the influence of the intramolecular hydrogen-bond on the CD spectra, N-methylation of the amides was performed. Binaphthyl amides **3a**–**j** were methylated with sodium hydride and iodomethane in DMSO to give the corresponding *N*-methyl derivatives **4a**–**j** in excellent yields (Scheme 2). In contrast with the CD spectra of **3a** and **3b**, those of the *N*-methyl derivatives **4a** and **4b** in CH_3CN showed simple diagnostic split curves centered at 225 nm (Fig. 3). In the CD spectra of *N*-methyl derivatives **4c**–**j**, the same simple split curves were noted. In all cases, *N*-methyl derivatives with an (*R*)-configuration exhibited positive exciton chirality, while those with an (*S*)-configuration exhibited negative exciton chirality (Table 2). It should be noted that the wavelengths of the marker bands used for the derivatives **4a**–**j** were different from those for **3a**–**j**. These results indicate that the CD bands observed for **3a**–**j** were not the values expected in the ECCD method, in which the exciton coupling between the two ^1B_b electric transition moments of the 2-naphthyl groups is considered. In fact, the replacement of the amide hydrogen with a methyl group gave rise to the diagnostic split CDs that enabled us to determine the clear exciton chirality listed in Table 2. Therefore, it is implied that the intramolecular hydrogen-bonding of the binaphthyl amides affects their CD spectra.

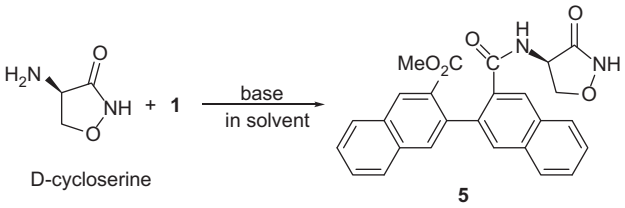
The MM calculations revealed that the screw sense of the most stable conformer of each *N*-methyl amides **4a**–**j** is antipole, for example, the most stable conformer for **3a** has the CC turn, while that for **4a** is C (Fig. 2). Thus, the replacement of the amide hydrogen with a methyl group has results not only in the CD spectrum but also in the conformational stability of the compound. This change might be attributable to the loss of hydrogen bonding and/or the steric effect of the methyl group. For the most stable conformers of *N*-methyl amides **4a** and **4b**, the calculated screw senses between the two ^1B_b electric transition moments of the naphthyl groups were in good accordance with those expected from their exciton chiralities (Fig. 2), that is, *N*-methyl amide **4a** with a positive exciton chirality had a C turn, whereas **4b** with a negative exciton chirality had a CC turn. These results suggested that the N-methylation could be established as a novel alternative method for the determination of the absolute configuration of compounds that have a primary amine based on induced CD exciton chirality. In the following section, the potential of the method is demonstrated.

2.5. Application of the ICD method to D- and L-cycloserines

2.5.1. Derivatization of D- and L-cycloserines to the corresponding binaphthyl amides

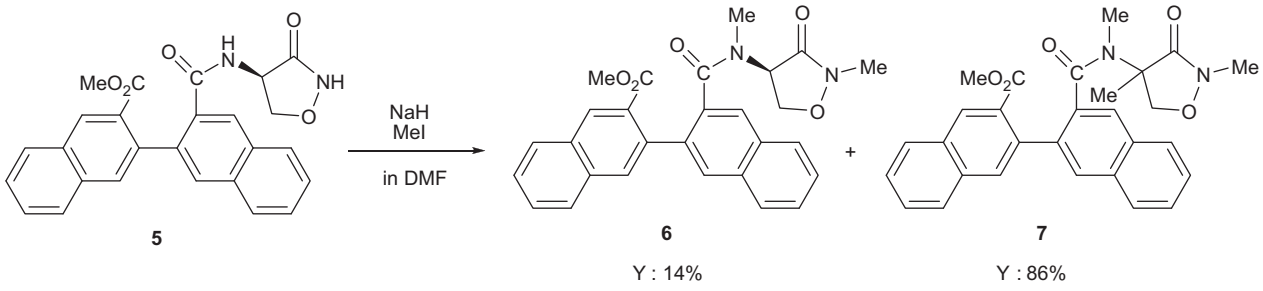
The ICD method with N-methylation was applied to natural products with a primary amine. D-Cycloserine was hardly derivatized in MeCN even at 50 °C due to its insolubility in MeCN. The optimum reaction conditions for D-cycloserine were thus determined (Table 3). The reaction was carried out in MeCN/DMF/H_2O (2/2/1) for 24 h at ambient temperature to give binaphthyl amide **5** in 40% yield (entry 6). When DMF or DMSO was employed as the dipolar aprotic solvent, the reaction was found to proceed almost quantitatively (entries 8 and 9). Unfortunately, DMSO was difficult to remove from the product. Therefore, DMF was used in the subsequent derivatizations. For L-cycloserine, the derivatized product was obtained in 98% yield.

Table 3
Derivatization of D-cycloserine to the corresponding binaphthyl amides **5**[a]



Entry	Solvent	Temp (°C)	Base	Time (h)	HPLC area%[b]			Yield[c] (%)
					5	**1**	Others	
1	MeCN	rt	—	1	ND[d]	97.6	2.4	—
2	MeCN	50 °C	—	1	2.0	96.2	1.8	—
3	MeCN	rt	DMAP (3.0)	1	15.6	14.4	70.0	—
4	MeCN	rt	Et_3N (3.0)	1	23.5	5.5	71.0	—
5	MeCN/DMF/H_2O	rt	—	1	55.2	37.9	6.9	—
6	MeCN/DMF/H_2O	rt	—	24	89.3	0.3	10.4	40
7	MeCN/H_2O	rt	—	24	10.9	82.5	6.6	—
8	DMF	rt	—	24	96.6	0.2	3.2	98
9	DMSO	rt	—	24	92.9	1.1	6.0	—[e]

[a] D-Cycloserine: 20 mg.
[b] Column: Cosmosil ARII 4.6 mm × 150 mm; temp: 40 °C; detection: UV 254 nm; eluent: MeOH/H_2O/MSA = 90/10/0.1; flow rate: 1 mL/min.
[c] Isolated yield.
[d] Not detected.
[e] DMSO could not be removed completely from the product.



Scheme 3. Preparation of *N*-methyl binaphthyl derivative **6**.

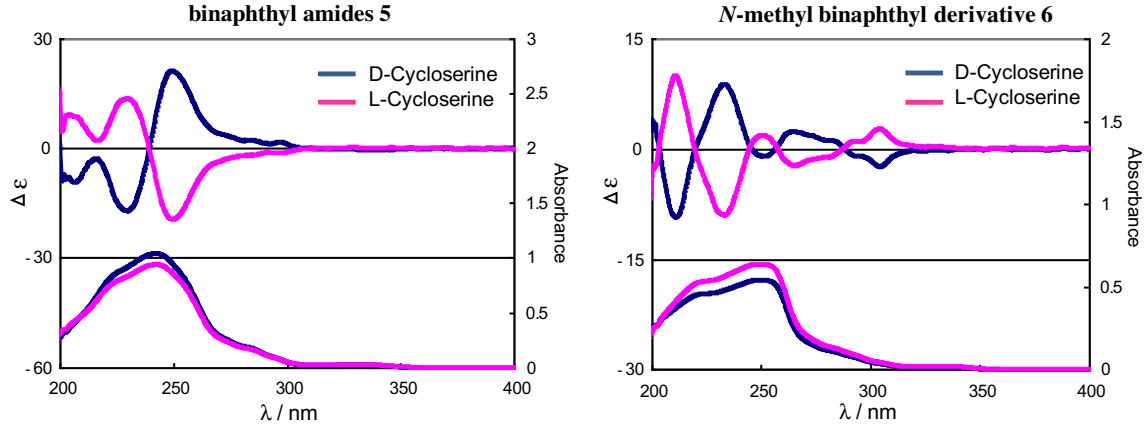


Figure 4. UV and CD spectra of binaphthyl amide **5** and *N*-methyl binaphthyl derivative **6** in MeOH.

2.5.2. N-Methylation of binaphthyl amides

Similar to the case of the amines described above, the N-methylation of cycloserine binaphthyl derivatives was performed in order to investigate the influence of the amide hydrogen atom on the CD spectra (Scheme 3). The expected *N*-methylated derivative **6** was furnished in only 14% yield, along with a large amount of by-product **7** in which a third methyl group was introduced onto the α-position of the isoxazolidinone moiety of cycloserine. The

CD of by-product **7** was found to be inactive. On the other hand, the CD spectrum of *N*-methylated derivative **6** showed the typical diagnostic split centered at 225 nm, which was in good agreement with the other amines studied here; the D-cycloserine derivative with an (*R*)-configuration showed positive exciton chirality whereas the L-cycloserine derivative with an (*S*)-configuration exhibited a negative one (Fig. 4). It is worth noting that when *N*-methylated derivative **6** was exposed to methylation conditions (NaH, MeI/DMF), no reaction took place. Recovered compound **6** was found to maintain its enantiomeric purity by comparing the intensity of the Cotton effects. This result could be interpreted as follows: once generated, the *N*-methylated derivative **6** resisted further methylation due to $A^{1,3}$-strain in its enolate form, although enolization was presumed to proceed faster than N-methylation.

3. Conclusion

Bisignate CD curves were observed at around 240 nm for all of the binaphthyl amides examined. In a conformational analysis based on MM calculations for each derivative, a strong correlation was obtained between the signs of the exciton chirality and the screw sense of the two 2-naphthoyl groups (positive/clockwise; negative/counterclockwise) in the most stable conformer. Semi-empirical molecular orbital calculations (AM1) suggested the existence of an intramolecular hydrogen-bond in the binaphthyl amide. After N-methylation, the center of the bisignate CD curve shifted to 225 nm, which showed excellent correlation between the signs of exciton chirality and the absolute configurations of the amines [positive/(*R*)-configuration; negative/(*S*)-configuration] for all of the *N*-methyl derivatives. Furthermore, the calculated screw senses between the electric transition moments of the binaphthyl system in the *N*-methyl derivatives were in good accordance with those expected from their exciton chiralities. The ICD method was proven to be applicable to natural products possessing a primary amine, such as D- and L-cycloserines. This method will be a powerful tool to determine the absolute configurations of various natural products with an amino group.

4. Experimental

4.1. General

Unless otherwise noted, the following procedures were adopted. Non-aqueous reactions were carried out under an inert atmosphere of dry N_2 and/or Ar. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz in $CDCl_3$ with TMS as the internal reference (0.00 ppm). Chemical shifts are reported in ppm (δ) and coupling constants, *J*, are reported in Hz. Infrared spectra of samples in $CHCl_3$ solution were recorded on a Shimadzu FTIR-8300 spectrometer. Peaks are reported in units of cm^{-1} with the following relative intensities: br (broad), s (strong 67–100%), m (medium 33–67%), or w (weak 0–33%). UV spectra were recorded on a Shimadzu UV-1600 spectrometer and data are given in λ_{max} (ε) (nm). CD and UV spectra were measured on a JASCO J-725 spectrometer and data are given in λ_{ext} ($\Delta\varepsilon$) (nm). Mass spectra (MS) and high-resolution MS (HRMS) were recorded on a JEOL JMS-SX 102A QQ, a Shimadzu GCMS-Q505, and a JEOL JMS-GC-mate mass spectrometer. MS (EI) were recorded with the ionization voltage of 70 eV. MS (FAB) were recorded with NBA as the matrix. Data are reported in the form of *m/z* (intensity relative to base = 100%). Column chromatography was carried out with silica gel (Wakogel C-200). Recycling high performance liquid chromatography (RHPLC) was performed on JAI LC-908 with a JAIGEL H column using $CHCl_3$ as the mobile phase. For thin-layer chromatography (TLC), Merck precoated plates GF_{254} were used. Spots were monitored under UV light (254 nm) and then developed by spraying 10% H_2SO_4 and/or 5% phosphomolybdic acid ethanol solution and heating the plate at 100 °C until coloration took place. Preparative TLC (PTLC) was performed with precoated silica gel plates, Merck 60 F_{254} (0.5 mm thick). Elemental analyses were performed by Kyoto Pharmaceutical University. Chemical purity was determined by HPLC (Shimadzu LC-2010C HT system; UV (254 nm), Cosmosil C18AR-II 4.6 mm × 150 mm, 5 μm, 90.0% MeOH in H_2O, 35 min; flow rate 1.0 mL/min; 40 °C).

4.2. Preparation of the binaphthyl-type chromophoric reagent 1

4.2.1. Dinaphtho[2,3-*c*:2′,3′-*e*]oxepine-6,8-dione

A stirred suspension of 2,2′-binaphthalene-3,3′-dicarboxylic acid (4.77 g, 13.90 mmol) in acetic anhydride (48 mL) was heated at reflux for 2.5 h. After cooling down to below 10 °C, the reaction mixture was stirred at the same temperature for 2.5 h. The precipitated crystals were collected by filtration and washed with diethyl ether. After being dried in vacuo at room temperature, dinaphtho[2,3-*c*:2′,3′-*e*]oxepine-6,8-dione (3.43 g, 76%) was obtained as an ochreous solid that was used in the following step without further purification.

4.2.2. 3′-(Methoxycarbonyl)-2,2′-binaphthalene-3-carboxylic acid

A stirred suspension of dinaphtho[2,3-*c*:2′,3′-*e*]oxepine-6,8-dione (3.40 g, 10.54 mmol) in methanol (68 mL) was heated at reflux for 4 h, followed by removal of the solvent in vacuo. The residue was dissolved in methanol (25 mL) and chloroform (80 mL) at 60 °C. After the addition of activated carbon (3.0 g), the solution was stirred at 60 °C for 1.5 h. Next, the activated carbon was filtered off with heating and washed with chloroform/methanol (3:1, v/v). The combined filtrates were concentrated to dryness. After precipitation by the addition of ethyl acetate (10 mL), the solvent was evaporated to give 3′-(methoxycarbonyl)-2,2′-binaphthalene-3-carboxylic acid (3.47 g, 92%), which was used in the following step without further purification.

4.2.3. Methyl 3′-(cyanocarbonyl)-2,2′-binaphthalene-3-carboxylate 1 (improved procedure)

To a stirred suspension of 3′-(methoxycarbonyl)-2,2′-binaphthalene-3-carboxylic acid (2.40 g, 6.73 mmol) in methylene chloride (50 mL) were added dropwise thionyl chloride (2.40 g, 20.20 mmol) and pyridine (0.11 g, 1.35 mmol), and the reaction mixture was stirred at temperatures below 10 °C for 2 h. After the confirmation of complete dissolution, the solvent was removed in vacuo. To a solution of the crude acid chloride in dichloromethane (60 mL) were added trimethylsilyl cyanide (2.00 g, 20.2 mmol) and zinc iodide (0.02 g, 0.07 mmol) at temperatures below 10 °C, and the reaction mixture was stirred at the same temperature for 2 h and then at room temperature for 1 h. After removal of the solvent in vacuo, the crude product was stirred in cyclopentyl methyl ether (12 mL) at room temperature for 1 h. The precipitated crystals were collected by filtration and washed with cyclopentyl methyl ether (7 mL). Drying the crystals in vacuo at room temperature gave methyl 3′-(cyanocarbonyl)-2,2′-binaphthalene-3-carboxylate **1** (1.75 g, 71% over two steps), which was almost pure and did not need further purification.

4.3. General procedure

4.3.1. Amidation

To a solution of amine (ca. 0.03 mmol) in acetonitrile (0.5 mL) was added acyl cyanide **1** (1.1 equiv) and the whole mixture was

stirred at room temperature for 2–3 h under an argon atmosphere. After removal of the solvent in vacuo, the crude product was purified by silica gel chromatography to give the corresponding binaphthyl amides in 97–100% yields.

4.3.2. *N*-Methylation

To a suspension of 60% sodium hydride (6 equiv) in dimethyl sulfoxide (0.5 mL) was added a solution of binaphthyl amide (ca. 10–20 mg) and then methyl iodide (20 equiv), after which the whole mixture was stirred at room temperature for 1 day. The reaction was quenched with ice-water and adjusted to pH 3–4 with solid ammonium chloride. The resulting aqueous solution was extracted with diethyl ether (20 mL × 3) and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography to give *N*-methyl amides in 90–97% yields.

4.3.2.1. Methyl 3′-{[(1*R*)-1-cyclohexylethyl]carbamoyl}-2,2′-binaphthalene-3-carboxylate 3a. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)): 0.39. HPLC purity: 100.0%; Anal. Calcd for $C_{31}H_{31}NO_3$: C, 79.97; H, 6.71; N, 3.01. Found: C, 79.19; H, 6.99; N, 3.11. IR (film) ν 2920 m, 2845 m, 1705 m, 1643 m, 1519 m, 897 w, 890 w, 747 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.29 (s, 0.58H), 8.24 (s, 0.42H), 7.98–7.93 (m, 2H), 7.82 (t, J = 7.8 Hz, 2H), 7.80–7.74 (m, 1H), 7.63–7.50 (m, 5H), 6.52 (br d, J = 8.8 Hz, 0.58H), 6.45 (br d, J = 8.8 Hz, 0.42H), 3.80 (m, 0.58H), 3.77 (s, 1.74H), 3.76 (s, 1.26H), 3.71 (m, 0.42H), 1.71–1.39 (m, 1.38H), 1.32–1.19 (m, 0.58H), 1.12–0.97 (m, 3.1H), 0.91 (d, J = 6.3 Hz, 1.74H), 0.94–0.69 (m, 2.94H), 0.63–0.42 (m, 1.74H), 0.32–0.15 (m, 1.26H), 0.25 (d, J = 6.3 Hz, 1.26H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 228.2 (22,400), 333.0 (700); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 214.0 (−11.6), 219.5 (0), 228.8 (+27.9), 244.1 (0), 258.6 (−10.0), 288.4 (−2.8), 300.6 (−3.9); $[\alpha]_D^{28} = -15.7$ (c 0.216, $CHCl_3$); ESI-MS m/z 465 (M^+, 22), 339 (100), 296 (44), 295 (48), 281 (38), 280 (72), 252 (27); HRMS (ESI) Anal. Calcd for $C_{31}H_{31}NO_3$ m/z 465.2304 $[M]^+$. Found: 465.2308.

4.3.2.2. Methyl 3′-{[(1*S*)-1-cyclohexylethyl]carbamoyl}-2,2′-binaphthalene-3-carboxylate 3b. Pale yellow gum. R_f (hexane/EtOAc, 2/1 (v/v)): 0.39; HPLC purity: 100.0%; Anal. Calcd for $C_{31}H_{31}NO_3$: C, 79.97; H, 6.71; N, 3.01. Found: C, 79.19; H, 6.99; N, 3.11. IR (film) ν cm^{-1} 2920 m, 2845 w, 1701 m, 1645 m, 1520 m, 747 m; ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.29 (s, 0.58H), 8.24 (s, 0.42H), 7.98–7.93 (m, 2H), 7.82 (t, J = 7.8 Hz, 2H), 7.80–7.74 (m, 1H), 7.63–7.50 (m, 5H), 6.52 (br d, J = 8.8 Hz, 0.58H), 6.45 (br d, J = 8.8 Hz, 0.42H), 3.80 (m, 0.58H), 3.77 (s, 1.74H), 3.76 (s, 1.26H), 3.71 (m, 0.42H), 1.71–1.39 (m, 1.38H), 1.32–1.19 (m, 0.58H), 1.12–0.97 (m, 3.1H), 0.91 (d, J = 6.3 Hz, 1.74H), 0.94–0.69 (m, 2.94H), 0.63–0.42 (m, 1.74H), 0.32–0.15 (m, 1.26H), 0.25 (d, J = 6.3 Hz, 1.26H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 227.6 (22,400), 333.0 (800); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 214.6 (+9.8), 219.5 (0), 228.8 (−28.9), 244.1 (0), 258.8 (+10.3), 289.2 (+2.7), 301.0 (+3.5); $[\alpha]_D^{28} = +17.5$ (c 0.230, $CHCl_3$); ESI-MS m/z 465 (M^+, 25),339 (100), 296 (41), 295 (47), 281 (38), 280 (70); HRMS (ESI) Anal. Calcd for $C_{31}H_{31}NO_3$ m/z $[M]^+$ 465.2304. Found: 465.2303.

4.3.3.1. Methyl 3′-{[(2*R*)-3,3-dimethylbutan-2-yl]carbamoyl]-2,2′-binaphthalene-3-carboxylate 3c. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.49. HPLC purity: 99.6%; Anal. Calcd for $C_{29}H_{29}NO_3$: C, 79.24; H, 6.65; N, 3.19. Found: C, 79.01; H, 6.66; N, 3.21. IR (film) ν 3342 w, 3059 w, 2955 m, 1711 m, 1647 m, 1529 m, 901 w, 839 w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 0.3H), 8.43 (s, 0.7H), 8.30 (s, 0.3H), 8.23 (s, 0.7H), 7.97–7.95 (m, 2H), 7.84–7.77 (m, 3H), 7.63–7.51 (m, 5H), 6.57 (d, J = 9.6 Hz, 0.5H), 6.37 (d, J = 9.6 Hz, 0.5H), 3.83–3.79 (m, 0.3H), 3.76 (s, 1.8H), 3.75 (s, 1.2H), 3.73–3.69 (m, 0.7H), 0.89 (d, J = 6.9 Hz, 1.4H), 0.74 (s, 5.2H), 0.28 (s, 3.7H), 0.12 (d, J = 6.9 Hz, 1.6H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 227.0 (21,200), 334.8 (700); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 212.6 (+6.9), 216.9 (0), 223.6 (−19.3), 233.7 (0), 234.8 (+0.8), 240.0 (−0.8), 260.2 (+3.5), 287.4 (+1.0), 298.8 (+2.1); $[\alpha]_D^{23} = +8.4$ (c 1.000, $CHCl_3$); ESI-MS m/z 439 (M^+, 0.7), 382 (35), 339 (100), 295 (70), 280 (71), 252 (31); HRMS (ESI) Anal. Calcd for $C_{29}H_{29}NO_3$ m/z 439.2147 $[M]^+$. Found: 439.2150.

4.3.3.2. Methyl 3′-{[(2*S*)-3,3-dimethylbutan-2-yl]carbamoyl]-2,2′-binaphthalene-3-carboxylate 3d. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.49. HPLC purity: 99.6%; Anal. Calcd for $C_{29}H_{29}NO_3$: C, 79.24; H, 6.65; N, 3.19. Found: C, 78.97; H, 6.61; N, 3.30. IR (film) ν 3342 w, 3059 w, 2957 m, 1711 m, 1647 m, 1529 m, 901 w, 768 w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 0.3H), 8.43 (s, 0.7H), 8.30 (s, 0.3H), 8.23 (s, 0.7H), 7.97–7.95 (m, 2H), 7.84–7.77 (m, 3H), 7.63–7.51 (m, 5H), 6.57 (d, J = 9.6 Hz, 0.5H), 6.37 (d, J = 9.6 Hz, 0.5H), 3.83–3.79 (m, 0.3H), 3.76 (s, 1.8H), 3.75 (s, 1.2H), 3.73–3.69 (m, 0.7H), 0.89 (d, J = 6.9 Hz, 1.4H), 0.74 (s, 5.7H), 0.28 (s, 3.3H), 0.12 (d, J = 6.9 Hz, 1.6H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 226.8 (21,700), 335.0 (800); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 211.2 (−10.3), 217.7 (0), 224.0 (+16.7), 231.9 (0), 234.6 (−2.1), 259.8 (−4.3), 287.0 (−2.0), 299.4 (−3.2); $[\alpha]_D^{24} = -8.5$ (c 1.030, $CHCl_3$); ESI-MS m/z 439 (M^+, 0.8), 382 (33), 339 (100), 295 (69), 280 (66); HRMS (ESI) Anal. Calcd for $C_{29}H_{29}NO_3$ m/z 439.2147 $[M]^+$. Found: 439.2151.

4.3.3.3. Methyl 3′-[(2*R*)-butan-2-ylcarbamoyl]-2,2′-binaphthalene-3-carboxylate 3e. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.30. HPLC purity: 100.0%; IR (film) ν 3000 m, 2960 m, 2915 w, 1706 m, 1646 m, 1631 m, 1525 m, 893 w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.45, 8.25 (each s, 0.42H), 8.44, 8.23 (each s, 0.58H), 7.98–7.93 (m, 2H), 7.85–7.76 (m, 3H), 7.63–7.55 (m, 3H), 7.55–7.51 (m, 2H), 6.47 (br d, J = 8.3 Hz, 0.58H), 6.40 (br d, J = 8.3 Hz, 0.42H), 3.77 (m, 1H), 3.77 (s, 3H), 1.23 (m, 1.17H), 0.92 (d, J = 6.4 Hz, 1.25H), 0.80 (m, 0.83H), 0.76 (t, J = 7.3 Hz, 1.75H), 0.29 (d, J = 6.4 Hz, 1.75H), 0.20 (t, J = 7.3 Hz, 1.25H); UV $\lambda_{max}(\varepsilon)$ nm 226.8 (22,200), 333.6 (1000); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 211.6 (+3.9), 217.1 (0), 223.6 (−8.8), 239.5 (0), 256.8 (+2.5), 288.0 (+1.0), 298.8 (+1.5); $[\alpha]_D^{30} = -2.4$ (c 0.206, $CHCl_3$); ESI-MS m/z 411 (M^+, 57), 339 (100), 296 (64), 295 (57), 281 (43), 280 (88), 252 (36); HRMS (ESI) Anal. Calcd for $C_{27}H_{25}NO_3$ m/z 411.1834 $[M]^+$. Found: 411.1830.

4.3.3.4. Methyl 3′-[(2*S*)-butan-2-ylcarbamoyl]-2,2′-binaphthalene-3-carboxylate 3f. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.30; HPLC purity: 100.0%; IR (film) ν 3000 m, 2955 m, 2920 m, 1711 s, 1647 s, 1631 m, 1531 m, 892 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.45, 8.25 (each s, 0.42H), 8.44, 8.23 (each s, 0.58H), 7.98–7.93 (m, 2H), 7.85–7.76 (m, 3H), 7.63–7.55 (m, 3H), 7.55–7.51 (m, 2H), 6.47 (br d, J = 8.3 Hz, 0.58H), 6.40 (br d, J = 8.3 Hz, 0.42H), 3.77 (m, 1H), 3.77 (s, 3H), 1.23 (m, 1.17H), 0.92 (d, J = 6.4 Hz, 1.25H), 0.80 (m, 0.83H), 0.76 (t, J = 7.3 Hz, 1.75H), 0.29 (d, J = 6.4 Hz, 1.75H), 0.20 (t, J = 7.3 Hz, 1.25H); UV $\lambda_{max}(\varepsilon)$ nm 226.6 (22,200), 333.6 (1000); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 213.4 (−4.3), 217.1 (0), 224.4 (+9.4), 238.4 (+0.9), 242.1 (0), 256.6 (−1.6), 277.8 (+0.5), 298.6 (−0.8); $[\alpha]_D^{30} = +2.5$ (c 0.238, $CHCl_3$); ESI-MS m/z 411 (M^+, 59), 339 (100), 296 (63), 295 (55), 281 (42), 280 (87), 252 (36); HRMS (ESI) Anal. Calcd for $C_{27}H_{25}NO_3$ m/z 411.1834 $[M]^+$. Found: 411.1835.

4.3.3.5. Methyl 3′-[(2*R*)-hexan-2-ylcarbamoyl]-2,2′-binaphthalene-3-carboxylate 3g. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.54. HPLC purity: 99.5%; Anal. Calcd for $C_{29}H_{29}NO_3$: C, 79.24; H, 6.65; N, 3.19. Found: C, 79.07; H, 6.60; N, 3.23. IR (film) ν 3337 w, 3059 m, 2957 m, 2932 m, 2858 m,

1711 m, 1647 m, 1535 m, 901 w, 787 w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.25 (d, J = 10.1 Hz, 1H), 7.97–7.95 (m, 2H), 7.84–7.77 (m, 3H), 7.60–7.52 (m, 5H), 6.50 (d, J = 10.5 Hz, 0.5H), 6.48 (d, J = 10.5 Hz, 0.5H), 3.83–3.75 (m, 1H), 3.78 (s, 1.8H), 3.77 (s, 1.2H), 1.16–1.10 (m, 2H), 0.94 (d, J = 6.4 Hz, 1.6H), 0.80 (t, J = 6.4 Hz, 1.3H), 0.75–0.46 (m, 4H), 0.39 (t, J = 7.3 Hz, 1.7H), 0.30 (d, J = 6.9 Hz, 1.4H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 226.6 (21,900), 334.0 (900); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 214.2 (−7.0), 220.1 (0), 229.0 (+13.7), 240.7 (0), 255.4 (−6.0), 290.2 (−1.8), 301.0 (−2.3); $[\alpha]_D^{20} = -17.7$ (c 0.884, $CHCl_3$); ESI-MS m/z 440 (M^+, 12), 439 (33), 339 (90), 296 (61), 295 (65), 281 (71), 280 (100), 252 (39); HRMS (ESI) Anal. Calcd for $C_{29}H_{29}NO_3$ m/z 439.2147 $[M]^+$. Found: 439.2152.

4.3.3.6. Methyl 3′-[(2*S*)-hexan-2-ylcarbamoyl]-2,2′-binaphthalene-3-carboxylate 3h. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.54. HPLC purity: 99.7%; Anal. Calcd for $C_{29}H_{29}NO_3$: C, 79.24; H, 6.65; N, 3.19. Found: C, 79.13; H, 6.49; N, 3.26. IR (film) ν 3335 w, 3059 m, 2955 m, 2932 m, 2856 m, 1711 m, 1647 m, 1535 m, 901 w, 787 w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.25 (d, J = 10.1 Hz, 1H), 7.97–7.95 (m, 2H), 7.84–7.77 (m, 3H), 7.60–7.52 (m, 5H), 6.50 (d, J = 10.5 Hz, 0.5H), 6.48 (d, J = 10.5 Hz, 0.5H), 3.83–3.75 (m, 1H), 3.78 (s, 1.8H), 3.77 (s, 1.2H), 1.16–1.09 (m, 2H), 0.94 (d, J = 6.4 Hz, 1.6H), 0.80 (t, J = 6.9 Hz, 1.3H), 0.75–0.46 (m, 4H), 0.39 (t, J = 6.9 Hz, 1.7H), 0.30 (d, J = 6.4 Hz, 1.4H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 226.8 (22,500), 334.0 (900); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 213.8 (+3.5), 218.3 (0), 228.6 (−16.8), 242.1 (0), 256.8 (+5.0), 289.22 (+0.5), 300.4 (+1.0); $[\alpha]_D^{20} = +15.4$ (c 0.739, $CHCl_3$); ESI-MS m/z 440 (M^+, 13), 439 (37), 339 (100), 296 (67), 295 (72), 281 (71), 280 (95), 252 (41); HRMS (ESI) Anal. Calcd for $C_{29}H_{29}NO_3$ m/z 439.2147 $[M]^+$. Found: 439.2142.

4.3.3.7. Methyl 3′-{[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]carbamoyl}-2,2′-binaphthalene-3-carboxylate 3i. Colorless amorphous R_f (hexane/EtOAc, 2/1 (v/v)) 0.31. HPLC purity: 98.6%; IR (film) ν 2995 m, 2910 m, 2860 m, 1710 s, 1646 s, 1584 m, 1534 m, 897 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 0.42H), 8.42 (s, 0.58H), 8.27 (s, 1H), 7.98–7.93 (m, 2H), 7.85–7.76 (m, 3H), 7.63–7.51 (m, 5H), 6.71 (br d, J = 8.3 Hz, 0.58H), 6.58 (br d, J = 8.3 Hz, 0.42H), 4.07 (m, 1H), 3.78 (s, 1.74H), 3.77 (s, 1.26H), 2.50 (m, 0.58H), 2.17 (m, 0.58), 2.09–1.95 (m, 1H), 1.80 (m, 0.58H), 1.61 (m, 1.16H), 1.47–1.34 (m, 2.10H), 1.07 (s, 1.74H), 1.05 (s, 1.26H), 1.00 (d, J = 7.3 Hz, 1.26H), 0.86 (s, 3H), 0.63 (m, 0.58H), 0.38 (d, J = 9.8 Hz, 0.58H), 0.29 (m, 0.42H), 0.20 (d, J = 7.3 Hz, 1.74H), 0.13 (d, J = 9.8 Hz, 0.42H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 227.8 (21,000), 331.4 (1100); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 212.8 (−4.5), 217.1 (0), 225.6 (+15.1), 242.7 (0), 257.6 (−5.3), 286.6 (−1.8), 299.4 (−2.3); $[\alpha]_D^{30} = -20.9$ (c 0.238, $CHCl_3$); ESI-MS m/z 491 (M^+, 46), 339 (100), 296 (48), 295 (61), 281 (59), 280 (77); HRMS (ESI) Anal. Calcd for $C_{33}H_{33}NO_3$ m/z 491.2460 $[M]^+$. Found: 491.2461.

4.3.3.8. Methyl 3′-{[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]carbamoyl}-2,2′-binaphthalene-3-carboxylate 3j. Colorless amorphous R_f (hexane/EtOAc, 2/1 (v/v)) 0.35. HPLC purity: 99.6%; Anal. Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 79.19; H, 6.99; N, 3.11. IR (film) ν 3325 w, 2945 m, 2915 m, 2870 m, 1702 m, 1640 m, 1638 m, 1524 m, 895 m, 748 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 0.42H), 8.42 (s, 0.58H), 8.27 (s, 1H), 7.98–7.93 (m, 2H), 7.85–7.76 (m, 3H), 7.63–7.51 (m, 5H), 6.71 (br d, J = 8.3 Hz, 0.58H), 6.58 (br d, J = 8.3 Hz, 0.42H), 4.07 (m, 1H), 3.78 (s, 1.74H), 3.77 (s, 1.26H), 2.50 (m, 0.58H), 2.17 (m, 0.58), 2.09–1.95 (m, 1H), 1.80 (m, 0.58H), 1.61 (m, 1.16H), 1.47–1.34 (m, 2.10H), 1.07 (s, 1.74H), 1.05 (s, 1.26H), 1.00 (d, J = 7.3 Hz, 1.26H), 0.86 (s, 3H), 0.63 (m, 0.58H), 0.38 (d, J = 9.8 Hz, 0.58H), 0.29 (m, 0.42H), 0.20 (d, J = 7.3 Hz, 1.74H), 0.13 (d, J = 9.8 Hz, 0.42H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 227.6 (21,800), 330.6 (1300); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 209.6 (+3.2), 216.9 (0), 225.4 (−15.8), 242.7 (0), 258.8 (+5.6), 287.6 (+1.6), 299.6 (+2.0); $[\alpha]_D^{30} = +25.2$ (c 0.266, $CHCl_3$); ESI-MS m/z 491 (M^+, 46), 339 (100), 296 (47), 295 (60), 281 (59), 280 (76); HRMS (ESI) Anal. Calcd for $C_{33}H_{33}NO_3$ m/z 491.2460 $[M]^+$. Found: 491.2460.

4.3.3.9. Methyl 3′-{[(1*R*)-1-cyclohexylethyl](methyl)carbamoyl}-2,2′-binaphthalene-3-carboxylate 4a. Colorless amorphous. R_f ($CHCl_3$/EtOAc, 9/1 (v/v)) 0.48. HPLC purity: 98.7%; IR (film) ν 2925 m, 2850 m, 1725 m, 1623 m, 750 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58–8.38 (m, 1H), 8.17–7.71 (m, 6H), 7.64–7.47 (m, 5H), 4.29 (m, 0.7H), 3.69 (s, 2.1H), 3.68 (s, 0.9H), 3.52 (m, 0.3H), 2.67 (br s, 0.9H), 2.48 (br s, 2.1H), 1.79–0.48 (m, 13.1H), 0.12 (br d, J = 4.4 Hz, 0.9H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 223.0 (15,600), 257.0 (18,300), 334.4 (500); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 216.0 (−20.4), 226.1 (0), 236.6 (+24.8), 251.3 (0), 256.8 (−3.8), 263.1 (0), 278.0 (+2.2), 286.5 (0), 292.6 (−4.1), 303.8 (−9.0); $[\alpha]_D^{24} = +20.6$ (c 0.206, $CHCl_3$); ESI-MS m/z 479 (M^+, 34), 339 (100), 295 (57), 281 (35), 280 (64); HRMS (ESI) Anal. Calcd for $C_{32}H_{33}NO_3$ m/z 479.2460 $[M]^+$. Found: 479.2458.

4.3.3.10. Methyl 3′-{[(1*S*)-1-cyclohexylethyl](methyl)carbamoyl}-2,2′-binaphthalene-3-carboxylate 4b. Colorless amorphous. R_f ($CHCl_3$/EtOAc, 9/1 (v/v)) 0.50. HPLC purity: 99.1%; IR (film) ν 2925 m, 2850 m, 1724 m, 1617 m, 1615 m, 888 w, 749 m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58–8.38 (m, 1H), 8.17–7.71 (m, 6H), 7.64–7.47 (m, 5H), 4.29 (m, 0.7H), 3.69 (s, 2.1H), 3.68 (s, 0.9H), 3.52 (m, 0.3H), 2.67 (br s, 0.9H), 2.48 (br s, 2.1H), 1.79–0.48 (m, 13.1H), 0.12 (br d, J = 4.4 Hz, 0.9H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 223.0 (16,600), 257.0 (19,400), 335.2 (600); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 216.2 (+21.1), 225.9 (0), 236.8 (−27.8), 251.3 (0), 256.8 (+4.3), 263.7 (0), 275.8 (−2.4), 286.5 (0), 293.0 (+4.8), 303.8 (+10.0); $[\alpha]_D^{25} = -23.8$ (c 0.248, $CHCl_3$); ESI-MS m/z 479 (M^+, 32), 339 (100), 295 (59), 281 (33), 280 (64); HRMS (ESI) Anal. Calcd for $C_{32}H_{33}NO_3$ m/z 479.2460 $[M]^+$. Found: 479.2464.

4.3.3.11. Methyl 3′-{[(2*R*)-3,3-dimethylbutan-2-yl](methyl)carbamoyl]-2,2′-binaphthalene-3-carboxylate 4c. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.46. HPLC purity: 99.0%; Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.19; H, 6.99; N, 3.11. IR (film) ν 2953 m, 1720 m, 1609 m, 897 w, 754 w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 0.6H), 8.43 (s, 0.4H), 8.05–7.80 (m, 6H), 7.61–7.50 (m, 5H), 4.59–4.57 (m, 0.5H), 3.70 (s, 3H), 3.76–3.69 (m, 0.5H), 2.73 (s, 1.2H), 2.62 (s, 1.8H), 1.25 (s, 1.2H), 1.00–0.80 (m, 0.5H), 0.74 (s, 7.8H), 0.10–0.01 (m, 2.5H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 221.8 (17,200), 257.4 (16,900), 335.0 (700); CD λ_{ext}(nm)($\Delta\varepsilon$)(cyclohexane) 216.6 (−20.9), 227.1 (0), 237.0 (+21.0), 269.8 (+1.8), 287.5 (0), 287.5 (0), 294.0 (−5.3), 304.6 (−9.7); $[\alpha]_D^{26} = +10.8$ (c 1.870, $CHCl_3$); ESI-MS m/z 453 (M^+, 0.5), 396 (33), 339 (100), 295 (77), 280 (74); HRMS (ESI) Anal. Calcd for $C_{30}H_{31}NO_3$ m/z 453.2304 $[M]^+$. Found: 453.2299.

4.3.3.12. Methyl 3′-{[(2*S*)-3,3-dimethylbutan-2-yl](methyl)carbamoyl]-2,2′-binaphthalene-3-carboxylate 4d. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.46. HPLC purity: 99.2%; Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.77; H, 6.93; N, 3.09. IR (film) ν 3059 m, 1722 m, 1603 m, 897 w, 727 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.52 (s, 0.6H), 8.43 (s, 0.4H), 8.04–7.80 (m, 6H), 7.61–7.50 (m, 5H), 4.58–4.56 (m, 0.5H), 3.70 (s, 3H), 3.76–3.69 (m, 0.5H), 2.73 (s, 1.2H), 2.62 (s, 1.8H), 1.25 (s, 1.2H), 1.00–0.80 (m, 0.5H), 0.74 (s, 7.8H), 0.10–0.01 (m, 2.5H); UV (cyclohexane) $\lambda_{max}(\varepsilon)$ nm 221.6 (17,400), 257.4 (17,100),

334.8 (700); CD λ_{ext}(nm)(Δε)(cyclohexane) 216.2 (+17.9), 227.5 (0), 237.2 (−22.8), 287.3 (0), 295.0 (+4.4), 304.6 (+8.7); $[\alpha]_D^{26} = -10.0$ (*c* 2.180, $CHCl_3$); ESI-MS *m/z* 453 (M^+, 0.7), 396 (40), 340 (26), 339 (100), 295 (68), 280 (59); HRMS (ESI) Anal. Calcd for $C_{30}H_{31}NO_3$ *m/z* 453.2304 $[M]^+$. Found: 453.2301.

4.3.3.13. Methyl 3′-[(2*R*)-butan-2-yl(methyl)carbamoyl]-2,2′-binaphthalene-3-carboxylate 4e. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.38. HPLC purity: 100.0%; IR (film) *ν* 2953 m, 2936 m, 1722 m, 1614 m, 895 w, 721 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.50 (s, 0.8H), 8.46 (s, 0.2H), 7.99–7.79 (m, 6H), 7.61–7.50 (m, 5H), 4.60–4.50 (m, 1H), 3.71 (s, 3H), 2.66 (s, 1.2H), 2.47 (s, 1.8H), 1.40–1.20 (m, 2.3H), 1.10–0.60 (m, 3.2H), 0.30–0.20 (m, 2.5H); UV (cyclohexane) λ_{max}(ε) nm 221.8 (18,000), 257.2 (18,700), 336.2 (900); CD λ_{ext}(nm)(Δε)(cyclohexane) 216.0 (−16.3), 226.7 (0), 236.6 (+18.1), 253.1 (0), 256.0 (−1.6), 261.5 (0), 274.2 (+2.4), 287.1 (0), 293.2 (−3.1), 304.0 (−7.0); $[\alpha]_D^{23} = -8.0$ (*c* 0.891, $CHCl_3$); ESI-MS *m/z* 425 (M^+, 30), 339 (42), 310 (39), 295 (63), 280 (100), 252 (40); HRMS (ESI) Anal. Calcd for $C_{28}H_{27}NO_3$ *m/z* 425.1991 $[M]^+$. Found: 425.1986.

4.3.3.14. Methyl 3′-[(2*S*)-butan-2-yl(methyl)carbamoyl]-2,2′-binaphthalene-3-carboxylate 4f. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.38. HPLC purity: 100.0%; IR (film) *ν* 2953 m, 2936 m, 1722 m, 1612 m, 895 w, 725 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.50 (s, 0.8H), 8.46 (s, 0.2H), 7.99–7.79 (m, 6H), 7.61–7.50 (m, 5H), 4.60–4.50 (m, 1H), 3.70 (s, 3H), 2.66 (s, 1.2H), 2.47 (s, 1.8H), 1.40–1.20 (m, 2.3H), 1.10–0.60 (m, 3.2H), 0.30–0.20 (m, 2.5H); UV (cyclohexane) λ_{max}(ε) nm 221.8 (17,700), 257.2 (18,600), 335.2 (1000); CD λ_{ext}(nm)(Δε)(cyclohexane) 215.4 (+15.3), 226.7 (0), 236.4 (−17.7), 257.0 (+2.5), 286.3 (0), 293.2 (+3.7), 304.0 (+7.6); $[\alpha]_D^{20} = +9.0$ (*c* 0.748, $CHCl_3$); ESI-MS *m/z* 425 (M^+, 30), 339 (44), 310 (40), 295 (59), 281 (36), 280 (100), 252 (42); HRMS (ESI) Anal. Calcd for $C_{28}H_{27}NO_3$ *m/z* 425.1991 $[M]^+$. Found: 425.1999.

4.3.3.15. Methyl 3′-[(2*R*)-hexan-2-yl(methyl)carbamoyl]-2,2′-binaphthalene-3-carboxylate 4g. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.49. HPLC purity: 99.2%; Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.16; H, 7.00; N, 3.20. IR (film) *ν* 2955 m, 2932 m, 1722 m, 1614 m, 895 w, 721 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.50 (s, 0.8H), 8.46 (s, 0.2H), 7.95–7.78 (m, 6H), 7.59–7.51 (m, 5H), 4.61–4.56 (m, 1H), 3.70 (s, 1.8H), 3.69 (s, 1.2H), 2.66 (s, 1.2H), 2.47 (s, 1.8H), 1.36–0.22 (m, 12H); UV (cyclohexane) λ_{max}(ε) nm 221.6 (17,700), 257.2 (18,100), 335.0 (900); CD λ_{ext}(nm)(Δε)(cyclohexane) 215.4 (−20.7), 226.5 (0), 236.6 (+23.47), 250.7 (0), 257.2 (−4.9), 264.1 (0), 279.0 (+1.7), 285.7 (0), 293.0 (−5.1), 303.8 (−9.9); $[\alpha]_D^{26} = +7.4$ (*c* 1.870, $CHCl_3$); ESI-MS *m/z* 454 (M^+, 11), 453 (35), 339 (56), 310 (43), 295 (68), 281 (39), 280 (100), 252 (40); HRMS (ESI) Anal. Calcd for $C_{30}H_{31}NO_3$ *m/z* 453.2304 $[M]^+$. Found: 453.2310.

4.3.3.16. Methyl 3′-[(2*S*)-hexan-2-yl(methyl)carbamoyl]-2,2′-binaphthalene-3-carboxylate 4h. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.49. HPLC purity: 99.7%; Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.91; H, 6.89; N, 3.17. IR (film) *ν* 2955 m, 2932 m, 1722 m, 1612 m, 895 w, 721 w, cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.49 (s, 0.8H), 8.45 (s, 0.2H), 7.94–7.77 (m, 6H), 7.61–7.50 (m, 5H), 4.60–4.58 (m, 1H), 3.70 (s, 1.8H), 3.69 (s, 1.2H), 2.65 (s, 1.2H), 2.47 (s, 1.8H), 1.36–0.21 (m, 12H); UV (cyclohexane) λ_{max}(ε) nm 221.8 (17,800), 257.2 (18,300), 334.8 (900); CD λ_{ext}(nm)(Δε)(cyclohexane) 215.4 (+18.1), 225.7 (0), 236.8 (−24.6), 251.7 (0), 257.0 (+4.0), 262.7 (0), 279.6 (−2.6), 286.9 (0), 293.2 (+4.2), 303.8 (+9.0); $[\alpha]_D^{26} = -7.7$ (*c* 1.760, $CHCl_3$); ESI-MS *m/z* 454 (M^+, 18), 453 (53), 339 (71), 310 (52), 295 (73), 281 (38), 280 (100), 252 (35); HRMS (ESI) Anal. Calcd for $C_{30}H_{31}NO_3$ *m/z* 453.2304 $[M]^+$. Found: 453.2308.

4.3.3.17. Methyl 3′-{methyl[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-carbamoyl}-2,2′-binaphthalene-3-carboxylate 4i. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.57. HPLC purity: 99.0%; IR (film) *ν* 2951 m, 2924 m, 1722 m, 1620 m, 895 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.50 (s, 1H), 8.03–7.77 (m, 6H), 7.60–7.51 (m, 5H), 5.20–5.00 (m, 1H), 3.70 (s, 3H), 2.84 (s, 0.5H), 2.65 (s, 2.5H), 2.22–2.20 (m, 1H), 1.70–1.50 (m, 2.3H), 1.32–1.19 (m, 2.8H), 1.13 (s, 3H), 1.10–1.00 (m, 1H), 1.02 (s, 3H), 0.90–0.83 (m, 1.4H), 0.74 (d, *J* = 10.9 Hz, 1H), 0.70–0.55 (m, 0.5H); UV (cyclohexane) λ_{max}(ε) nm 222.6 (18,200), 256.8 (19,400), 335.2 (700); CD λ_{ext}(nm)(Δε)(cyclohexane) 215.2 (−5.6), 222.9 (0), 235.4 (+13.1), 245.3 (0), 255.2 (−5.0), 267.3 (0), 271.4 (+0.3), 283.1 (0), 291.6 (−2.1), 302.8 (−3.9); $[\alpha]_D^{26} = +0.2$ (*c* 2.020, $CHCl_3$);ESI-MS *m/z* 505 (M^+, 58), 339 (100), 310 (33), 295 (77), 280 (87); HRMS (ESI) Anal. Calcd for $C_{34}H_{35}NO_3$ *m/z* 505.2617 $[M]^+$. Found: 505.2612.

4.3.3.18. Methyl 3′-{methyl[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-carbamoyl}-2,2′-binaphthalene-3-carboxylate 4j. Colorless amorphous. R_f (hexane/EtOAc, 2/1 (v/v)) 0.57. HPLC purity: 98.8%; IR (film) *ν* 2951 m, 2924 m, 1722 m, 1620 m, 894 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.50 (s, 1H), 8.01–7.77 (m, 6H), 7.60–7.51 (m, 5H), 5.20–5.00 (m, 1H), 3.70 (s, 3H), 2.84 (s, 0.5H), 2.65 (s, 2.5H), 2.24–2.19 (m, 1H), 1.70–1.50 (m, 2.3H), 1.30–1.19 (m, 2.8H), 1.13 (s, 3H), 1.10–1.00 (m, 1H), 1.02 (s, 3H), 0.90–0.83 (m, 1.4H), 0.74 (d, *J* = *J* = 10.9 Hz, 1H), 0.70–0.55 (m, 0.5H); UV (cyclohexane) λ_{max}(ε) nm 222.6 (17,400), 256.8 (18,300), 335.6 (700); CD λ_{ext}(nm)(Δε)(cyclohexane) 215.4 (+3.8), 220.9 (0), 235.4 (−12.1), 245.5 (0), 256.2 (+4.0), 266.1 (0), 278.4 (−0.6), 285.5 (0), 290.4 (+1.1), 302.0 (+2.9); $[\alpha]_D^{26} = -0.7$ (*c* 1.640, $CHCl_3$); ESI-MS *m/z* 505 (M^+,23), 339 (58), 295 (71), 280 (100), 252 (36); HRMS (ESI) Anal. Calcd for $C_{34}H_{35}NO_3$ *m/z* 505.2617 $[M]^+$. Found: 505.2609.

4.3.3.19. Methyl 3′-{[(4*R*)-3-oxoisoxazolidin-4-yl]carbamoyl}-2,2′-binaphthalene-3-carboxylate 5. Colorless amorphous. R_f (hexane/EtOAc, 1/3 (v/v)) 0.41. HPLC purity: 100.0%; IR (film) *ν* 3296 m, 3059 m, 2953 m, 2933 m, 1715 m, 1663 m, 1508 m, 901 w, 667 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.54 (s, 0.5H), 8.48 (s, 0.5H), 8.24 (s, 0.5H), 8.21 (s, 0.5H), 7.98–7.94 (m, 2H), 7.84–7.75 (m, 3H), 7.67–7.53 (m, 5H), 7.20–7.16 (m, 1H), 4.71–4.65 (m, 1H), 4.44–4.37 (m, 1H), 3.88–3.85 (m, 0.5H), 3.76 (s, 1.5H), 3.74 (s, 1.5H), 3.13–3.08 (m, 0.5H); UV (cyclohexane) λ_{max}(ε) nm 242.0 (10,400), 333.0 (300); CD λ_{ext}(nm)(Δε)(cyclohexane) 205.6 (−9.3), 229.8 (−17.2), 239.4 (0), 249.2 (+21.2); $[\alpha]_D^{26} = -6.2$ (*c* 4.220, $CHCl_3$); ESI-MS *m/z* 440 (M^+, 11), 296 (100), 280 (39); HRMS (ESI) Anal. Calcd for $C_{26}H_{20}N_2O_5$ *m/z* 440.1372 $[M]^+$. Found: 440.1379.

4.3.3.20. 3′-{Methyl[(4*R*)-2-methyl-3-oxoisoxazolidin-4-yl]carbamoyl}-2,2′-binaphthalene-3-carboxylate 6. Colorless amorphous. R_f (hexane/EtOAc, 1/3 (v/v)) 0.79; HPLC purity: 100.0%; IR (film) *ν* 3059 w, 3026 w, 1713 m, 1663 m, 1512 m, 895 w cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.54 (s, 0.6H), 8.45 (s, 0.4H), 8.06–7.80 (m, 6H), 7.63–7.55 (m, 5H), 5.40–5.32 (m, 0.5H), 4.35–4.21 (m, 0.5H), 3.88 (s, 1.5H), 3.77 (s, 1.5H), 3.73 (s, 3H), 3.31–3.24 (m, 2H), 2.74 (s, 1.2H), 2.56 (s, 1.8H); UV (cyclohexane) λ_{max}(ε) nm 224.2 (5400), 248.6 (5400), 335.0 (200); CD λ_{ext}(nm)(Δε)(cyclohexane) 213.6 (−8.1), 219.8 (0), 233.0 (+8.9), 245.6 (0), 250.4 (−0.9), 256.4 (0), 265.6 (+2.5), 288.4 (0), 304.6 (−2.3); $[\alpha]_D^{30} = +51.2$ (*c* 0.430, $CHCl_3$); ESI-MS *m/z* 468 (M^+, 30), 310 (94), 295 (76), 281 (48), 280 (100); HRMS (ESI) Anal. Calcd for $C_{28}H_{24}N_2O_5$ *m/z* 468.1691 $[M]^+$. Found: 468.1685.

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15. Calculations were performed with CONFLEX and MOPAC implemented in CAChe *ver*. 4.1.1 for Apple Macintosh; Fujitsu Co., Ltd, Chiba, Japan. Conformational analysis using CONFLEX was carried out under the following conditions: search limit: 0.01%; maximum configurations: 5000; highest steric energy: 25.0 kcal/mol; energy comparison: 1.5 kcal/mol; dihedral comparison: 10.0°; force field: augmented MM2; optimization: conjugate gradient for no more than 3000 updates or until convergence to 0.001 kcal/mol; cut-off distance for vdw interactions: 9.0 Å.
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