Tetrahedron: *Asymmetry* 26 (2015) 710–720

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Formal synthesis of (−)-flustramine B and its absolute configuration assignment by vibrational circular dichroism exciton chirality

Reyna E. Cordero-Rivera [a], Myriam Meléndez-Rodríguez [a,*], Oscar R. Suárez-Castillo [a,*], Claudia I. Bautista-Hernández [a], Nayely Trejo-Carbajal [a], Julián Cruz-Borbolla [a], Luis E. Castelán-Duarte [a], Martha S. Morales-Ríos [b], Pedro Joseph-Nathan [b]

[a] *Área Académica de Química, Universidad Autónoma del Estado de Hidalgo, Mineral de la Reforma, Hidalgo 42184, Mexico*
[b] *Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México, D. F. 07000, Mexico*

ARTICLE INFO

Article history:
Received 20 April 2015
Accepted 18 May 2015
Available online 9 June 2015

ABSTRACT

A formal synthesis of the natural product (−)-flustramine B (**3**) is described, together with an easy and reliable approach for the absolute configuration assignment of a series of (3*R*,14*S*)- and (3*S*,14*S*)-oxindolylacetylphenyloxazolidinones **4**, **6**, **13a–c**, and amides (+)- and (−)-**14** by evaluation of the vibrational circular dichroism bisignated couplet resulting from the interaction of the C2 and C9 carbonyl groups. The absolute configuration assignment was validated by ^{1}H NMR spectra and X-ray diffraction, and therefore (−)-flustramine B **3** was established as (3a*S*,8a*R*)-**3**.

1. Introduction

Oxindole derivatives **1** (Fig. 1) are important compounds of considerable interest as starting materials or intermediates for the total synthesis of terrestrial and marine alkaloids containing furo- and pyrroloindole skeletons **2**,[1] such as (−)-flustramine B **3** isolated from the bryozoa *Flustra foliacea* (L.),[2a,b] which has shown skeletal and smooth muscle relaxant activity.[2c] Although (−)-**3** has been synthesized in enantiomerically pure form, its absolute configuration and that of related compounds have been assigned only by chemical correlation using diverse synthetical approaches.[3] Due to the optical activity of oxindole, furoindole, and pyrroloindole derivatives such as **1**, **2**, and **3**, suitable and fast methods to assign their absolute configuration are required. We have recently shown that ^{1}H NMR spectroscopy is a useful tool for establishing the absolute configuration of chiral 2-(2-oxo-3-indolyl)acetic acid derivatives, such as **4**, using (*S*)-phenyl-2-oxazolidinone **5** as the chiral derivatizing agent (CDA) (Fig. 2).[4] The systematic variation of $\Delta\delta^{RS}$ values allowed the assumption that (3*S*,14*S*)-**4** presents the H4-H7 and H16-H20 signals at lower frequency values ($+\Delta\delta^{RS}$) and the H8A signal at a higher frequency value ($-\Delta\delta^{RS}$) than the corresponding (3*R*,14*S*)-**4** diastereomer. It was evidenced that the chemical shift nonequivalences arising from the mutual diamagnetic influence of the aromatic (*S*)-oxazolidinone and oxindole moieties on the ^{1}H NMR signals is present in (3*S*,14*S*)-**4**, but not in the (3*R*,14*S*)-**4** diastereomer, as shown in Figure 2. The absolute configuration of (3*R*,14*S*)- and (3*S*,14*S*)-**4** was independently determined using the time consuming protocol

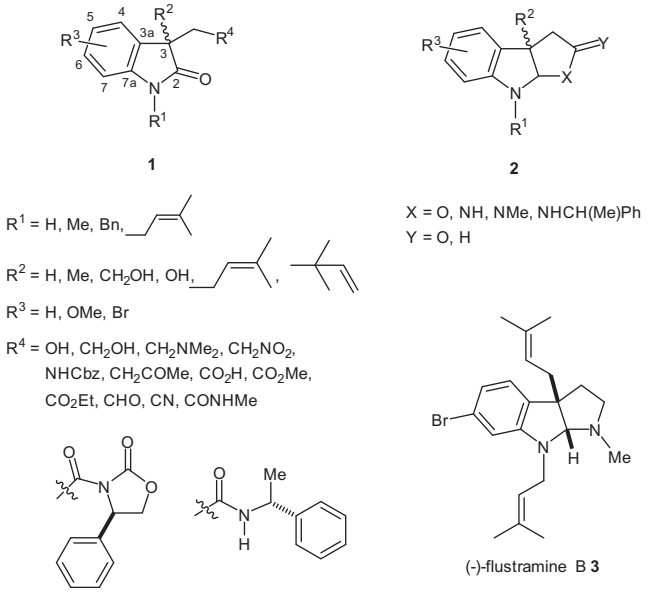


Figure 1. Synthetic and natural oxindole **1**, furoindole **2** and pyrroloindole **3** derivatives.

* Corresponding authors. Tel.: +52 771 71 72000x2206; fax: +52 771 71 72000x6502.
E-mail address: osuarez@uaeh.edu.mx (O.R. Suárez-Castillo).

http://dx.doi.org/10.1016/j.tetasy.2015.05.009
0957-4166/

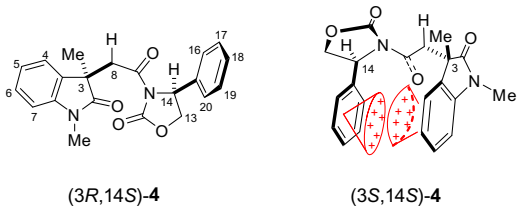


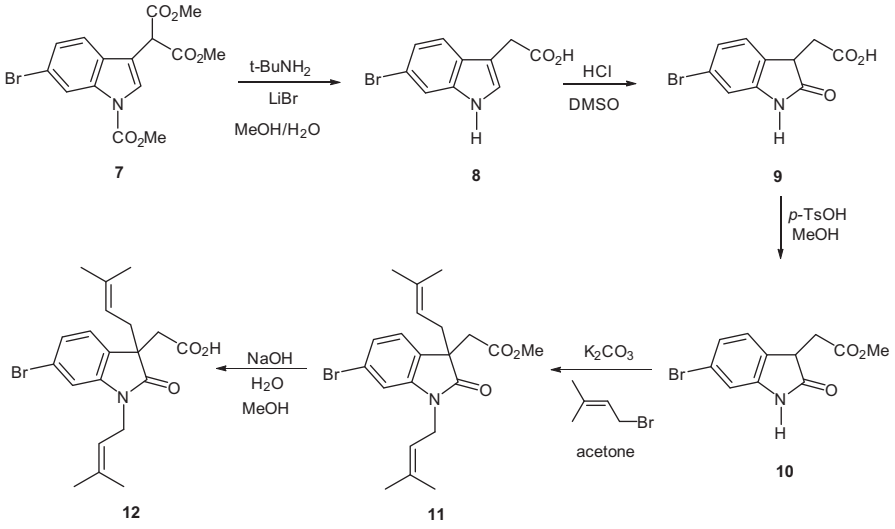
Figure 2. Mutual anisotropic effect of the aromatic rings of (3*S*,14*S*)-**4**.

needed to compare experimental vibrational circular dichroism (VCD) spectra with those calculated using density functional theory, which showed good agreement.[5]

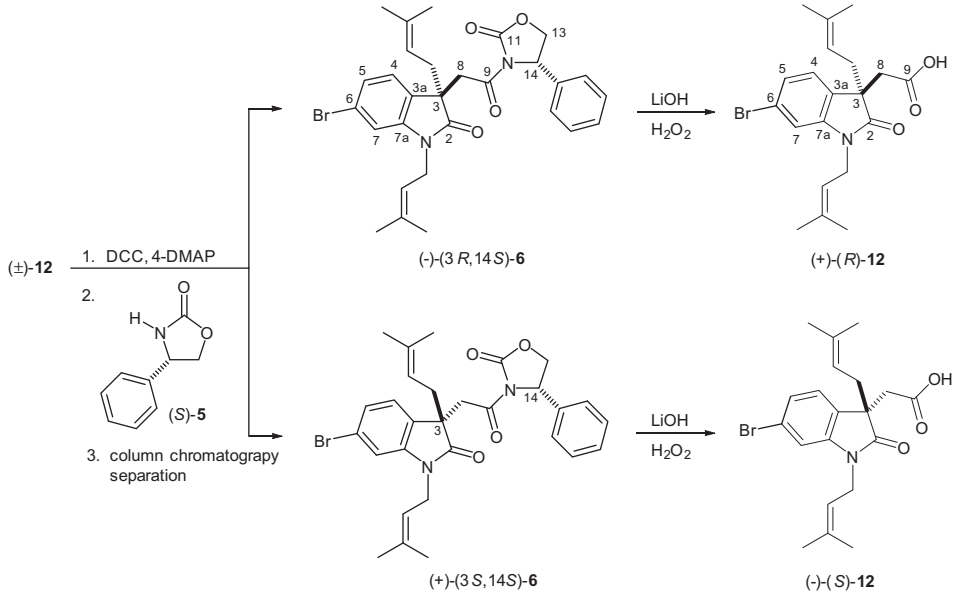
In continuation of our studies aimed at the synthesis of flustramines[6] and the determination of the absolute configuration of indole and oxindole derivatives,[4,7] we herein report that the absolute configuration of (3*R*,14*S*)- and (3*S*,14*S*)-6-bromooxindolylacetylphenyloxazolidinones **4**, **6**, **13a**–**c**, and (3*R*)- and (3*S*)-amides **14**, an intermediate in the formal synthesis of flustramine,[3b] can be assigned solely by VCD exciton chirality (VCDEC)[8] considering the bisignate couplets that originate from the through-space interaction of the C2 and C9 amide carbonyl groups. The absolute configuration in both diastereomers was also assigned when comparing specific VCD bands in the (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a**–**c** series.

2. Results and discussion

Compounds (3*R*,14*S*)- and (3*S*,14*S*)-bromooxindolylacetylphenyloxazolidinones **6** were synthesized according to Schemes 1 and 2. Thus, 6-bromoindole malonate **7**[9] was treated with *t*-BuNH$_2$/LiBr/MeOH/H$_2$O to obtain 2-(6-bromoindolyl)acetic acid **8** in 96% yield. Acid **8** was converted, in 49% overall yield, into ester



Scheme 1. Synthesis of (±)-6-bromooxoindolinacetic acid **12**.



Scheme 2. Resolution of (±)-6-bromooxoindolinacetic acid **12** with (*S*)-phenyl-2-oxazolidinone **5**.

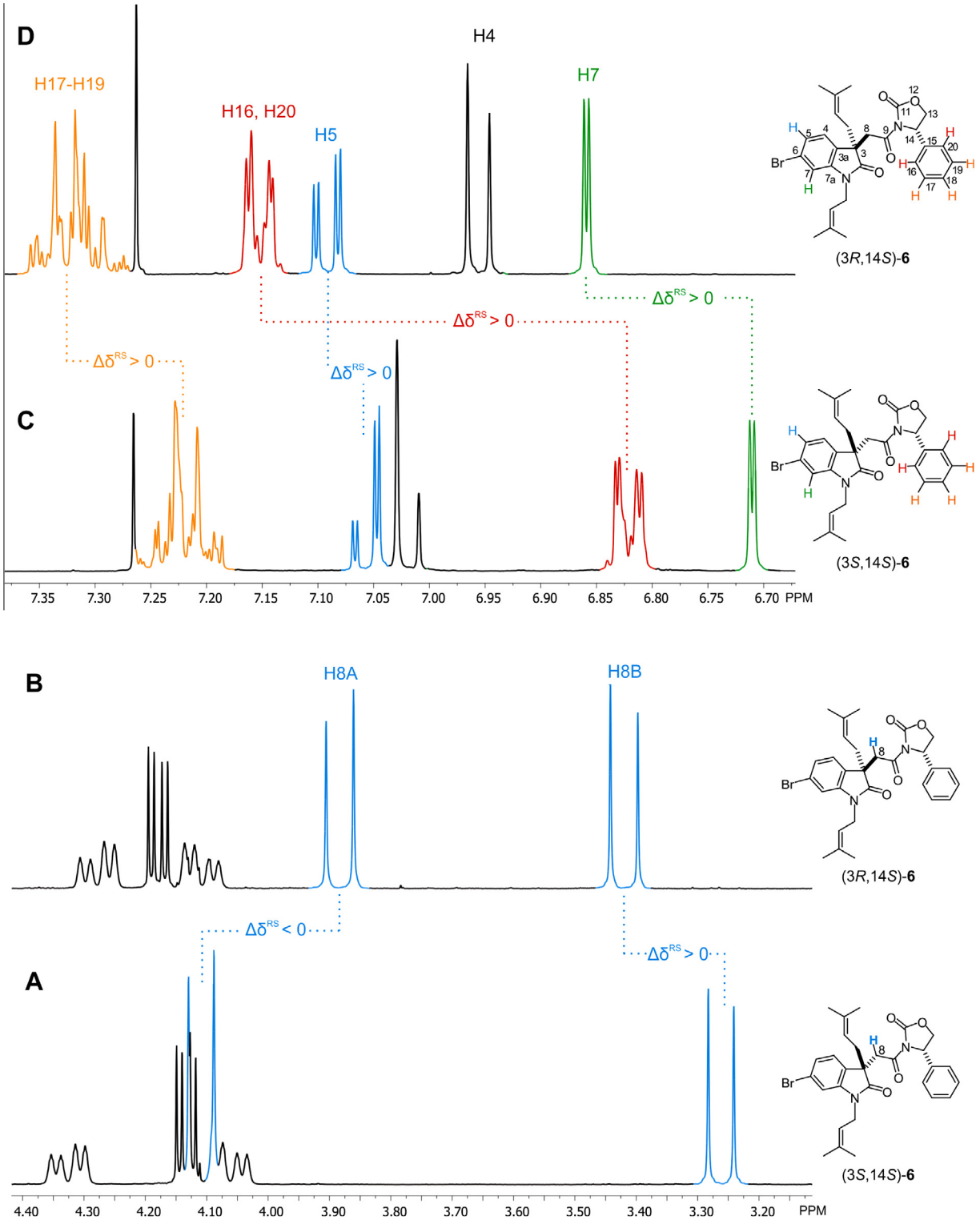


Figure 3. $\Delta\delta^{RS}$ values for the aromatic H5, H7, H16-H20 and H8 atoms of (3*R*,14*S*)- and (3*S*,14*S*)-**6** ($\Delta\delta^{RS} = \delta_R - \delta_S$, where the *R* and *S* descriptors refer to the C3 configuration at the oxindole moiety).

10 by oxidation with HCl/DMSO to give oxindole **9** followed by esterification. Dialkylation of **10** with prenyl bromide using K_2CO_3/acetone gave N1,C3-diprenyloxindol **11** in 92% yield, which was saponified with NaOH/H_2O/MeOH followed by acidification with HCl/H_2O to obtain **12** in 97% yield (Scheme 1). Derivatization of a racemic sample of **12** into oxazolidinones **6** was carried out with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (4-DMAP),[4] followed by reaction with phenyloxazolidinone (*S*)-**5** to give an equimolar diastereomeric mixture of (3*R*,14*S*)- and (3*S*,14*S*)-**6**, as was evidenced by ^{1}H NMR analysis of the reaction crudes. Phenyloxazolidinones (3*R*,14*S*)- and (3*S*,14*S*)-**6** were easily separated by column chromatography to afford pure isomers with >99% diastereomeric excess as determined by ^{1}H NMR measurements.

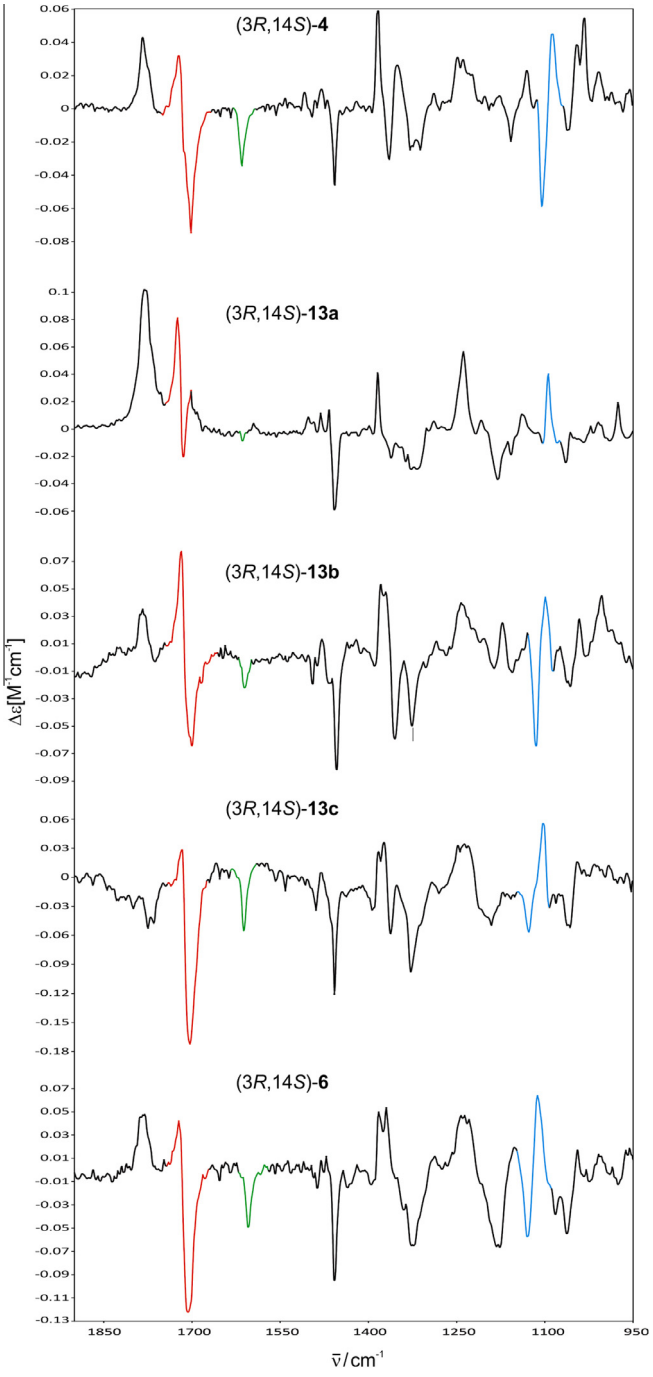


Figure 4. Comparison of the VCD spectra of (3*R*,14*S*)-**4**, **13a–c**, and **6**.

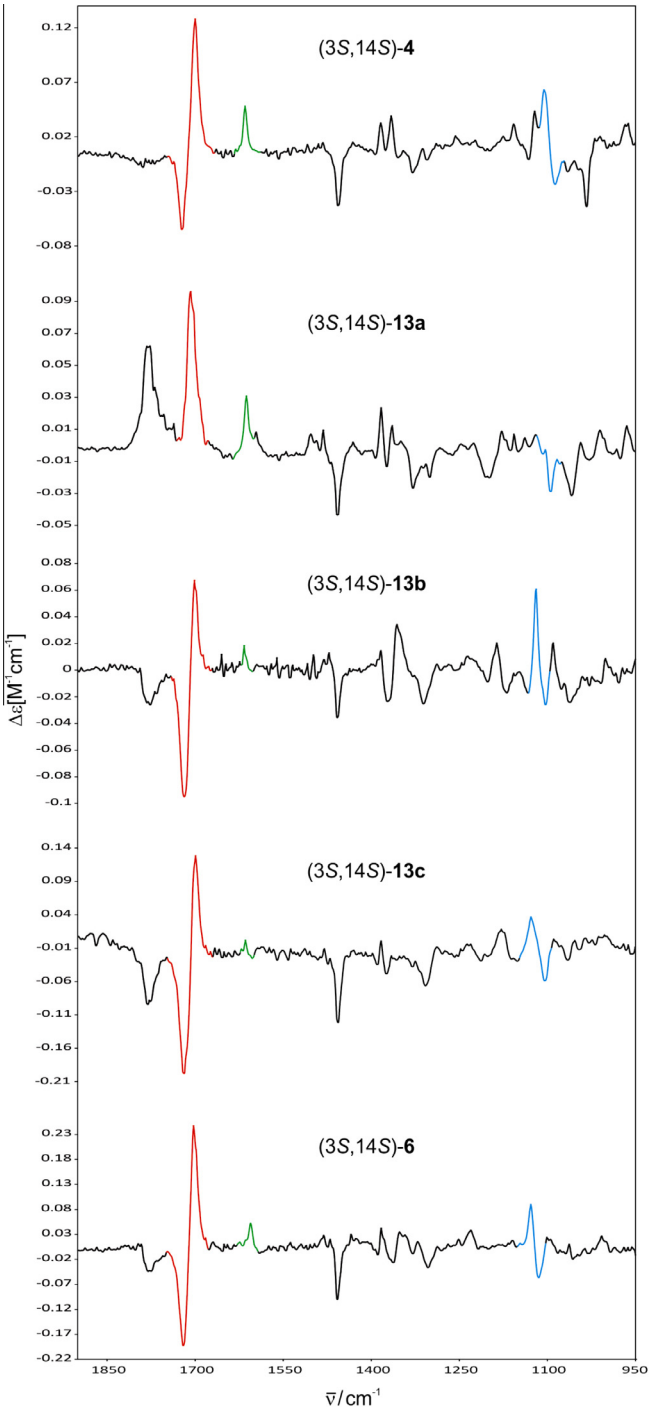


Figure 5. Comparison of the VCD spectra of (3*S*,14*S*)-**4**, **13a–c**, and **6**.

The ^{1}H NMR spectra comparison of (3*R*,14*S*)- and (3*S*,14S)-**6** showed positive $\Delta\delta^{RS}$ values ($\Delta\delta^{RS} = \delta_R - \delta_S$, where the *R* and *S* descriptors refer to the C3 configuration at the oxindole moiety) for the aromatic H5, H7, H16-H20 and H8B signals as a consequence of the orientation of the magnetic anisotropy imposed by both phenyl groups of the (*S*)-oxazolidinyl and oxindolyl moieties, as is depicted in Figure 3. On the contrary, negative $\Delta\delta^{RS}$ shifts occurred for H4 and H8A. The $\Delta\delta^{RS}$ values have the same sign distribution for H5, H7, H16-H20 and H8B as those obtained for (3*R*,14*S*)- and (3*S*,14*S*)-**4**, which suggests that diastereomers with the same configuration, such as (3*R*,14*S*)-**6** and (3*R*,14*S*)-**4**, and (3*S*,14S)-**6** and (3*S*,14S)-**4**, adopt similar conformations at the C8—(C9═O)—N10—C11═O fragment.[4] In Figure 3, colours are used to identify the same proton signals of both diastereoisomers.

With the precedent of the absolute configuration of (3*R*,14*S*)- and (3*S*,14S)-**6** assigned, according to our own experience by ^{1}H NMR spectroscopy, we next assessed the applicability of VCD as a confident method to assign the absolute configuration of diastereomers **6** and other structurally related compounds. The assignment of the absolute configuration using vibrational spectroscopy is not a simple task since normal vibrational modes may contain complex combinations of individual molecular conformation. Thus, although time consuming, the conformational analysis, geometry optimization at different levels of theory, and VCD spectra calculation is essential. Therefore, in search of a faster methodology to assign the absolute configuration of oxindole

Table 1
VCDEC couplets for (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **13a–c**, **6**

Compound	M	$\Delta\varepsilon_1$ (υ(cm^{-1}))[a]	$\Delta\varepsilon_2$ (υ(cm^{-1}))[a]	A[b]
(3*R*,14*S*)-**4**	0.095	−0.074 (1701)	0.032 (1722)	−0.106
(3*R*,14*S*)-**6**	0.078	−0.122 (1706)	0.042 (1724)	−0.164
(3*R*,14*S*)-**13a**	0.068	−0.020 (1714)	0.081 (1724)	−0.101
(3*R*,14*S*)-**13b**	0.045	−0.064 (1701)	0.077 (1718)	−0.141
(3*R*,14*S*)-**13c**	0.046	−0.172 (1703)	0.026 (1716)	−0.198
(3*S*,14*S*)-**4**	0.091	0.128 (1699)	−0.065 (1722)	0.193
(3*S*,14*S*)-**6**	0.088	0.247 (1703)	−0.192 (1720)	0.438
(3*S*,14*S*)-**13a**	0.091	0.096(1708)[c]	—	—
(3*S*,14*S*)-**13b**	0.052	0.067 (1701)	−0.095 (1718)	0.162
(3*S*,14*S*)-**13c**	0.041	0.129 (1699)	−0.197 (1718)	0.326

[a] In M^{-1} cm^{-1}.
[b] $\Delta\varepsilon_1 - \Delta\varepsilon_2$.
[c] For (3*S*,14*S*)-**13a** only a positive monosignate signal was detected.

derivatives, the experimental VCD spectra of oxindolylacetylphenyloxazolidinones **13a–c** were acquired and compared with those of **4** and **6** (Figs. 4 and 5). As can be seen, a great similarity of oxazolidinones (3*R*,14*S*)- and (3*S*,14*S*)-**6** with their respective analogues **4**, **13a–c** is evident, since the achiral alkyl groups at C3 have no relevant contributions to the VCD spectra.[10]

The VCD spectra of (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a–c** shown in Figures 4 and 5 evidence some particular features attributed to each family. For example, (3*R*,14*S*)-**4**, **6**, **13a–c** show common VCD bands in the 1087–1110, 1103–1130, 1230–1247, 1311–1328, 1382, 1456–1458, 1604–1614, 1701–1714, and 1716–1724 cm^{-1} ranges (Fig. 4), while for the (3*S*,14*S*)-**4**, **6**, **13a–c** diastereomers the common VCD bands appear in the 1085–1114, 1103–1128, 1301–1328, 1382–1384, 1456–1458, 1604–1616, 1699–1708, and 1718–1722 cm^{-1} ranges (Fig. 5). The VCD bands in the 1085–1130, 1604–1616, and 1699–1724 cm^{-1} ranges are very sensitive to the absolute configuration in both (3*R*,14*S*)- and (3*S*,14*S*)-oxazolidinone **4**, **6**, **13a–c** series, as similar absorption bands are shown, but with an opposite sign. The negative sign of the band at 1604–1616 cm^{-1} and the negative/positive combination from low to high wave numbers at 1085–1130 cm^{-1} account for the (3*R*)-configuration, whereas the opposite situation corresponds to the (3*S*)-configuration.

Both (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a–c** diastereomeric series show strong sharp bisignate VCDEC signals around 1699–1714 and 1716–1724 cm^{-1} which evidence the through-space coupling of the C2 and C9 carbonyl groups.[8a] As shown in Figures 4 and 5, and in Table 1, these bisignate VCDEC signals are, in general, more intense in the (3*S*,14*S*)-(*A* values from 0.162 to 0.438) series than in the (3*R*,14*S*)-**4**, **6**, **13a–c** (*A* values from −0.101 to −0.198) series. Accordingly, Monde et al.[8a] studied the influence of carbonyl groups' spatial arrangement on the amplitude *A*, concluding that dihedral angles close to 0° and 180°, or a larger interchromophoric distance could attenuate the coupling. A negative-lower to positive-higher wave numbers signal twist generated by the interaction of the electric transition moments of the C2 and C9 carbonyl groups in (3*R*,14*S*)-**4**, **6**, **13a–c** was observed, while a positive-lower to negative-higher wave numbers signal twist was observed for (3*S*,14*S*)-**4**, **6** and **13a–c**. According to the model proposed by Monde and Taniguchi,[8a] (3*R*,14*S*)-**4**, **6**, **13a–c** should display a counterclockwise ($-180° < \theta < 0°$, negative twist) chromophoric orientation of the C2 and C9 carbonyl groups (Fig. 6A), while diastereomers (3*S*,14*S*)-**4**, **6**, **13a–c** should present a clockwise ($0° < \theta < +180°$, positive twist) disposition (Fig. 6B) as a consequence of their C3 absolute configuration. It is worth noting that for (3*S*,14*S*)-**13a** only a positive monosignate signal was detected at 1708 cm^{-1}, which could evidence that no coupling between the C2 and C9 carbonyl groups would exist. However, its position coincides with that of the first negative Cotton effect signal (1714 cm^{-1}) for the (3*R*,14*S*)-**13a** diastereoisomer (Fig. 7), indicating that even for (3*S*,14*S*)-**13a** the absolute configuration could be assigned by comparison at the 1650–1750 cm^{-1} VCD spectral region. Furthermore, it has been demonstrated that when no through-space interaction between two carbonyl groups in chiral compounds is possible, the VCD signals are 20–25 times less intense.[8a]

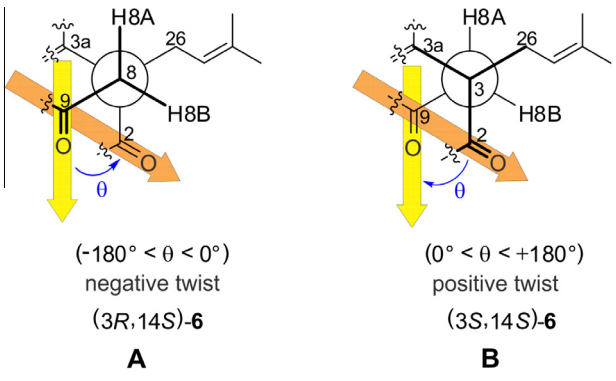
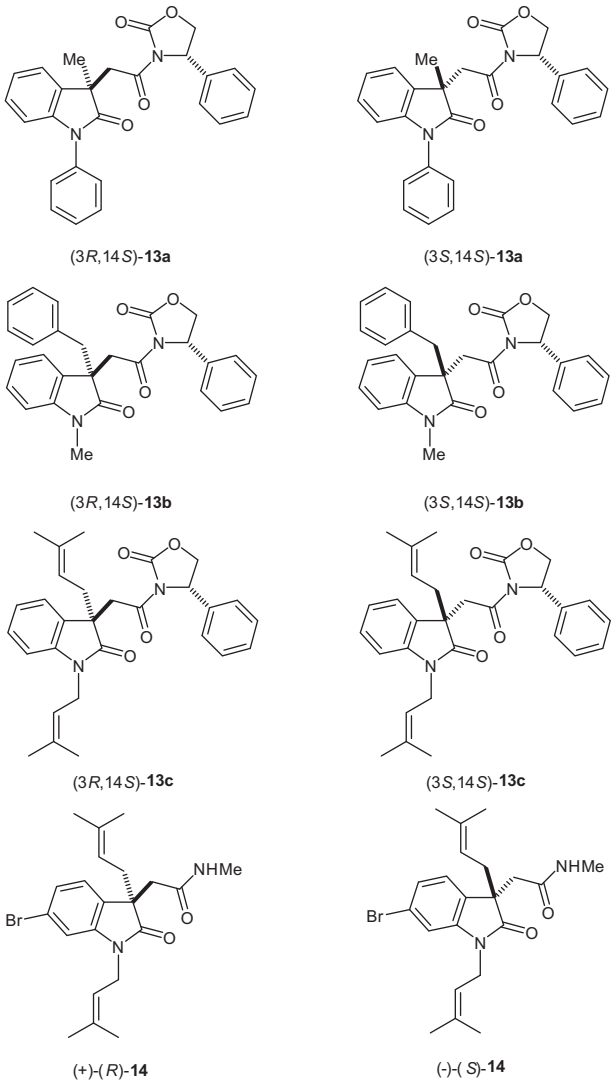


Figure 6. Twist sense for the electric transition moments of the C2 (orange arrows) and C9 (yellow arrows) carbonyl groups in (3*R*,14*S*)- and (3*S*,14*S*)-**6**.



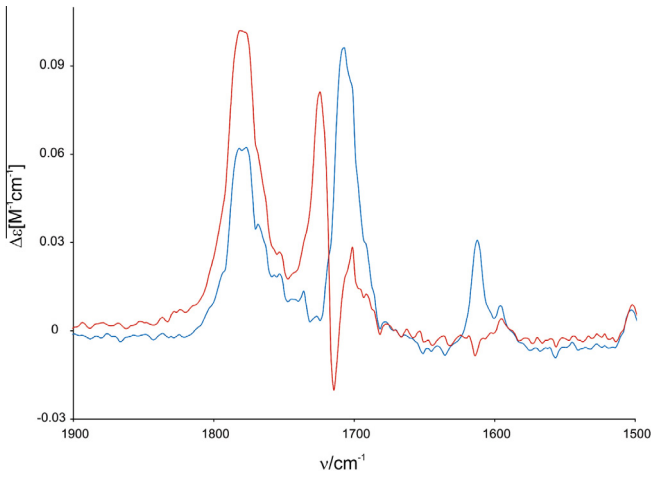


Figure 7. VCD spectral region of the bisignate couplet for compounds (3*R*,14*S*)-**13a** (red trace) and (3*S*,14*S*)-**13a** (blue trace) showing that the positive monosignate signal (1708 cm^{-1}) in (3*S*,14*S*)-**13a** coincides with the negative first Cotton effect (1714 cm^{-1}) for the (3*R*,14*S*)-**13a**.

In addition to the bisignate signal in the VCD spectra of (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a**–**c** shown in Figures 4 and 5, a third signal in the 1774–1784 cm^{-1} range appeared. This signal is due to the C11 carbonyl group and although its phase sign is not systematic in each group of spectra, it does not perturb the sense of sign variation for the bisignate signal in each group. Although it has been demonstrated that the presence of three carbonyl groups could generate a strong bisignate VCD signal,[8c] this does not occur in the (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a**–**c** series because of the distinct absorption of the C11 carbonyl group.

In order to evaluate the preferred orientation of the C2 and C9 carbonyl groups, a conformational search and geometry optimization for (3*R*,14*S*)- and (3*S*,14*S*)-**6** was carried out. Thus, a molecular modeling protocol with Monte Carlo searching[11] using the MMFF94[12] molecular mechanics force field method, as implemented in the Spartan08[13] program, gave 116 conformers for (3*R*,14*S*)-**6** and 128 conformers for (3*S*,14*S*)-**6** within the first 10 kcal/mol energy window. With the aim to avoid the possibility of overlooking relevant conformers, all conformers were submitted to single-point energy calculations at the DFT B3LYP/6-31G(d)[14] level of theory to afford 106 conformers for (3*R*,14*S*)-**6** and 118 conformers for the (3*S*,14*S*)-**6** appearing in 9.49 kcal/mol and 9.64 kcal/mol energy gaps, respectively. The meaningful 50 conformers for (3*R*,14*S*)-**6** and 82 conformers for (3*S*,14*S*)-**6** found in the initial 5.0 kcal/mol gap, contributing in both cases to 99.9% of the total conformational population, were optimized at the B3LYP/DGDZVP[15] level of theory to provide 45 conformers for (3*R*,14*S*)-**6** and 65 conformers for (3*S*,14*S*)-**6** in the 5.63 kcal/mol for both diastereoisomers. As can be seen in Figures 8 and 9, the most stable 23 conformers (79.1% of the total population) for (3*R*,14*S*)-**6** (Fig. 8, A, C) and 33 conformers (81.4% of the total population) for (3*S*,14*S*)-**6** (Fig. 9, A, C) show the O=C2—C3—C8—C9=O fragment almost in the same spatial disposition. It is evident that the large number of conformers is due to the conformational freedom of the flexible prenyl groups at the N1 and C3 positions. The chromophoric orientation of the C2 and C9 carbonyl groups is better appreciated, for the most stable conformer in each group, when the prenyl and phenyloxazolidinone groups are omitted for clarity. A counterclockwise twist of these groups appears for (3*R*,14*S*)-**6** (Fig. 8, B, D) while a clockwise twist is evident for the (3*S*,14*S*)-**6** isomer (Fig. 9, B, D). The distances between the two carbonyl groups are in the 3.2–3.3 Å range. Thus, computational results reinforce the absolute configuration assignment in (3*R*,14*S*)- and (3*S*,14*S*)-**6** based on the bisignate VCDEC couplets originated by the two amide carbonyl groups in **4**, **6**, and **13a**–**c**.

Subsequently, hydrolysis of (3*R*,14*S*)- and (3*S*,14*S*)-**6** with $LiOH/H_2O_2$[16] afforded the corresponding (+)-(*R*)- and (−)-(*S*)-acids **12**, in 74% and 72% yield, respectively (Scheme 2) which were transformed into (+)-(*R*)-(54%) and (−)-(*S*)-amides **14** (51%) through the mixed anhydrides after treatment with pentafluorophenol, 1-ethyl-3-(3-dimethylamino propyl)carbodiimide (EDC) and methylamine.[16] We were able to obtain single crystals of (*S*)-**14** which provided the X-ray structure shown in Figure 10 (top). The absolute configuration structure was established by taking advantage of the heavy atom at C6 by evaluation of the Flack[17a] [−0.002(7), (*R*)-enantiomer 1.015(16)] and the Hooft[17b] parameters [0.006(2), (*R*)-enantiomer 1.008(2)]. As can also be seen in Figure 9 (bottom), in the solid state a clockwise twist is evident for the (−)-(3*S*)-**14** isomer with a C2=O, C9=O distance of 3.2 Å.

The VCD spectra of (3*R*)- and (3*S*)-**14** are shown in Figure 11 with their respective bisignate couplets. A counterclockwise twist of the C2 and C9 carbonyl groups is evident in (3*R*)-**14** (Fig. 11, top) while a clockwise twist is evident for (3*S*)-**14** (Fig. 11, bottom). This result confirms that the additional carbonyl at the phenyloxazolidinone moiety (C14) in (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a**–**c** does not perturb the twist sign of the C2 and C9 carbonyl groups.

Since the synthesis of the natural product (−)-flustramine B **3** has been carried out from (−)-(*S*)-**14**,[3b] and taking into account the well known *cis*-configuration of the C3a/C8a ring fusion,[2] the absolute configuration follows as (3a*S*,8a*R*)-**3**.

3. Conclusions

We have demonstrated that the absolute configuration of oxindole derivatives **4**, **6**, **13a**–**c**, and **14** can easily be assigned by considering the twist of their VCDEC bisignate couplet and other characteristic signals. A general assumption for the absolute configuration assignment is: (3*R*)-oxindole derivatives **4**, **6**, **13a**–**c**, **14** show a positive twist of the C2 and C9 carbonyl groups, while (3*S*)-**4**, **6**, **13a**–**c**, **14** show a negative twist. This approach could be useful for the absolute configuration assignment of natural and synthetic furo- and pyrroloindoles, as shown for (−)-(3a*S*,8a*R*)-flustramina B **3**.

4. Experimental

4.1. General

The melting point was determined on a Büchi B-545 apparatus. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrophotometer. The 400 and 100 MHz ^1H and ^{13}C NMR spectra were obtained on a Varian VNMRS 400 spectrometers using $CDCl_3$ as the solvent and TMS as the internal reference. For complete assignments gHSQC and gHMBC spectra were measured. Data are reported as follows: chemical shift in ppm from TMS, integration, multiplicity (s = singlet, d = doublet, t = triplet, 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), programed from 70 °C to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. Optical rotation measurements were performed on a Perkin–Elmer 341 polarimeter. Microanalytical determinations were performed on a Perkin Elmer 2400 Series CHNS/O apparatus. Analytical thin-layer chromatography (TLC) was carried out on silica gel F_{254} coated aluminum sheets (0.25 mm thickness)

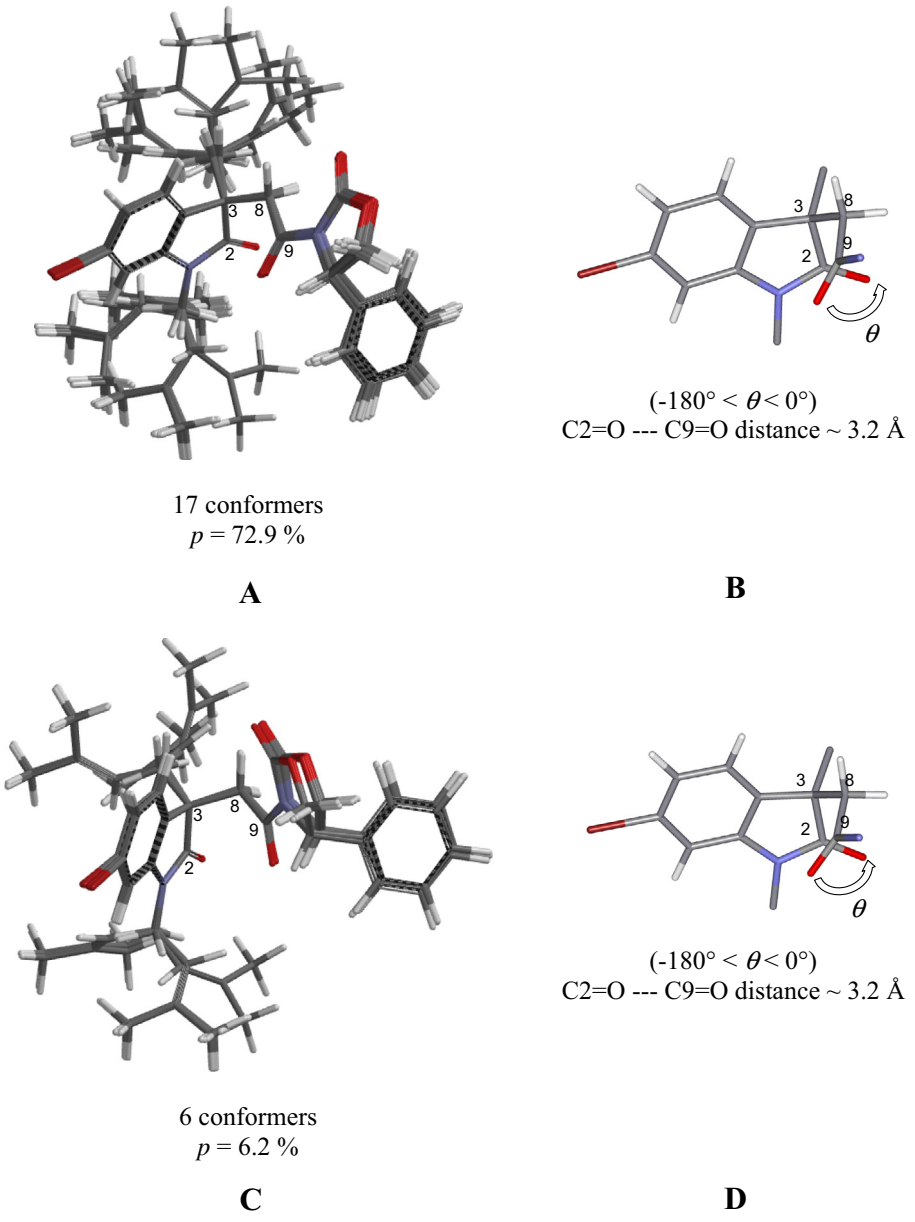


Figure 8. DFT B3LYP/DGDZVP optimized geometries for (3*R*,14*S*)-**6** showing the preferred orientation of the C2 and C9 carbonyl groups in the most stable conformers (A, C). Prenyl and phenyloxazolidinone groups in B, D were omitted for clarity.

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. Preparation of 2-(6-bromo-1*H*-indol-3-yl)acetic acid 8

To a solution of **7** (0.32 g, 0.83 mmol) in MeOH (2.5 mL) was added *t*-BuNH$_2$ (0.88 mL, 8.37 mmol) and LiBr (0.22 g, 2.53 mmol dissolved in 5 mL of H$_2$O), and the mixture was stirred at reflux for 3.5 h. After cooling to room temperature, the volatiles were evaporated under reduced pressure and the residue was diluted with EtOAc (50 mL), washed with a saturated solution of NaHCO$_3$ (5 × 20 mL) and brine (2 × 15 mL). The combined aqueous solutions were acidified to pH ca. 1 with a 1 M aqueous solution of HCl and extracted with EtOAc (5 × 20 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated to dryness in vacuum to give acid **8** as a pale yellow oil (0.20 g, 95%). The spectroscopic data of **8** were consistent with those reported.[18]

4.3. Preparation of methyl 2-(6-bromo-2-oxoindolin-3-yl)acetate 10

To a solution of acid **8** (0.30 g, 1.18 mmol) in DMSO (5 mL, 10 mmol) was added an aqueous solution (36%) of HCl (5 mL) and the mixture was stirred for 12 h at room temperature, diluted with water (15 mL), neutralized with a saturated solution of NaHCO$_3$, and extracted with EtOAc (5 × 20 mL). The organic layer was washed with brine (3 × 15 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated to dryness in vacuum. The residue containing acid **9** was dissolved in MeOH (5 mL) and *p*-toluenesulfonic acid (0.010 g, 0.05 mmol) was added, and the mixture heated at reflux for 2.5 h. After cooling to room temperature, MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with a saturated solution of NaHCO$_3$ (2 × 20 mL), brine (2 × 15 mL), dried over Na$_2$SO$_4$, and evaporated to dryness in vacuum. The resultant crude product was purified by flash column chromatography on silica gel

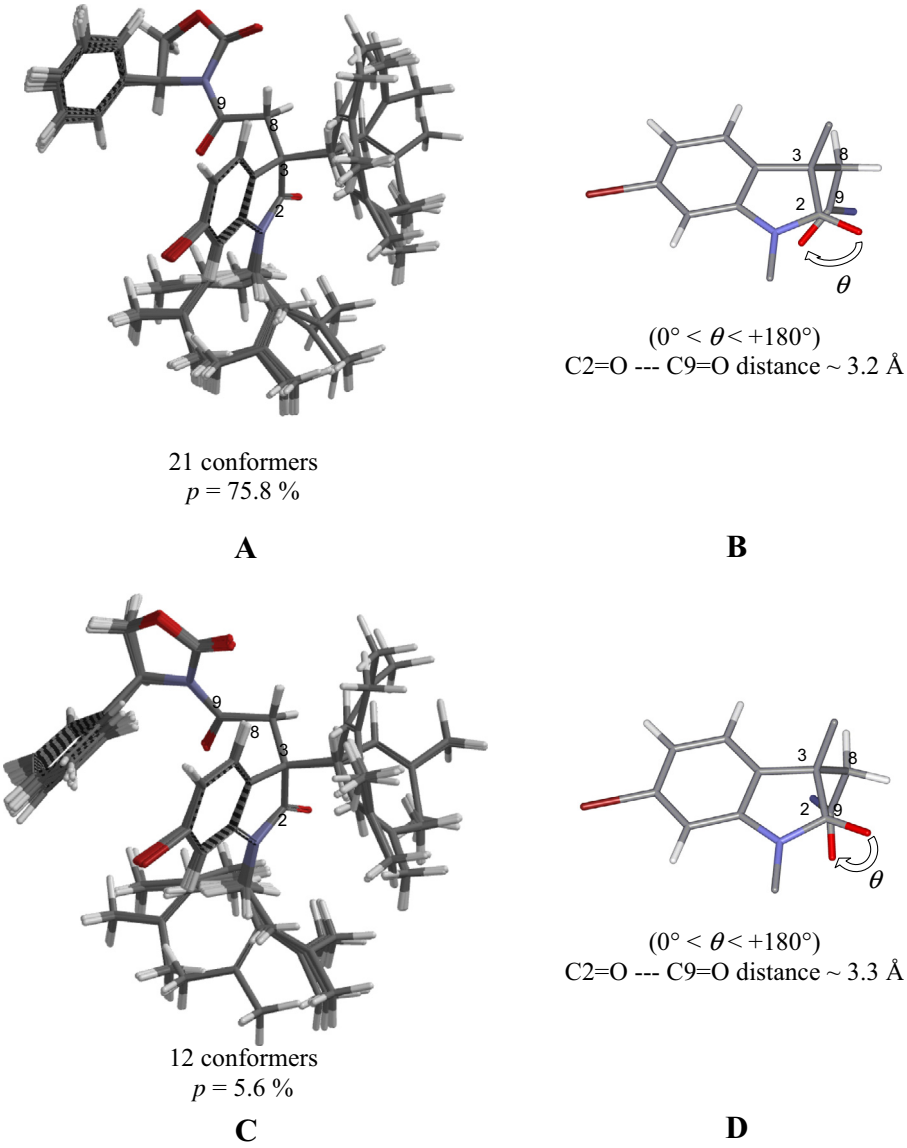


Figure 9. DFT B3LYP/DGDZVP optimized geometries for (3*S*,14*S*)-**6** showing the preferred orientation of the C2 and C9 carbonyl groups in the most stable conformers (A, C). Prenyl and phenyloxazolidinone groups in B, D were omitted for clarity.

eluting with EtOAc/hexanes 1:3 to give ester **10** as white crystals (0.16 g, 66%). The spectroscopic data of **10** match those reported.[6d]

4.4. Preparation of methyl 2-(6-bromo-1,3-bis(3-methylbut-2-enyl)-2-oxoindolin-3-yl)acetate 11

To a solution of **10** (0.26 g, 0.92 mmol) in acetone (12 mL) was added K_2CO_3 (0.92 g, 6.67 mmol) and the mixture stirred for 30 min at room temperature. Then, 4-bromo-2-methyl-2-butene (0.38 g, 2.55 mmol) was added and the resulting mixture was stirred for 2.5 h at reflux. After cooling to room temperature, the volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/hexanes (1:5) to obtain ester **11** as a pale yellow oil (0.35 g, 91%). The spectroscopic data of **11** were consistent with those reported.[19]

4.5. Preparation of 2-(6-bromo-1,3-bis(3-methylbut-2-enyl)-2-oxoindolin-3-yl)acetic acid 12

To a solution of ester **11** (0.32 g, 0.76 mmol) in MeOH (16 mL) was added an aqueous solution (15%) of NaOH (8 mL) and the mixture stirred for 40 min at 50–60 °C. After cooling in an ice/water bath, the mixture was acidified to pH 1 with a 1 M HCl aqueous solution and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give **11** as a pale yellow oil (0.30 g, 97%). Although **11** is known,[3b] it is spectroscopically not yet characterized. Thus, NMR data follow: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (1H, dd, J = 7.9, 1.7 Hz, H5), 7.00 (1H, d, J = 7.9 Hz, H4), 6.90 (1H, d, J = 1.7 Hz, H7), 5.03 (1H, tsept, J = 6.6, 1.3 Hz, H16), 4.74 (1H, tsept, J = 7.7, 1.3 Hz, H11), 4.36 (1H, dd, J = 15.7, 6.6 Hz, H15A), 4.17 (1H, dd, J = 15.7, 6.6 Hz, H15B), 3.04 and 2.80 (2H, AB system, J = 16.7 Hz, H8), 2.42 (2H, d, J = 7.7 Hz, H10), 1.81 (3H, br s, Me18), 1.72 (3H, br s, Me19), 1.57 (3H, br s, Me13), 1.45 (3H, br s, Me14); ^{13}C NMR (100 MHz,

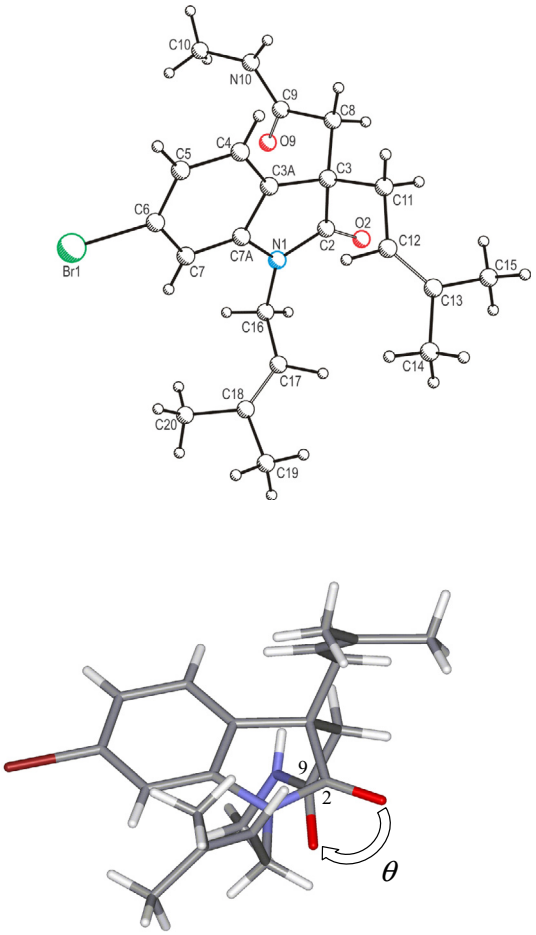


Figure 10. X-ray diffraction structure of (3*S*)-**14** (top). Twist direction of the C2 and C9 carbonyl groups in the solid state (bottom).

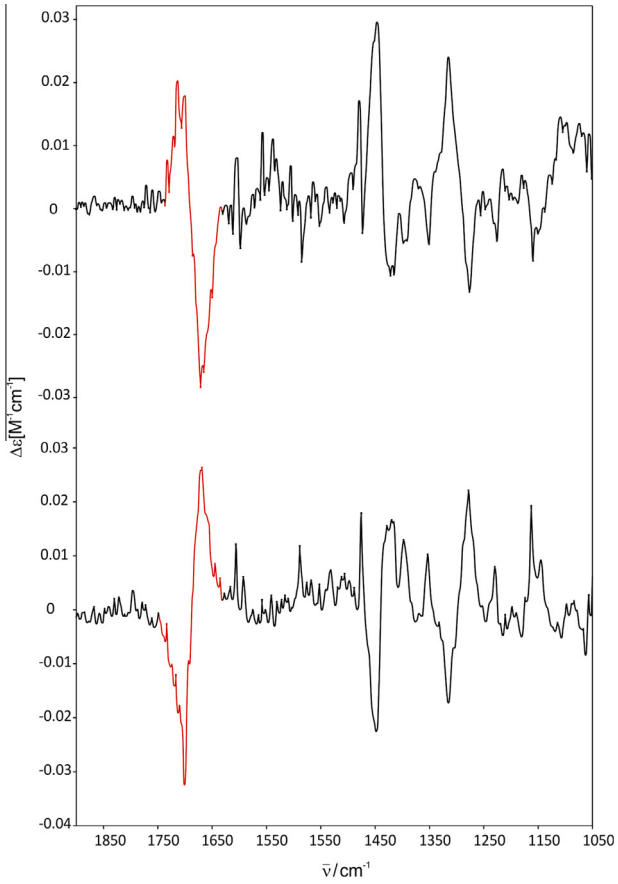


Figure 11. VCD spectra of (3*R*)-**14** (top) and (3*S*)-**14** (bottom) showing the carbonyl groups bisignate couplet in the 1632–1753 cm^{-1} region.

$CDCl_3$): δ179.0 (C2), 174.0 (C9), 144.7 (C7a), 137.1 (C17), 137.0 (C12), 130.1 (C3a), 125.1 (C5), 124.2 (C4), 121.8 (C6), 117.9 (C16), 116.4 (C11), 112.3 (C7), 49.5 (C3), 39.8 (C8), 38.4 (C15), 36.3 (C10), 26.0 (C13), 25.8 (C19), 18.3 (C18), 18.1 (C14); IR (KBr) ν_{max} 3434, 2972, 2927, 1716, 1605, 1488, 1434, 1378, 1176 cm^{-1}.

4.6. General procedure for the preparation of diastereomeric imides 6

To a solution of acid **12** (0.25 g, 0.62 mmol) in CH_2Cl_2 (15 mL) were added 4-DMAP (0.16 g, 1.31 mmol), DCC (0.15 g, 0.73 mmol) and (*S*)-(+)-4-phenyloxazolidinone **5** (0.10 g, 0.61 mmol). The reaction mixture was stirred at room temperature for 24 h, filtered, and the solvent evaporated in vacuum. The residue containing the (3*R*,14*S*)- and (3*S*,14*S*)-**6** diastereomeric pair was purified by flash column chromatography on silica gel using EtOAc/hexanes 1:2.

4.6.1. (*S*)-3-(2-((*R*)-6-Bromo-1,3-bis(3-methylbut-2-enyl)-2-oxoindolin-3-yl)acetyl)-4-phenyloxazolidin-2-one (3*R*,14*S*)-6

Prepared from **12** as white solid (0.12 g, 35%), mp: 146–147 °C (EtOAc/hexanes). $[\alpha]_D^{20}$ = −9.2 (*c* 1.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.27 (3H, overlapped, H17-H19), 7.15 (2H, dm, *J* = 7.9 Hz, H16, H20), 7.09 (1H, dd, *J* = 7.8, 1.7 Hz, H5), 6.96 (1H, d, *J* = 7.8 Hz, H4), 6.86 (1H, d, *J* = 1.7 Hz, H7), 5.21 (1H, dd, *J* = 8.7, 3.7 Hz, H14), 4.98 (1H, tsept, *J* = 6.6, 1.4 Hz, H22), 4.78 (1H, tsept, *J* = 7.7, 1.4 Hz, H27), 4.57 (1H, t, *J* = 8.8 Hz, H13A), 4.29 (1H, br dd, *J* = 15.9, 6.7 Hz, H21A), 4.19 (1H, dd, *J* = 8.8, 3.7 Hz, H13B), 4.12 (1H, br dd, *J* = 15.9, 6.4 Hz, H21B), 3.89 and 3.43 (2H, AB system, *J* = 17.9 Hz, H8), 2.46 (1H, dd, *J* = 13.5, 6.9 Hz, H26A), 2.41 (1H, dd, *J* = 13.5, 7.9 Hz, H26B), 1.73 (3H, d, *J* = 0.9 Hz, Me24), 1.67 (3H, d, *J* = 1.2 Hz, Me25), 1.58 (3H, d, *J* = 0.9 Hz, Me29), 1.48 (3H, d, *J* = 1.1 Hz, Me30); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5 (C2), 168.8 (C9), 154.0 (C11), 145.1 (C7a), 138.5 (C15), 136.8 (C28), 136.6 (C23), 130.8 (C3a), 129.3 (C17, C19), 128.7 (C18), 125.7 (C16, C20), 124.5 (C5), 123.6 (C4), 121.5 (C6), 118.3 (C22), 116.6 (C27), 112.1 (C7), 70.3 (C13), 57.3 (C14), 49.5 (C3), 41.1 (C8), 38.2 (C21), 36.8 (C26), 26.0 (C29), 25.8 (C25), 18.2 (C24), 18.1 (C30); IR (KBr) ν_{max} 2970, 2915, 2857, 1782, 1712, 1605, 1488, 1439, 1382, 1322, 1248, 1199 cm^{-1}; EIMS *m*/*z* (relative intensity) 550/552 ($[M]^+$ 5.7/5.3), 483/485 (98/86), 387/389 (49/58), 345/347 (56/44), 321 (73.4), 319 (100), 292 (83), 265 (39), 263 (52), 252 (69), 250 (80), 164 (66), 133 (44), 104 (89), 105 (37), 91 (35), 69 (27), 41 (45), 39 (45). Anal. Calcd for $C_{29}H_{31}BrN_2O_4$; C, 63.16; H, 5.67; N, 5.08. Found: C, 62.69; H, 5.80; N, 5.54.

4.6.2. (*S*)-3-(2-((*S*)-6-Bromo-1,3-bis(3-methylbut-2-enyl)-2-oxoindolin-3-yl)acetyl)-4-phenyloxazolidin-2-one (3*S*,14*S*)-6

Prepared from **12** as yellow oil (0.11 g, 32%). $[\alpha]_D^{20}$ = +92.6 (*c* 1.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.19 (3H, overlapped, H17-H19), 7.06 (1H, dd, *J* = 7.9, 1.7 Hz, H5), 7.02 (1H, d, *J* = 8.0 Hz, H4), 6.82 (2H, dm, *J* = 7.9 Hz, H16, H20), 6.71 (1H, br d, *J* = 1.6 Hz, H7), 5.23 (1H, dd, *J* = 8.6, 3.6 Hz, H14), 4.91 (1H, tsept, *J* = 6.4, 1.4 Hz, H22), 4.77 (1H, tsept, *J* = 7.6, 1.4 Hz, H27), 4.59

(1H, t, J = 8.9 Hz, H13A), 4.33 (1H, br dd, J = 15.8, 6.4 Hz, H21A), 4.14 (1H, dd, J = 8.9, 3.5 Hz, H13B), 4.06 (1H, br dd, J = 15.8, 6.4 Hz, H21B), 4.11 and 3.27 (2H, AB system, J = 16.7 Hz, H8), 2.47 (1H, dd, J = 13.8, 7.4 Hz, H26A), 2.42 (1H, dd, J = 13.8, 8.0 Hz, H26B), 1.76 (3H, d, J = 0.8 Hz, Me24), 1.67 (3H, d, J = 1.1 Hz, Me25), 1.57 (3H, br s, Me29), 1.47 (3H, d, J = 0.8 Hz, Me30); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7 (C2), 168.7 (C9), 153.9 (C11), 145.1 (C7a), 138.3 (C15), 136.7 (C28), 136.3 (C23), 130.0 (C3a), 129.0 (C17, C19), 128.4 (C18), 125.3 (C16, C20), 124.5 (C5), 124.0 (C4), 121.6 (C6), 118.4 (C22), 116.6 (C27), 112.1 (C7), 70.1 (C13), 57.4 (C14), 50.1 (C3), 40.4 (C8), 38.2 (C21), 36.7 (C26), 26.0 (C29), 25.7 (C25), 18.3 (C24), 18.1 (C30); IR (KBr) ν_{max} 2972, 2916, 2858, 1781, 1712, 1605, 1488, 1432, 1382, 1322, 1251, 1201 cm^{-1}; EIMS m/z (relative intensity) 550/552 ($[M]^+$, 2.1/2.0), 483/485 (84/84), 387/389 (22/19), 345/347 (27/19), 319/321 (55/50), 292 (48), 265 (17), 263 (22), 251/253 (44/47), 164 (15), 133 (60), 104 (100), 105 (50), 91 (29), 69 (36), 41 (60), 39 (62).

4.7. Preparation of (+)- and (−)-2-(6-bromo-1,3-bis(3-methylbut-2-enyl)-2-oxoindolin-3-yl)acetic acids (+)-12 and (−)-12

To a solution of (3*R*,14*S*)- or (3*S*,14*S*)-**6**, (0.11 g, 0.20 mmol) in THF (2 mL) was added LiOH (0.20 g, 8.35 mmol) dissolved in an aqueous solution (29–32%) of H_2O_2 (0.13 mL, 4.24 mmol) and H_2O (1 mL), and the mixture stirred at room temperature for 24 h. The reaction mixture was treated with an aqueous saturated solution of Na_2SO_3 for 20 min followed by extraction with EtOAc (3 × 15 mL). The organic phase was washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt–hexanes 1:2 to give (+)-**12** as a pale yellow oil (0.060 g, 74%), $[\alpha]_D^{20}$ = +18.3 (*c* 1, $CHCl_3$), or (−)-**12** as a pale yellow oil (0.058 g, 72%), $[\alpha]_D^{20}$ = −18.3 (*c* 1, $CHCl_3$).

4.8. VCD measurements

IR and VCD spectra were measured using a BioTools Chiral*IR* spectrophotometer equipped with dual photoelastic modulation. Samples of (3*R*,14*S*)- and (3*S*,14*S*)-**4**, **6**, **13a**–**c**, and **14** 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} during 4–20 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.

4.9. X-ray diffraction analyses

Data for (3*S*)-**14** were acquired on an Agilent Technologies Gemini A CCD diffractometer using Mo Kα radiation (λ = 0.7073 Å). Crystal data were $C_{21}H_{27}BrN_2O_2$ M = 419.35, orthorhombic, space group $P2_12_12_1$ a = 9.1141(3) Å, b = 10.1139(2) Å, c = 24.0163(7) Å, V = 2213.80(11) Å^3, Z = 4, ρ = 1.26 mg/mm^3, μ(Mo Kα) = 1.872 mm^{-1}, total reflections = 96675, unique reflections 5967 (R_{int} 0.0001%), observed reflections 4230, final R indices [$I > 2\sigma(I)$] R_1 = 3.9%, wR_2 = 8.3%. The structure was solved by direct methods using the SHELXS-97[20] program, included in the WINGX v1.6[21] package, and refined 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. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ, UK. Fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments

We are pleased to acknowledge the financial support from CONACYT (Mexico) grants 183481, 152994 and 132048. R.E.C.R. and C.I.B.H. thank CONACYT for fellowships 330632 and 237689, respectively.

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) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523–5528; (g) Fréchard, A.; Fabre, N.; Péan, C.; Montaut, S.; Fauvel, M.-T.; Rollin, P.; Fourasté, I. *Tetrahedron Lett.* **2001**, *42*, 9015–9017; (h) Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *J. Org. Chem.* **2006**, *71*, 8559–8564; (i) Cravotto, G.; Giovenzana, G. B.; Palmisano, G.; Penoni, A.; Pilati, T.; Sisti, M.; Stazi, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3070–3074; (j) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Trends Heterocycl. Chem.* **1999**, *6*, 111–124; (k) Morales-Ríos, M. S.; Suárez-Castillo, O. R. *Nat. Prod. Commun.* **2008**, *3*, 629–642; (l) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem. Eur. J.* **2011**, *17*, 1388–1408.
2. (a) Carlé, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012–4013; (b) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586–1589; (c) Christophersen, C. *Acta Chem. Scand.* **1985**, *B39*, 517–529.
3. (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482–5487; (b) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420–422; (c) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543–5549; (d) Morales-Ríos, M. S.; Rivera-Becerril, E.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2493–2499.
4. Suárez-Castillo, O. R.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Zúñiga-Estrada, E. A.; Cruz-Borbolla, J.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2011**, *22*, 2085–2098.
5. Debie, E.; De Gussem, E.; Dukor, R. K.; Herrebout, W.; Nafie, L. A.; Bultinck, P. *ChemPhysChem* **2011**, *12*, 1542–1549.
6. (a) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *J. Org. Chem.* **1999**, *64*, 1086–1087; (b) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Trujillo-Serrato, J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186–1192; (c) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Tetrahedron* **2002**, *58*, 1479–1484; (d) Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Aquino-Torres, E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Heterocycles* **2007**, *71*, 1539–1551.
7. (a) Suárez-Castillo, O. R.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Sánchez-Zavala, M.; Rivera-Becerril, E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2009**, *20*, 2374–2389; (b) Vázquez-Arredondo, R. M.; Suárez-Castillo, O. R.; Meléndez-Rodríguez, M.; Sánchez-Zavala, M.; Cano-Escudero, I. C.; Bautista-Hernández, C. I.; Cruz-Borbolla, J.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2012**, *23*, 1279–1293.
8. (a) Taniguchi, T.; Monde, K. *J. Am. Chem. Soc.* **2012**, *134*, 3695–3698; (b) Batista, J. M.; Batista, A. N. L.; Mota, J. S.; Cass, Q. B.; Kato, M. J.; Bolzani, V. S.; Freedman, T. B.; López, S. N.; Furlan, M.; Nafie, L. A. *J. Org. Chem.* **2011**, *76*, 2603–2612; (c) Massa, A.; Rizzo, P.; Monaco, G.; Zanasi, R. *Tetrahedron Lett.* **2013**, *54*, 6242–6246; (d) Komori, K.; Taniguchi, T.; Mizutani, S.; Monde, K.; Kuramochi, K.; Tsubaki, K. *Org. Lett.* **2014**, *16*, 1386–1389; (e) Asai, T.; Taniguchi, T.; Yamamoto, T.; Monde, K.; Oshima, Y. *Org. Lett.* **2013**, *15*, 4320–4323; (f) Buendía-Trujillo, A. I.; Torres-Valencia, J. M.; Joseph-Nathan, P.; Burgueño-Tapia, E. *Tetrahedron: Asymmetry* **2014**, *25*, 1418–1423; (g) Sánchez-Castellanos, M.; Bucio, M. A.; Hernández-Barragán, A.; Joseph-Nathan, P.; Cuevas, G.; Quijano, L. *Chirality* **2015**, *27*, 247–252; (h) Joseph-Nathan, P.; Gordillo-Román, B. Vibrational Circular Dichroism Absolute Configuration Determination of Natural Products In *Progress in the Chemistry of Organic Natural Products*; Kinghorn, A. D., Falk, H., Kobayashi, J., Eds.; Springer International Publishing: Switzerland, 2015; Vol. 100, pp 311–451.
9. Suárez-Castillo, O. R.; Meléndez-Rodríguez, M.; Beiza-Granados, L.; Cano-Escudero, I. C.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Nat. Prod. Commun.* **2011**, *6*, 451–456.
10. Reina, M.; Burgueño-Tapia, E.; Bucio, M. A.; Joseph-Nathan, P. *Phytochemistry* **2010**, *71*, 810–815.
11. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
12. (a) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490–519; (b) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 520–552; (c) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 553–586; (d) Halgren, T. A.; Nachbar, R. B. *J. Comput. Chem.* **1996**, *17*, 587–615; (e) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 616–641.
13. As implemented in Spartan08, Windows v 1.2.0; Wavefunction Inc.: Irvine, CA, USA, 2009.

14. Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
15. (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.
16. Kawasaki, T.; Shinada, M.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem.* **2008**, *73*, 5959–5964.
17. (a) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; (b) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41*, 96–103.
18. Brogan, J. T.; Stoops, S. L.; Lindsley, C. W. *ACS Chem. Neurosci.* **2012**, *3*, 658–664.
19. Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328–7331.
20. Sheldrick, G. M. *Programs for Crystal Structure Analysis*; Institüt für Anorganische Chemie der Universität; University of Göttingen: Göttingen, Germany, 1988.
21. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.