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Absolute configuration assignment of oxindole derivatives by vibrational circular dichroism exciton coupling

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ABSTRACT

A convenient and reliable approach for the absolute configuration assignment of oxindole derivatives **2a**–**m** by vibrational circular dichroism (VCD) measurements and evaluation of the VCD bisignated couplet resulting from the interaction of the C2 and C9 carbonyl groups is presented. The absolute configuration assignments were further tested by ^{1}H NMR measurements and by X-ray diffraction analysis.

1. Introduction

Chiral oxindole derivatives, mainly 1,3,3-trisubtituted **1** molecules (Fig. 1), have been widely used in the total synthesis of chiral or racemic terrestrial and marine natural products.[1] For this purpose, we recently assigned the absolute configuration of chiral 2-(2-oxo-3-indolyl)acetic acid derivatives by ^{1}H NMR spectroscopy using enantiomerically pure (*R*)-phenylethylamine or (*S*)-phenyl-2-oxazolidinone as chiral derivatizing agents.[2] As shown for compounds **2** and **3** (Fig. 2), experimental data demonstrated that the phenyl ring of phenylethylamine shields the *N*1–Me group in (3*R*,11*R*)-**2** and the C3–Me group in (3*S*,11*R*)-**2** diastereoisomers,[2a] while (3*S*,14*S*)-**3** presents the H4-H7 and H16-H20 signals at lower frequency values and the H8A signal at higher values than the corresponding signals for the (3*R*,14*S*)-**3** diastereomer due to the mutual diamagnetic influence of the aromatic (*S*)-oxazolidinone and oxindole moieties on the ^{1}H NMR signals.[2b] Thus, the $\Delta\delta^{RS}$ parameter allowed us to assign the absolute configuration of diastereoisomers **2** and **3** as shown in Figure 2. The absolute configuration of (3*S*,14*S*)-**3** and (3*R*,14*S*)-**3** were independently determined using a time consuming protocol needed to compare the experimental vibrational circular dichroism (VCD) spectra with those calculated using DFT, which showed good agreement.[2b]

In a continuation of our studies aimed at the determination of the absolute configuration of oxindole derivatives,[3] we herein report that the absolute configuration of (3*R*)-**2a**–**m** and (3*S*)-**2a**–**m** can be assigned solely by VCD exciton coupling (VCDEC)[4] by considering the bisignate couplets that originate from the through-space interaction of the C2 and C9 amide carbonyl groups. We also demonstrate that the absolute configurations of (3*R*)-**2a**–**m** and (3*S*)-**2a**–**m** can be assigned by this method independent of the chiral derivatizing amine used, thus avoiding the need of having an aromatic group that is capable of producing an efficient and

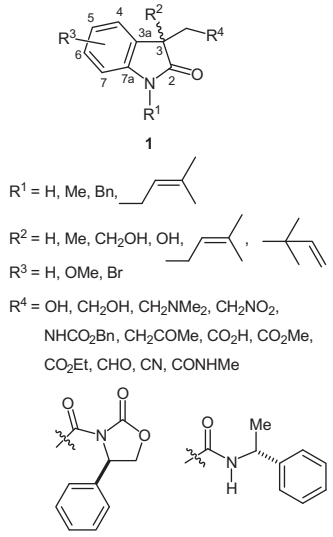

Figure 1. Natural and synthetic oxindoles **1**.

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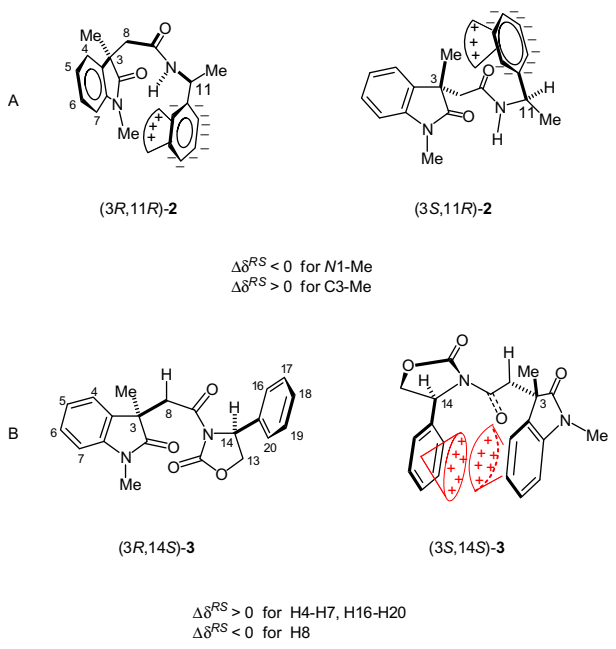


Figure 2. Anisotropic effect of the aromatic rings in (*R*)-phenylethylamine (A) and (*S*)-phenyl-2-oxazolidinone (B) on the oxindole moiety subsituents.

space-oriented anisotropic effect to selectively affect substituents in the substrate. This absolute configuration assignment methodology was confirmed by single-crystal X-ray diffraction analysis.

2. Results and discussion

In order to investigate the utility of VCDEC for the absolute configuration assignment in a series of 2-oxo-3-indolylacetic acid derivatives **2a**–**e**[2a] (Fig. 3) and **2f**–**m** containing a variety of alkyl groups at the *N*1 and C3 positions, and different chiral amine fragments at the carboxyl group, their experimental VCD spectra were acquired. For this goal, racemic carboxylic acids **4** were derived into the corresponding amides **2f**–**k** by activation with Et_3N and $ClCO_2Et$,[2a] followed by reaction with different chiral amines **5f**–**k** (Scheme 1) to give equimolar diastereomeric mixtures of (3*R*)-**2f**–**k** (28–46%) and (3*S*)-**2f**–**k** (29–43%), which were easily separated by column chromatography to afford enantiomerically pure isomers (de >99%) as determined by ^1H NMR.

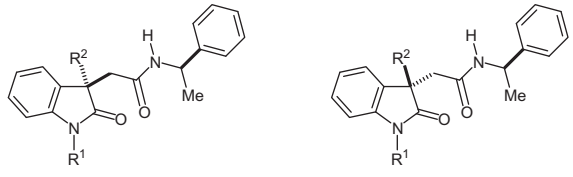
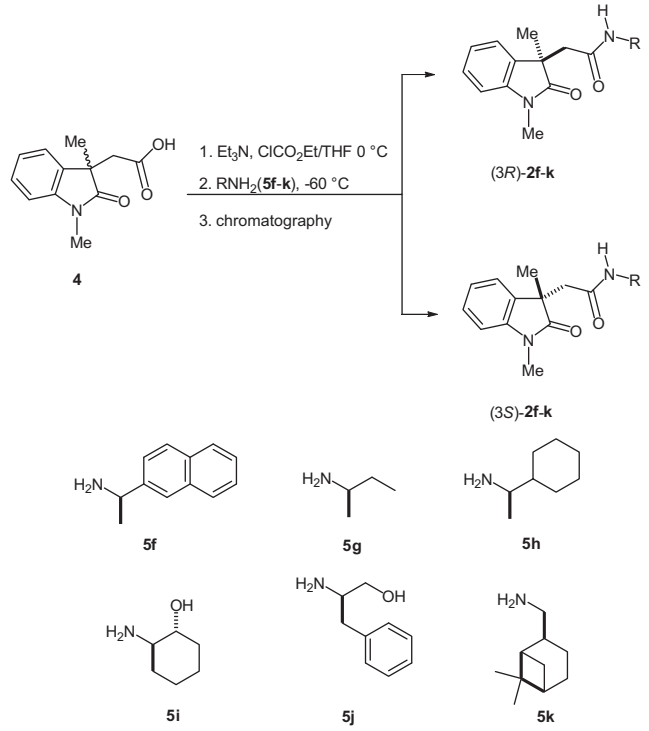


Figure 3. Formulas of (3*R*)-**2a**–**e** and (3*S*)-**2a**–**e**.

The ^1H NMR spectra comparison of the less polar (3*R*)-**2f** and the more polar (3*S*)-**2f** showed large enough chemical shift differences ($\Delta\delta^{RS} = \delta_R - \delta_S$, where the *R* and *S* descriptors refer to the C3 configuration at the oxindole moiety) for the aromatic H7, *N*1-Me and C3-Me groups. As shown in Figure 2A, the $\Delta\delta^{RS}$ values would arise from the diamagnetic influence of the aromatic (*R*)-naphthyl moiety on the NMR signals of H7 and the *N*1-Me and C3-Me groups in the (3*R*)- and (3*S*)-stereogenic centers of the oxindole skeleton in **2f**. It is worth noting that in diastereoisomers (3*R*)-**2f** and (3*S*)-**2f**, the signals for the aromatic fragments are more scattered than those of compounds (3*R*)-**2a** and (3*S*)-**2a** (Fig. 4). Furthermore, the $\Delta\delta^{RS}$ values for H7 (−0.24) and *N*1-Me (−0.44) are greater for diastereoisomers **2f** than in **2a** (−0.06, −0.18) (Figs. 4 and 5), which indicate a stronger aromatic magnetic cone projection of the naphthyl ring towards H7 and *N*1-Me than that of the phenyl ring.[5] In order to ensure that the $\Delta\delta^{RS}$ values for H7, *N*1-Me and C3-Me are mainly due to the anisotropic effect of the naphthyl aromatic ring, the ^1H NMR spectra of (3*R*)-**2f** and (3*S*)-**2f** were obtained in $CDCl_3$ at different concentrations (Fig. 6); we found that the chemical shifts for H7 and *N*1-Me in (3*R*)-**2f** are more concentration dependent than those of (3*S*)-**2f**, but the chemical shifts caused by this effect are incomparable with those caused by the anisotropic effect.



Scheme 1. Synthesis of diastereoisomeric amides **2f**–**k**.

It is well known that ^1H NMR spectroscopy is a useful method for the absolute configuration assignment of monofunctional and polyfunctional compounds as long as the chiral derivatizing agents have aromatic or carbonyl groups that selectively produce an efficient and space-oriented anisotropic effect on the substituent at the asymmetric unit of the substrate.[6] Thus, although the ^1H NMR spectra of diastereoisomers (3*R*)-**2g**–**k** and (3*S*)-**2g**–**k** did not shown any systematic variation of the $\Delta\delta^{RS}$ values for H7, *N*1-Me and C3-Me, we found a direct relationship between the chemical shifts difference for the AB system at H8 ($\Delta\delta_{H8A\text{-}H8B}$) and the polarity in each diastereoisomer with the configuration at C3 of amides **2a**–**k** (Table 1). We noticed that the $\Delta\delta_{H8A\text{–}H8B}$ values tended to be greater in the more polar amides (3*S*)-**2a**–**h** than in the less polar (3*R*)-**2a**–**h** ones,[2a] although this trend was reversed in amides **2i**–**k** as evidenced when these diastereoisomers where synthesized from enantiomerically pure (3*S*)-**4**. Thus, the resolution of (±)-**4**

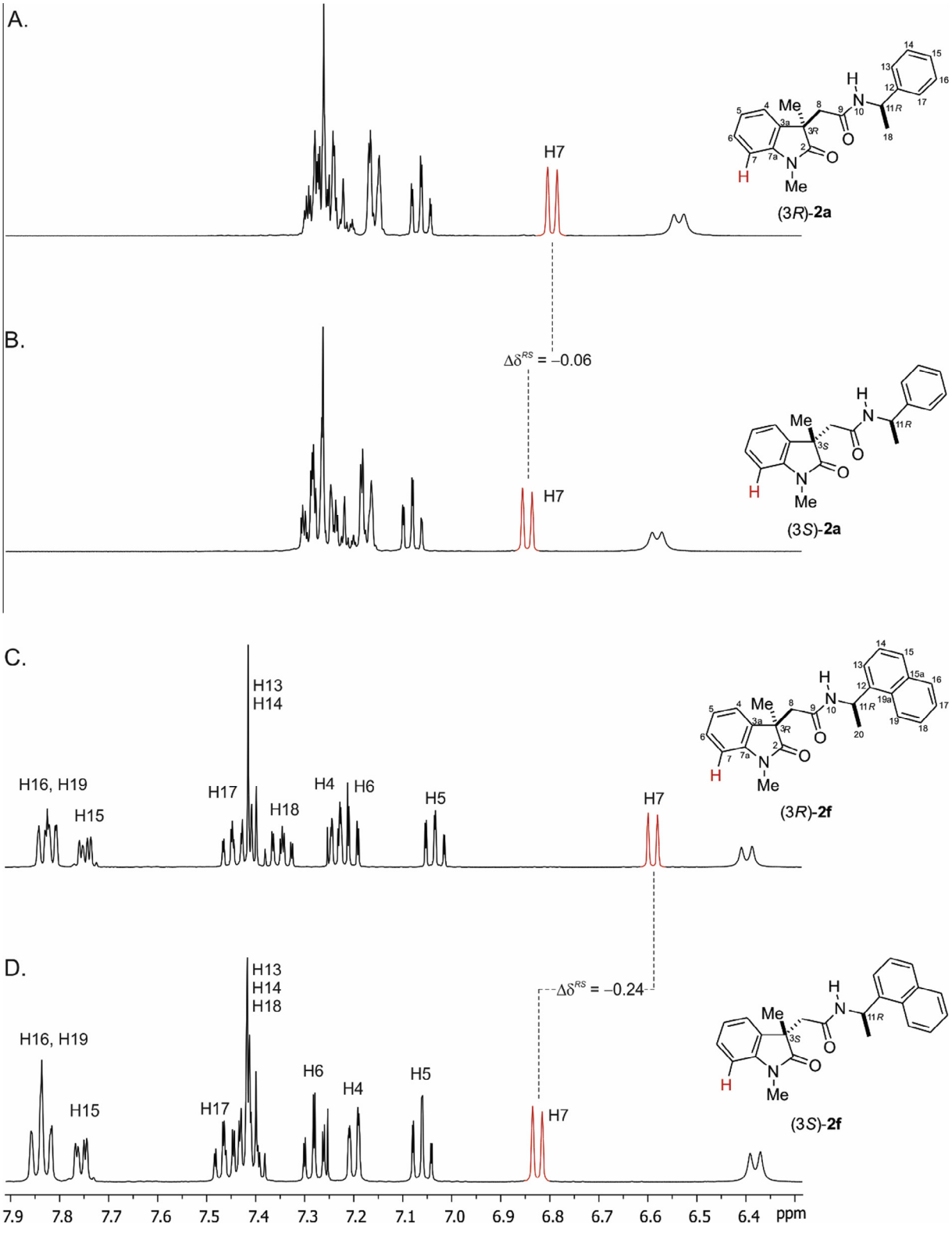


Figure 4. $\Delta\delta^{RS}$ values for H7 of (3*R*)- and (3*S*)-**2a**,**2f**.

with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 4-dimethylaminopyridine (DMAP), followed by reaction with (*R*)-4-phenyl-2-oxazolidinone **6**, gave a diastereomeric mixture of the less polar (3*S*,14*R*)-**7** and the more polar (3*R*,14*R*)-**7** in 22% and 23% yields, respectively (Scheme 2), whose absolute configurations were established after analysis of their ^{1}H NMR spectra.[2b] Subsequent hydrolysis of (3*S*,14*R*)-**7** and (3*R*,14*R*)-**7** with $LiOH/H_2O_2$[3] afforded the corresponding (3*S*)-**4** and (3*R*)-**4** acids in 90% and 85% yields, respectively (Scheme 2). Finally, acid (*S*)-**4** was transformed into the corresponding amides (3*S*)-**2i**–**k** by activation with $ClCO_2Et$ and Et_3N,[2a] followed by reaction with chiral amines **5i**–**k** (Scheme 3). TLC analysis

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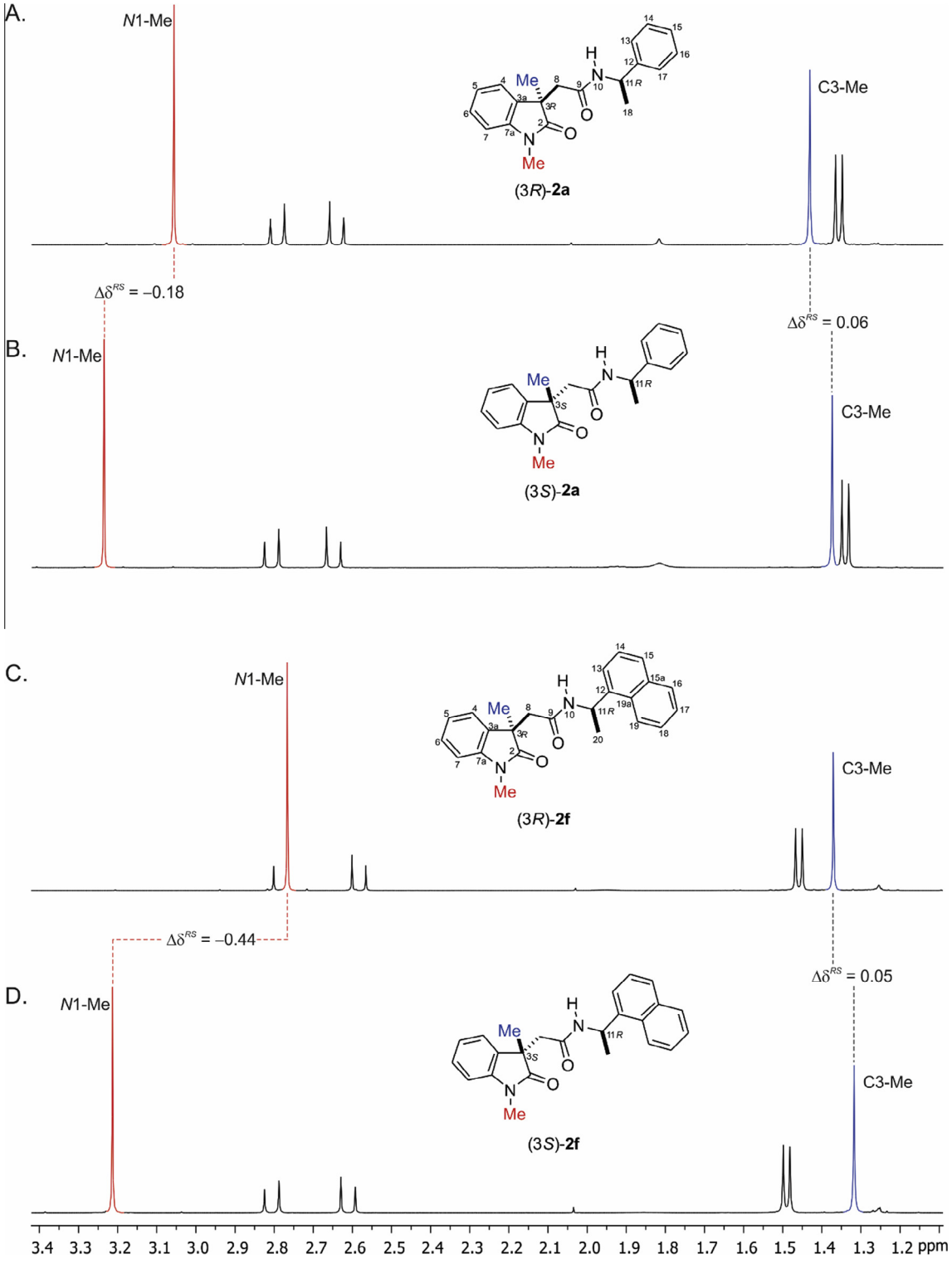

Figure 5. $\Delta\delta^{RS}$ values for the *N*1-Me and C3-Me signals of (3*R*)- and (3*S*)-**2a**,**2f**.

showed that (3*S*)-**2i**–**k** correspond to the less polar amides when compared with those obtained from racemic (±)-**4** and thus, the R_f and $\Delta\delta_{H8A\text{-}H8B}$ values in Table 1 were justified.

As is evident for oxindoles **2a**–**f**, ^{1}H NMR spectroscopy is an easy and reliable approach for the absolute configuration assignment of chiral oxindoles, provided that the aromatic amines are used as chiral derivatizing agent. However, when this condition is not fulfilled, as in the case of **2g**–**k**, this methodology does not work. Therefore, we sought a more confident and general method for the assignment of the absolute configuration of chiral 2-(2-oxo-3-indolyl)acetic acid derivatives **2a**–**k** that would not be restricted to the presence of aromatic chiral derivatizing agents.[6] Thus, the experimental VCD spectra of **2a**–**k** were acquired and compared with each other (Figs. 7, 8, 10 and 11). We first analyzed the VCD spectra of (3*R*)- and (3*S*)-**2a**–**e** in which the amide fragment is the same, but the *N*1 and C3 substituents are different. As can be

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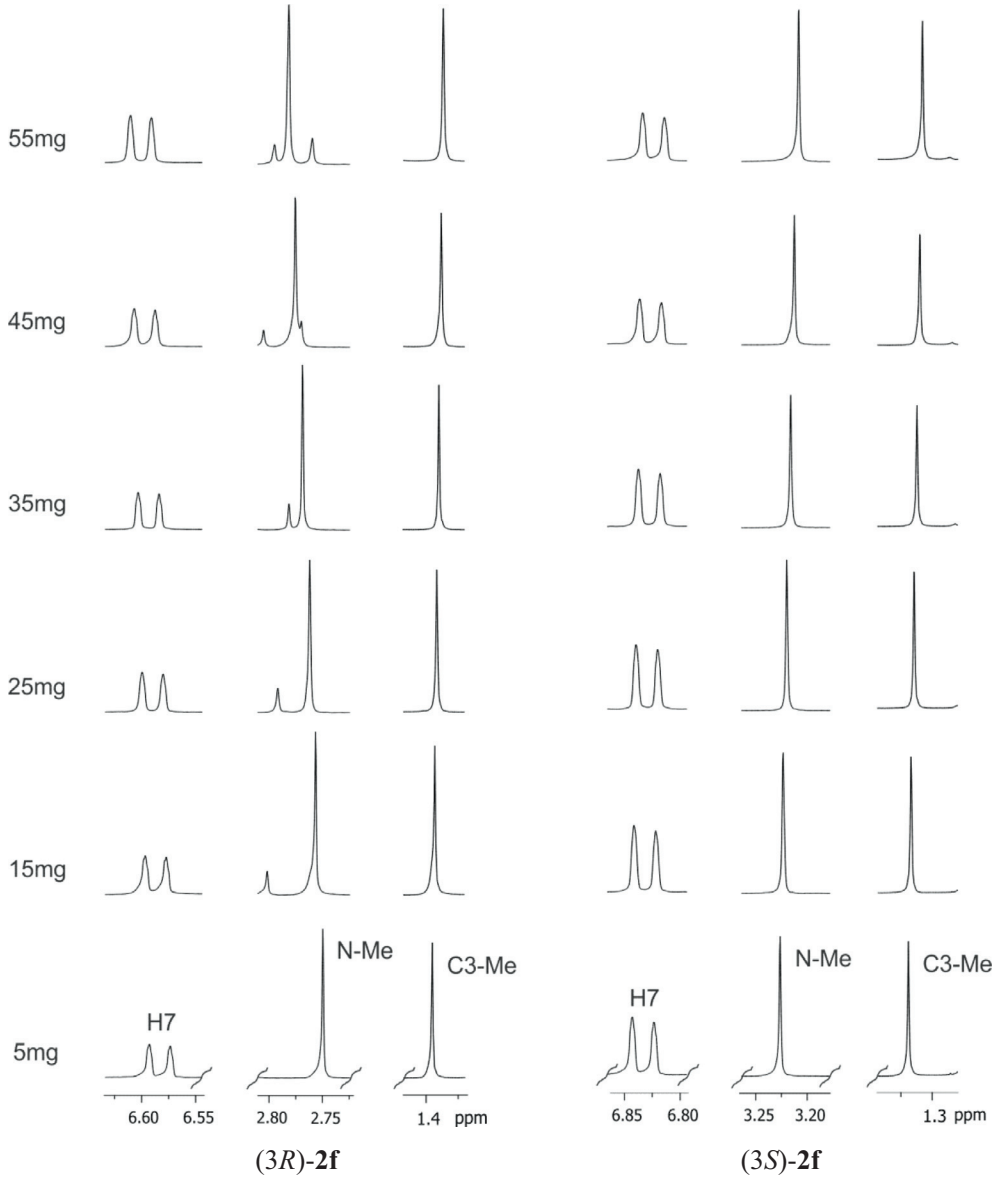

Figure 6. Concentration dependence of the H7, N-Me and C3-Me chemical shift of (3*R*)- and (3*S*)-**2f**.

Table 1
$\Delta\delta_{H8A-H8B}$ and R_f[a] values of diastereoisomeric amides **2a**–**k**

Compound	(3*R*)-**2a**–**k**		(3*S*)-**2a**–**k**	
	R_f	$\Delta\delta_{H8A-H8B}$	R_f	$\Delta\delta_{H8A-H8B}$
2a	0.62	0.13	0.47	0.14
2b	0.69	0.13	0.49	0.13
2c	0.64	0.15	0.47	0.17
2d	0.82	0.12	0.64	0.14
2e	0.73	0.20	0.56	0.19
2f	0.47	0.14	0.40	0.16
2g	0.69	0.20	0.56	0.20
2h	0.64	0.16	0.47	0.19
2i	0.09	0.10	0.22	0.18
2j	0.18	0.14	0.36	0.19
2k	0.58	0.15	0.60	0.16

[a] Determined by TLC (Silica gel F_{254} coated aluminum sheets 0.25 mm thickness) using EtOAc.

seen, with the exception of the oxindole derivatives (3*R*)- and (3*S*)-**2e** (Figs. 7 and 8), all other compounds presented the same sign for the band around 1600 cm^{-1}. For amides (3*R*)-**2a**–**d** the sign is negative, while for (3*S*)-**2a**–**d** it is positive. Since there was no great similarity in the 1550–950 cm^{-1} range for (3*R*)-**2a**–**e** (Fig. 7) and for (3*S*)-**2a**–**e** (Fig. 8), this indicated that although achiral, the different alkyl groups at the C3 and N1 positions make important changes in this VCD region. In both (3*R*)- and (3*S*)-diastereomeric series of **2a**–**e**, there are intense bisignate VCDEC signals around 1626–1747 cm^{-1} which indicate the through-space coupling of the C2 and C9 carbonyl groups.[3,7] As shown in Figures 7 and 8, and in Table 2, these bisignate VCDEC signals are generally as intense in both the (3*R*)- (*A* values from −0.039 to −0.101) and the (3*S*)-**2a**–**e** (*A* values from 0.047 to 0.089) series. A negative-lower to positive-higher wave numbers signal twist (negative Cotton effect) generated by the interaction of the electric transition moments of the C2 and C9 carbonyl groups in (3*R*)-**2a**–**e** was observed, while a positive/negative combination from low to high wave numbers signal twist (positive Cotton effect) was observed for (3*S*)-**2a**–**e**. According to the model proposed by Monde and Taniguchi,[4a] (3*R*)-**2a**–**e** should display a counterclockwise ($-180° < \theta < 0°$, negative twist) chromophoric orientation of the C2 and C9 carbonyl groups (Fig. 9A), while diastereoisomers

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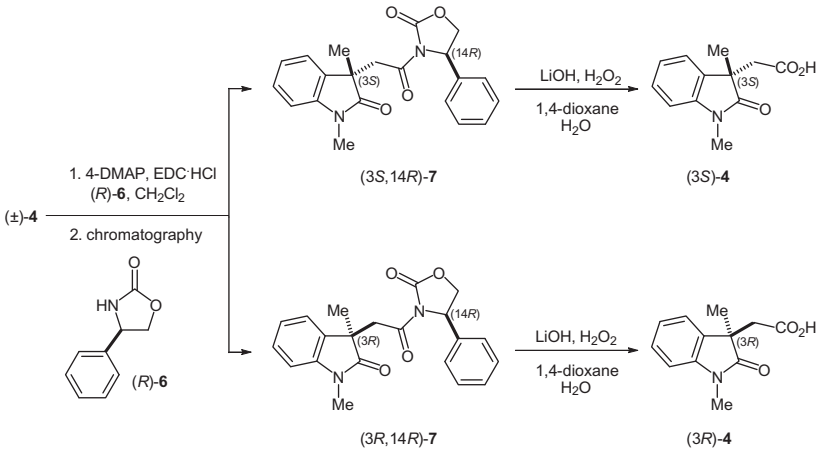
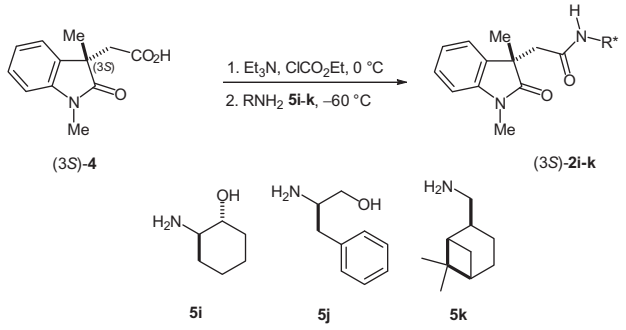


Scheme 2. Enantiomer separation of (±)-**4**.



Scheme 3. Synthesis of enantiomerically pure amides (3*S*)-**2i**–**k**.

(3*S*)-**2a**–**e** should present a clockwise ($0° < \theta < +180°$, positive twist) disposition (Fig. 9B) thus revealing their C3 absolute configuration. Although for (3*R*)-**2d** only a negative monosignate signal was detected at 1655 cm^{-1} (Fig. 7), its position coincides with that of the first negative Cotton effect signal (1655–1665 cm^{-1}) for the (3*R*)-**2a**–**c**,**e** diastereoisomers (Fig. 7), thus indicating that even for (3*R*)-**2d**, the absolute configuration could be assigned at the 1655–1699 cm^{-1} VCD spectroscopic region.

The applicability of the methodology was further evaluated with the VCD spectroscopic comparison of oxindole derivatives (3*R*)-**2a**,**f**–**k** and (3*S*)-**2a**,**f**–**k** containing methyl groups at the *N*1 and C3 positions, but with different amide residues (Figs. 10 and 11). Both series of spectra show the same sign for the band around 1600 cm^{-1} as those shown for (3*R*)-**2a**–**d** and (3*S*)-**2a**–**d**. As opposed to these latter, oxindoles (3*R*)-**2f**–**k** and (3*S*)-**2f**–**k** were very similar in the 1550–950 cm^{-1} region, which indicates that a change of the amide fragment has less influence on the VCD spectra than the substituents at *N*1 and C3 (Figs. 7 and 8). Meanwhile, the VCDEC signals twist around 1626–1747 cm^{-1} in (3*R*)-**2f**–**k** and (3*S*)-**2f**–**k** is not altered due to the presence of the chiral amine, and is consistent with those of (3*R*)-**2a**–**e** and (3*S*)-**2a**–**e**, but their intensity *A* is smaller for (3*R*)-**2f**–**k** (−0.028 to −0.045, Table 2) and similar for (3*S*)-**2f**–**k** (0.043–0.119). Just as for (3*R*)-**2d**, compounds (3*R*)-**2f**,**g**,**h** and (3*S*)-**2g** present only negative or positive monosignate signals but their position coincides with that of the first or second negative or positive Cotton effect signal for the other oxindoles in the series. The VCD spectra of (3*R*)- and (3*S*)-**2a**,**f**–**k** in Figures 10 and 11 show common absorption bands in the 1466–1471, 1448–1460, 1379–1392, 1352–1356, 1240–1246, 1088–1098, 1059–1065, 1032–1036 cm^{-1} ranges, which are also very sensitive to the absolute configuration in both the (3*R*)- and (3*S*)-**2a**,**f**–**k** series since opposite signs are shown for these signals. Furthermore, the VCD spectra of oxindole **2k**, containing an amine fragment with a stereogenic center in the β-position, were similar to those of the (3*R*)- or (3*S*)-**2a**,**f**–**j** series. These results undoubtedly indicate the low influence of the amide fragment in the VCD spectra of the oxindoles **2a**,**f**–**k** series.

It is important to note that when comparing the VCD spectra of the (3*R*)-**2a**–**e** and (3*R*)-**2f**–**k** series (Figs. 7 and 10) or those of the (3*S*)-**2a**–**e** and (3*S*)-**2f**–**k** series (Figs. 8 and 11), the plots are more different when the substituents at the *N*1 and C3 positions are changed, than when the chiral amine is changed. This was conclusively demonstrated when the VCD spectra of the enantiomeric esters **8** were obtained (Scheme 4, Fig. 12). It is evident that the VCD spectrum of the ester (3*R*)-**8** (Fig. 12A) seems more similar to those of the (3*R*)-**2a**,**f**–**k** series than those to the (3*R*)-**2b**–**e** series. Similarly, the VCD spectrum of ester (3*S*)-**8** (Fig. 12B) seems more like those of the (3*S*)-**2a**,**f**–**k** series than those of the (3*S*)-**2b**–**e** series. We also observed in the VCD spectra shown in Figures 7 and 8 that a substituent change at the C3 position modifies the spectra more than a change at the *N*1 position. For example the VCD spectra of compounds (3*R*)-**2a**,**b**,**d** are more similar when compared with the spectra of (3*R*)-**2c**,**e** (Fig. 7). The same applies when comparing the VCD spectra of (3*S*)-**2a**,**b**,**d** with those of (3*S*)-**2c**,**e** (Fig. 8). This observation was reaffirmed with the spectra comparison of oxindoles (3*R*)-**2f**,**l**,**m** and (3*S*)-**2f**,**l**,**m** (Figs. 13 and 14, Scheme 5) in which the C3-Me substituted oxindoles are more alike as compared with the C3-Et substituted counterparts.

Lastly, the reliability in the absolute configuration assignment by means of evaluation of the bisignate VCDEC signals in the carbonyl region was supported by the X-ray diffraction analysis of oxindoles (3*R*)-**2f**,**g**,**h** and (3*S*)-**2j** (Fig. 15). In the solid state a counterclockwise twist of the chromophoric orientation of the C2 and C9 carbonyl groups appears for (3*R*)-**2f**,**g**,**h**, while a clockwise twist is evident for (3*S*)-**2i**. As shown in Figure 15, the chromophoric orientation of these groups is better appreciated when the substituent on the amide nitrogen is omitted.

3. Conclusions

We have demonstrated that the stereochemistry of oxindole derivatives **2a**–**m** can easily be established by considering the sign of their VCDEC bisignate couplet signals irrespective of the substituents at the *N*1 and C3 positions and on the chiral amide used. A significant advantage of this methodology is that no aromatic chiral derivatizing agent is necessary to establish the absolute configuration in these oxindoles. The VCDEC technique seems reliable

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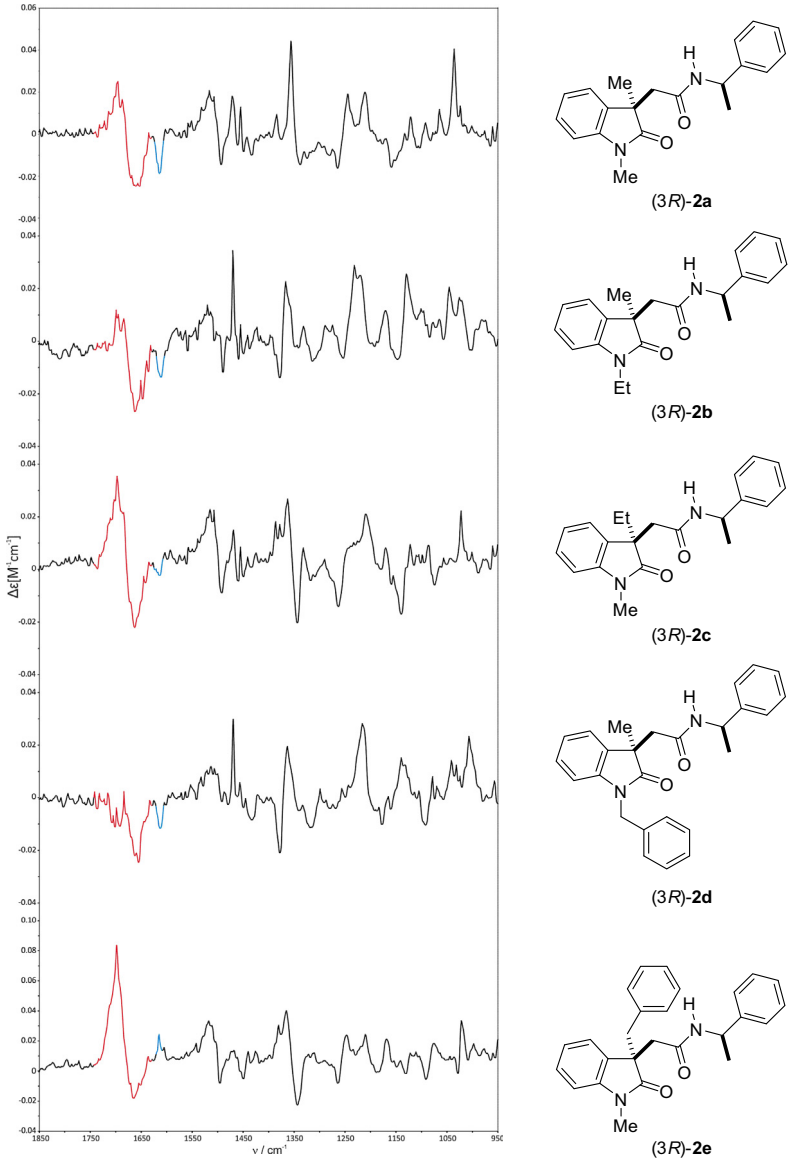

Figure 7. Comparison of the VCD spectra of (3*R*)-**2a**-**e**.

and could be of general value to assign the absolute configuration of C3-chiral oxindole derivatives, thus avoiding the need for time consuming DFT calculation protocols.

4. Experimental

4.1. General

Melting points were determined on a Büchi B-540 apparatus. IR spectra were recorded on a Perkin–Elmer GX FT-IR spectrophotometer. The 400 and 100 MHz ^{1}H and ^{13}C NMR spectra were obtained on a Varian VNMRS 400 spectrometer using DMSO-d_6, and $CDCl_3$ as the solvents and TMS or the signal of the undeterated solvents as the internal reference.[8] Solutions of 35 mg/0.7 mL of deuterated solvent were used to obtain the ^{1}H and ^{13}C NMR spectra. For complete assignments, gCOSY, gHSQCAD, HSQCHT, gHMBCAD and HMBCHT spectra were measured. Data are reported as follows: chemical shift in ppm from TMS, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, m = multiplet, br = broad), coupling constant (Hz), and assignment. GC/MS analyses were conducted on a Varian CP 3800 GC equipped with a Varian Saturn 2000 selective mass detector and a 30 m, 0.25 mm i.d., 0.25 mm CP-SIL capillary column, using helium as the carrier gas (1 mL/min), programmed from 70 °C to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. MS were obtained in the electron impact (EI) mode at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF-QII mass spectrometer. Microanalytical determinations were performed on a Perkin–Elmer 2400 Series PCII. Optical rotation measurements were performed on a Perkin–Elmer 341 polarimeter. Analytical thin-layer chromatography (TLC) was carried out on silica gel F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was done using silica gel 60 (230–400 mesh) from Aldrich.[9]

4.2. Preparation of oxindoles (*R*)-4 and (*S*)-4

To a solution of (3*S*,14*R*)-**7** or (3*R*,14*R*)-**7** (0.25 g, 0.69 mmol) in 1,4-dioxane/H_2O (8 mL/4 mL) was added a solution of LiOH (66 mg, 2.74 mmol) dissolved in an aqueous solution (29–32%) of H_2O_2

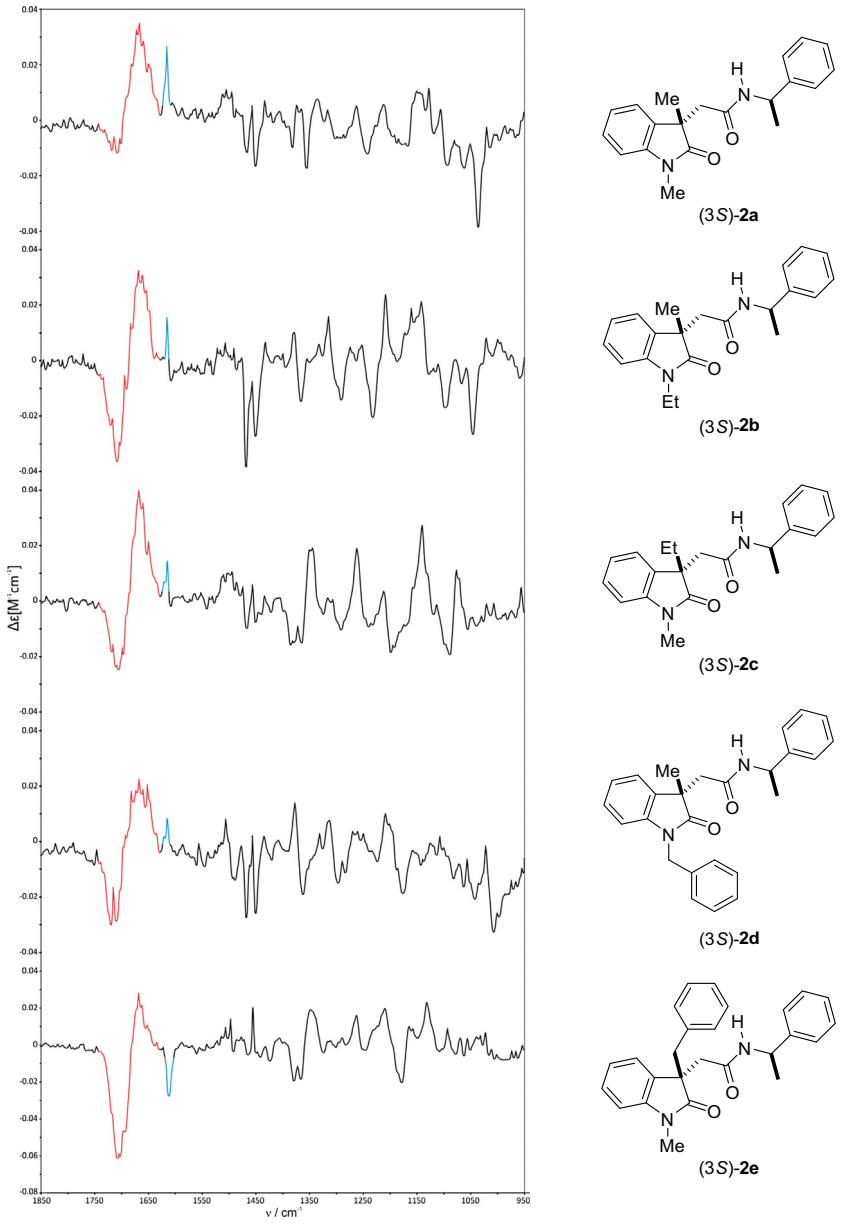

Figure 8. Comparison of the VCD spectra of (3*S*)-**2a**-**e**.

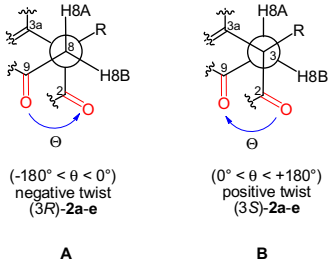

Figure 9. Twist sense for the electric transition moments of the C2 and C9 carbonyl groups in (3*R*)- and (3*S*)-**2a**–**e**.

(0.460 mL, 5.49 mmol) and the mixture was stirred at 0 °C for 18 h. Next, an aqueous saturated solution of Na_2SO_3 (15 mL) was added and the mixture was stirred at rt for 20 min, followed by extraction with EtOAc (3 × 15 mL). The aqueous phase was treated with an aqueous solution of HCl (1 M), followed by extraction with EtOAc (2 × 15 mL). The organic phases were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

4.2.1. (*R*)-(−)-2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetic acid (*R*)-4

Prepared from (3*R*,14*R*)-**7** as a white solid (0.128 g, 85%), mp: 215–217 °C (EtOAc/hexanes). $[\alpha]_D^{20} = -15.5$ (*c* 1.0, EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.02 (1H, br s, OH), 7.34 (1H, ddd, *J* = 7.2, 1.2, 0.5 Hz, H4), 7.24 (1H, td, *J* = 7.7, 1.3 Hz, H6), 7.00 (1H, td, *J* = 7.7, 1.0 Hz, H5), 6.98 (1H, d, *J* = 7.7 Hz, H7), 3.12 (3H, s, NMe), 2.92, 2.80 (2H, AB system, *J* = 16.6 Hz, H8), 1.22 (3H, s, C3-Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.2 (C2), 170.9 (C9), 143.4 (C7a), 133.2 (C3a), 127.6 (C6), 122.1 (C4), 121.7 (C5), 108.0 (C7), 44.7 (C3), 40.9 (C8), 26.0 (NMe), 24.3 (C3-*Me*). IR (KBr) ν_{max} 3443, 2974, 2720, 2637, 2594, 1724, 1672, 1613, 1197 cm^{-1}. EIMS *m*/*z* (relative intensity) 219 ([M]$^+$, 100), 174 (53), 160 (38), 132 (21), 117 (13). HRMS (ESI) *m*/*z* calculated for $C_{12}H_{14}NO_3$ [M+H]$^+$: 220.0968, found: 220.0975.

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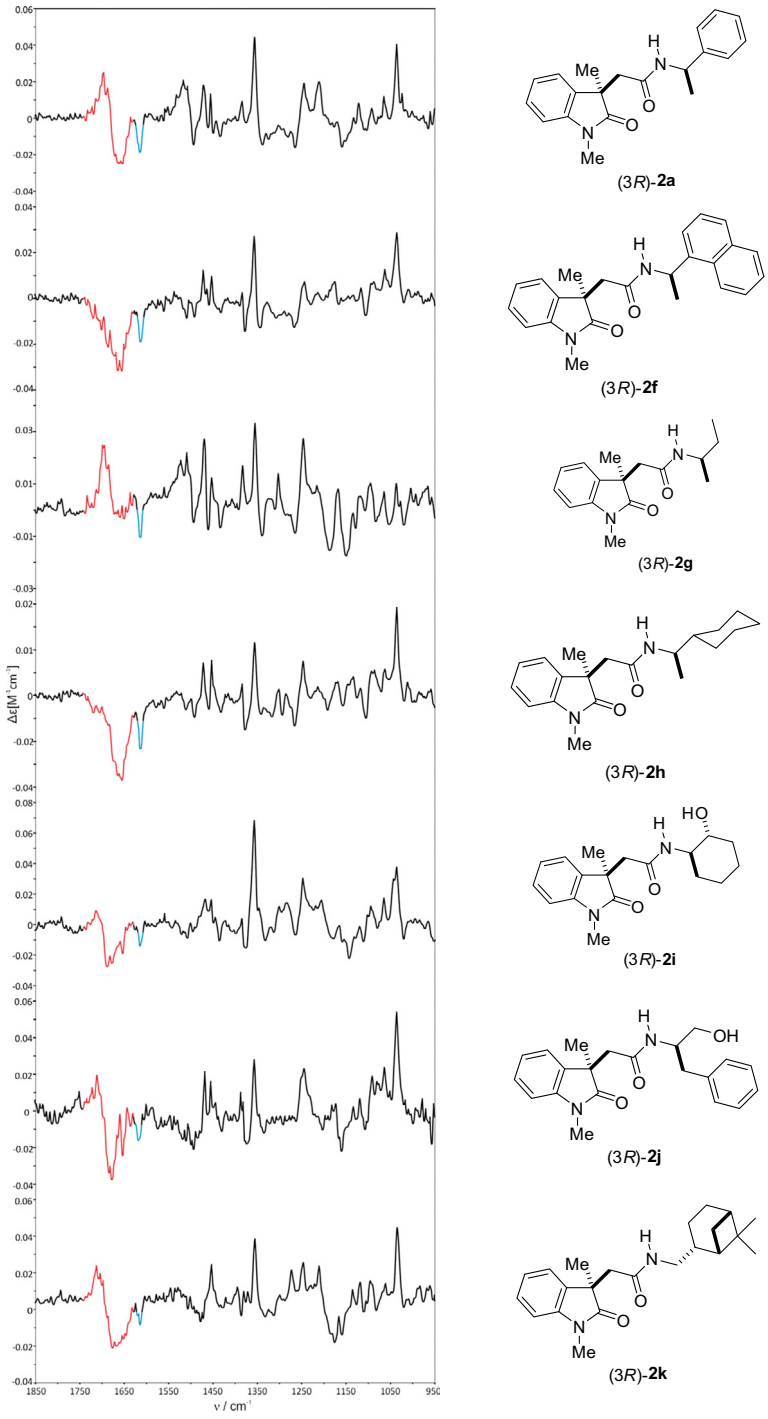


Figure 10. Comparison of the VCD spectra of (3*R*)-**2a**,**f**–**k**.

4.2.2. (*S*)-(+)-2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetic acid (*S*)-4

Prepared from (3*S*,14*R*)-**7** as a white solid (0.136 g, 90%), mp: 214–216 °C (EtOAc/hexanes). Lit.[10] 175.0–175.5 °C. $[\alpha]_D^{20}$ = +15.0 (*c* 1.0, EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (1H, br s, OH), 7.33 (1H, dd, *J* = 7.3, 0.7 Hz, H4), 7.24 (1H, td, *J* = 7.7, 1.2 Hz, H6), 7.00 (1H, td, *J* = 7.7, 1.0 Hz, H5), 6.98 (1H, d, *J* = 7.7 Hz, H7); 3.12 (3H, s, NMe); 2.92, 2.79 (2H, AB system, *J* = 16.6 Hz, H8); 1.22 (3H, s, C3-Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.2 (C2), 170.9 (C9), 143.4 (C7a), 133.2 (C3a), 127.5 (C6), 122.1 (C4), 121.6 (C5), 108.0 (C7), 44.7 (C3), 40.9 (C8), 26.0 (NMe), 24.3 (C3-*Me*). IR (KBr) ν_{max} 2974, 2720, 2637, 2601, 1724, 1674, 1613, 1197 cm^{-1}. EIMS *m*/*z* (relative intensity) 219 ([M]$^+$, 100), 174 (70), 160 (76), 132 (31), 117 (17). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}NO_3$ [M+H]$^+$: 220.0968, found: 220.0974.

4.3. General procedure for the esterification of oxindoles (*R*)-4 and (*S*)-4

To a solution of the appropriate acid (*S*)-**4** or (*R*)-**4** (0.075 g, 0.34 mmol) in MeOH (5 mL) was added concentrated H_2SO_4 (0.05 mL) and heated at reflux for 5 h. After cooling to the room temperature, MeOH was evaporated under reduced pressure and

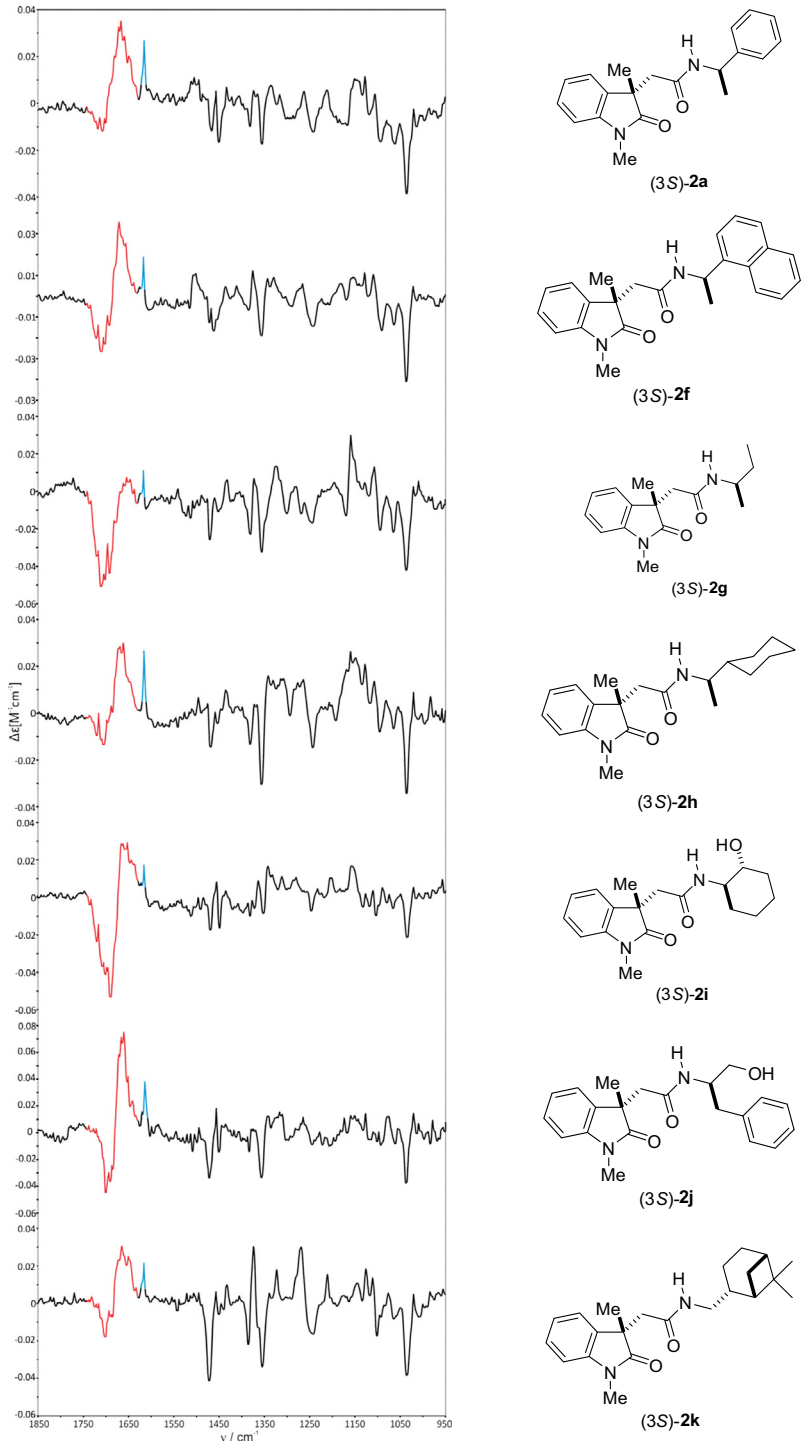


Figure 11. Comparison of the VCD spectra of (3*S*)-**2a**,**f**–**k**.

the residue was dissolved in EtOAc (15 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4 and evaporated in vacuum.

4.3.1. Methyl (*R*)-2-(1,3-dimethyl-2-oxoindolin-3-yl)acetate (*R*)-8

Prepared from (3*R*)-**4** as a colorless oil[2a,11] (0.079 g, 99%). $[\alpha]_D^{20} = -23.5$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (1H, td, *J* = 7.6, 1.3 Hz, H6), 7.20 (1H, ddd, *J* = 7.4, 1.2, 0.4 Hz, H4), 7.04 (1H, td, *J* = 7.5, 1.0 Hz, H5), 6.87 (1H, d, *J* = 7.8 Hz, H7), 3.45 (1H, s, OMe), 3.26 (3H, s, NMe), 3.01, 2.86 (2H, AB system, *J* = 16.4 Hz, H8), 1.38 (3H, s, C3-Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.9 (C2), 170.3 (C9), 143.6 (C7a), 132.9 (C3a), 128.2 (C6), 122.4 (C5), 122.2 (C4), 108.1 (C7), 51.6 (OMe), 45.5 (C3), 41.4 (C8), 26.4 (NMe), 24.2 (C3-*Me*). IR (film) ν_{max} 3056, 2953, 2929, 1739, 1715, 1614, 1249, 1202 cm^{-1}. EIMS *m*/*z* (relative intensity) 233 ($[M]^+$, 81), 174 (20), 160 (100), 132 (22).

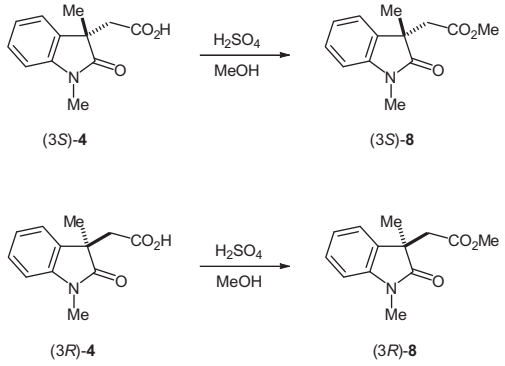
4.3.2. Methyl (*S*)-2-(1,3-dimethyl-2-oxoindolin-3-yl)acetate (*S*)-8

Prepared from (3*S*)-**4** as a pale yellow oil[2a,11] (0.079 g, 99%). $[\alpha]_D^{20} = +23.3$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28

Table 2
VCDEC couplets for (3*R*)- and (3*S*)-**2a-k**

Compound	M	$\Delta\varepsilon_1$[a] (ν[cm^{-1}])	$\Delta\varepsilon_2$[a] (ν[cm^{-1}])	A[b]
(3*R*)-**2a**	0.1055	−0.025 (1655)	0.025 (1697)	−0.050
(3*R*)-**2b**	0.1030	−0.027 (1662)	0.012 (1699)	−0.039
(3*R*)-**2c**	0.1248	−0.022 (1663)	0.035 (1697)	−0.057
(3*R*)-**2d**	0.0937	−0.024 (1655)[c]	–	–
(3*R*)-**2e**	0.0987	−0.017 (1663)	0.084 (1697)	−0.101
(3*R*)-**2f**	0.1163	−0.003 (1650)	0.025 (1695)	−0.028
(3*R*)-**2g**	0.1531	−0.031 (1655)[c]	–	–
(3*R*)-**2h**	0.1299	−0.037 (1655)[c]	–	–
(3*R*)-**2i**	0.1096	−0.025 (1678)	0.009 (1712)	−0.034
(3*R*)-**2j**	0.0908	−0.037 (1678)	0.020 (1711)	−0.057
(3*R*)-**2k**	0.0790	−0.021 (1676)	0.024 (1713)	−0.045
(3*R*)-**2l**	0.1345	−0.008 (1653)	0.021 (1699)	−0.029
(3*R*)-**2m**	0.1087	−0.008 (1653)	0.051 (1699)	−0.059
(3*R*)-**8**	0.1429	−0.014 (1712)	0.010 (1738)	−0.024
(3*S*)-**2a**	0.1199	0.035 (1666)	−0.012 (1709)	0.047
(3*S*)-**2b**	0.1030	0.032 (1668)	−0.036 (1709)	0.068
(3*S*)-**2c**	0.1149	0.040 (1668)	−0.024 (1705)	0.064
(3*S*)-**2d**	0.1004	0.023 (1668)	−0.028 (1709)	0.051
(3*S*)-**2e**	0.1138	0.028 (1668)	−0.061 (1709)	0.089
(3*S*)-**2f**	0.1360	0.036 (1670)	−0.027 (1709)	0.063
(3*S*)-**2g**	0.0729	0.007 (1653)	−0.051 (1711)	0.058
(3*S*)-**2h**	0.1218	0.030 (1663)	−0.013 (1705)	0.043
(3*S*)-**2i**	0.1264	0.029 (1653)	−0.053 (1690)	0.082
(3*S*)-**2j**	0.1003	0.075 (1661)	−0.044 (1701)	0.119
(3*S*)-**2k**	0.0940	0.031 (1664)	−0.018 (1701)	0.049
(3*S*)-**2l**	0.1225	0.050 (1670)[c]	–	–
(3*S*)-**2m**	0.1121	0.062 (1668)	−0.024 (1703)	0.086
(3*S*)-**8**	0.1286	0.015 (1716)	−0.028 (1736)	0.043

[a] In M^{-1} cm^{-1}.
[b] $\Delta\varepsilon_1 - \Delta\varepsilon_2$.
[c] For (3*R*)-**2d**,**g**,**h** and (3*S*)-**2l** only monosignate signals were detected.



Scheme 4. Synthesis of enantiomerically pure esters (3*S*)- and (3*R*)-**8**.

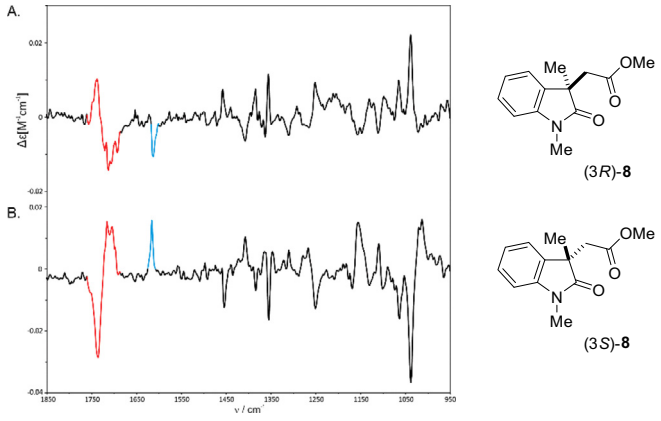


Figure 12. VCD spectra of esters (3*R*)-**8** (A) and (3*S*)-**8** (B).

(1H, td, J = 7.7, 1.2 Hz, H6), 7.20 (1H, dd, J = 7.4, 0.8 Hz, H4), 7.04 (1H, td, J = 7.5, 0.9 Hz, H5), 6.87 (1H, d, J = 7.8 Hz, H7), 3.46 (1H, s, OMe), 3.26 (3H, s, NMe), 3.01, 2.86 (2H, AB system, J = 16.4 Hz, H8), 1.38 (3H, s, C3-Me). ^{13}C NMR (100 MHz, $CDCl_3$), δ 179.9 (C2), 170.3 (C9), 143.6 (C7a), 132.9 (C3a), 128.2 (C6), 122.4 (C5), 122.2 (C4), 108.1 (C7), 51.6 (OMe), 45.5 (C3), 41.4 (C8), 26.4 (NMe), 24.2 (C3-*Me*). IR (film) ν_{max} 3056, 2967, 2953, 2930, 1739, 1715, 1614, 1204 cm^{-1}. EIMS m/z (relative intensity) 233 ([M]$^+$, 91), 174 (19), 160 (100), 132 (23). Anal. Calcd for $C_{13}H_{15}N_1O_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.08; H, 6.09; N, 5.90.

4.4. General procedure for the preparation of diastereomeric amides 2f–m

A cooled solution (0 °C) of the appropriate acid **4** [(*i*) (0.15 g, 0.68 mmol) or (*ii*) (0.25 g, 1.14 mmol)], **9a** [(*iii*) (0.25 g, 1.07 mmol)] or **9b** [(*iv*) (0.25 g, 1.07 mmol)] in THF (20 mL) was treated dropwise with Et_3N (1 equiv). The mixture was stirred for 15 min after which $ClCO_2Et$ (1.4 equiv) was added dropwise and stirred for additional 1 h. After cooling to −60 °C, one equiv of (*R*)-**5f** for *i*, *iii* and *iv*, (*R*)-**5g** for *ii*, (*R*)-**5h** for *ii*, (1*R*,2*R*)-**5i** for *i*, (*R*)-**5j** for *ii* and (1*S*,2*R*,5*S*)-**5k** for *i* were added and the reaction mixture stirred for 1 h. After warming to room temperature, EtOAc was added (25 mL) and the organic layer was washed with a saturated aqueous solution of NH_4Cl (2 × 15 mL), brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness in vacuum. The crude products were purified by flash column chromatography on silica gel with EtOAc/hexanes 1:2 for **2f**, EtOAc/hexanes 2:3 for **2h** and **2k**, EtOAc/hexanes 1:1 for **2g**, **2l** and **2m**, and EtOAc for **2i** and **2j**.

4.4.1. 2-((*R*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)acetamide (3*R*)-2f

Prepared from **4** (*i*) as white crystals (0.115 g, 45%), mp: 221–223 °C (EtOAc/hexanes). $[\alpha]_D^{20}$ = +64.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (1H, br d, J = 8.2 Hz, H16), 7.82 (1H, m, H19), 7.75 (1H, br dd, J = 6.7, 2.7 Hz, H15), 7.45 (1H, ddd, J = 8.2, 6.8, 1.1 Hz, H17), 7.40–7.42 (2H, overlapped, H13, H14), 7.35 (1H, ddd, J = 8.4, 6.8, 1.4 Hz, H18), 7.24 (1H, ddd, J = 7.4, 1.2, 0.5 Hz, H4), 7.21 (1H, td, J = 7.7, 1.2 Hz, H6), 7.04 (1H, td, J = 7.6, 1.0 Hz, H5), 6.59 (1H, d, J = 7.7 Hz, H7), 6.40 (1H, br d, J = 8.7 Hz, H10), 5.74 (1H, dq, J = 8.7, 6.8 Hz, H11), 2.78, 2.58 (2H, AB system, J = 14.0 Hz, H8), 2.77 (3H, s, NMe), 1.46 (3H, d, J = 6.8 Hz, H20), 1.37 (3H, s, C3-Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (C2); 166.6 (C9), 141.6 (C7a), 137.1 (C12), 132.7 (C15a), 131.6 (C3a), 130.0 (C19a), 127.5 (C16), 127.1 (C15), 127.0 (C6), 125.6 (C18), 124.7 (C17), 124.2 (C14), 122.3 (C19), 121.8 (C4), 121.7 (C5), 121.4 (C13), 107.4 (C7), 45.6 (C3), 43.0 (C8), 42.8 (C11), 24.8 (NMe), 23.1 (C3-*Me*), 19.5 (C20). IR (KBr) ν_{max} 3406, 3281, 3051, 2964, 2927, 1709, 1647, 1609, 1542 cm^{-1}. EIMS m/z (relative intensity) 372 ([M]$^+$, 6), 212 (14), 174 (22), 170 (100), 160 (17), 154 (14). Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.21; H, 6.52; N, 7.20.

4.4.2. 2-((*S*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)acetamide (3*S*)-2f

Prepared from **4** (*i*) as white crystals (0.110 g, 43%), mp: 156–158 °C (EtOAc/hexanes). $[\alpha]_D^{20}$ = +34.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.82 (2H, overlapped, H16, H19), 7.76 (1H, br dd, J = 7.0, 2.2 Hz, H15), 7.46 (1H, ddd, J = 8.0, 6.8, 1.2 Hz, H17), 7.42–7.40 (2H, overlapped, H13, H14), 7.41 (1H, ddd, J = 8.4, 6.9, 1.6 Hz, H18), 7.28 (1H, td, J = 7.7, 1.2 Hz, H6), 7.20 (1H, ddd, J = 7.4, 1.2, 0.4 Hz, H4), 7.06 (1H, td, J = 7.6, 1.0 Hz, H5),

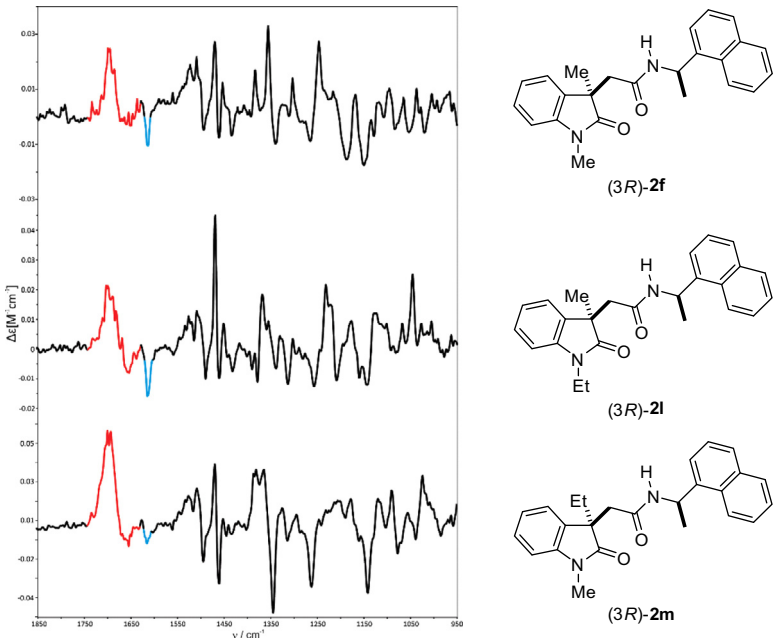


Figure 13. Comparison of the VCD spectra of (3*R*)-**2f**,**l**,**m**.

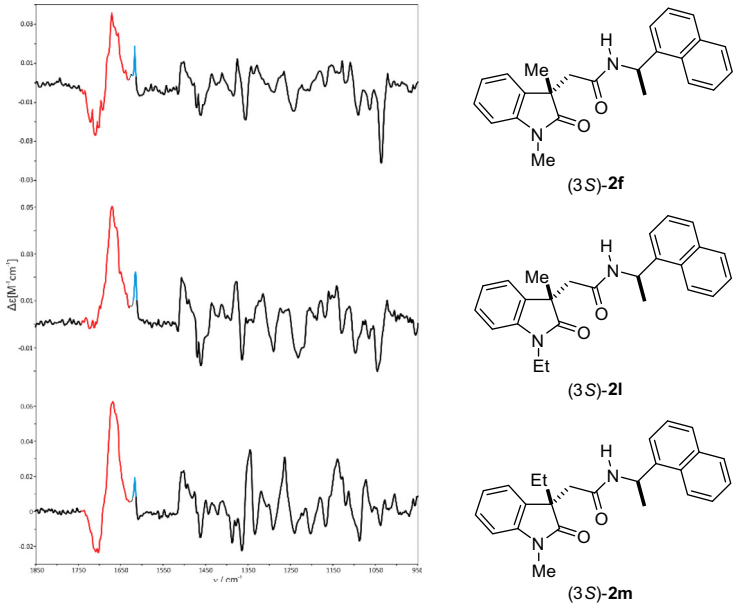
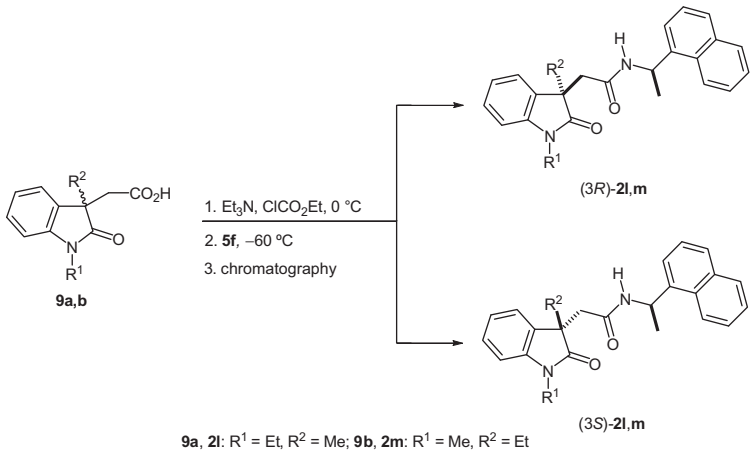


Figure 14. Comparison of the VCD spectra of (3*S*)-**2f**,**l**,**m**.

6.83 (1H, d, *J* = 7.7 Hz, H7), 6.38 (1H, br d, *J* = 8.3 Hz, H10), 5.72 (1H, dq, *J* = 8.2, 6.7 Hz, H11), 3.21 (3H, s, NMe), 2.81, 2.61 (2H, AB system, *J* = 14.7 Hz, H8), 1.49 (3H, d, *J* = 6.8 Hz, H20), 1.32 (3H, s, C3-Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4 (C2), 167.6 (C9), 142.9 (C7a), 138.0 (C12), 133.8 (C15a), 133.1 (C3a), 131.0 (C19a), 128.6 (C16), 128.2 (C15), 128.1 (C6), 126.5 (C18), 125.7 (C17), 125.2 (C14), 123.5 (C19), 122.7 (C4), 122.6 (C5), 122.5 (C13), 108.3 (C7), 46.3 (C3), 44.3 (C11), 43.9 (C8), 26.4 (NMe), 23.9 (C3-*Me*), 20.6 (C20). IR (KBr) ν_{max} 3453, 3302, 3063, 2963, 2923, 1709, 1648, 1615, 1549 cm^{-1}. EIME *m*/*z* (relative intensity) 373 ([M+H]$^+$, 100), 372 (42), 354 (12), 195 (20), 170 (82), 154 (13), 130 (13). HRMS (ESI) *m*/*z* calcd for $C_{24}H_{25}N_2O_2$ [M+H]$^+$: 373.1916, found: 373.1909.

4.4.3. *N*-((*R*)-*sec*-Butyl)-2-((*R*)-1,3-dimethyl-2-oxoindolin-3-yl) acetamide (3*R*)-2g

Prepared from **4** (*ii*) as white crystals (0.117 g, 37%), mp: 149–151 °C (EtOAc/hexanes). $[\alpha]_D^{20}$ = +23.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.18 (2H, overlapped, H4, H6), 7.00 (1H, tm, *J* = 7.6 Hz, H5), 6.78 (1H, d, *J* = 7.6 Hz, H7), 6.04 (1H, br d, *J* = 7.8 Hz, H10), 3.65 (1H, dsext, *J* = 8.3, 6.7 Hz, H11), 3.16 (3H, s, NMe), 2.71, 2.57 (2H, AB system, *J* = 14.5 Hz, H8), 1.35 (3H, s, C3-Me), 1.25 (2H, q, *J* = 7.3 Hz, H12), 0.91 (3H, d, *J* = 6.7 Hz, H14), 0.71 (3H, t, *J* = 7.5 Hz, H13). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5 (C2), 168.1 (C9), 142.8 (C7a), 133.2 (C3a), 128.1 (C6), 122.8 (C4), 122.7 (C5), 108.2 (C7), 46.4 (C11, C3), 44.1 (C8), 29.5 (C12), 26.4 (NMe), 23.7 (C3-*Me*), 20.1 (C14), 10.2 (C13). IR (KBr) ν_{max} 3439,



Scheme 5. Synthesis of diastereoisomeric amides (3*R*)-**2l**,**m** and (3*S*)-**2l**,**m**.

3321, 2969, 2930, 2874, 1703, 1656, 1612, 1546 cm^{-1}. EIMS *m*/*z* (relative intensity) 274 ([M]$^+$, 25), 186 (17), 174 (100), 160 (38). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{23}N_2O_2$ [M+H]$^+$: 275.1760, found: 275.1754.

4.4.4. *N*-((*R*)-*sec*-Butyl)-2-((*S*)-1,3-dimethyl-2-oxoindolin-3-yl) acetamide (3*S*)-2g

Prepared from **4** (*ii*) as white crystals (0.111 g, 35%), mp: 133–135 °C (EtOAc/hexanes). $[\alpha]_D^{20} = -37.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (1H, dd, *J* = 6.5, 1.3 Hz, H4), 7.20 (1H, ddd, *J* = 9.0, 7.7, 1.3 Hz, H6), 7.00 (1H, td, *J* = 7.4, 1.0 Hz, H5), 6.78 (1H, dd, *J* = 7.7, 0.9 Hz, H7), 6.03 (1H, br d, *J* = 8.0 Hz, H10), 3.64 (1H, dsext, *J* = 8.3, 6.6 Hz, H11), 3.17 (3H, s, NMe), 2.72, 2.56 (2H, AB system, *J* = 14.5 Hz, H8), 1.35 (3H, s, C3-Me), 1.26 (2H, q, *J* = 7.4 Hz, H12), 0.89 (3H, d, *J* = 6.6 Hz, H14), 0.72 (3H, t, *J* = 7.5 Hz, H13). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0 (C2), 168.3 (C9), 143.0 (C7a), 133.3 (C3a), 128.3 (C6), 123.0 (C4), 122.9 (C5), 108.4 (C7), 46.3 (C11, C3), 44.4 (C8), 29.6 (C12), 26.5 (NMe), 23.9 (C3-*Me*), 20.4 (C14), 10.4 (C13). IR (KBr) ν_{max} 3322, 3058, 2967, 2937, 1710, 1702, 1659, 1540 cm^{-1}. EIMS *m*/*z* (relative intensity) 275 (100), 274 ([M]$^+$, 61), 259 (22), 200 (13), 186 (37), 174 (79), 160 (38). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{23}N_2O_2$ [M+H]$^+$: 275.1760, found: 275.1754.

4.4.5. *N*-((*R*)-1-Cyclohexylethyl)-2-((*R*)-1,3-dimethyl-2-oxoindolin-3-yl)acetamide (3*R*)-2h

Prepared from **4** (*ii*) as a white solid (0.170 g, 45%), mp: 161–163 °C (EtOAc/hexanes). $[\alpha]_D^{20} = +48.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (1H, ddd, *J* = 7.4, 1.2, 0.6 Hz, H4), 7.27 (1H, td, *J* = 7.7, 1.2 Hz, H6), 7.07 (1H, td, *J* = 7.6, 1.0 Hz, H5), 6.85 (1H, d, *J* = 7.6 Hz, H7), 6.12 (1H, br d, *J* = 8.9 Hz, H10), 3.67 (1H, dq, *J* = 8.8, 6.6 Hz, H11), 3.24 (3H, s, NMe), 2.81, 2.65 (2H, AB system, *J* = 14.5 Hz, H8), 1.71–1.67 (2H, overlapped, H14*e*, H16*e*), 1.63–1.54 (3H, overlapped, H13*e*, H15*e*, H17*e*), 1.42 (3H, s, C3-Me), 1.21–1.01 (4H, overlapped, H12, H14*a*, H15*a*, H16*a*), 0.94 (3H, d, *J* = 6.8 Hz, H18), 0.90–0.76 (2H, overlapped, H13*a*, H17*a*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5 (C2), 168.1 (C9), 142.7 (C7a), 133.1 (C3a), 128.1 (C6), 122.9 (C4), 122.8 (C5), 108.2 (C7), 49.2 (C11), 46.4 (C3), 44.1 (C8), 42.8 (C12), 28.8, 28.7 (C13, C17), 26.4 (NMe), 26.3 (C15), 26.2, 26.1 (C14, C16), 24.0 (C3-*Me*), 17.6 (C18). IR (KBr) ν_{max} 3397, 3317, 2961, 2925, 2851, 1709, 1659, 1547 cm^{-1}. EIMS *m*/*z* (relative intensity) 329 ([M+H]$^+$, 16), 245 (12), 219 (10), 202 (17), 174 (100), 160 (22), 146 (13). HRMS ESI *m*/*z* calcd for $C_{20}H_{29}N_2O_2$ [M+H]$^+$: 329.2229, found: 329.2224.

4.4.6. *N*-((*R*)-1-Cyclohexylethyl)-2-((*S*)-1,3-dimethyl-2-oxoindolin-3-yl)acetamide (3*S*)-2h

Prepared from **4** (*ii*) as a white solid (0.157 g, 42%), mp: 188–190 °C (EtOAc/hexanes). $[\alpha]_D^{20} = -8.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (1H, ddd, *J* = 7.3, 1.3, 0.7 Hz, H4), 7.27 (1H, ddd, *J* = 8.9, 7.7, 1.3 Hz, H6), 7.07 (1H, ddd, *J* = 7.8, 7.3, 1.0 Hz, H5), 6.85 (1H, ddd, *J* = 7.7, 0.8, 0.8 Hz, H7), 6.04 (1H, br d, *J* = 8.9 Hz, H10), 3.66 (1H, dq, *J* = 8.8, 6.7 Hz, H11), 3.24 (3H, s, NMe), 2.82, 2.63 (2H, AB system, *J* = 14.4 Hz, H8), 1.69–1.66 (2H, overlapped, H14*e*, H16*e*), 1.62–1.53 (3H, overlapped, H13*e*, H15*e*, H17*e*), 1.43 (3H, s, C3-Me), 1.21–1.01 (4H, overlapped, H12, H14*a*, H15*a*, H16*a*), 0.91 (3H, d, *J* = 6.8 Hz, H18), 0.89–0.75 (2H, overlapped, H13*a*, H17*a*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5 (C2), 167.9 (C9), 142.9 (C7a), 133.1 (C3a), 128.1 (C6), 122.8 (C4), 122.7 (C5), 108.2 (C7), 49.1 (C11), 46.4 (C3), 44.4 (C8), 42.8 (C12), 28.8, 28.7 (C13, C17), 26.4 (NMe), 26.3 (C15), 26.1 (C14, C16), 23.9 (C3-*Me*), 17.7 (C18). IR (KBr) ν_{max} 3406, 3267, 2967, 2926, 2852, 1711, 1647, 1560 cm^{-1}. EIMS *m*/*z* (relative intensity) 329 ([M+H]$^+$, 24), 245 (11), 219 (13), 202 (19), 174 (100), 160 (27). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{29}N_2O_2$ [M+H]$^+$: 329.2229, found: 329.2224.

4.4.7. 2-((*R*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-((1*R*,2*R*)-2-hydroxycyclohexyl)acetami de (3*R*)-2i

Prepared from **4** (*i*) as a colorless oil (0.101 g, 47%). $[\alpha]_D^{20} = +43.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.27 (2H, overlapped, H4, H6), 7.10 (1H, td, *J* = 7.7, 0.9 Hz, H5), 6.87 (1H, dd, *J* = 7.4, 1.0 Hz, H7), 6.61 (1H, br d, *J* = 7.0 Hz, H10), 3.49 (1H, m, H11), 3.25 (3H, s, NMe), 3.22 (1H, m, H12), 2.81, 2.71 (2H, AB system, *J* = 14.3 Hz, H8), 1.99 (1H, m, H13*e*), 1.80 (1H, m, H16*e*), 1.69–1.63 (2H, overlapped, H14*e*, H15*e*), 1.44 (3H, s, C3-Me), 1.27–1.12 (4H, overlapped, H13*a*, H14*a*, H15*a*, H16*a*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.8 (C2), 170.3 (C9), 142.8 (C7a), 133.2 (C3a), 128.2 (C6), 122.8 (C5), 122.7 (C4), 108.5 (C7), 74.3 (C12), 55.3 (C11), 46.4 (C3), 44.0 (C8), 34.1 (C13), 31.3 (C16), 26.4 (NMe), 24.5, 24.1 (C14, C15), 23.8 (C3-*Me*). IR (KBr) ν_{max} 3433, 3092, 2932, 2858, 1697, 1647, 1554 cm^{-1}. EIMS *m*/*z* (relative intensity) 317 ([M+H]$^+$, 100), 299 (6), 202 (7), 174 (16). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}N_2O_3$ [M+H]$^+$: 317.1860, found: 317.1873.

4.4.8. 2-((*S*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-((1*R*,2*R*)-2-hydroxycyclohexyl)acetami de (3*S*)-2i

Prepared from **4** (*i*) as a colorless oil (0.094 g, 43%). $[\alpha]_D^{20} = -24.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (1H, td, *J* = 7.7, 1.3 Hz, H6), 7.28 (1H, ddd, *J* = 7.3, 1.2, 0.5 Hz, H4), 7.08 (1H, td, *J* = 7.6, 1.0 Hz, H5), 6.87 (1H, d, *J* = 7.7 Hz, H7), 6.48 (1H, br d,

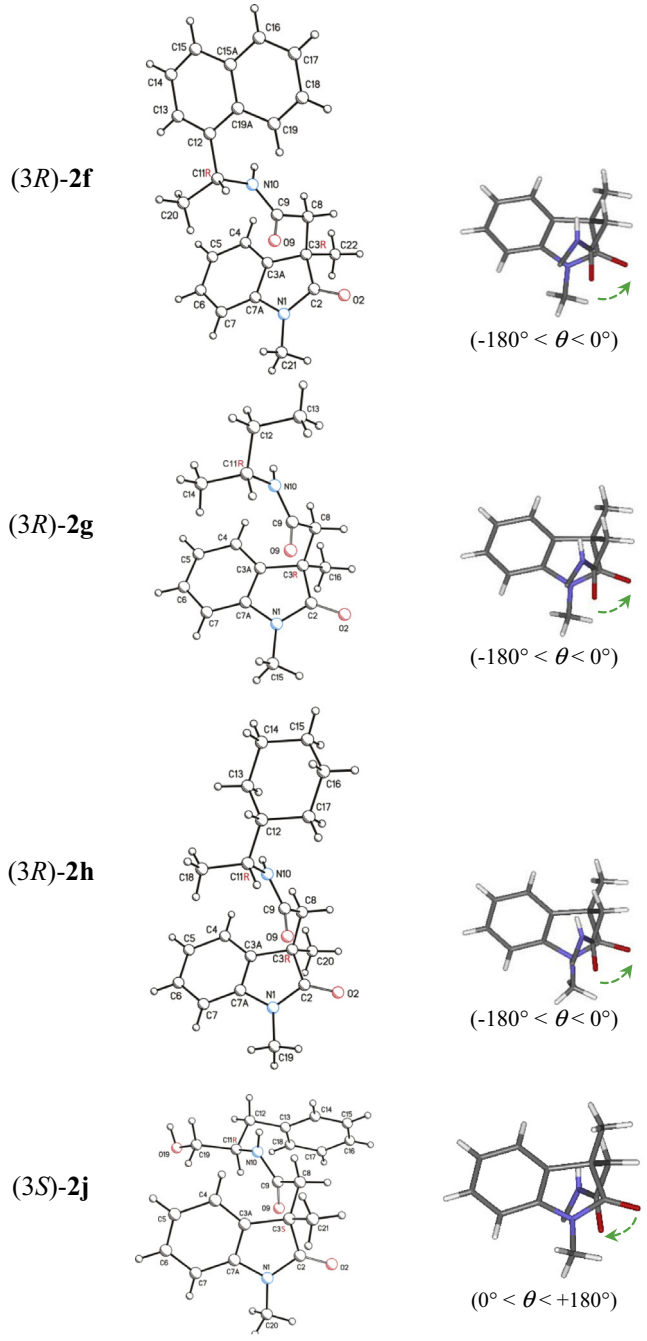


Figure 15. X-ray diffraction structures of (3*R*)-**2f**,**g**,**h** and (3*S*)-**2j**. The insert, on the right, shows the twist direction of the C2 and C9 carbonyl groups in the solid state. The substituent on the amide nitrogen is omitted for the sake of clarity.

J = 7.6 Hz, H10), 3.58–3.50 (2H, overlapped, H11, OH), 3.26 (1H, m, H12), 3.24 (3H, s, NMe), 2.80, 2.62 (2H, AB system, *J* = 14.3 Hz, H8), 2.01 (1H, m, H13*e*), 1.82 (1H, m, H16*e*), 1.71–1.64 (2H, overlapped, H14*e*, H15*e*), 1.47 (3H, s, C3-Me), 1.33–1.07 (4H, overlapped, H13*a*, H14*a*, H15*a*, H16*a*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6 (C2), 170.2 (C9), 142.6 (C7a), 133.3 (C3a), 128.3 (C6), 122.9 (C5), 122.8 (C4), 108.4 (C7), 74.6 (C12), 55.5 (C11), 46.3 (C3), 44.0 (C8), 33.9 (C13), 31.3 (C16), 26.4 (NMe), 24.5, 24.0 (C14, C15), 23.2 (C3-*Me*). IR (film) ν_{max} 3409, 3302, 2933, 2860, 1698, 1648, 1545 cm^{-1}. EIMS *m*/*z* (relative intensity) 317 ([M+H]$^+$, 100), 299 (5), 202 (18), 174 (11). HRMS ESI *m*/*z* calcd for $C_{18}H_{25}N_2O_3$ [M+H]$^+$: 317.1860, found: 317.1855.

4.4.9. 2-((*R*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-hydroxy-3-phenylpropan-2-yl)acetamide (3*R*)-2j

Prepared from **4** (*ii*) as a white solid (0.136 g, 34%), mp: 88–90 °C. $[\alpha]_D^{20}$ = +45.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (1H, br d, *J* = 8.2 Hz, H10), 7.23–7.12 (5H, overlapped, H4, H6, H15, H16, H17), 7.04 (2H, dd, *J* = 8.3, 1.5 Hz, H18, H14), 6.94 (1H, td, *J* = 7.6, 1.0 Hz, H5), 6.92 (1H, dd, *J* = 7.4, 1.0 Hz, H7), 4.71 (1H, t, *J* = 5.5 Hz, OH), 3.64 (1H, m, H11), 3.22 (1H, dt, *J* = 10.7, 5.2 Hz, H19A), 3.17 (1H, dt, *J* = 10.7, 5.5 Hz, H19B), 3.10 (3H, s, NMe), 2.71, 2.57 (2H, AB system, *J* = 15.0 Hz, H8), 2.61 (1H, dd, *J* = 13.8, 6.1 Hz, H12A), 2.33 (1H, dd, *J* = 13.8, 7.7 Hz, H12B), 1.16 (3H, s, C3-Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.5 (C2), 169.1 (C9), 144.3 (C7a), 140.0 (C13), 134.3 (C3a), 129.9 (C18, C14), 129.0 (C17, C15), 128.3 (C6), 126.8 (C16), 123.5 (C4), 122.5 (C5), 108.9 (C7), 63.1 (C19), 53.0 (C11), 46.2 (C3), 43.3 (C8), 37.2 (C12), 27.0 (NMe), 25.1 (C3-*Me*). IR (KBr) ν_{max} 3424, 2920, 2852, 1702, 1635, 1613, 1561 cm^{-1}. EIMS *m*/*z* (relative intensity) 353 ([M+H]$^+$, 100), 335 (11), 174 (12). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}N_2O_3$ [M+H]$^+$: 353.1860, found: 353.1854.

4.4.10. 2-((*S*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-hydroxy-3-phenylpropan-2-yl)acetamide (3*S*)-2j

Prepared from **4** (*ii*) as a white solid (0.123 g, 31%), mp: 150–152 °C. $[\alpha]_D^{20}$ = +8.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (1H, td, *J* = 7.7, 1.2 Hz, H6), 7.26 (1H, m, H4), 7.25–7.23 (2H, overlapped, H15, H17), 7.18 (1H, m, H16), 7.16–7.14 (2H, overlapped, H18, H14), 7.06 (1H, td, *J* = 7.6, 1.0 Hz, H5), 6.85 (1H, d, *J* = 7.8 Hz, H7), 6.50 (1H, br d, *J* = 8.0 Hz, H10), 4.04 (1H, m, H11), 3.49 (1H, dd, *J* = 11.2, 3.4 Hz, H19A), 3.39 (1H, dd, *J* = 11.2, 4.9 Hz, H19B), 3.23 (1H, br s, OH), 3.21 (3H, s, NMe), 2.77 (1H, dd, *J* = 13.8, 7.3 Hz, H12A), 2.71 (1H, dd, *J* = 13.7, 7.0 Hz, H12B), 2.76, 2.57 (2H, AB system, *J* = 14.3 Hz, H8), 1.42 (3H, s, C3-Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5 (C2), 169.3 (C9), 142.7 (C7a), 137.8 (C13), 133.3 (C3a), 129.1 (C18, C14), 128.5 (C17, C15), 128.2 (C6), 126.4 (C16), 122.8 (C5), 122.7 (C4), 108.4 (C7), 63.3 (C19), 52.6 (C11), 46.3 (C3), 43.9 (C8), 36.7 (C12), 26.4 (NMe), 23.3 (C3-*Me*). IR (KBr) ν_{max} 3425, 3373, 2935, 2913, 2866, 1706, 1646, 1536 cm^{-1}. EIMS *m*/*z* (relative intensity) 353 ([M+H]$^+$, 100), 335 (28), 174 (37). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.55; H, 6.92; N, 8.34.

4.4.11. 2-((*R*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)acetamide (3*R*)-2k

Prepared from **4** (*i*) as a white solid (0.067 g, 28%), mp: 145–147 °C. $[\alpha]_D^{20}$ = +14.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.26 (2H, overlapped, H4, H6), 7.08 (1H, t, *J* = 7.8 Hz, H5), 6.85 (1H, dd, *J* = 7.3, 1.0 Hz, H7), 6.32 (1H, br s, H10), 3.24 (3H, s, NMe), 3.11 (2H, dd, *J* = 7.8, 5.8 Hz, H11), 2.79, 2.64 (2H, AB system, *J* = 14.6 Hz, H8), 2.30 (1H, m, H18A), 2.01 (1H, m, H12), 1.93–1.80 (4H, overlapped, H15, H16, H17*e*), 1.75 (1H, m, H13), 1.42 (3H, s, C3-Me), 1.36 (1H, m, H17*a*), 1.14 (3H, s, H20), 0.96 (3H, s, H19), 0.82 (1H, d, *J* = 9.6 Hz, H18B). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6 (C2), 168.8 (C9), 142.7 (C7a), 133.2 (C3a), 128.1 (C6), 122.8 (C4, C5), 108.3 (C7), 46.3 (C3), 45.1 (C11), 43.9 (C8), 43.6 (C13), 41.2 (C12,15), 38.6 (C14), 33.2 (C18), 27.9 (C20), 26.4 (*N*Me), 25.9 (C16), 23.7 (C3-*Me*), 23.1 (C19), 19.8 (C17). IR (KBr) ν_{max} 3333, 2966, 2924, 2866, 1702, 1676, 1551 cm^{-1}. EIMS *m*/*z* (relative intensity) 355 ([M+H]$^+$, 16), 218 (26), 174 (100), 160 (40), 146 (16). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.36; H, 8.78; N, 8.32.

4.4.12. 2-((*S*)-1,3-Dimethyl-2-oxoindolin-3-yl)-*N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)acetamide (3*S*)-2k

Prepared from **4** (*i*) as a pale yellow oil (0.071 g, 29%). $[\alpha]_D^{20}$ = −34.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (1H, dd, *J* = 7.5, 1.3 Hz, H4), 7.28 (1H, td, *J* = 7.9, 1.2 Hz, H6), 7.09

(1H, td, J = 7.6, 1.0 Hz, H5), 6.86 (1H, dd, J = 8.0, 1.0 Hz, H7), 6.28 (1H, br t, J = 5.3 Hz, H10), 3.23 (3H, s, NMe), 3.15 (1H, ddd, J = 13.3, 8.1, 5.9 Hz, H11A), 3.07 (1H, ddd, J = 13.3, 7.6, 5.7 Hz, H11B), 2.80, 2.64 (2H, AB system, J = 14.5 Hz, H8), 2.29 (1H, m, H18A), 2.00 (1H, m, H12), 1.93–1.80 (4H, overlapped, H15, H16, H17*e*), 1.65 (1H, m, H13); 1.43 (3H, s, C3-Me), 1.36 (1H, m, H17*a*), 1.09 (3H, s, H20), 0.95 (3H, s, H19), 0.82 (1H, d, J = 9.5 Hz, H18B). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7 (C2), 168.9 (C9), 142.6 (C7a), 133.1 (C3a), 128.1 (C6), 123.0 (C5), 122.9 (C4), 108.3 (C7), 46.4 (C3), 45.0 (C11), 43.8 (C8), 43.4 (C13), 41.3 (C15), 41.2 (C12), 38.5 (C14), 33.2 (C18), 27.9 (C20), 26.4 (NMe), 25.9 (C16), 23.8 (C3-*Me*), 23.0 (C19), 19.8 (C17). IR (film) ν_{max} 3317, 2924, 2868, 1705, 1651, 1550 cm^{-1}. EIMS m/z (relative intensity) 354 ([M]$^+$, 5), 218 (28), 174 (100), 160 (43), 146 (17). HRMS (ESI) m/z calcd for $C_{22}H_{31}N_2O_2$ [M+H]$^+$: 355.2380. Found: 355.2386.

4.4.13. 2-((*R*)-1-Ethyl-3-methyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)acetamide (3*R*)-2l

Prepared from **9a** (*iii*) as a white solid (0.193 g, 47%), mp: 159–161 °C. $[\alpha]_D^{20}$ = +62.0 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, J = 8.5 Hz, H19), 7.81 (1H, m, H16), 7.75 (1H, m, H15), 7.45 (1H, ddd, J = 8.0, 6.9, 1.2 Hz, H17), 7.42–7.40 (2H, overlapped, H13, H14), 7.39 (1H, ddd, J = 8.3, 6.8, 1.4 Hz, H18), 7.25 (1H, dd, J = 7.4, 0.7 Hz, H4), 7.23 (1H, td, J = 7.7, 1.2 Hz, H6), 7.02 (1H, td, J = 7.7, 1.0 Hz, H5), 6.69 (1H, d, J = 7.8 Hz, H7), 6.53 (1H, br d, J = 8.6 Hz, H10), 5.77 (1H, dq, J = 8.5, 6.8 Hz, H11), 3.55 (1H, dq, J = 14.5, 7.3 Hz, CH_2CH_3A), 3.31 (1H, dc, J = 14.3, 7.2 Hz, CH_2CH_3B), 2.76, 2.58 (2H, AB system, J = 14.3 Hz, H8), 1.46 (3H, d, J = 6.8 Hz, H20), 1.39 (3H, s, C3-Me), 1.10 (3H, t, J = 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2 (C2), 168.0 (C9), 142.0 (C7a), 138.5 (C12), 134.0 (C15a), 133.4 (C3a), 131.3 (C19a), 128.8 (C16), 128.4, 128.3 (C15, C6), 126.8 (C18), 126.0 (C17), 125.4 (C14), 123.7 (C19), 123.4 (C4), 122.8 (C5, C13), 108.8 (C7), 46.6 (C3), 44.3 (C11), 44.1 (C8), 34.7 (CH_2CH_3), 24.2 (C3-*Me*), 20.8 (C20), 12.7 (CH_2CH_3). IR (KBr) ν_{max} 3271, 3049, 2980, 2963, 2940, 1702, 1650, 1608, 1538 cm^{-1}. EIME m/z (relative intensity) 386 ([M]$^+$, 17), 188 (19), 170 (100), 155 (16), 128 (18). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.19; H, 6.85; N, 6.96.

4.4.14. 2-((*S*)-1-Ethyl-3-methyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)acetamide (3*S*)-2l

Prepared from **9a** (*iii*) as a white solid (0.186 g, 45%), mp: 152–154 °C. $[\alpha]_D^{20}$ = +13.3 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, J = 8.3 Hz, H19), 7.83 (1H, dm, J = 8.2 Hz, H16), 7.76 (1H, dd, J = 7.0, 2.3 Hz, H15), 7.47 (1H, ddd, J = 8.0, 6.8, 1.2 Hz, H17), 7.45–7.38 (3H, overlapped, H13, H14, H18), 7.27 (1H, td, J = 7.7, 1.2 Hz, H6), 7.21 (1H, ddd, J = 7.4, 1.2, 0.4 Hz, H4), 7.04 (1H, td, J = 7.5, 0.9 Hz, H5), 6.85 (1H, d, J = 7.8 Hz, H7), 6.55 (1H, br d, J = 8.2 Hz, H10), 5.74 (1H, dq, J = 8.1, 6.8 Hz, H11), 3.84 (1H, dq, J = 14.5, 7.3 Hz, CH_2CH_3A), 3.69 (1H, dq, J = 14.3, 7.2 Hz, CH_2CH_3B), 2.78, 2.62 (2H, AB system, J = 14.8 Hz, H8), 1.50 (3H, d, J = 6.8 Hz, H20), 1.31 (3H, s, C3-Me), 1.27 (3H, t, J = 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3 (C2), 168.0 (C9), 142.2 (C7a), 138.4 (C12); 134.1 (C15a), 133.7 (C3a), 131.2 (C19a), 128.9 (C16), 128.4, 128.3 (C15, C6), 126.7 (C18), 126.0 (C17), 125.5 (C14), 123.7 (C19), 123.2 (C4), 122.8 (C5, C13), 108.7 (C7), 46.5 (C3), 44.6 (C11), 44.0 (C8), 35.0 (CH_2CH_3), 24.2 (C3-*Me*), 20.9 (C20), 12.9 (CH_2CH_3). IR (KBr) ν_{max} 3259, 3051, 2975, 2935, 1703, 1653, 1612, 1548 cm^{-1}. EIMS m/z (relative intensity) 387 ([M+H]$^+$, 25), 188 (16), 170 (100), 155 (17), 128 (22). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.29; H, 6.89; N, 7.26.

4.4.15. 2-((*R*)-3-Ethyl-1-methyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)acetamide (3*R*)-2m

Prepared from **9b** (*iv*) as a white solid (0.182 g, 44%), mp: 212–214 °C. $[\alpha]_D^{20}$ = +62.8 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.79 (2H, overlapped, H16, H19), 7.74 (1H, m, H15), 7.44 (1H, ddd, J = 8.0, 6.8, 1.0 Hz, H17), 7.41–7.39 (2H, overlapped, H13, H14), 7.33 (1H, ddd, J = 8.4, 6.8, 1.3 Hz, H18), 7.21 (1H, td, J = 7.7, 1.3 Hz, H6), 7.20 (1H, m, H4), 7.04 (1H, td, J = 7.5, 1.0 Hz, H5), 6.56 (1H, d, J = 7.6 Hz, H7), 6.29 (1H, br d, J = 8.8 Hz, H10), 5.71 (1H, dq, J = 8.7, 6.8 Hz, H11), 2.78, 2.58 (2H, AB system, J = 14.0 Hz, H8), 2.74 (3H, s, NMe), 1.87 (1H, dq, J = 13.7, 7.4 Hz, CH_2CH_3A), 1.77 (1H, dq, J = 13.5, 7.4 Hz, CH_2CH_3B), 1.42 (3H, d, J = 6.8 Hz, H20), 0.53 (3H, t, J = 7.4 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (C2), 167.9 (C9), 143.8 (C7a), 138.5 (C12), 134.0 (C15a), 131.3 (C19a), 130.8 (C3a), 128.8 (C16), 128.4 (C15, C6), 126.9 (C18), 126.0 (C17), 125.4 (C14), 123.7 (C19), 123.4 (C4), 122.9 (C5), 122.7 (C13), 108.4 (C7), 51.8 (C3), 44.1 (C11), 43.7 (C8), 31.3 (CH_2CH_3), 25.9 (NMe), 20.7 (C20), 8.4 (CH_2CH_3). IR (KBr) ν_{max} 3292, 3051, 2971, 2936, 1709, 1655, 1609, 1547 cm^{-1}. EIMS m/z (relative intensity) 386 ([M]$^+$, 14), 188 (15), 170 (100), 146 (15). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.73; H, 6.94; N, 6.80.

4.4.16. 2-((*S*)-3-Ethyl-1-methyl-2-oxoindolin-3-yl)-*N*-((*R*)-1-(naphthalen-1-yl)ethyl)acetamide (3*S*)-2m

Prepared from **9b** (*iv*) as a white solid (0.186 g, 45%), mp: 164–166 °C. $[\alpha]_D^{20}$ = +30.3 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.80 (2H, overlapped, H16, H19), 7.75 (1H, m, H15), 7.47 (1H, ddd, J = 8.1, 6.9, 1.2 Hz, H17), 7.43–7.38 (3H, overlapped, H13, H14, H18), 7.29 (1H, td, J = 7.6, 1.3 Hz, H6), 7.15 (1H, ddd, J = 7.5, 1.3, 0.5 Hz, H4), 7.06 (1H, td, J = 7.5, 0.9 Hz, H5), 6.81 (1H, d, J = 7.8 Hz, H7), 6.30 (1H, br d, J = 8.3 Hz, H10), 5.67 (1H, dq, J = 8.1, 6.8 Hz, H11), 3.21 (3H, s, NMe), 2.81, 2.61 (2H, AB system, J = 14.6 Hz, H8), 1.83 (1H, dq, J = 13.6, 7.4 Hz, CH_2CH_3A), 1.74 (1H, dq, J = 13.5, 7.4 Hz, CH_2CH_3B), 1.47 (3H, d, J = 6.8 Hz, H20), 0.53 (3H, t, J = 7.4 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0 (C2), 167.9 (C9), 144.2 (C7a), 138.2 (C12), 134.0 (C15a), 131.3 (C19a, C3a), 128.9 (C16), 128.4 (C15, C6), 126.7 (C18), 126.0 (C17), 125.4 (C14), 123.7 (C19), 123.2 (C4), 122.9, 122.8 (C5, C13), 108.3 (C7), 51.4 (C3), 44.6 (C11), 43.5 (C8), 31.2 (CH_2CH_3), 26.5 (NMe), 20.7 (C20), 8.4 (CH_2CH_3). IR (KBr) ν_{max} 3269, 3051, 2971, 2932, 1703, 1650, 1545 cm^{-1}. EIMS m/z (relative intensity) 387 ([M+H]$^+$, 21), 188 (12), 170 (100), 146 (17). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.63; H, 6.93; N, 6.76.

4.5. VCD measurements

IR and VCD spectra were measured using a BioTools Chiral*IR* spectrophotometer equipped with dual photoelastic modulation. Samples of (3*R*)-**2a**–**m** and (3*S*)-**2a**–**m** were dissolved in 150 μL of $CDCl_3$, placed in a BaF_2 cell with a path length of 100 μm and data were acquired at a resolution of 4 cm^{-1} over 6 h. Baseline corrections were done by subtracting the spectra from the solvent. The stability of the samples was monitored by ^{1}H NMR immediately prior and after VCD measurements.

4.6. X-ray diffraction analyses

Data for (3*R*)-**2f**–**h**, (3*S*)-**2i** were acquired on an Agilent Technologies Gemini A CCD diffractometer using Mo Kα radiation (λ = 0.7073 Å). The structures were solved by direct methods using the SHELXS-97[12] program included in the WINGX v1.6 package.[13] Structural refinements were carried out by full-matrix least squares on F^2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters are in deposit at the Cambridge Crystallographic Data Center. Table 3 summarizes the relevant data and the CCDC deposition numbers.

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Table 3
Crystal data for (3*R*)-**2f**, (3*R*)-**2g**, (3*R*)-**2h** and (3*S*)-**2i**

	(3*R*)-**2f**	(3*R*)-**2g**	(3*R*)-**2h**	(3*S*)-**2j**
Empirical formula	$C_{24}H_{24}N_2O_2$	$C_{16}H_{22}N_2O_2$	$C_{20}H_{28}N_2O_2$	$C_{21}H_{24}N_2O_3$
Formula weight	372.45	274.36	328.44	352.42
Crystal size (mm)	0.40 × 0.20 × 0.20	0.40 × 0.20 × 0.15	0.45 × 0.35 × 0.30	0.45 × 0.35 × 0.25
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system	monoclinic	orthorhombic	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
Unit cell dimensions				
a (Å)	8.5281(4)	8.437(2)	8.4199(3)	6.922(1)
b (Å)	10.4698(4)	10.331(2)	10.3450(2)	12.485(3)
c (Å)	12.1072(5)	19.071(4)	11.3849(3)	22.139(4)
β (deg)	102.929(4)	90	100.752(3)	90
Volume ($Å^3$)	1053.62(8)	1662.4(6)	974.26(5)	1913.4(7)
Z, calculated density (mg/mm^3)	2, 1.174	4, 1.096	2, 1.120	4, 1.223
Absorption coefficient (mm^{-1})	0.075	0.073	0.072	0.082
F(000)	396	592	356	752
θ range for data collection (deg)	3.13–29.38	3.22–29.68	3.15–29.58	3.08–29.52
Limiting indices	$-11 \leqslant h \leqslant 11$, $-14 \leqslant k \leqslant 12$, $0 \leqslant l \leqslant 16$	$-11 \leqslant h \leqslant 11$, $-14 \leqslant k \leqslant 14$, $-26 \leqslant l \leqslant 25$	$-11 \leqslant h \leqslant 11$, $-14 \leqslant k \leqslant 14$, $-15 \leqslant l \leqslant 15$	$-9 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 17$, $0 \leqslant l \leqslant 30$
Collected reflections	12,668	79,096	84,604	65,279
Unique reflections	4926	4545	5225	5173
Completeness to *θ* (%)	92.1	96.9	97.7	98.0
Data/restraints/parameters	3039/1/264	3378	4125	3826
Goodness-of-fit on F^2	0.980	1.032	1.033	1.028
Final *R* indices [*I* > 2sigma (*I*)] (%)	R_1 = 3.8, wR_2 = 6.0	R_1 = 4.2, wR_2 = 10.9	R_1 = 3.9, wR_2 = 9.1	R_1 = 4.0, wR_2 = 8.0
R indices (all data) (%)	R_1 = 8.2, wR_2 = 7.3	R_1 = 6.6, wR_2 = 12.3	R_1 = 5.9, wR_2 = 10.3	R_1 = 7.1, wR_2 = 9.7
Largest diff. peak and hole (e $Å^3$)	0.104 and −0.112	0.162 and −0.126	0.172 and −0.105	0.133 and −0.119
CCDC deposition No.	1468092	1468093	1468095	1468096

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