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Absolute configuration determination of 2-(2-oxo-3-indolyl)acetamide derivatives

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ABSTRACT

We describe a reliable method for determining the absolute configuration of 2-(2-oxo-3-indolyl)acetamides based on analysis of the ^{1}H NMR spectra of their phenylethylamide diastereomers. The conformational preferences for two diastereomeric amides were calculated by DFT, which matched well with the experimental results. X-ray diffraction analysis allowed us to validate the method.

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1. Introduction

The oxindole ring system is a very important structural unit found in many natural products and biologically active compounds.[1] In particular, 1,3,3-trisubtituted oxindole derivatives **1** have been widely applied in the total synthesis of terrestrial and marine natural products containing the furo- and pyrroloindole skeletons **2**[2] (Fig. 1). The reduction of oxindoles **1** containing acid, ester, or amide functionalities on a C3 chain is the frequently used strategy to synthesize the corresponding systems **2**. Many oxindole derivatives **1** are often found in Nature as optically active compounds in which a key problem is to find a suitable and easy method to assign their absolute configuration. NMR spectroscopy is a widely used method for the absolute configuration assignment of monofunctional and polyfunctional compounds, such as alcohols, amines, and carboxylic acids, when using Chiral Derivatizing Agents (CDAs), which contain an aryl ring that selectively directs its anisotropic cone toward a substituent on the asymmetric unit of the substrate, thereby reflecting their spatial relationship with respect to the aryl ring and absolute configuration.[3] Although predictions of absolute configuration of α-chiral carboxylic acids by this means are very well documented, the absolute configuration assignment of chiral β-branched carboxylic acids has scarcely been investigated.[4] Among several CDAs available for the configurational assignment of α- and β-branched carboxylic acids, 1-arylethylamines are the most widely used reagents due to the conformational properties of the resulting RC(=O)NHCH–(Me)Ar substructural unit.[4a,b,5] As 2-(2-oxo-3-indolyl)acetic acid derivatives **1** represent a very important structural unit in natural product synthesis and biological important targets, herein we show that inexpensive enantiomerically pure phenylethylamine (FEA) could be used as a reliable reagent to determine the absolute configuration of C3-chiral oxindoles of type **1**. To pursue this achievement, we used molecular mechanics and DFT calculations to predict the conformational preferences of two diastereomeric amides and compared these data with those obtained by ^{1}H NMR spectroscopy. This absolute configuration assignment methodology was confirmed by X-ray diffraction analysis.

2. Results and discussion

To investigate the utility of (*R*)-phenylethylamine [(*R*)-FEA] as a CDA for the absolute configuration assignment of the C3 stereogenic center in 2-oxo-3-indolylacetic acid derivatives **9a–e** containing a variety of alkyl groups at the *N*1 and C3 positions, diastereomeric amides **11a–e** were synthesized according to Scheme 1. Thus, treatment of **3** with KOH/TBAB/THF and subsequent alkylation with MeI, EtBr, or BnBr gave *N*-alkylindoles **4a–c** in 92%, 90%, or 87% yield, respectively, which were oxidized with DMSO/HCl[6] at room temperature to afford the corresponding 2-(2-oxo-3-indolyl)acetic acid derivatives **5a–c** (68–71%) together with methyl 2-(2-oxo-3-indolyl)acetate derivatives **6a–c** (21–25%). Methyl esterification of oxindoles **5a–c** with MeOH/H$^+$ at reflux[6] afforded esters **6a–c** (83–86% overall yield from **4a–c**). Subsequent C3 alkylation of **6a–c** and **8** with the corresponding alkyl halide MeI, EtBr, or BnBr using K_2CO_3/acetone gave *N*1,C3-dialkyloxindole derivatives **7a–e** (86–91% yields).[7] Alkaline hydrolysis of esters **7a–e** (NaOH/H_2O/MeOH) followed by acidification with HCl/H_2O gave carboxylic acids **9a–e** (85–89% yields).

With racemic samples of **9a–e** now being readily available, amide derivatization with (*R*)-α-FEA **10** [(*R*)-**10**] was carried out by activation of carboxylic acids **9** with $ClCO_2Et$ and Et_3N[8] followed

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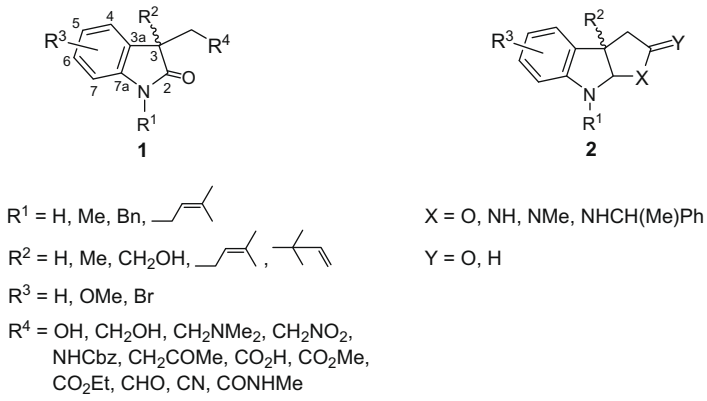


Figure 1.

by reaction with the amine to give equimolar diastereomeric mixtures of (3*R*,11*R*)-**11a**–**e** (41–43%) and (3*S*,11*R*)-**11a**–**e** (40–42%), as evidenced by ^{1}H NMR of the reaction crudes, which indicated that no kinetic resolution occurred in any case. The diastereomeric amides (3*R*,11*R*)-**11a**–**e** and (3*S*,11*R*)-**11a**–**e** were easily separated by column chromatography due to their different R_f values (Table 1) to afford enantiomerically pure isomers (de >99% as determined by ^{1}H NMR).

Interpretation of the ^{1}H NMR spectra of the two resulting sets of diastereomers (3*R*,11*R*)-**11a**–**e** and (3*S*,11*R*)-**11a**–**e**, combined with the evaluation of their representative low energy conformations, allowed absolute configuration assignment at the C3 stereogenic center of the chiral oxindole unit substrate. Thus, both diastereomeric amides **11a** were used as representative models for this goal. The ^{1}H NMR spectra allowed discrimination of the amides (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a** since these compounds showed large enough chemical shift differences ($\Delta\delta^{RS} = \delta_R - \delta_S$, where the *R* and *S* descriptors refer to the stereogenic C3 configuration in the oxindole moiety[4c]) for diagnostic signals *N*1-Me, C3-Me, and H8A (Table 2). Essentially, these $\Delta\delta^{RS}$ values arise from the diamagnetic influence of the aromatic (*R*)-FEA moiety on the NMR signals of *N*1-Me and C3-Me groups in the (3*R*)- and (3*S*)-stereogenic centers of the oxindole skeleton. As shown in Figure 2 the signals due to *N*1-Me anisochronous protons, which are far from the C3 stereogenic C_β-center, show a higher chemical shift difference [and sign ($-\Delta\delta^{RS}$)] than those of the closer C3-Me group ($+\Delta\delta^{RS}$) (Fig. 2, Table 2). Also, considering the polarity of diastereoisomeric amides **11a** (Table 1), it is shown that the *N*1-Me group signal of the less polar (3*R*,11*R*)-**11a** appears at lower frequency than that of the more polar (3*S*,11*R*)-**11a** (Fig. 2), while the C3-Me signal for the more polar (3*S*,11*R*)-**11a** appears at lower frequency than that of the less polar (3*R*,11*R*)-**11a**.

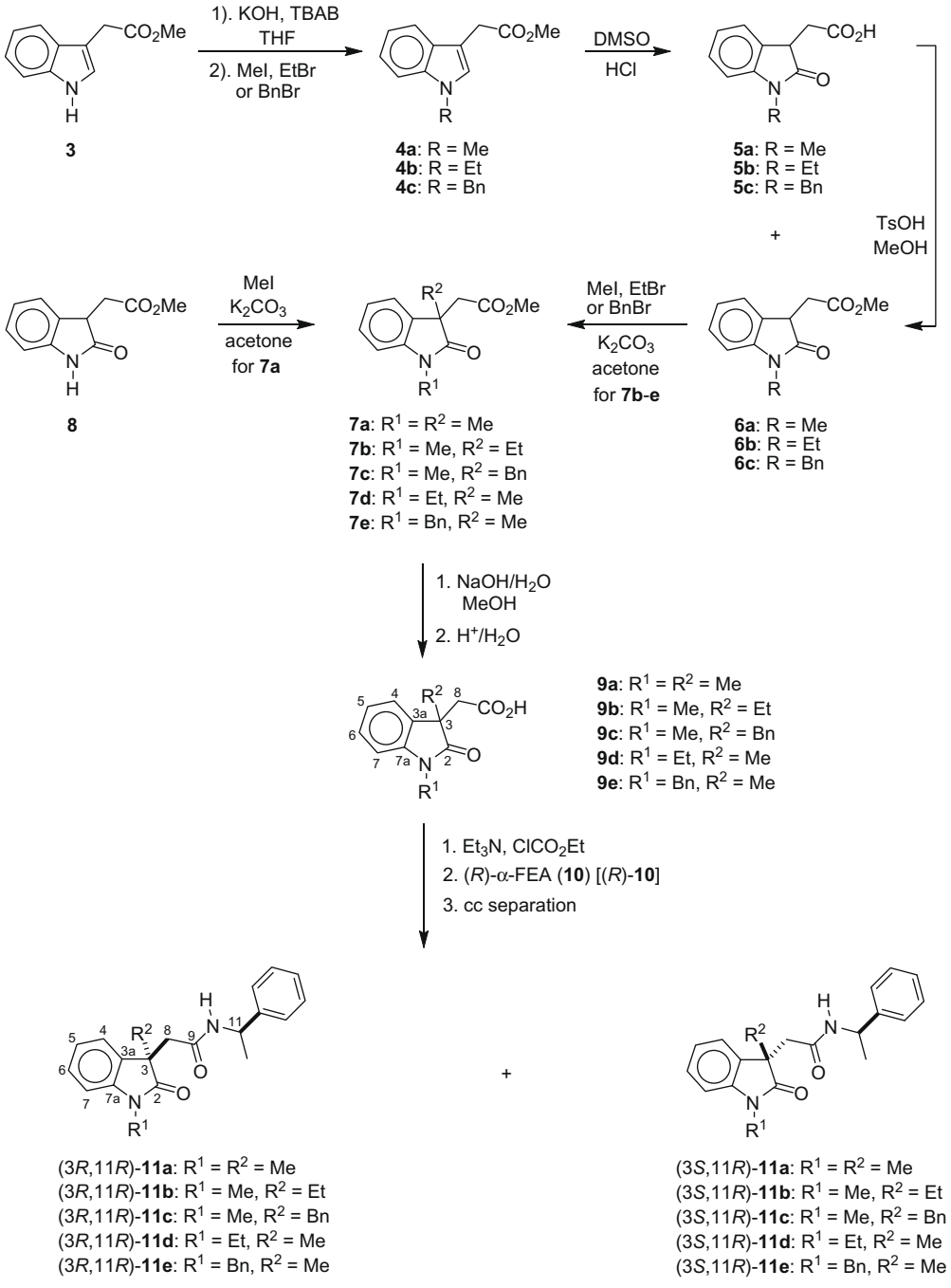
The assumption that the aromatic (*R*)-FEA moiety influences the chemical shifts of *N*1-Me and C3-Me groups in **11a**–**e** is reinforced when considering the δ values (range 3.17–3.29 ppm)[2b–f,9] for the *N*-Me group signals in several derivatives of type **1** without an aromatic moiety at the C_α-phenyethylacetamide unit at C3. The observed signs for $\Delta\delta^{RS}$ between both diastereomers of **11a** could be accounted for by using the representation proposed in Figure 3, where the substituent arrangement around C3 in (3*R*,11*R*)-**11a** shows that the dominating conformation of the amide should be that in which the orientation of the magnetic anisotropy imposed by the phenyl group of the (*R*)-FEA moiety should spend enough time to shield the protons of the *N*1-Me group, whereas those in the C3-Me group remain unaffected. In the (3*S*,11*R*)-**11a** derivative, the C3-Me group is protected while the *N*1-Me group is unaffected (Fig. 3). Therefore, the *N*1-Me group will be more shielded in (3*R*,11*R*)-**11a** than in (3*S*,11*R*)-**11a**, while the C3-Me group will be more shielded in (3*S*,11*R*)-**11a** than in (3*R*,11*R*)-**11a**.

Using conformational arguments, the structures in Figure 4 (3*R*,11*R*)-**11a** (A) and (3*S*,11*R*)-**11a** (B) always have *anti-periplanar* (*ap*) (C=O)–(N–H)–(C–H) arrays (χ and θ angles).[5] These *ap* conformations were supported by X-ray crystallographic analyses and DFT calculations of both diastereomers of **11a**. As shown in Figure 4, free rotation around the C8–C=O bond generates the three main conformers **I**–**III**. In conformer **II**, the shift of the *N1*-Me protons of the (3*R*,11*R*)-**11a** diastereomer and the C3-Me protons of the (3*S*,11*R*)-**11a** diastereomer should always be upfield as a result of the anisotropic shielding of the phenyl ring. Therefore conformer **II** is the predominant rotamer of diastereomeric amides **11a**.

The above-mentioned methodology of ^{1}H NMR configuration assignment was extended to include 2-oxindole carboxylic amides with substituents other than a methyl group at *N*1 and C3 positions, including the substrates shown in Table 2; the results confirm the applicability of the methodology. The $\Delta\delta^{RS}$ values obtained for amides **11b**–**e** have the same sign for the *N*1–CH_2–R and C3–CH_2–R groups and for the C8 AB system, as those obtained for **11a**, which suggests that amides **11a**–**e** adopt similar conformations at the C3–C8–C(=O)–N(H)–C11 fragment (φ, ϕ, χ, and θ angles). As shown in Table 2, the $+\Delta\delta^{RS}$ magnitude values (0.03–0.07) for the C3–CH_2–R group in oxindole-amides **11a**–**e** are comparable to those reported for other types of amides containing FEA as a CDA and a methyl group at the β-position.[4a,b] However, the $-\Delta\delta^{RS}$ magnitude values (0.09–0.23) for the *N*1–CH_2–R group are longer than the $\Delta\delta$ values reported for the substituents at positions other than the β position in β-branched substituted carboxylic acids,[4a,b] suggesting that in our case, FEA is a more reliable reagent to assign the absolute configuration of chiral amides **11a**–**e**.

Further evidence to explain the $\Delta\delta^{RS}$ values observed in Figure 2 and Table 2 was provided when a systematic molecular modeling protocol with Monte Carlo searching[10–12] and geometry optimization using DFT calculations at the B3LYP/6–31G(d),[5,12,13] and B3LYP/DGDZVP[14,15] levels of theory was applied to amides (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a**.[16] According to the conformer contribution,[17,18] only 5 conformers arose as relevant components (99.3%) for amide (3*R*,11*R*)-**11a** and only 4 conformers (99.7%) for amide (3*S*,11*R*)-**11a**, which are shown in Figures 5 and 6, respectively.

It is worth noting that an *anti*-disposition between C11–H and *N*10–H was invariably detected as the most stable conformer irrespective of the diastereomeric amide studied showing θ values between −135.7° and 172.6° for the (3*R*,11*R*)-**11a** conformers and between −137.2° and 168.5° for the (3*S*,11*R*)-**11a** conformers. This result implies that the *Z*-conformer at the C=O–NCH_α moiety is always significantly preferred over the *E*-conformer and leaves the free conformation around the φ and ϕ angles (Fig. 4) as the dominating process in both diastereomers. Conformers **11a*A*** and **11a*B*** are depicted as the most populated in the conformational equilibria



Scheme 1. Synthesis of diastereomeric amides **11a–e**.

for both diastereomeric amides (3*R*,11*R*)-**11a** (64.9% and 20.4%) (Fig. 5) and (3*S*,11*R*)-**11a** (69.2% and 17.6%) (Fig. 6), while the remaining conformers are minor contributors. It is interesting to note that for (3*R*,11*R*)-**11a**, the global minimum structure **11a*A*** has the CDA phenyl ring pointing toward the *N*1-Me group in exact coincidence with conformer **II** presented in Figure 4, trace A. Regarding (3*S*,11*R*)-**11a**, the global minimum structure **11a*A*** has the CDA phenyl group oriented in close proximity to the C3-Me group and also in coincidence with conformer **II** as shown in Figure 4, trace B. In both cases, the global minimum of both amides corresponded very well with those predicted in Figure 4 and with the experimental results. Thus, computational results reinforce the assignment of the absolute configuration in (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a**.

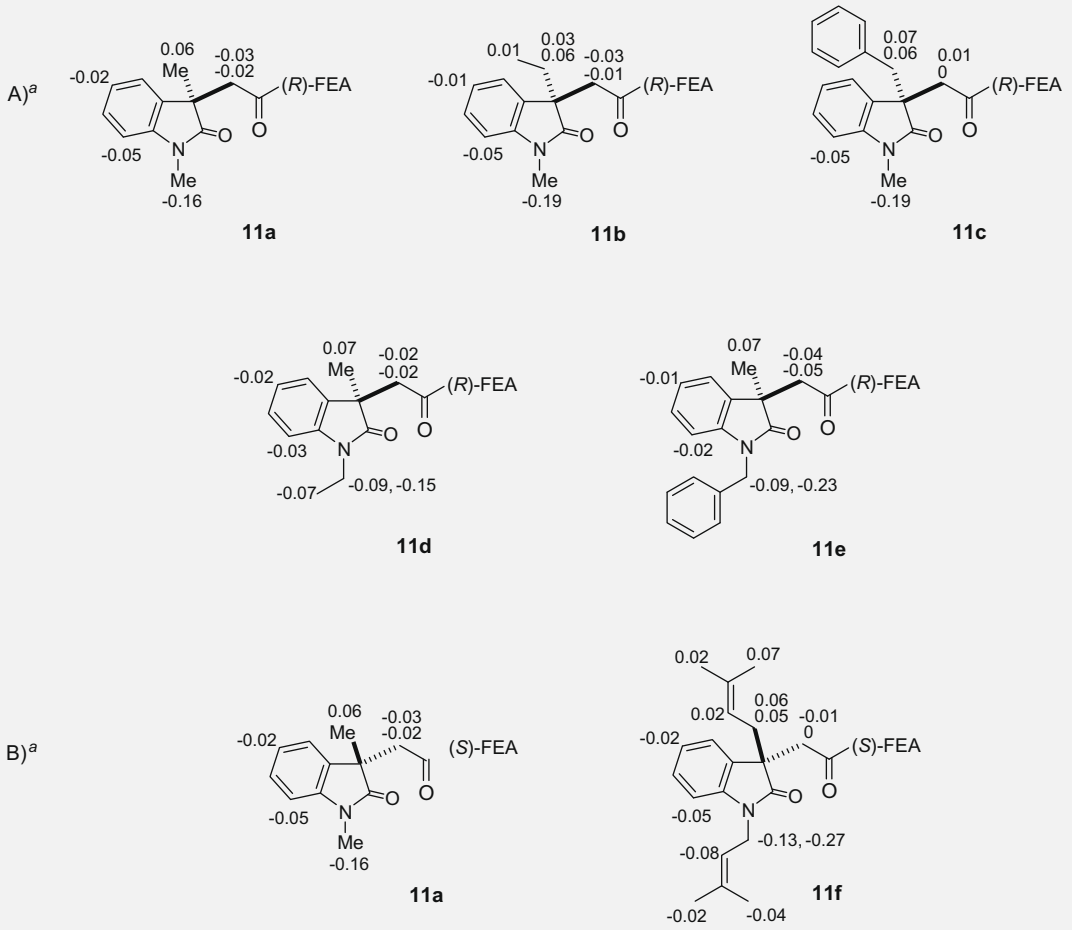
Table 1
R_f[a] values of diastereomeric amides **11a–e**

Compound	(3*R*,11*R*)-Diastereomer R_f	(3*S*,11*R*)-Diastereomer R_f
11a	0.34	0.18
11b	0.38	0.28
11c	0.48	0.32
11d	0.44	0.24
11e	0.58	0.40

[a] Determined by TLC (Silica gel F_{254} coated aluminum sheets 0.25 mm thickness) using EtOAc/hexane (1:2, v/v).

From the minimum energy conformational analysis of (3*R*,11*R*)-**11a**, a hydrogen bond between the amide hydrogen and the carbonyl oxygen atom would be expected, but a detailed analysis of the geometry of this fragment revealed that such a hydrogen bond is only allowed for conformer (3*R*,11*R*)-**11aB** (Fig. 5). In the case of amide (3*S*,11*R*)-**11a** such a hydrogen bond is formed for the most

Table 2
Significant $\Delta\delta^{RS}$ values for (3*R*,11*R*)-**11a–e** and (3*S*,11*R*)-**11a–e**, and $\Delta\delta^{SR}$ for (3*S*,11*S*)-**11a**,**f** and (3*R*,11*S*)-**11a**,**f**



[a] $\Delta\delta^{RS}$ Values ($\delta_R - \delta_S$) were calculated by subtracting the proton chemical shifts of (3*S*)-oxyndole-(11*R*)-FEA from those of (3*R*)-oxyndole-(11*R*)-FEA (A) while $\Delta\delta^{SR}$ values ($\delta_S - \delta_R$) were calculated by subtracting the proton chemical shifts of (3*R*)-oxyndole-(11*S*)-FEA from those of (3*S*)-oxyndole-(11*S*)-FEA (B).[4c]

abundant (3*S*,11*R*)-**11a*A*** conformer (Fig. 6). Thus, we envisioned that the solvent polarity, apart from intramolecular interactions, should govern the orientation of the substituents in amides **11a–e**. Therefore, we next examined the ^{1}H NMR spectra of amides (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a**, using $Cl_2CDCDCl_2$, CD_3OD, DMSO-d_6, CD_3CN, and acetone-d_6 (Table 3). The δ values of diagnostic signals in both diastereomeric amides in $Cl_2CDCDCl_2$ are consistent with trends observed in $CDCl_3$, although δ decreased smoothly. However, in solvents more polar than $CDCl_3$ no significant differences in δ for the *N*1-Me and C3-Me protons were observed between both (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a** diastereomers. An additional point of interest in Table 3 is related to the chemical shifts for protons H8. The chemical shifts of these AB system vary notably between amides (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a** when the spectra were obtained in CD_3OD and CD_3CN (Table 3), and the same trend was observed between amides (3*R*,11*R*)-**11c–e** and (3*S*,11*R*)-**11c–e** (Table 4). In the case of amides **11a**,**c–e** the difference in chemical shift for the H8A and H8B signals ($\Delta\delta$) was always higher in amides (3*S*,11*R*)-**11a**,**c–e** than in the (3*R*,11*R*)-**11a**,**c–e** stereoisomer (Tables 3 and 4). Furthermore, in amides **11a–e** the average chemical shift for H8A and H8B was always higher in (3*S*,11*R*)-**11a–e** than in (3*R*,11*R*)-**11a–e**. Thus, we can initially predict the relative configuration of each amide **11** by inspection of the chemical shift difference for the C8 AB protons when measured in CD_3OD or in CD_3CN.

The reliability of our methodology for the absolute configuration assignment of 2-(2-oxo-3-indolyl)acetamide derivatives **11a–e** by ^{1}H NMR was supported by X-ray diffraction analysis of amides (3*R*,11*R*)-**11a**, (3*S*,11*R*)-**11a**, (3*S*,11*R*)-**11b**, (3*S*,11*R*)-**11c**, (3*R*,11*R*)-**11d**, and (3*S*,11*R*)-**11d** whose absolute configuration structures are shown in Figure 7. Thus, these results validate the method for the assignment of the absolute configuration of oxindole carboxylic amides **11a–e** by ^{1}H NMR using (*R*)-FEA as a CDA.

As Nature usually produces only one chiral enantiomer or diastereomer, it was important to use (*S*)-FEA [(*S*)-**10**] as a CDA to resolve a mixture of (±)-**9a** and to study its effect on the chemical shifts for *N*1-Me and C3-Me signals in order to establish the absolute configuration of chiral acid derivatives of type **9** using both FEA enantiomers. As expected, preferential shielding of the *N*1-Me group was observed in the diastereomer (3*S*,11*S*)-**11a** ($\Delta\delta^{SR} = -0.16$), whereas preferential shielding of the C3-Me group was observed in the (3*R*,11*S*)-**11a** one ($\Delta\delta^{SR} = 0.06$) (Table 2). Amides (3*R*,11*S*)-**11a** and (3*S*,11*S*)-**11a** gave suitable crystals for X-ray diffraction analysis and the corresponding absolute configuration structures are shown in Figure 8. According to the aforementioned methodology, it is now possible to establish the absolute configuration of reported amides[8] (3*S*,11*S*)-**11f** and (3*R*,11*S*)-**11f** (Table 2). In the less polar (3*S*,11*S*)-**11f** diastereomer ($R_f = 0.60$, EtOAc/hexane, 1:1 v/v), the *N*1–CH_2–R group appears at lower frequency than that of the more polar (3*R*,11*S*)-**11f** ($R_f = 0.27$, EtOAc/

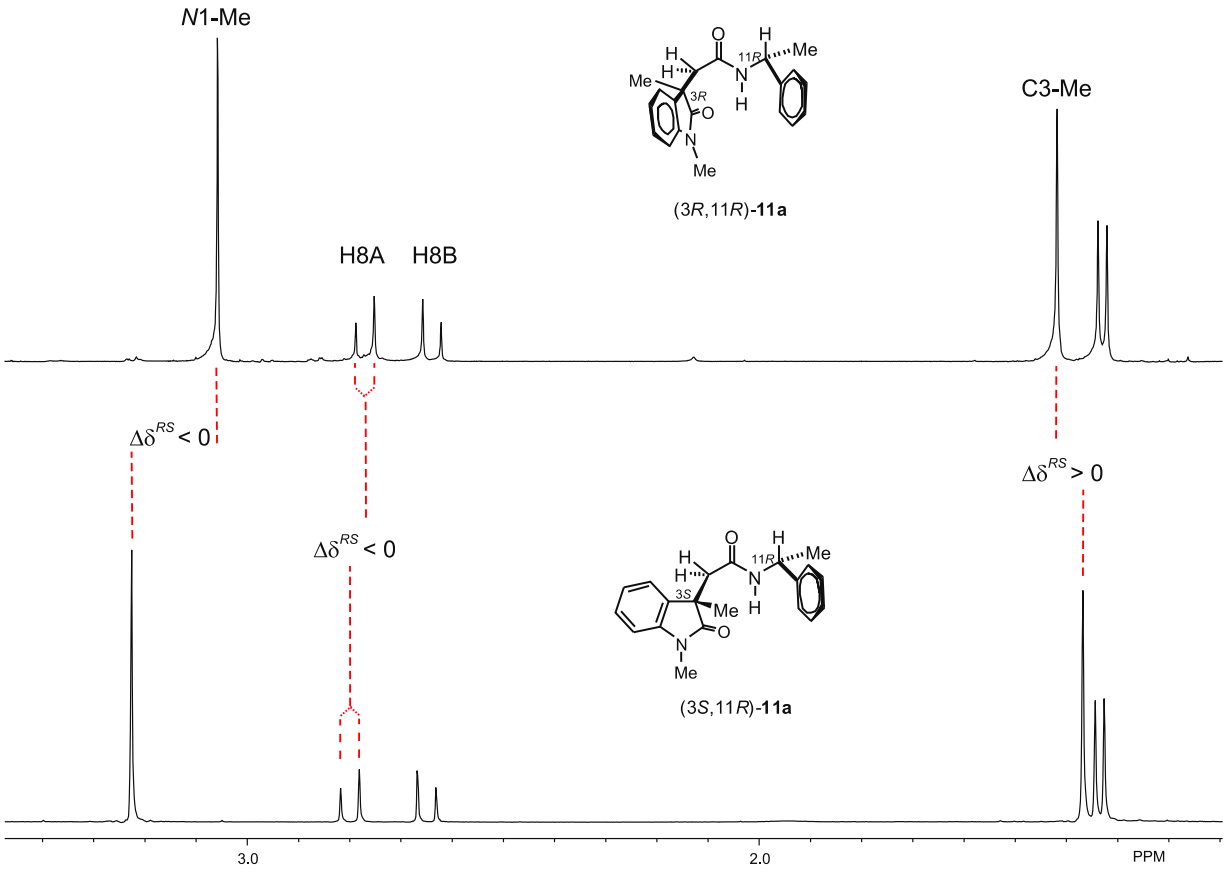


Figure 2. Partial ^{1}H NMR spectra illustrating the $\Delta\delta^{RS}$ for *N*1-Me, H8A, and C3-Me in (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a**.

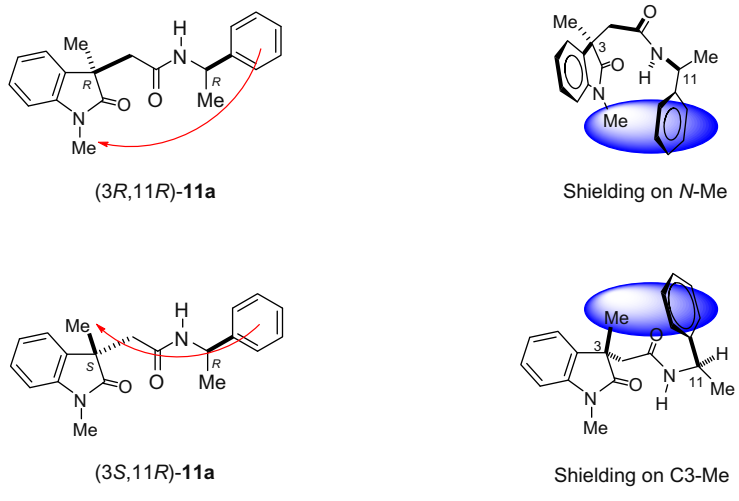


Figure 3. *N*1-Me and C3-Me anisotropic shielding in amides (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a**.

hexane, 1:1 v/v) compound. On the contrary, the C3–CH_2–R signal for the more polar (3*R*,11*S*)-**11f** appears at lower frequency than that of the less polar (3*S*,11*S*)-**11f**.

3. Conclusion

In conclusion, we have demonstrated that the absolute configuration assignment of 2-(2-oxo-3-indolyl)acetic acid derivatives **9** could be achieved by its derivatization with either commercially available enantiomer of FEA (*R*)-**10** or (*S*)-**10** and subsequent ^{1}H NMR analysis of their corresponding amides **11**. A general assumption might be made for the configuration assignment as follows: (3*R*,11*R*)- and (3*S*,11*S*)- stereoisomers of amides of type **11** will present the *N*1–CH_2–R proton signal at a lower frequency value ($-\Delta\delta^{RS}$ or $-\Delta\delta^{SR}$) and the C3–CH_2–R proton signal at a higher frequency value ($+\Delta\delta^{RS}$ or $+\Delta\delta^{SR}$) when compared to their corresponding (3*S*,11*R*)- and (3*R*,11*S*)-diastereomers.

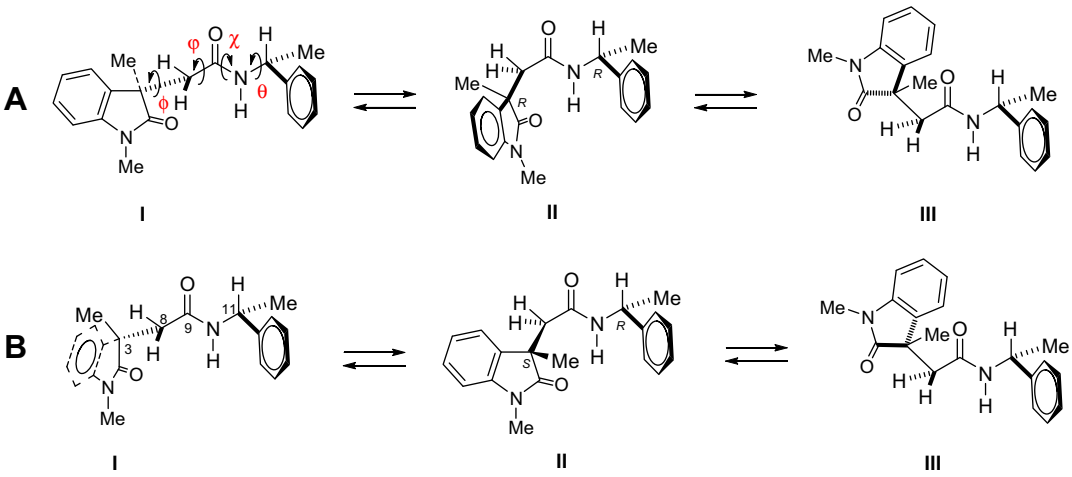


Figure 4. Preferred conformations of amides (3*R*,11*R*)-**11a** (A) and (3*S*,11*R*)-**11a** (B).

4. Experimental

4.1. General experimental procedures

Melting points were determined on a Büchi B-540 apparatus. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrophotometer. The 400 and 100 MHz ^{1}H and ^{13}C NMR spectra were obtained on a JEOL Eclipse 400 spectrometer and the 300 and 75 MHz ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer using $CDCl_3$, DMSO-d_6, $Cl_2CDCDCl_2$, CD_3OD, CD_3CN, or acetone-d_6 as the solvents and TMS as the internal reference. For complete assignments 2D NMR, HMQC, HSQC, HETCOR, and HMBC spectra were used. Data are reported as follows: chemical shift in ppm from TMS, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quintet, 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 carrier gas (1 mL/min), programed from 70 °C to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. MS analyses were obtained in the electron impact (EI) mode at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química, UNAM-México and at the UCR Mass Spectrometry Facility, University of California, Riverside. Microanalytical determinations were performed on a Perkin–Elmer 2400 series PCII apparatus. Optical rotation measurements were performed on a Perkin–Elmer 341 polarimeter. Analytical thin-layer chromatography (TLC) was done 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.

4.2. General procedure for the preparation of *N*-alkyl indoles 4a–c

To a solution of indole-3-acetic acid methyl ester **3** (2 g, 10.6 mmol) in dry THF (20 mL) were added the appropriate alkyl halide (MeI, 2.6 mL, EtBr, 3.2 mL, or BnBr, 5.0 mL, 42 mmol), TBAB (212 mg, 0.66 mmol), and KOH (2.35 g, 42 mmol). The mixture was stirred at room temperature over 8 h and filtered off through a Celite pad. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 mL), washed with H_2O (1 × 10 mL), saturated solution of $NaHCO_3$ (1 × 10 mL), brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. Resultant crudes **4a–c** were purified by flash column chromatography on silica gel with EtOAc/hexane 1:10 for **4a** and **4b** and 1:8 for **4c**.

4.3. Methyl 2-(1-methyl-1*H*-3-indol-3-yl)acetate 4a

Prepared from **3** as a yellow oil (1.98 g, 92%).[19] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (1H, br d, J = 7.7 Hz, H4), 7.27 (1H, br d, J = 8.0 Hz, H7), 7.21 (1H, td, J = 7.4, 1.1 Hz, H6), 7.11 (1H, td, J = 7.4, 1.5 Hz, H5), 7.00 (1H, s, H2), 3.75 (2H, s, H8), 3.70 (3H, s, H11), 3.67 (3H, s, H10); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (C9), 136.8 (C7a), 127.6 (C2), 127.5 (C3a), 121.7 (C6), 119.1 (C5), 118.8 (C4), 109.2 (C7), 106.6 (C3), 51.8 (C10), 32.5 (C11), 31.0 (C8).

4.4. Methyl 2-(1-ethyl-1*H*-3-indol-3-yl)acetate 4b

Prepared from **3** as a yellow oil (2.06 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, ddd, J = 7.8, 1.4, 0.8 Hz, H4), 7.29 (1H, dt, J = 8.3, 1.1 Hz, H7), 7.20 (1H, ddd, J = 8.1, 6.9, 1.1 Hz, H6), 7.10 (1H, ddd, J = 8.0, 6.9, 1.4 Hz, H5), 7.07 (1H, br s, H2), 4.08 (2H, q, J = 7.3 Hz, H11), 3.75 (2H, d, J = 0.8 Hz, H8), 3.67 (3H, s, H10), 1.41 (3H, t, J = 7.3 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (C9), 135.8 (C7a), 127.7 (C3a), 125.9 (C2), 121.5 (C6), 119.0 (C5), 118.9 (C4), 109.3 (C7), 106.7 (C3), 51.8 (C10), 40.7 (C11), 31.0 (C8), 15.3 (C12); IR ($CHCl_3$) ν_{max} 3056, 2953, 2920, 2850, 1730, 1613, 1467 cm^{-1}; EIMS *m/z* (relative intensity) 217 (M^+, 41), 158 (100), 130 (10). FAB-HRMS *m/z* calcd for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1099.

4.5. Methyl 2-(1-benzyl-1*H*-3-indol-3-yl)acetate 4c

Prepared from **3** as a yellow oil (2.56 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (1H, br d, J = 6.8 Hz, H4), 7.27–7.17 (4H, m, H7, H14–H16), 7.15 (1H, td, J = 7.0, 1.5 Hz, H6), 7.10 (1H, br t, J = 7.3 Hz, H5), 7.07 (2H, dd, J = 6.6, 2.2 Hz, H13, H17), 7.06 (1H, br s, H2), 5.19 (2H, s, H11), 3.75 (2H, s, H8), 3.65 (3H, s, H10); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (C9), 137.3 (C12), 136.4 (C7a), 128.6 (C14,C16), 127.8 (C3a), 127.5 (C15), 127.0 (C2), 126.7 (C13,C17), 121.9 (C6), 119.3 (C5), 119.0 (C4), 109.7 (C7), 107.4 (C3), 51.8 (C10), 49.8 (C11), 31.0 (C8); IR ($CHCl_3$) ν_{max} 3059, 3030, 2950, 2918, 1736, 1615, 1467 cm^{-1}; EIMS *m/z* (relative intensity) 279 (M^+, 65), 221 (100), 91 (38). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.05; H, 6.19; N, 5.41.

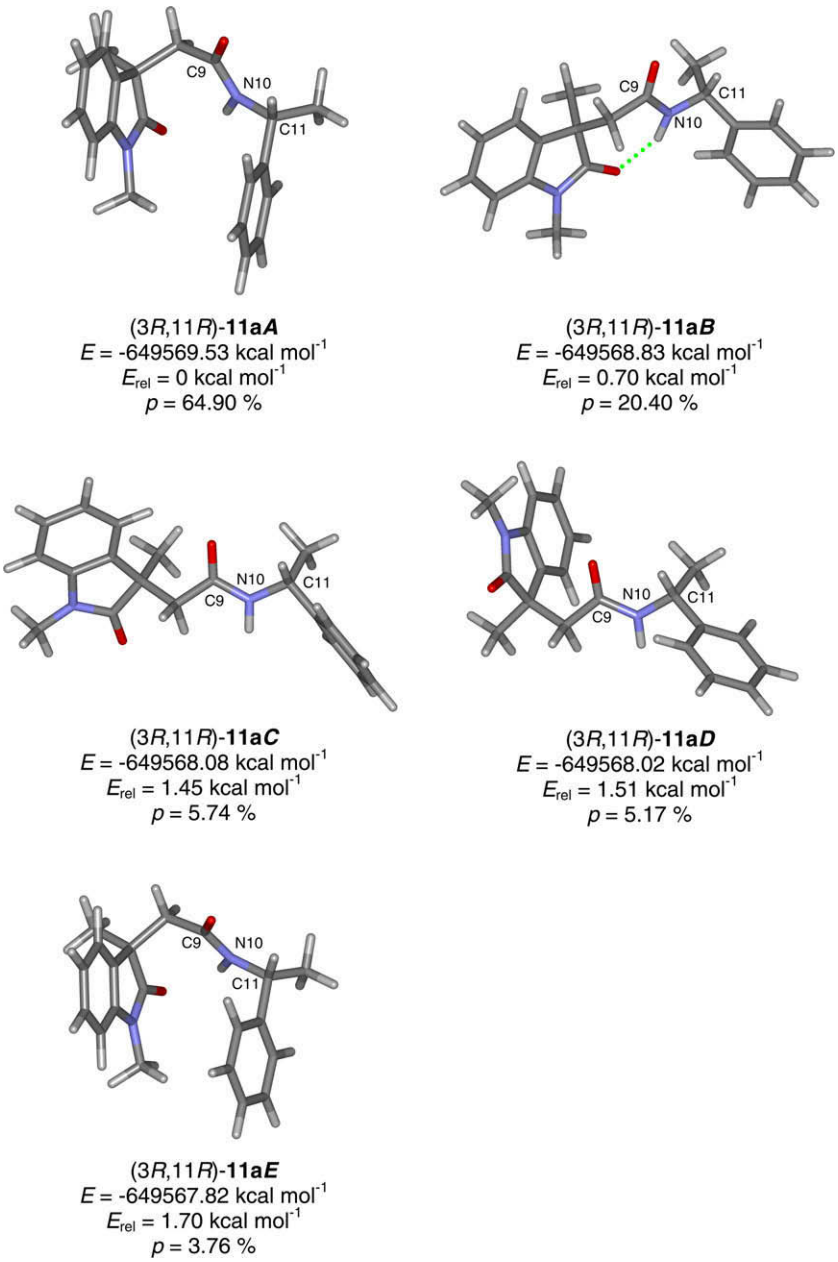


Figure 5. Optimized geometries, calculated energies (E/kcal/mol), relative energy differences (E_{rel}/kcal/mol) and populations (p in %) for (3*R*,11*R*)-**11a*A–E*** conformers obtained at the DFT B3LYP/DGDZVP level of theory.

4.6. General procedure for the preparation of oxindoles 5a–c and 6a–c from 4a–c

To a solution of the appropriate indoles **4a–c** (0.02 mol) in DMSO (7 mL, 10 mmol) was added an aqueous solution (36%) of HCl (46 mL, 0.54 mol) and the solution was stirred at room temperature for 2.5 h. The mixture was diluted with water (100 mL), neutralized with a saturated solution of $NaHCO_3$, and extracted with EtOAc (6×70 mL). The organic layer was washed with brine (2×100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness in vacuum. The resultant crude products **6a–c** were purified by flash column chromatography on silica gel eluting with EtOAc/hexane 1:3.

The aqueous phase was acidified to pH 1 with aqueous HCl and extracted with EtOAc (4×30 mL). The combined organic layers were washed with brine (2×30 mL), dried over anhydrous Na_2SO_4, filtrated, and evaporated to dryness in vacuum. The resultant crude products **5a–c** were purified by flash chromatography on silica gel using EtOAc/hexane 3:2 for **5a** and **5b** and 1:1 for **5c**.

4.7. General procedure for the esterification of oxindoles 5a–c

To a solution of the appropriate oxindoles **5a–c** (13.2 mmol) in MeOH (30 mL) was added *p*-toluenesulfonic acid (100 mg) and heated at reflux for 4 h. After cooling to room temperature the MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc (30 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (3×20 mL), brine (3×20 mL), dried over Na_2SO_4 and evaporated to dryness in vac-

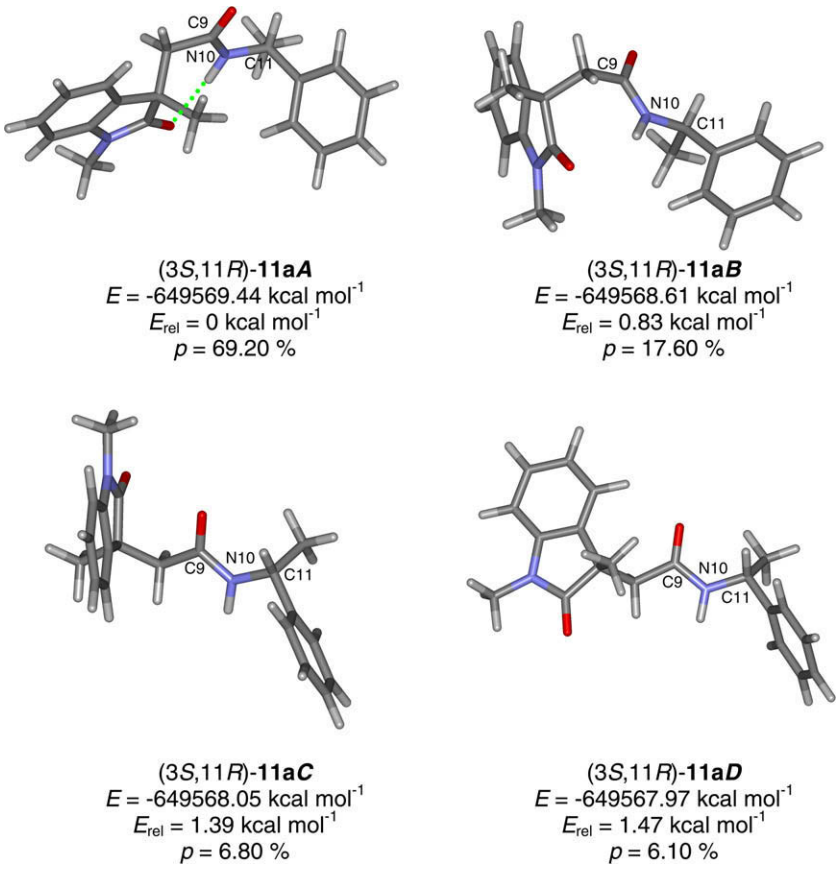


Figure 6. Optimized geometries, calculated energies (E/kcal/mol), relative energy differences (E_{rel}/kcal/mol) and population (p in %) for (3*S*,11*R*)-**11a*A–D*** conformers obtained at the DFT B3LYP/DGDZVP level of theory.

Table 3
Diagnostic chemical shifts (δ)[a] for *N*1-Me, C3-Me, and CH_2 groups and $\Delta\delta$ values for the AB system in (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a** using various solvents

Solvent	Chemical shift, δ (ppm)							
	(3*R*,11*R*)-**11a**				(3*S*,11*R*)-**11a**			
	*N*1-Me	C3-Me	H8A, H8B	$\Delta\delta$	*N*1-Me	C3-Me	H8A, H8B	$\Delta\delta$
$CDCl_3$	3.06	1.42	2.77, 2.64	0.13	3.22	1.36	2.80, 2.66	0.14
$Cl_2CDCDCl_2$	3.01	1.32	2.71, 2.53	0.18	3.12	1.28	2.76, 2.54	0.22
CD_3OD	3.22	1.36	2.84	0	3.21	1.35	2.91, 2.88	0.03
DMSO-d_6	3.06	1.20	2.76, 2.61	0.15	3.05	1.20	2.81, 2.68	0.13
CD_3CN	3.12	1.30	2.75	0	3.12	1.28	2.81, 2.77	0.04
$(CD_3)_2CO$	3.13	1.30	2.79, 2.70	0.09	3.18	1.32	2.86, 2.79	0.07

[a] Room temperature measurements at 300 MHz.

Table 4
Chemical shift (δ, ppm) and $\Delta\delta$ (ppm) values for H8 of (3*R*,11*R*)-**11b–e** and (3*S*,11*R*)-**11b–e** in CD_3OD and CD_3CN[a]

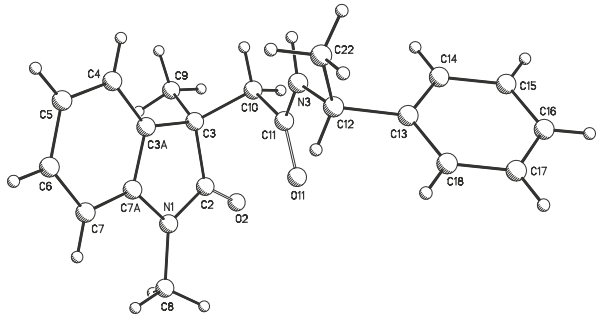
Compound	Chemical shift, δ (ppm)			
	CD_3OD		CD_3CN	
	H8A, H8B	$\Delta\delta$	H8A, H8B	$\Delta\delta$
(3*R*,11*R*)-**11b**	2.83	0	2.71	0
(3*S*,11*R*)-**11b**	2.88	0	2.77, 2.75	0.02
(3*R*,11*R*)-**11c**	3.00, 2.98	0.02	2.86, 2.84	0.02
(3*S*,11*R*)-**11c**	3.06, 3.01	0.05	2.93, 2.86	0.07
(3*R*,11*R*)-**11d**	2.83	0	2.71	0
(3*S*,11*R*)-**11d**	2.88, 2.85	0.03	2.77, 2.74	0.03
(3*R*,11*R*)-**11e**	2.90	0	2.80	0
(3*S*,11*R*)-**11e**	2.96, 2.92	0.04	2.87, 2.82	0.05

[a] Room temperature measurements at 300 MHz.

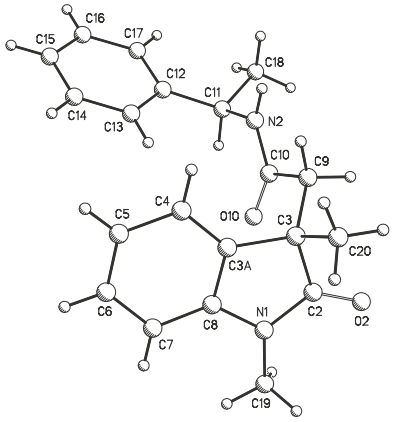
uum. The resultant crude products **6a–c** were purified by flash column chromatography on silica gel eluting with EtOAc/hexane 1:3.

4.8. 2-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 5a

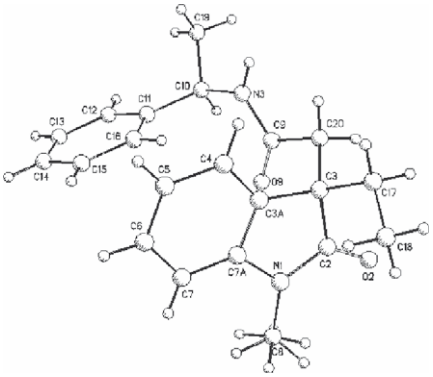
Prepared from **4a** as colorless crystals (2.91 g, 71%), mp: 167–168 °C (EtOAc/hexane). Lit.[20] 168–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.0 (1H, br s, H10), 7.31 (1H, br d, J = 7.3 Hz, H4), 7.30 (1H, br t, J = 8.1 Hz, H6), 7.04 (1H, br t, J = 7.4 Hz, H5), 7.00 (1H, br d, J = 7.7 Hz, H7), 3.72 (1H, dd, J = 6.6, 5.1 Hz, H3), 3.15 (3H, s, H11), 2.97 (1H, dd, J = 17.1, 4.6 Hz, H8A), 2.77 (1H, dd, J = 17.2, 6.9 Hz, H8B); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.4 (C2), 173.2 (C9), 145.4 (C7a),



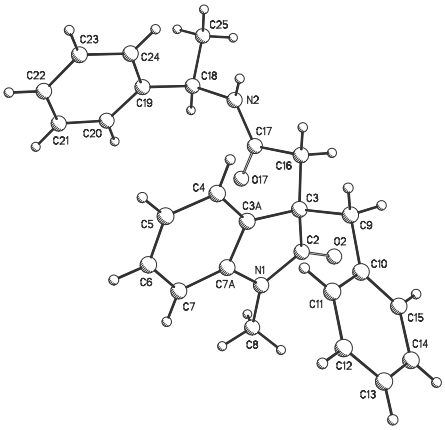
(3*R*,11*R*)-**11a**



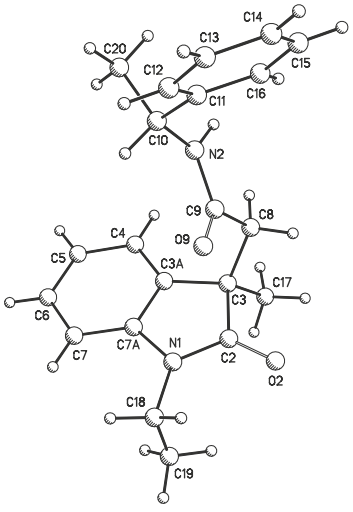
(3*S*,11*R*)-**11a**



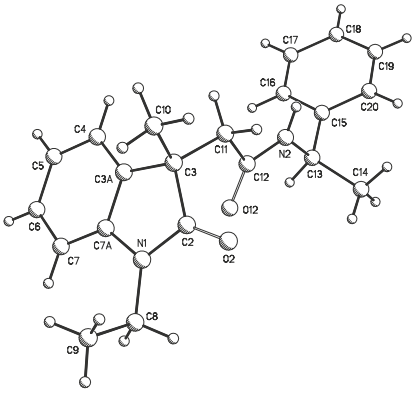
(3*S*,11*R*)-**11b**



(3*S*,11*R*)-**11c**



(3*R*,11*R*)-**11d**



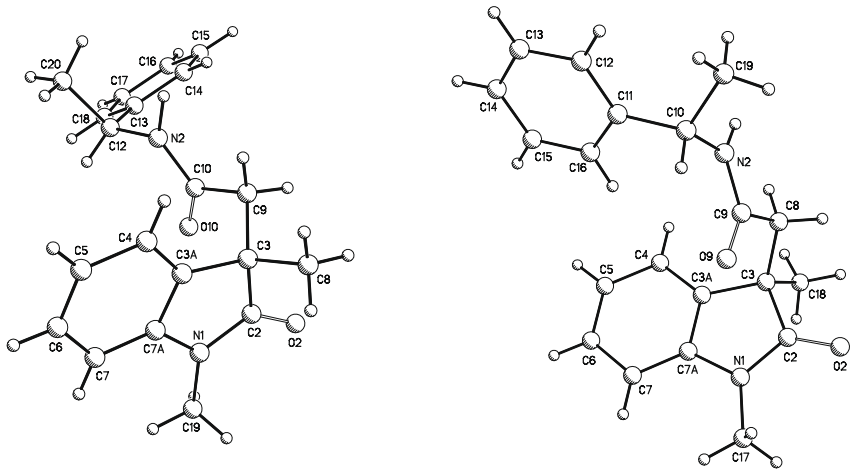
(3*S*,11*R*)-**11d**

Figure 7. X-ray diffraction structures of (3*R*,11*R*)-**11a**, (3*S*,11*R*)-**11a**, (3*S*,11*R*)-**11b**, (3*S*,11*R*)-**11c**, (3*R*,11*R*)-**11d**, and (3*S*,11*R*)-**11d**.

129.6 (C3a), 128.9 (C6), 124.4 (C4), 122.9 (C5), 109.3 (C7), 42.4 (C3), 35.2 (C8), 27.1 (C11); IR (KBr) ν_{max} 3440, 2923, 2889, 2595, 2525, 1725, 1671, 1611, 1200, 1177 cm^{-1}; EIMS *m/z* (relative intensity) 205 (M^+, 47), 159 (100).

4.9. 2-(1-Ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 5b

Prepared from **4b** as colorless crystals (3.10 g, 71%), mp: 182–184 °C (EtOAc/hexane). ^1H NMR (400 MHz, DMSO-d_6): δ 12.00



(3*S*,11*S*)-**11a** (3*R*,11*S*)-**11a**

Figure 8. X-ray diffraction structures of (3*S*,11*S*)-**11a** and (3*R*,11*S*)-**11a**.

(1H, br s, H10), 7.31 (1H, d, J = 7.3 Hz, H4), 7.28 (1H, t, J = 8.0 Hz, H6), 7.02 (1H, d, J = 7.3 Hz, H7), 7.01 (1H, t, J = 8.0 Hz, H5), 3.75–3.61 (3H, m, H3 y H11), 2.94 (1H, dd, J = 16.9, 4.4 Hz, H8A), 2.76 (1H, dd, J = 16.9, 6.6 Hz, H8B), 1.12 (3H, t, J = 7.3 Hz, H12); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.2 (C2), 172.2 (C9), 143.5 (C7a), 128.8 (C3a), 128.0 (C6), 123.6 (C4), 121.8 (C5), 108.4 (C7), 41.4 (C3), 34.2 (C8,C11), 12.5 (C12); IR (KBr) ν_{max} 3434, 3030, 2970, 2927, 1728, 1654, 1609, 1467 cm^{-1}; EIMS m/z (relative intensity) 219 (M$^+$, 35), 173 (100), 160 (28), 159 (62), 158 (92). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.56; H, 5.98; N, 6.34.

4.10. 2-(1-Benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 5c

Prepared from **4c** as colorless crystals (3.85 g, 68%), mp: 126–127 °C (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.69 (1H, br s, H10), 7.32–7.20 (6H, m, H4, H13–H17), 7.16 (1H, br t, J = 7.6 Hz, H6), 7.00 (1H, td, J = 7.5, 0.9 Hz, H5), 6.71 (1H, br d, J = 7.8 Hz, H7), 4.99, 4.85 (2H, AB system, J = 15.7 Hz, H11), 3.87 (1H, dd, J = 7.5, 4.7 Hz, H3), 3.16 (1H, dd, J = 17.3, 4.7 Hz, H8A), 2.95 (1H, dd, J = 17.3, 7.5 Hz, H8B); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0 (C2), 176.1 (C9), 143.2 (C7a), 135.5 (C12), 128.7 (C14,C16), 128.3 (C6), 127.7 (C15), 127.6 (C3a), 127.2 (C13,C17), 123.8 (C4), 122.7 (C5), 109.3 (C7), 43.9 (C11), 41.6 (C3), 34.5 (C8); IR ($CHCl_3$) ν_{max} 3061, 3031, 2928, 1712, 1614, 1490, 1467 cm^{-1}; EIMS m/z (relative intensity) 281 (M$^+$, 69), 235 (94), 91 (100). FABHRMS m/z calcd for $C_{17}H_{14}NO_3$ (M−H$^+$): 280.0974, found: 280.097.

4.11. Methyl (1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate 6a[21]

Prepared from **4a** (0.92 g, 21%) and from **5a** (2.46 g, 85%) as a white solid, mp: 70–72 °C (Et_2O/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (1H, br t, J = 7.4 Hz, H6), 7.28 (1H, br d, J = 6.6 Hz, H4), 7.05 (1H, br t, J = 7.3 Hz, H5), 6.87 (1H, br d, J = 8.0 Hz, H7), 3.77 (1H, dd, J = 8.1, 4.4 Hz, H3), 3.70 (3H, s, H10), 3.23 (3H, s, H11), 3.09 (1H, dd, J = 16.9, 4.4 Hz, H8A), 2.78 (1H, dd, J = 16.8, 8.0 Hz, H8B); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (C2), 170.9 (C9), 143.7 (C7a), 127.7 (C6), 127.6 (C3a), 123.1 (C4), 121.8 (C5), 107.5 (C7), 51.3 (C10), 41.1 (C3), 34.0 (C8), 25.6 (C11); IR ($CHCl_3$) ν_{max} 3056, 2953, 1737, 1712, 1614 cm^{-1}; EIMS m/z (relative intensity) 219 (M$^+$, 59), 159 (100). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 65.72; H, 6.01; N, 6.32.

4.12. Methyl (1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate 6b

Prepared from **4b** (1.03 g, 22%) and from **5b** (2.56 g, 83%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (1H, t, J = 7.7 Hz, H6), 7.25 (1H, d, J = 7.7 Hz, H4), 7.02 (1H, t, J = 7.3 Hz, H5), 6.87 (1H, d, J = 7.7 Hz, H7), 3.85–3.71 (3H, m, H3, H11), 3.67 (3H, s, H10), 3.08 (1H, dd, J = 16.8, 4.4 Hz, H8A), 2.80 (1H, dd, J = 16.9, 8.1 Hz, H8B), 1.27 (3H, t, J = 7.3 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3 (C2), 171.5 (C9), 143.4 (C7a), 128.4 (C3a), 128.3 (C6), 124.0 (C4), 122.3 (C5), 108.3 (C7), 52.0 (C10), 41.8 (C3), 34.8 (C11), 34.7 (C8), 12.6 (C12); IR ($CHCl_3$) ν_{max} 3056, 2977, 2953, 2935, 1739, 1715, 1614, 1468 cm^{-1}; EIMS m/z (relative intensity) 233 (M$^+$, 64), 174 (54), 173 (100), 158 (56). FABHRMS m/z calcd for $C_{13}H_{15}NO_3$: 233.1052, found: 233.1050.

4.13. Methyl 2-(1-benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetate 6c

Prepared from **4c** (1.48 g, 25%) and from **5c** (3.35 g, 86%) as a white solid, mp: 107–108 °C (Et_2O/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.22 (5H, m, H13–H17), 7.24 (1H, br d, J = 7.0 Hz, H4), 7.15 (1H, br t, J = 7.7 Hz, H6), 6.98 (1H, br t, J = 7.3 Hz, H5), 6.72 (1H, br d, J = 7.7 Hz, H7), 4.93, 4.91 (2H, AB system, J = 15.8 Hz, H11), 3.87 (1H, dd, J = 8.0, 4.7 Hz, H3), 3.65 (3H, s, H10), 3.13 (1H, dd, J = 16.8, 4.7 Hz, H8A), 2.88 (1H, dd, J = 16.8, 8.0 Hz, H8B); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8 (C2), 171.5 (C9), 143.6 (C7a), 135.9 (C12), 128.8 (C14,C16), 128.3 (C6), 128.2 (C3a), 127.7 (C15), 127.4 (C13,C17), 123.9 (C4), 122.6 (C5), 109.2 (C7), 52.0 (C10), 44.0 (C11), 42.0 (C3), 34.8 (C8); IR ($CHCl_3$) ν_{max} 3032, 2951, 1737, 1712, 1614, 1489, 1467, 1211 cm^{-1}; EIMS m/z (relative intensity) 295 (M$^+$, 100), 235 (74), 158 (12), 91 (79). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.11; H, 5.70; N, 4.76.

4.14. General procedure for the preparation of *N*1,*C*3 dialkylated oxindoles 7a–e

To a solution of the appropriate oxindoles **6a–c** or **8** (4.57 mmol) in acetone (20 mL) was added K_2CO_3 (4.70 g, 34 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was treated with the appropriate alkyl halide MeI (4.6 mL, 73.2 mmol for **6b**,**c** and **8**), EtBr (5.5 mL, 73.2 mmol for **6a**), or BnBr (8.7 mL, 73.2 mmol for **6a**) and heated at reflux for 8 h.

After cooling to room temperature, additional MeI was added (4.6 mL) for **6b**,**c** and **8**, and additional EtBr was added (5.5 mL) for **6a.** The mixtures were heated at reflux for further 8 h. After cooling to room temperature, the acetone was evaporated under reduced pressure and the mixture was diluted with water (40 mL) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL) and the combined organic layers were washed with brine (2 × 25 mL), dried over Na_2SO_4, filtrated, and evaporated to dryness in vacuum. Crudes **7a**–**d** were purified by flash column chromatography on silica gel with EtOAc/hexane 1:3 for **7a**, 1:4 for **7b**,**c**, and 1:5 for **7d**,**e**.

4.15. Methyl 2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate 7a

Prepared from **8** as a yellow oil (0.92 g, 86%).[7]

4.16. Methyl 2-(1-methyl-3-ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetate 7b

Prepared from **6a** as a yellow oil (1.01 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (1H, br t, J = 7.7 Hz, H6), 7.16 (1H, br d, J = 7.3 Hz, H4), 7.04 (1H, br t, J = 7.4 Hz, H5), 6.86 (1H, br d, J = 7.3 Hz, H7), 3.41 (3H, s, H10), 3.25 (3H, s, H11), 3.00, 2.87 (2H, AB system, J = 16.2 Hz, H8), 1.88 (1H, dq, J = 13.2, 7.3 Hz, H12A), 1.80 (1H, dq, J = 13.2, 7.3 Hz, H12B), 0.58 (3H, t, J = 7.3 Hz, H13); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C2), 170.2 (C9), 144.5 (C7a), 130.8 (C3a), 128.1 (C6), 122.4 (C4), 122.2 (C5), 107.8 (C7), 51.4 (C10), 50.1 (C3), 40.8 (C8), 31.0 (C12), 26.1 (C11), 8.0 (C13); IR ($CHCl_3$) ν_{max} 3055, 2966, 2936, 1740, 1715, 1614, 1494 cm^{-1}; EIMS m/z (relative intensity) 247 (M^+, 100), 232 (20), 219 (20), 176 (46), 159 (54), 130 (21). FABHRMS m/z calcd for $C_{14}H_{17}NO_3$: 247.1208, found: 247.1209.

4.17. Methyl 2-(1-methyl-3-benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate 7c

Prepared from **6a** as colorless crystals (1.21 g, 86%), mp: 105–107 °C (EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (1H, td, J = 7.7, 1.5 Hz, H6), 7.11–7.02 (4H, m, H4, H15–H17), 6.99 (1H, td, J = 7.3, 0.7 Hz, H5), 6.80 (2H, dd, J = 8.0, 1.4 Hz, H14, H18), 6.59 (1H, d, J = 7.7 Hz, H7), 3.43 (3H, s, H10), 3.16, 2.96 (2H, AB system, J = 16.7 Hz, H8), 3.03 (2H, s, H12), 2.99 (3H, s, H11); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5 (C2), 170.2 (C9), 144.2 (C7a), 134.9 (C13), 130.3 (C3a), 130.1 (C14,C18), 128.3 (C6), 127.6 (C15,C17), 126.8 (C16), 123.3 (C4), 122.0 (C5), 107.9 (C7), 51.7 (C10), 51.3 (C3), 44.0 (C12), 40.3 (C8), 26.1 (C11); IR ($CHCl_3$) ν_{max} 3057, 3030, 2952, 1740, 1713, 1614 cm^{-1}; EIMS m/z (relative intensity) 309 (M^+, 69), 233 (32), 218 (34), 176 (100), 91 (32). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.69; H, 6.26; N, 4.56.

4.18. Methyl 2-(1-ethyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate 7d

Prepared from **6b** as a yellow oil (1.03 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (1H, td, J = 7.7, 1.4 Hz, H6), 7.20 (1H, dd, J = 7.4, 0.6 Hz, H4), 7.02 (1H, td, J = 7.4, 1.1 Hz, H5), 6.88 (1H, br d, J = 7.7 Hz, H7), 3.86 (1H, dq, J = 14.1, 7.1 Hz, H11A), 3.74 (1H, dq, J = 14.1, 7.1 Hz, H11B), 3.44 (3H, s, H10), 3.02, 2.85 (2H, AB system, J = 16.2 Hz, H8), 1.37 (3H, s, H13), 1.29 (3H, t, J = 7.3 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.4 (C2), 170.1 (C9), 142.5 (C7a), 133.0 (C3a), 128.0 (C6), 122.3 (C4), 122.1 (C5), 108.2 (C7), 51.4 (C10), 45.3 (C3), 41.3 (C8), 34.6 (C11), 24.3 (C13), 12.3 (C12); IR ($CHCl_3$) ν_{max} 3055, 2976, 2952, 1741, 1713, 1613 cm^{-1}; EIMS m/z (relative intensity) 247 (M^+, 97), 232 (20), 204 (28), 188 (19), 174 (100), 146 (19), 130 (17). FABHRMS m/z calcd for $C_{14}H_{17}NO_3$: 247.1208, found: 247.1213.

4.19. Methyl 2-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate 7e

Prepared from **6c** as a yellow oil (1.24 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 7.40–7.22 (5H, m, H13–H17), 7.20 (1H, br dd, J = 7.4, 1.1 Hz, H4), 7.15 (1H, td, J = 7.8, 1.3 Hz, H6), 7.00 (1H, td, J = 7.5, 1.0 Hz, H5), 6.74 (1H, br d, J = 7.7 Hz, H7), 4.97, 4.94 (2H, AB system, J = 15.8 Hz, H11), 3.42 (3H, s, H10), 3.10, 2.91 (2H, AB system, J = 16.3 Hz, H8), 1.44 (3H, s, H18); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.9 (C2), 170.2 (C9), 142.5 (C7a), 136.0 (C12), 132.8 (C3a), 128.6 (C14,C16), 128.0 (C6), 127.4 (C15), 127.3 (C13,C17), 122.4 (C5), 122.2 (C4), 109.1 (C7), 51.5 (C10), 45.5 (C3), 43.9 (C11), 41.2 (C8), 24.8 (C18); IR ($CHCl_3$) ν_{max} 3059, 3032, 2952, 2927, 1740, 1714, 1613 cm^{-1}; EIMS m/z (relative intensity) 309 (M^+, 96), 250 (15), 236 (22), 208 (30), 207 (100), 130 (25), 91 (66). FABHRMS m/z calcd for $C_{19}H_{19}NO_3$: 309.1365, found: 309.1366.

4.20. General procedure for the preparation of 2-oxindoleacetic acids 9a–e

To a solution of the appropriate oxindoles **7a**–**e** (3.24 mmol) in MeOH (12 mL) was added a solution of aqueous NaOH (15%, 3.4 mL) and the mixture was stirred at 50 °C for 1.5 h. After cooling to 0 °C, the mixture was treated with an aqueous solution of HCl (1 M) to pH 1 and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over Na_2SO_4, filtrated, and evaporated to dryness in vacuum. The resultant crude products **9a**–**e** were purified by flash chromatography on silica gel using EtOAc/hexane 2:1 for **9a**,**b**,**d** and 3:2 for **9c**,**e**.

4.21. 2-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 9a

Prepared from **7a** as colorless crystals (0.62 g, 88%), mp: 181–182 °C (EtOAc/hexane). Lit.[2b] 179–180.5 °C.

4.22. 2-(1-Methyl-3-ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 9b

Prepared from **7b** as a brown solid (0.64 g, 85%), mp: 109–110 °C (EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (1H, br s, H10), 7.26 (1H, td, J = 7.7, 1.4 Hz, H6), 7.13 (1H, br d, J = 7.3 Hz, H4), 7.04 (1H, t, J = 7.5, H5), 6.82 (1H, br d, J = 7.7 Hz, H7), 3.17 (3H, s, H11), 2.94, 2.78 (2H, AB system, J = 16.3 Hz, H8), 1.84 (1H, dq, J = 13.7, 7.3 Hz, H12A), 1.76 (1H, dq, J = 13.7, 7.3 Hz, H12B), 0.54 (3H, t, J = 7.5 Hz, H13); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (C2), 174.3 (C9), 144.3 (C7a), 130.9 (C3a), 128.4 (C6), 122.8 (C4), 122.7 (C5), 108.3 (C7), 50.3 (C3), 40.9 (C8), 31.0 (C12), 26.4 (C11), 8.1 (C13); IR (KBr) ν_{max} 3432, 2985, 2931, 1737, 1722, 1674, 1610 cm^{-1}; EIMS m/z (relative intensity) 233 (M^+, 100), 188 (36), 174 (22), 160 (80), 159 (40), 146 (43), 130 (26). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.65; H, 6.51; N, 5.86.

4.23. 2-(1-Methyl-3-benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 9c

Prepared from **7c** as colorless crystals (0.85 g, 89%), mp: 90–91 °C (Et_2O/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.52 (1H, br s, H10), 7.16 (1H, td, J = 7.8, 0.9 Hz, H6), 7.10 (1H, br d, J = 7.3 Hz, H4), 7.07–6.98 (4H, m, H5, H15–H17), 6.73 (2H, br dd, J = 8.0, 1.8 Hz, H14, H18), 6.54 (1H, br d, J = 7.8 Hz, H7), 3.11, 2.89 (2H,

AB system, J = 16.5 Hz, H8), 2.99 (2H, br s, H12), 2.89 (3H, s, H11); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8 (C2), 174.0 (C9), 143.7 (C7a), 134.5 (C13), 129.8 (C3a,C14,C18), 128.2 (C6), 127.4 (C15,C17), 126.7 (C16), 123.1 (C4), 122.2 (C5), 108.0 (C7), 51.0 (C3), 43.7 (C12), 40.0 (C8), 26.0 (C11); IR (KBr) ν_{max} 3436, 3033, 2919, 1733, 1665 cm^{-1}. EIMS m/z (relative intensity) 295 (M^+, 26), 277 (25), 262 (18), 237 (20), 221 (18), 105 (17), 91 (100), 44 (50). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.85; H, 5.82; N, 4.61.

4.24. 2-(1-Ethyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 9d

Prepared from **7d** as a brown solid (0.66 g, 87%), mp: 250 °C decomp. (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.53 (1H, br s, H10), 7.25 (1H, td, J = 7.7, 1.4 Hz, H6), 7.16 (1H, dd, J = 7.4, 0.8 Hz, H4), 7.02 (1H, td, J = 7.7, 1.1 Hz, H5), 6.84 (1H, br d, J = 7.7 Hz, H7), 3.83 (1H, dq, J = 14.3, 7.2 Hz, H11A), 3.63 (1H, dq, J = 14.3, 7.2 Hz, H11B), 2.97, 2.78 (2H, AB system, J = 16.7 Hz, H8), 1.31 (3H, s, H13), 1.18 (3H, t, J = 7.4 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.7 (C2), 174.7 (C9), 142.2 (C7a), 132.9 (C3a), 128.1 (C6), 122.4 (C5), 122.3 (C4), 108.4 (C7), 45.1 (C3), 41.2 (C8), 34.6 (C11), 24.0 (C13), 11.9 (C12); IR ($CHCl_3$) ν_{max} 3056, 2978, 2935, 2876, 1712, 1612 cm^{-1}; EIMS m/z (relative intensity) 233 (M^+, 100), 188 (53), 174 (48), 146 (25), 130 (16). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.73; H, 6.56; N, 5.72.

4.25. 2-(1-Benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid 9e

Prepared from **7e** as colorless crystals (0.84 g, 88%), mp: 154–155 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.59 (1H, br s, H10), 7.30- 7.22 (5H, m, H13–H17), 7.17 (1H, dd, J = 7.3, 0.7 Hz, H4), 7.12 (1H, td, J = 7.7, 1.2 Hz, H6), 6.99 (1H, td, J = 7.5, 1.0 Hz, H5), 6.67 (1H, br d, J = 7.5 Hz, H7), 4.98, 4.83 (2H, AB system, J = 15.8 Hz, H11), 3.08, 2.88 (2H, AB system, J = 16.8 Hz, H8), 1.40 (3H, s, H18); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0 (C2), 175.0 (C9), 142.3 (C7a), 135.7 (C12), 132.6 (C3a), 128.7 (C14,C16), 128.1 (C6), 127.5 (C15), 127.1 (C13,C17), 122.6 (C5), 122.2 (C4), 109.5 (C7), 45.3 (C3), 43.9 (C11), 40.9 (C8), 24.9 (C18); IR (KBr) ν_{max} 3420, 3208, 3058, 2971, 2925, 2909, 1742, 1677, 1614, 1494, 1469 cm^{-1}; EIMS m/z (relative intensity) 295 (M^+, 100), 236 (17), 222 (20), 207 (25), 130 (15), 91 (49). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.88; H, 5.63; N, 4.64.

4.26. General procedure for the preparation of diastereomeric amides 11a–e

A cooled solution (0 °C) of the appropriate acids **9a–e** (2.36 mmol) in THF (20 mL) was treated dropwise with Et_3N (0.32 mL, 2.3 mmol). The mixture was stirred for 15 min and $ClCO_2Et$ (0.32 mL, 3.3 mmol) was added dropwise and stirred for additional 1 h. After cooling to −60 °C, (*R*)- or (*S*)-FEA (0.64 mL, 5.0 mmol) was added dropwise and the reaction mixture was stirred for 1 h. After warming to room temperature, EtOAc was added (20 mL) and the organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness in vacuum. The crude products **11a–e** were purified by flash column chromatography on silica gel with EtOAc/hexane 2:3 for **11a**, **11b**, and **11d**, and with EtOAc/hexane 1:2 for **11c** and **11e**.

4.27. (3*R*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl) acetamide (3*R*,11*R*-11a)

Prepared from **9a** as colorless crystals (0.32 g, 42%), mp: 157–159 °C (EtOAc/hexane). $[\alpha]_D^{20} = +87.3$ (c 1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.19 (5H, m, H4, H6, H15–H17), 7.15 (2H, br d, J = 7.7 Hz, H14, H18), 7.05 (1H, td, J = 7.5, 1.0 Hz, H5), 6.79 (1H, br d, J = 7.7 Hz, H7), 6.64 (1H, br d, J = 8.0 Hz, H10), 4.96 (1H, q, J = 7.3 Hz, H11), 3.06 (3H, s, H19), 2.77, 2.64 (2H, AB system, J = 14.3 Hz, H8), 1.42 (3H, s, H20), 1.33 (3H, d, J = 7.0 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3 (C2), 167.8 (C9), 143.0 (C13), 142.6 (C7a), 132.9 (C3a), 128.4 (C15,C17), 128.0 (C6), 127.0 (C16), 126.1 (C14,C18), 122.8 (C4), 122.7 (C5), 108.2 (C7), 48.2 (C11), 46.3 (C3), 43.8 (C8), 26.1 (C19), 23.7 (C20), 21.4 (C12); IR ($CHCl_3$) ν_{max} 3300, 3059, 2970, 2927, 1701, 1652, 1614, 1542, 1471 cm^{-1}. EIMS m/z (relative intensity) 322 (M^+, 17), 174 (31), 160 (21), 130 (10), 120 (100). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.23; H, 6.93; N, 8.49.

4.28. (3*S*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl) acetamide (3*S*,11*R*-11a)

Prepared from **9a** as colorless crystals (0.32 g, 42%), mp: 126–127 °C (EtOH). $[\alpha]_D^{20} = +160.2$ (c 1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.18 (5H, m, H4, H6, H15–H17), 7.14 (2H, d, J = 7.3 Hz, H14, H18), 7.07 (1H, td, J = 7.5, 0.8 Hz, H5), 6.84 (1H, d, J = 8.0 Hz, H7), 6.67 (1H, br d, J = 6.2 Hz, H10), 4.93 (1H, q, J = 7.0 Hz, H11), 3.22 (3H, s, H19), 2.80, 2.66 (2H, AB system, J = 14.6 Hz, H8), 1.36 (3H, s, H20), 1.33 (3H, d, J = 7.0 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5 (C2), 167.9 (C9), 142.9 (C13), 142.7 (C7a), 133.0 (C3a), 128.4 (C15,C17), 128.1 (C6), 127.0 (C16), 126.0 (C14,C18), 122.7 (C5), 122.6 (C4), 108.2 (C7), 48.4 (C11), 46.3 (C3), 43.9 (C8), 26.3 (C19), 23.6 (C20), 21.6 (C12); IR ($CHCl_3$) ν_{max} 3301, 3059, 2970, 2928, 1704, 1651, 1614, 1471 cm^{-1}; EIMS m/z (relative intensity) 322 (M^+, 17), 174 (10), 130 (11), 120 (100), 105 (11). FABHRMS m/z calcd for $C_{20}H_{23}N_2O_2$ ($M+H^+$): 323.1760, found: 323.1760.

4.29. (3*S*,1′*S*)-*N*-(1′-Phenylethyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl) acetamide (3*S*,11*S*-11a)

Prepared from **9a** as colorless crystals (0.31 g, 41%), mp: 157–158 °C (EtOH). $[\alpha]_D^{20} = -87.9$ (c 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.19 (5H, m, H4, H6, H15–H17), 7.15 (2H, br d, J = 7.2 Hz, H14, H18), 7.05 (1H, td, J = 7.5, 0.7 Hz, H5), 6.79 (1H, br d, J = 7.5 Hz, H7), 6.68 (1H, br d, J = 7.6 Hz, H10), 4.94 (1H, br q, J = 7.2 Hz, H11), 3.06 (3H, s, H19), 2.77, 2.64 (2H, AB system, J = 14.3 Hz, H8), 1.42 (3H, s, H20), 1.32 (3H, d, J = 6.9 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3 (C2), 167.8 (C9), 143.0 (C13), 142.6 (C7a), 132.9 (C3a), 128.4 (C15,C17), 128.0 (C6), 127.0 (C16), 126.0 (C14,C18), 122.8 (C4), 122.6 (C5), 108.2 (C7), 48.2 (C11), 46.3 (C3), 43.8 (C8), 26.1 (C19), 23.7 (C20), 21.4 (C12). IR ($CHCl_3$) ν_{max} 3301, 3059, 3029, 2970, 2927, 2870, 1702, 1651, 1614 cm^{-1}; EIMS m/z (relative intensity) 322 (M^+, 16), 174 (28), 160 (21), 130 (9), 120 (100). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.10; H, 6.89; N, 8.59.

4.30. (3*R*,1′*S*)-*N*-(1′-Phenylethyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl) acetamide (3*R*,11*S*-11a)

Prepared from **9a** as colorless crystals (0.32 g, 42%), mp: 126–127 °C (EtOAc/hexane). $[\alpha]_D^{20} = -159.5$ (c 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.20 (5H, m, H4, H6, H15–H17), 7.15 (2H, d, J = 7.5 Hz, H14, H18), 7.07 (1H, td, J = 7.5, 0.9 Hz, H5), 6.84 (1H, br d, J = 7.6 Hz, H7), 6.64 (1H, br d, J = 7.8 Hz, H10), 4.94 (1H, q, J = 7.2 Hz, H11), 3.22 (3H, s, H19), 2.80, 2.66 (2H, AB system, J = 14.6 Hz, H8), 1.36 (3H, s, H20), 1.33 (3H, d, J = 6.9 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.5 (C2), 167.9 (C9), 142.9 (C13), 142.8 (C7a), 133.1 (C3a), 128.4 (C15,C17), 128.1 (C6), 127.0 (C16), 126.0 (C14,C18), 122.8 (C5), 122.7 (C4), 108.2 (C7), 48.4 (C11), 46.3 (C3), 44.0 (C8), 26.3 (C19), 23.6 (C20), 21.6 (C12); IR

($CHCl_3$) ν_{max} 3300, 3059, 2969, 2925, 1702, 1652, 1614 cm^{-1}; EIMS *m/z* (relative intensity) 322 (M^+, 17), 174 (25), 160 (18), 120 (100). FABHRMS *m/z* calcd for $C_{20}H_{23}N_2O_2$ ($M+H^+$): 323.1760, found: 323.1753.

4.31. (3*R*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-methyl-3-ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide (3*R*,11*R*-11b)

Prepared from **9b** as colorless crystals (Et_2O/hexane) (0.34 g, 43%), mp: 131–132 °C (Et_2O/hexane). $[\alpha]_D^{20} = +73.0$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.18 (5H, m, H4, H6, H15–H17), 7.12 (2H, br dd, *J* = 8.3, 1.6 Hz, H14, H18), 7.06 (1H, td, *J* = 7.5, 1.0 Hz, H5), 6.78 (1H, br d, *J* = 7.9 Hz, H7), 6.50 (1H, br d, *J* = 7.0 Hz, H10), 4.92 (1H, br q, *J* = 7.3 Hz, H11), 3.03 (3H, s, H19), 2.79, 2.64 (2H, AB system, *J* = 14.2 Hz, H8), 1.92 (1H, dq, *J* = 13.6, 7.3 Hz, H20A), 1.85 (1H, dq, *J* = 13.6, 7.3 Hz, H20B), 1.30 (3H, br d, *J* = 7.0 Hz, H12), 0.57 (3H, t, *J* = 7.4 Hz, H21); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.7 (C2), 167.8 (C9), 143.6 (C7a), 143.0 (C13), 130.7 (C3a), 128.4 (C15,C17), 128.0 (C6), 127.0 (C16), 126.1 (C14,C18), 123.1 (C4), 122.6 (C5), 108.0 (C7), 51.3 (C3), 48.1 (C11), 43.3 (C8), 30.7 (C20), 25.9 (C19), 21.3 (C12), 8.1 (C21); IR ($CHCl_3$) ν_{max} 3303, 3059, 3030, 2969, 2932, 2878, 1699, 1648 cm^{-1}; EIMS *m/z* (relative intensity) 336 (M^+, 20), 321 (8), 200 (21), 188 (28), 146 (21), 120 (100), 105 (16). FABHRMS *m/z* calcd for $C_{21}H_{25}N_2O_2$ ($M+H^+$): 337.1916, found: 337.1909.

4.32. (3*S*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-methyl-3-ethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide [(3*S*,11*R*-11b)]

Prepared from **9b** as colorless crystals (0.33 g, 42%), mp: 111–112 °C (Et_2O/hexane). $[\alpha]_D^{20} = +143.1$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.17 (5H, m, H4, H6, H15–H17), 7.12 (2H, br dd, *J* = 8.0, 1.8 Hz, H14, H18), 7.07 (1H, td, *J* = 7.5, 1.0 Hz, H5), 6.83 (1H, br d, *J* = 7.8 Hz, H7), 6.47 (1H, br d, *J* = 7.8 Hz, H10), 4.91 (1H, q, *J* = 7.0 Hz, H11), 3.22 (3H, s, H19), 2.82, 2.65 (2H, AB system, *J* = 14.4 Hz, H8), 1.89 (1H, dq, *J* = 13.5, 7.3 Hz, H20A), 1.79 (1H, dq, *J* = 13.5, 7.3 Hz, H20B), 1.30 (3H, d, *J* = 6.9 Hz, H12), 0.56 (3H, t, *J* = 7.3 Hz, H21); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8 (C2), 167.8 (C9), 143.7 (C7a), 142.9 (C13), 130.9 (C3a), 128.4 (C15,C17), 128.1 (C6), 127.0 (C16), 126.0 (C14,C18), 123.0 (C4), 122.6 (C5), 108.0 (C7), 51.2 (C3), 48.3 (C11), 43.5 (C8), 30.6 (C20), 26.1 (C19), 21.5 (C12), 8.1 (C21); IR ($CHCl_3$) ν_{max} 3307, 3058, 3029, 2968, 2932, 1702, 1651 cm^{-1}; EIMS *m/z* (relative intensity) 336 (M^+, 24), 321 (10) 200 (24), 188 (33), 146 (21), 120 (100). FABHRMS *m/z* calcd for $C_{21}H_{25}N_2O_2$ ($M+H^+$): 337.1916, found: 337.1912.

4.33. (3*R*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-methyl-3-benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide (3*R*,11*R*-11c)

Prepared from **9c** as a white solid (0.39 g, 41%), mp: 137–138 °C (EtOAc/hexane). $[\alpha]_D^{20} = +29.1$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.14 (5H, m, H4, H6, H16, H23, H25), 7.11 (2H, br dd, *J* = 7.8, 1.8 Hz, H14, H18), 7.08–6.99 (5H, m, H5, H15, H17, H21, H24), 6.77 (2H, br dd, *J* = 7.8, 1.7 Hz, H22, H26), 6.51 (1H, br d, *J* = 7.8 Hz, H7), 6.41 (1H, br d, *J* = 7.6 Hz, H10), 4.96 (1H, q, *J* = 7.0 Hz, H11), 3.13, 3.09 (2H, AB system, *J* = 12.9 Hz, H20), 2.96, 2.76 (2H, AB system, *J* = 14.3 Hz, H8), 2.76 (3H, s, H19), 1.35 (3H, d, *J* = 6.9 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0 (C2), 167.7 (C9), 143.2 (C7a), 143.0 (C13), 134.9 (C21), 130.0 (C3a), 129.9 (C22, C26), 128.5 (C15,C17), 128.2 (C6), 127.4 (C23,C25), 127.1 (C16), 126.7 (C24), 126.1 (C14,C18), 123.9 (C4), 122.4 (C5), 108.0 (C7), 52.4 (C3), 48.3 (C11), 43.8 (C20), 42.8 (C8), 25.7 (C19), 21.4 (C12); IR ($CHCl_3$) ν_{max} 3301, 3060, 3030, 2972, 2927, 1698, 1649 cm^{-1}; EIMS *m/z* (relative intensity) 398 (M^+, 14), 321 (13), 276 (29), 236 (100), 160 (55), 105 (32). FABHRMS *m/z* calcd for $C_{26}H_{27}N_2O_2$ ($M+H^+$): 399.2073, found: 399.2066.

4.34. (3*S*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-methyl-3-benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide (3*S*,11*R*-11c)

Prepared from **9c** as colorless crystals (0.40 g, 42%), mp: 182–183 °C (CH_2Cl_2/hexane). $[\alpha]_D^{20} = +177.7$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–6.98 (11H, m, H4–H6, H14–H18, H23–H25), 6.74 (2H, br dd, *J* = 7.7, 1.3 Hz, H22, H26), 6.64 (1H, br d, *J* = 8.1 Hz, H10), 6.56 (1H, d, *J* = 7.8 Hz, H7), 4.94 (1H, q, *J* = 7.0 Hz, H11), 3.06, 3.03 (2H, AB system, *J* = 12.9 Hz, H20), 2.95 (3H, s, H19), 2.95, 2.76 (2H, AB system, *J* = 14.5 Hz, H8), 1.32 (3H, d, *J* = 6.9 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0 (C2), 167.7 (C9), 143.3 (C7a), 142.9 (C13), 134.8 (C21), 130.1 (C3a), 129.8 (C22, C26), 128.4 (C15,C17), 128.2 (C6), 127.4 (C23,C25), 127.0 (C16), 126.6 (C24), 126.0 (C14,C18), 123.7 (C4), 122.2 (C5), 107.9 (C7), 52.1 (C3), 48.3 (C11), 43.4 (C20), 42.7 (C8), 25.9 (C19), 21.5 (C12); IR ($CHCl_3$) ν_{max} cm^{-1} 3288, 3061, 3030, 2959, 2925, 2854, 1702, 1648; EIMS *m/z* (relative intensity) 398 (M^+, 17), 277 (14), 236 (100), 160 (67), 120 (34), 105 (37). FABHRMS *m/z* calcd for $C_{26}H_{27}N_2O_2$ ($M+H^+$): 399.2073, found: 399.2072.

4.35. (3*R*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-ethyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide (3*R*,11*R*-11d)

Prepared from **9d** as colorless crystals (0.33 g, 41%), mp: 126–127 °C (Et_2O/hexane). $[\alpha]_D^{20} = +74.8$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.19 (5H, m, H4, H6, H15–H17), 7.17 (2H, br dd, *J* = 7.2, 2.2 Hz, H14, H18), 7.04 (1H, td, *J* = 7.6, 1.0 Hz, H5), 6.83 (1H, dd, *J* = 8.5, 1.2 Hz, H7), 6.68 (1H, br d, *J* = 7.3 Hz, H10), 4.98 (1H, q, *J* = 7.0 Hz, H11), 3.73 (1H, dq, *J* = 14.1, 7.2 Hz, H19A), 3.58 (1H, dq, *J* = 14.2, 7.2 Hz, H19B), 2.76, 2.63 (2H, AB system, *J* = 14.4 Hz, H8), 1.43 (3H, s, H21), 1.35 (3H, d, *J* = 6.9 Hz, H12), 1.20 (3H, t, *J* = 7.2 Hz, H20); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0 (C2), 167.9 (C9), 143.1 (C13), 141.7 (C7a), 133.3 (C3a), 128.4 (C15,C17), 128.0 (C6), 127.0 (C16), 126.1 (C14,C18), 123.1 (C4), 122.6 (C5), 108.4 (C7), 48.4 (C11), 46.2 (C3), 43.8 (C8), 34.6 (C19), 23.6 (C21), 21.5 (C12), 12.5 (C20); IR ($CHCl_3$) ν_{max} 3310, 3059, 3030, 2973, 2928, 1698, 1652 cm^{-1}; EIMS *m/z* (relative intensity) 336 (M^+, 23), 188 (33), 174 (21), 128 (11), 120 (100). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.90; H, 7.18; N, 8.20.

4.36. (3*S*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-ethyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide (3*S*,11*R*-11d)

Prepared from **9d** as colorless crystals (0.33 g, 41%), mp: 152–153 °C (Et_2O/hexane). $[\alpha]_D^{20} = +145.8$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.20 (5H, m, H4, H6, H15–H17), 7.17 (2H, br dd, *J* = 7.3, 1.8 Hz, H14, H18), 7.06 (1H, td, *J* = 7.4, 0.9 Hz, H5), 6.86 (1H, br d, *J* = 7.6 Hz, H7), 6.71 (1H, br d, *J* = 7.6 Hz, H10), 4.96 (1H, q, *J* = 7.0 Hz, H11), 3.82 (1H, dq, *J* = 14.1, 7.3 Hz, H19A), 3.73 (1H, dq, *J* = 14.1, 7.3 Hz, H19B), 2.78, 2.65 (2H, AB system, *J* = 14.6 Hz, H8), 1.36 (3H, s, H21), 1.35 (3H, d, *J* = 7.9 Hz, H12), 1.27 (3H, t, *J* = 7.2 Hz, H20); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.1 (C2), 167.9 (C9), 143.0 (C13), 141.8 (C7a), 133.4 (C3a), 128.4 (C15,C17), 128.0 (C6), 127.0 (C16), 126.1 (C14,C18), 123.0 (C4), 122.5 (C5), 108.4 (C7), 48.5 (C11), 46.2 (C3), 43.9 (C8), 34.7 (C19), 23.6 (C21), 21.7 (C12), 12.6 (C20); IR ($CHCl_3$) ν_{max} 3307, 3057, 3030, 2968, 2932, 2878, 1704, 1651 cm^{-1}; EIMS *m/z* (relative intensity) 336 (M^+, 24), 321 (10), 200 (23), 188 (33), 146 (22), 120 (100), 105 (16). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.74; H, 7.31; N, 8.27.

4.37. (3*R*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetamide (3*R*,11*R*-11e)

Prepared from **9e** as a yellow solid on standing (0.39 g, 41%), mp: 64–65 °C. $[\alpha]_D^{20} = +66.7$ (*c* 1, EtOH). ^1H NMR (300 MHz, $CDCl_3$):

Table 5
Crystal data for (3*R*,11*R*)-**11a**, (3*S*,11*R*)-**11a**, (3*S*, 11*R*)-**11b**, and (3*S*, 11*R*)-**11c**

	(3*R*,11*R*)-**11a**	(3*S*,11*R*)-**11a**	(3*S*,11*R*)-**11b**	(3*S*,11*R*)-**11c**
Empirical formula	$C_{20}H_{22}N_2O_2$	$C_{20}H_{22}N_2O_2H_2O$	$C_{21}H_{24}N_2O_2$	$C_{26}H_{26}N_2O_2$
Formula weight	322.40	322.40 + 18.02	336.42	398.49
Crystal size (mm)	0.30 × 0.26 × 0.22	0.38 × 0.28 × 0.70	0.38 × 0.34 × 0.34	0.30 × 0.12 × 0.10
Wavelength (Å)	1.54184	0.71073	1.54184	0.71073
Crystal system, space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Tetragonal, $P4_32_12$
Unit cell dimensions				
a (Å)	8.4402(8)	12.7641(6)	12.421(3)	10.235(1)
b (Å)	10.323(3)	16.7665(9)	16.391(3)	10.235(1)
c (Å)	21.631(2)	17.6059(8)	18.089(3)	45.036(9)
Volume (Å$^{3)}$	1884.7(5)	3767.8(3)	3682.9(13)	4717.9(13)
Z, *Z*′, Calculated density (mg/mm^3)	4, 1, 1.136	4, 2, 1.168	4, 2, 1.213	8, 1, 1.122
Absorption coefficient (mm^{-1})	0.587	0.077	0.621	0.071
F(0 0 0)	688	1416	1440	1696
Theta range for data collection (°)	4.09–59.93	4.28–72.22	4.89–60.01	2.96–27.47
Limiting indices	$0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 11$, $2 \leqslant l \leqslant 23$	$-15 \leqslant h \leqslant 15$, $-17 \leqslant k \leqslant 20$, $-21 \leqslant l \leqslant 21$	$0 \leqslant h \leqslant 13$, $0 \leqslant k \leqslant 18$, $2 \leqslant l \leqslant 20$	$-13 \leqslant h \leqslant 12$, $-13 \leqslant k \leqslant 12$, $-57 \leqslant l \leqslant 49$
Reflections collected/unique	1462/1445 [*R*(int) = 0.0001]	25,267/7417 [*R*(int) = 0.0645]	2774/2661 [*R*(int) = 0.0001]	21,984/5214 [*R*(int) = 0.0001]
Completeness to theta = 59.93	88.7%	99.7%	86.4%	96.9%
Data/restraints/parameters	1365/0/226	3212/0/459	2522/0/467	2314/0/276
Goodness-of-fit on F^2	1.108	0.773	1.029	0.990
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 3.2%, wR_2 = 9.5%	R_1 = 3.7%, wR_2 = 6.4%	R_1 = 3.2%, wR_2 = 8.7%	R_1 = 5.5%, wR_2 = 10.3%
R indices (all data)	R_1 = 3.4%, wR_2 = 9.6%	R_1 = 12.4%, wR_2 = 7.9%	R_1 = 3.5%, wR_2 = 8.9%	R_1 = 17.6%, wR_2 = 12.8%
Largest diff. peak and hole	0.112 and −0.092 e A^{-3}	0.108 and −0.118 e Å^{-3}	0.093 and −0.110 e A^{-3}	0.123 and −0.091 e A^{-3}
CCDC Nos.	750097	750098	750200	750201

δ 7.34–7.22 (9H, m, H4, H15–H17, H21–H25), 7.20 (2H, br dd, J = 7.2, 1.9 Hz, H14, H18), 7.14 (1H, td, J = 7.5, 0.8 Hz, H6), 7.00 (1H, br t, J = 7.3 Hz, H5), 6.67 (1H, br d, J = 7.8 Hz, H7), 6.55 (1H, br d, J = 7.9 Hz, H10), 4.99 (1H, q, J = 8.0 Hz, H11), 4.97, 4.57 (2H, AB system, J = 15.9 Hz, H19), 2.82, 2.70 (2H, AB system, J = 14.5 Hz, H8), 1.50 (3H, s, H26), 1.33 (3H, d, J = 6.9 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6 (C2), 167.9 (C9), 143.1 (C13), 141.8 (C7a), 135.7 (C20), 133.1 (C3a), 128.7 (C22,C24), 128.5 (C15,C17), 128.0 (C6), 127.5 (C23), 127.1 (C16), 127.1 (C21,C25), 126.2 (C14,C18), 122.9 (C4), 122.8 (C5), 109.3 (C7), 48.4 (C11), 46.3 (C3), 43.9 (C8), 43.6 (C19), 23.9 (C26), 21.5 (C12); IR ($CHCl_3$) ν_{max} 3318, 3061, 3030, 2970, 2927, 2870, 1702, 1649 cm^{-1}; EIMS *m/z* (relative intensity) 398 (M^+, 20), 250 (24), 120 (100), 91 (56). FABHRMS *m/z* calcd for $C_{26}H_{26}N_2O_2$: 398.1993, found: 398.1994.

Table 6
Crystal data for (3*R*,11*R*)-**11d**, (3*S*,11*R*)-**11d**, (3*S*,11*S*)-**11a**, (3*R*,11*S*)-**11a**

	(3*R*,11*R*)-**11d**	(3*S*,11*R*)-**11d**	(3*S*,11*S*)-**11a**	(3*R*,11*S*)-**11a**
Empirical formula	$C_{21}H_{24}N_2O_2$	$C_{21}H_{24}N_2O_2$	$C_{20}H_{22}N_2O_2$	$C_{20}H_{22}N_2O_2{\cdot}H_2O$
Formula weight	336.42	336.42	322.40	322.40 + 18.02
Crystal size (mm)	0.42 × 0.40 × 0.36	0.40 × 0.34 × 0.34	0.40 × 0.34 × 0.30	0.36 × 0.32 × 0.63
Wavelength (Å)	1.54184	1.54184	1.54184	0.71073
Crystal system, space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$
Unit cell dimensions				
a (Å)	8.639(1)	10.179(4)	8.439(1)	12.7741(7)
b (Å)	10.190(5)	18.122(9)	10.325(3)	16.7934(8)
c (Å)	22.383(3)	20.578(4)	21.636(2)	17.6281(9)
Volume (Å^3)	1970.4(11)	3796(3)	1885.2(6)	3781.6(3)
Z, *Z*′, Calculated density (mg/mm^3)	4, 1, 1.134	4, 2, 1.177	4, 1, 1.136	4, 2, 1.164
Absorption coefficient (mm^{-1})	0.580	0.602	0.587	0.077
F(0 0 0)	720	1440	688	1416
Theta range for data collection (°)	3.95–59.91	4.30–60.00	4.09–59.91	2.31–25.98
Limiting indices	$0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 11$, $2 \leqslant l \leqslant 24$	$0 \leqslant h \leqslant 11$, $0 \leqslant k \leqslant 20$, $2 \leqslant l \leqslant 22$	$0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 11$, $2 \leqslant l \leqslant 23$	$-15 \leqslant h \leqslant 15$, $0 \leqslant k \leqslant 20$, $0 \leqslant l \leqslant 21$
Reflections collected/unique	1589/1514 [*R*(int) = 0.0001]	2804/2790 [*R*(int) = 0.0001]	1462/1441 [*R*(int) = 0.0001]	25,278/7400 [*R*(int) = 0.0001]
Completeness to theta = 59.93	89.1%	87.5%	88.4%	99.7%
Data/restraints/parameters	1350/0/234	2464/0/467	1392/0/226	3732/0/465
Goodness-of-fit on F^2	0.993	1.039	1.098	0.828
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 5.8%, wR_2 = 16.8%	R_1 = 3.2%, wR_2 = 8.4%	R_1 = 5.0%, wR_2 = 14.8%	R_1 = 3.8%, wR_2 = 8.0%
R indices (all data)	R_1 = 6.4%, wR_2 = 17.3%	R_1 = 3.9%, wR_2 = 8.7%	R_1 = 5.2%, wR_2 = 15.5%	R_1 = 9.0%, wR_2 = 9.5%
Largest diff. peak and hole	0.219 and −0.228 e A^{-3}	0.096 and −0.100 e A^{-3}	0.144 and −0.146 e A^{-3}	0.133 and −0.162 e A^{-3}
CCDC Nos.	950202	950203	750099	750100

4.38. (3*S*,1′*R*)-*N*-(1′-Phenylethyl)-2-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl) acetamide (3*S*,11*R*-11e)

Prepared from **9e** as a white solid (0.38 g, 40%), mp: 125–126 °C. $[\alpha]_D^{20} = +146.3$ (*c* 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.18 (9H, m, H4, H15–H17, H21–H25), 7.14 (2H, br dd, *J* = 7.8, 1.8 Hz, H14, H18), 7.14 (1H, td, *J* = 7.8, 1,3 Hz, H6), 7.01 (1H, td, *J* = 7.6, 1.0 Hz, H5), 6.69 (1H, br d, *J* = 7.5 Hz, H7), 6.57 (1H, br d, *J* = 7.8 Hz, H10), 5.06, 4.80 (2H, AB system, *J* = 15.8 Hz, H19), 4.97 (1H, q, *J* = 7.0 Hz, H11), 2.85, 2.71 (2H, AB system, *J* = 14.5 Hz, H8), 1.43 (3H, s, H26), 1.35 (3H, d, *J* = 6.9 Hz, H12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6 (C2), 167.9 (C9), 143.0 (C13), 141.9 (C7a), 135.7 (C20), 133.1 (C3a), 128.7 (C22,C24), 128.4 (C15,C17), 128.0 (C6), 127.5 (C23), 127.1 (C21,C25), 127.0 (C16), 126.1 (C14,C18), 122.8 (C4), 122.7 (C5), 109.3 (C7), 48.5 (C11), 46.3 (C3), 43.9 (C8), 43.7 (C19), 24.0 (C26), 21.6 (C12); IR ($CHCl_3$) ν_{max} 3316, 3060, 3029, 3005, 2971, 2927, 1702, 1656 cm^{-1}; EIMS *m*/*z* (relative intensity) 398 (M^+, 36), 250 (30), 120 (100), 105 (11), 91 (48), 77 (11). FABHRMS *m*/*z* calcd for $C_{26}H_{27}N_2O_2$ ($M+H^+$): 399.2073, found: 399.2064.

4.39. X-ray diffraction analyses

The studies for (3*S*,11*R*)-**11a,** (3*R*,11*S*)-**11a**, and (3*S*, 11*R*)-**11c** were carried out on a Bruker Smart 6000 CCD diffractometer using Mo Kα radiation (λ = 0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. These data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. An empirical absorption correction was applied. Data collections for (3*R*,11*R*)-**11a**, (3*S*,11*S*)-**11a**, (3*S*,11*R*)-**11b**, (3*R*,11*R*)-**11d**, and (3*S*,11*R*)-**11d** were done on a Bruker-Nonius CAD4 diffractometer using Cu Kα radiation (λ = 1.54184 Å). The structures for (3*S*,11*R*)-**11b** and (3*S*,11*R*)-**11c** were solved by direct methods using the SHELXS-97[22] program while the remaining compounds were solved using the SIR2004[23] software. Both programs are included in the WINGX v1.6 package.[24] The structural refinement was 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. Data for (3*S*,11*R*)-**11b** show a disordered methyl group.[25] Atomic coordinates, bond lengths, bond angles and anisotropic thermal parameters are in deposit at the Cambridge Crystallographic Data Center. Tables 5 and 6 summarize the relevant data of the X-ray procedures.

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References

1. (a) Kinashi, H.; Suzuki, Y.; Takeuchi, S.; Kawarada, A. *Agric. Biol. Chem.* **1976**, *40*, 2465–2470; (b) Suzuki, Y.; Kinashi, H.; Takeuchi, S.; Kawarada, A. *Phytochemistry* **1977**, *16*, 635–637; (c) Ohmoto, T.; Yamaguchi, K.; Ikeda, K. *Chem. Pharm. Bull.* **1988**, *36*, 578–581; (d) Dekker, T. G.; Fourie, T. G.; Matthee, E.; Snyckers, F. O. *Phytochemistry* **1987**, *26*, 1845–1846; (e) Monde, K.; Sasaki, K.; Shirata, A.; Takasugi, M. *Phytochemistry* **1991**, *30*, 2915–2917; (f) Ubaidullaev, K. A.; Shakirov, R.; Yunosov, S. Y. *Khim. Prir. Soedin* **1976**, *12*, 553–554; (g) Zhang, H.-p.; Kamano, Y.; Ichiharra, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523–5528; (h) Fréchard, A.; Fabre, N.; Péan, C.; Montaut, S.; Fauvel, M.-T.; Rollin, P.; Fourasté, I. *Tetrahedron Lett.* **2001**, *42*, 9015–9017; (i) Zhou, L.; Yang, J.-S.; Wu, X.; Zou, J.-H.; Xu, X.-D.; Tu, G.-Z. *Heterocycles* **2005**, *65*, 1409–1414; (j) Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Frye, S. V.; Gampe, R. T.; Harris, J. P. A.; Hassell, A.; Holmes, W. D.; Hunter, R. N.; Lackey, K. E.; Lovejoy, B.; Luzzio, M. J.; Montana, V.; Rocque, W. J.; Rusnak, D.; Shewchuk, L.; Veal, J. M.; Walker, D. H.; Kuyper, L. F. *J. Med. Chem.* **2001**, *44*, 4339–4358; (k) Woodard, C. L.; Li, Z.; Katchcart, A. K.; Terrell, J.; Gerena, L.; Lopez-Sanchez, M.; Kyle, D. E.; Bhattacharjee, A. K.; Nichols, D. A.; Ellis, W.; Prigge, S. T.; Geyer, J. A.; Waters, N. C. *J. Med. Chem.* **2003**, *46*, 3877–3882; (l) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641–4649; (m) Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *J. Org. Chem.* **2006**, *71*, 8559–8564.
2. (a) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Trends Heterocycl. Chem.* **1999**, *6*, 111–124. and references cited therein; (b) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3047–3051; (c) Yu, Q.-s.; Luo, W.-m.; Li, Y.-q. *Heterocycles* **1993**, *36*, 1279–1285; (d) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363–370; (e) Pei, X.-F.; Bi, S. *Heterocycles* **1994**, *39*, 357–360; (f) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503; (g) Morales-Ríos, M. S.; Suárez-Castillo, O. R. *Nat. Prod. Commun.* **2008**, *3*, 629–642. and references cited therein.
3. Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117. and references cited therein.
4. (a) Hoye, T. R.; Koltun, D. O. *J. Am. Chem. Soc.* **1998**, *120*, 4638–4643; (b) Hoye, T. R.; Hamad, A.-S. S.; Koltun, D. O.; Tennakoon, M. A. *Tetrahedron Lett.* **2000**, *41*, 2289–2293; (c) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397–404.
5. Avalos, M.; Babiano, R.; Barneto, J. L.; Cintas, P.; Clemente, F. R.; Jiménez, J. L.; Palacios, C. *J. Org. Chem.* **2003**, *68*, 1834–1842.
6. Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron* **2006**, *62*, 3040–3051.
7. Osman, F. H.; El-Samahy, F. A. *Phosphorus, Sulfur Silicon* **1998**, *134/135*, 437–446.
8. Morales-Ríos, M. S.; Rivera-Becerril, E.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2493–2499.
9. (a) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 881–882; (b) Luo, Y.-l.; Yu, Q.-s.; Chrisey, L.; Brossi, A. *Heterocycles* **1990**, *31*, 283–287; (c) Akai, S.; Tsujino, T.; Akiyama, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478–2486; (d) Yamazaki, S.; Yamamoto, M.; Morikawa, S. *Heterocycles* **2006**, *67*, 269–289.
10. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
11. (a) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 490–519; (b) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 520–552; (c) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 553–586; (d) Halgren, T.; Nachbar, R. B. *J. Comput. Chem.* **1996**, *17*, 587–615; (e) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 616–641.
12. As implemented in the computer package *Spartan′04*, Windows v 1.0.1; Wavefunction Inc. Irvine, CA, USA, 2004.
13. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. Ab Initio Molecular Orbital Theory; Wiley: New York, 1986.
14. (a) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can. J. Chem.* **1992**, *70*, 560–571; (b) Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280–1303.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Wallingford CT, 2004.
16. Monte Carlo searching protocol was applied to amides (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a** using the MMFF94 molecular mechanics force field method as implemented in the SPARTAN04 program. This protocol gave 14 conformers within 8.5 kcal/mol from the global minimum energy conformation for both diastereomeric amides. These structures were submitted to geometry optimization using DFT calculations at the B3LYP/6-31G(d) level of theory from which 9 conformers account for 99.8% in the case of amide (3*R*,11*R*)-**11a**, while 8 conformers (99.9%) account for amide (3*S*,11*R*)-**11a**, within 3.0 and 2.0 kcal/mol from the global minimum energy conformation, respectively. Further DFT geometry optimizations were carried out at the B3LYP/DGDZVP level of theory as implemented in the Gaussian 03 W program, giving rise to corresponding molecular model sets of 8 and 6 conformers for (3*R*,11*R*)-**11a** and (3*S*,11*R*)-**11a** amides, respectively, whose populations were estimated from the thermochemical parameters in the conformational equilibrium.
17. Cerda-García-Rojas, C. M.; Catalán, C. A. N.; Muro, A. C.; Joseph-Nathan, P. *J. Nat. Prod.* **2008**, *71*, 967–971.
18. Relative populations were calculated according to $\Delta G = \Delta H - T\Delta S$ and $\Delta G = -RT$ ln K equations. For conformational equilibria of (3*R*,11*R*)-**11a** equations $K_{1,2} = n_2/n_1$, $K_{2,3} = n_3/n_2$, $K_{3,4} = n_4/n_3$, $K_{4,5} = n_5/n_4$, $K_{5,6} = n_6/n_5$, $K_{6,7} = n_7/n_6$, $K_{7,8} = n_8/n_7$, and $n_1 + n_2 + n_3 + n_4 + n_5 + n_6 + n_7 + n_8 = 1$ were used while for (3*S*,11*R*)-**11a** equations $K_{1,2} = n_2/n_1$, $K_{2,3} = n_3/n_2$, $K_{3,4} = n_4/n_3$, $K_{4,5} = n_5/n_4$, $K_{5,6} = n_6/n_5$, and $n_1 + n_2 + n_3 + n_4 + n_5 + n_6 = 1$ were used, where $K_{i,j}$ stands for equilibrium constants and n_i stands for the molar fraction.
19. Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639–2641.

20. Amat-Guerri, F.; Martínez-Utrilla, R.; López-González, M. M. C. *J. Photochem. Photobiol., A* **1990**, *50*, 361–375.
21. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657–6660.
22. Sheldrick, G. M.. *Programs for Crystal Structure Analysis*. In *Institüt für Anorganische Chemie der Universität*; University of Göttingen: Göttingen, Germany, 1988.
23. Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381–388.
24. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
25. Stomberg, R.; Langer, V.; Hauteville, M. *Acta Crystallogr., Sect. E* **2002**, *58*, o1116–o1118.