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# One-pot synthesis of conformationally restricted spirooxindoles

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**Abstract**—Diastereomeric three-, five- and six-membered spirocycloalkyloxindoles were successfully synthesized in a rapid and convenient manner from readily accessible starting materials in moderate to high yields using 1-methyl-3-acetonitriloxindole after a one-pot base-mediated double-alkylation strategy. It was found that the diastereoselection is dependent on the reaction conditions and the spirocycloalkyl ring size, with the 3*R**,8*R** diastereomers being thermodynamically favored under the basic reaction conditions for three- and five-membered rings, and the 3*R**,8*S** diastereomer in the case of six-membered rings, as predicted by DFT calculations. The relative stereochemistry was supported by 2D NMR spectra and X-ray crystal structural analysis. The conformational rigidity of the spirocycloalkyloxindoles in solution was established based on NMR experimental and theoretical DFT approaches.


## 1. Introduction

Functionalized spirocycloalkyloxindoles are found in a variety of natural products and bioactive molecules.[1] Consequently, many synthetic methodologies have been developed for constructing these spirocycles, most of which were based on cycloaddition or condensation reactions.[2] Among them, cyclization reactions of dianions[3] with dielectrophiles constitute a useful strategy for the synthesis of carbo- and heterocyclic systems owing to their simplicity and synthetic usefulness.[4] However, cyclization reactions of dianions often suffer from side reactions, such as polymerization, decomposition, or formation of open-chain products. In order to prevent some side reactions, or tedious protection–deprotection sequences, selective sequential metalations and electrophilic condensations constitute a valuable alternative.[5] In particular, it has been known for many years that enolate alkylation of oxindoles with dibromides[6] results in the formation of spirooxindoles. Recently, this methodology has been proven powerful in the synthesis of the spirocyclohexenyloxindole SR 121463 A, a potent and selective vasopressin $V_2$ receptor antagonist.[7] As part of our continuing indole chemistry studies, we have profited from the acidic nature of oxindoles to introduce a variety of alkyl groups at C3 and applied them as intermediates in natural product synthesis.[8] In this paper we report, to the best of our knowledge, the first domino cyclization of sequential anionic species of 3-acetonitriloxindole with alkyl dibromides to provide a new convenient approach to a homologated series of conformationally restricted spirocycloalkyloxindoles.

## 2. Results and discussion

### 2.1. Preparation and conformational analysis of spirocyclopropyloxindoles, 4 and 5

The work began by establishing a general and practical method for the spirocyclization of oxindole **1** through coupling to alkyl dibromides $(CH_2)_nBr_2$ ($n$=1–4). The target molecules are anticipated to be derived from intermediates **2a–d**, which by bromide substitution reactions could generate a single C–C bond (path **A**), leading to the desired pairs of diastereomeric spirooxindoles **4/5**, **6/7**, **8/9**, and **10/11**, or alternatively to a C=C bond (path **B**) to give terminal alkenes **3b–d** (Scheme 1). Initial attempts to effect the coupling reaction of **1** and dibromomethane using 1.5 equiv of $K_2CO_3$ in DMSO at room temperature gave rise to a complex mixture in which the spirocyclopropyloxindoles **4** and **5** were evidenced in a diastereomeric ratio (dr) of 7:2 as determined by $^1$H NMR analysis of unpurified reaction products, along with a substantial amount of intermediate **2a** and a significant formation of undesired oxidized side product (3-hydroxy-1-methyl-2-oxo-2,3-dihydroindole-3-yl)-acetonitrile[9] (entry 1, Table 1). Substitution of the base for NaOH (15% aqueous NaOH in THF, rt) also proved to be unfruitful (entry 2). However, vastly improved yields of desired spirocyclopropyloxindoles **4** and **5** in a 3:1 dr (65.4%

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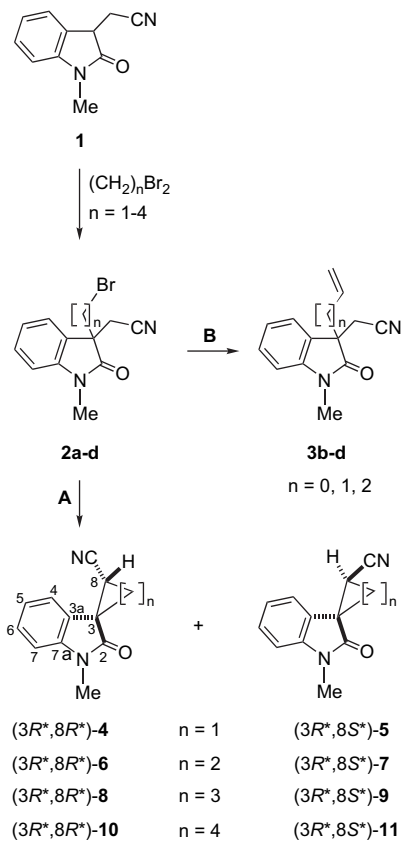
isolated combined yield) were obtained using 2.5 equiv of NaH in DMF at room temperature for 1 h, without interference of side reactions (entry 3). On the basis of experiments monitored by GC/MS and $^1$H NMR, completion of the equilibrated reaction was reached after 5 h leading to a 2:1 ratio in favor of **4**, evidencing that the kinetic product **4** epimerizes to **5** over time (entry 4). The same 2:1 dr was also reached by subjecting samples of pure **4** or **5** to the same basic reaction conditions (NaH in DMF). With the above evidence, it follows that the base-promoted double alkylation proceeded through initial $C_3$ alkylation of the $Na^+$ enolate derived from oxindole **1**, to give **2**, which undergoes an intramolecular nucleophilic attack of the nitrile-stabilized carbanion to yield the desired spirooxindoles **4/5**.




**Scheme 1**.

**Table 2**. Selected $^1$H NMR shifts ($\delta$), $^3J$(H,H) coupling constants (hertz), and NOESY correlations of **4**, **5**, **8**–**11** in $CDCl_3$

| Compound | $\delta$H4 | $\delta$H8 | $^3J_{8,9c}$ [a,b] | $^3J_{8,9t}$ [b,c] | H4 NOESY correlations |
|---|---|---|---|---|---|
| **4** | 7.20 | 2.44 | 6.9 | 9.4 | H9*c* |
| **5** | 6.86 | 2.36 | 7.4 | 9.4 | H8, H9*t* |
| **8** | 7.34 | 3.30 | 9.3 | 8.5 | H9*c*, H10*c*, H11*c* |
| **9** | 7.14 | 3.04 | 11.0 | 7.7 | H8, H11*t* |
| **10** | 7.61 | 3.08 | 11.3 | 4.1 | H9*c*, H11*c* |
| **11** | 7.16 | 2.86 | 12.6 | 3.6 | H8, H12*t* |

[a] In *anti* relationship.
[b] The diastereotopic methylene protons are designated as cis (*c*) or trans (*t*) with respect to the cyano group.
[c] In *gauche* relationship.

Spirocyclopropyloxindoles **4** and **5** were separated into individual diastereomerically pure compounds by flash chromatography on silica gel. The unambiguous attribution of their relative configuration was based on the anisotropic effect of the nitrile and carbonyl groups on $^1$H NMR chemical shifts of H4 and H8, respectively (Table 2), together with the spatial proximity determination of characteristic protons by using a NOESY sequence. Notably, the spirocycles 3*R**,8*R**-**4** and 3*R**,8*S**-**5**, have been previously prepared on the basis of a reductive cyclization of isomerized bromo derivative using the Baylis–Hillman approach.[10] Consistent with the experimental data, the conformational analysis carried out using density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory,[11] gave one optimized conformer for each diastereomer, with **4** being lower in energy by 2.7 kcal/mol,[12] in agreement with experimental data. The stereoelectronic repulsion between the C=O and CN groups seems to be responsible for diastereomer **5** being less stable than **4**.

## 2.2. Preparation and conformational analysis of spirocyclopentyloxindoles, 8 and 9

With an operative process identified, the scope of this synthetic method was explored by envisaging the construction of homologated spirocycloalkyloxindoles. As anticipated, only traces of the homologated analogue **6/7** could be detected after reaction of **1** with 1,2-dibromoethane (entry 5, Table 1), affording the vinyloxindole **3b** in 33% yield (path **B**) together with unreacted starting material. This result may be attributable to either the unfavorable cyclobutane ring strain or kinetic problems associated with its

**Table 1**. Reaction of **1** with alkyl dibromides

| Entry | $(CH_2)_nBr_2/n$ | Base/equiv | Time/h[a] | Product (yield/%) | dr[b] *R***R**:*R***S** |
|---|---|---|---|---|---|
| 1 | 1 | $K_2CO_3$/1.5 | 4[c] | **2a** (51), **4/5** (23),[d] Side product[e] (18) | 7:2 |
| 2 | 1 | NaOH/8.0[f] | 20[g] | **1** (17), **2a** (Traces), **4/5** (24),[d] side product[e] (25) | 7:2 |
| 3 | 1 | NaH/2.5 | 1 | **1** (28), **4/5** (65.4)[d] | 3:1 |
| 4 | 1 | NaH/2.5 | 5 | **4/5** (91)[d] | 2:1 |
| 5 | 2 | NaH/2.5 | 5 | **1** (42), **3b** (33), **6/7** (Traces)[h] | — |
| 6 | 3 | NaH/2.5 | 5 | **3c** (10.5),[h] **8/9** (52.6)[d] | 3:2 |
| 7 | 4 | NaH/3.5 | 10 | **3d** (2.3), **10/11** (52.2)[d] | 3:4 |

[a] Unless otherwise specified, reaction was carried out at rt in DMF.
[b] Determined by GC/MS and/or $^1$H NMR of crude reaction mixture.
[c] At rt in DMSO.
[d] Overall isolated yield.
[e] (3-Hydroxy-1-methyl-2-oxo-2,3-dihydroindole-3-yl)acetonitrile.[9]
[f] In the presence of $(t\text{-Bu})_4NHSO_4$.
[g] At rt in THF.
[h] Determined by $^1$H NMR integration after silica gel column chromatography.

formation. Conversely, the reaction involving **1** and 1,3-dibromopropane gives rise to a mixture of three isomeric products having an *m*/*z* of 226 in a 3:2:1 ratio, as shown by GC/MS. Analysis of the isomers by $^1$H NMR showed them to be the expected spirocyclopentyloxindoles **8** and **9**, in addition to terminal alkene **3c**, respectively. Product purification was extremely difficult owing to very similar chromatographic mobilities of side product **3c** and diastereomers **8/9**. Complete separation of **8** and **9** from undesired **3c** was achieved by slow fractional crystallization. It was also observed that stirring samples of pure **8** or **9** at room temperature in methanolic $K_2CO_3$ solution sufficed to induce slight epimerization.

Detailed conformational analysis of cyclopentane rings[13] often is precluded for pseudorotating ring molecules in which all geometrical parameters change significantly making it difficult to obtain sufficient information for setting up a Karplus relationship. Microwave[14] and electron diffraction[15] studies on cyanocyclopentane agreed that the cyano group prefers the equatorial position at the flap of an envelope conformation. Here we extended these studies to investigate the conformer preferences in solution of spirocyclopentanes **8** and **9**. As in the case of **4** and **5**, the key features which allow us to assign the relative stereochemistry of diastereomers **8** and **9** were based on the anisotropic effect of the nitrile and carbonyl groups on $^1$H chemical shifts of H4 and H8, respectively (Table 2), together with diagnostic sets of cross-peaks observed in the NOESY spectra between aromatic H4 ($\delta$=7.34) and the diastereotopic methylene protons cis to the cyano group (Table 2). In addition, the vicinal coupling constants for the H8 signal at $\delta$ 3.30 (dd, $^3J$=9.3, 8.5 Hz) suggest that the molecule exists in a preferred conformation.[16] Similarly, **9** appears to exist in solution as a preferred envelope conformer with the opposite orientation of the nitrile group as evidenced by the strong NOESY interaction between H4 ($\delta$=7.14) and H8 ($\delta$=3.04), as well as the magnitude of the observed vicinal coupling constants for the H8 signal (dd, $^3J$=11.0, 7.7 Hz). These data allowed to define the relative stereochemistry as 3*R**,8*R** for major product **8** and 3*R**,8*S** for **9** (Scheme 1). The structure and relative stereochemistry of major diastereomer **8** was confirmed by X-ray crystallography (Fig. 1). These data are in good agreement with the computational search, which gave single low-energy envelope conformation for **8** and **9**, with the cyano group disposed equatorial and **8** being lower in energy by 0.35 kcal/mol.[12]

### 2.3. Preparation and conformational analysis of spirocyclohexyloxindoles, 10 and 11

When 1,4-dibromobutane was used as dielectrophile, the reaction with **1**, using 2.5 equiv of NaH in DMF at room temperature for 5 h, gave rise to only one product having *m*/*z* 320/322, which was identified as brominated intermediate **2d**. Optimization of this reaction was achieved with 2.5 equiv of NaH for 3 h at room temperature and adding another 1.0 equiv with additional stirring for 7 h, thus affording diastereomers **10** and **11** together with terminal alkene **3d** in a 3:4:1 ratio, respectively, as determined by GC/MS of the crude reaction mixture. Both diastereomers were separated by careful column chromatography and crystallization procedures yielding **10** in 22.4% and **11** in 29.8% yields (entry 7, Table 1). Equilibration was also equally observed in **10/11**, for example, when minor isomer **10** was treated with NaH in DMF at room temperature, isomerization to **10/11** in a 3:4 ratio takes place proving the higher thermodynamic stability of **11** under these conditions. Despite the expected disfavored entropic factor involving the larger bromoalkylated chain of intermediate **2d**, which could favor increased amounts of debromohydrated product **3d**, the chemoselectivity is similar to that of **2c**.

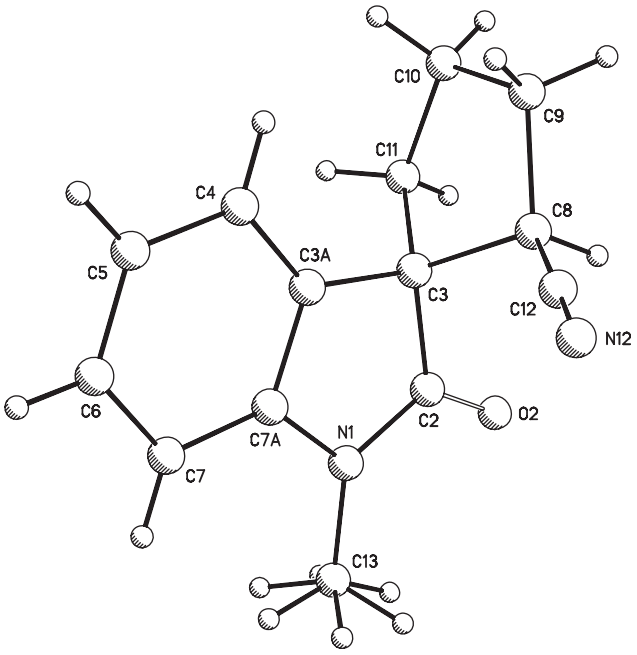



**Figure 1**. Crystal structure of **8**. The methyl group is disordered.[19]

The attribution of the relative configuration of **10** and **11** was based on $^1$H NMR analysis (Table 2) in combination with diagnostic sets of cross-peaks observed in the NOESY spectra. Thus, for **10** the proton signal pattern[17] for H8 at $\delta$ 3.08 (dd, $^3J$=11.3, 4.1 Hz) indicated their axial position at the spirocyclohexane ring based upon their axial and equatorial interactions with H9*c* and H9*t*, respectively (Table 2). Similarly, for **11** the proton signal pattern for H8 at $\delta$ 2.86 (dd, $^3J$=12.6, 3.6 Hz) and its NOESY interaction with H4 ($\delta$ 7.16) evidence equally the axial orientation for this hydrogen and confirms the equatorial disposition of the cyano group in solution. Therefore, the relative configurations of these diastereomers were 3*R**,8*R** for **10** and 3*R**,8*S** for major product **11** (Scheme 1). These data are predictive for a prioritary chair conformation for both **10** and **11** in solution. Single crystals of **10** and **11** could be obtained and the molecular structures shown in Figure 2 clearly reveal the chair conformation of the spirocyclohexane ring, with the cyano group in an equatorial position in accordance with NMR data, and further supported the relative stereochemistry of both diastereomers. The high stability of **11**, as determined using the B3LYP/6-31+G(d,p) basis set[18] with Gaussian 03W, may be rationalized in terms of minor 1,3-diaxial and electrostatic interactions and explains the observed conformational rigidity of diastereomer **11** in solution, as well as its higher product ratio.

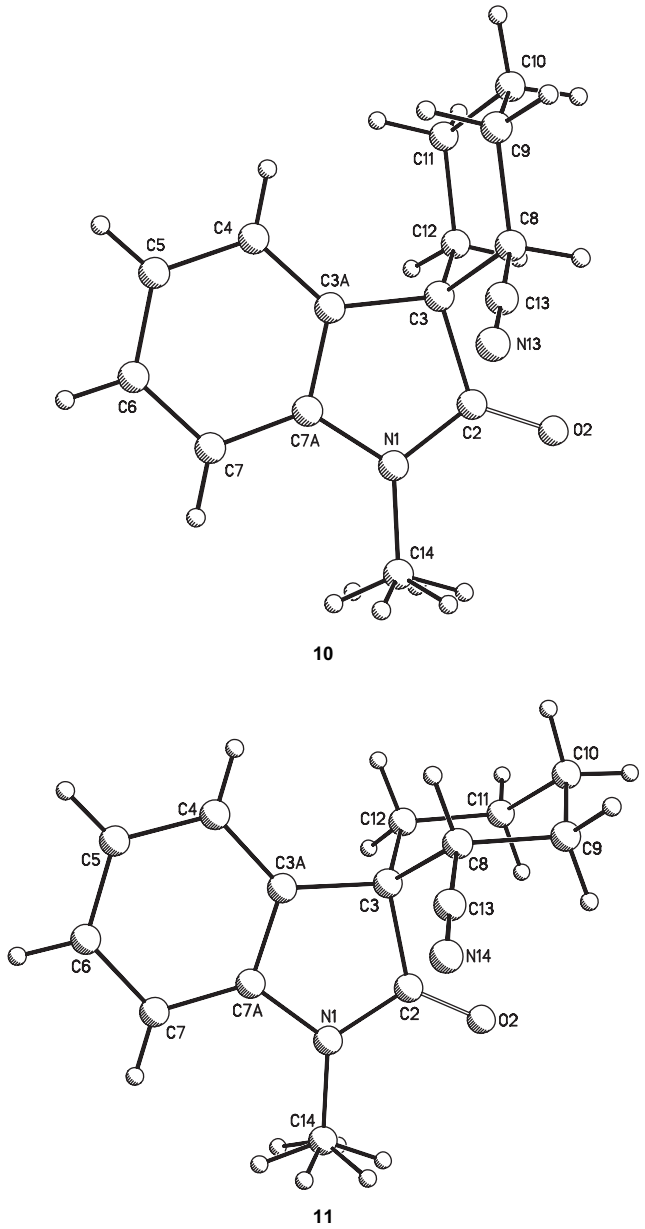



**Figure 2**. Crystal structures of **10** and **11**. The methyl group is disordered.[19]

## 3. Conclusions

A series of spirooxindoles were prepared by cyclization reaction of sequential anionic species derived from oxindole **1** with dielectrophiles in a one-pot procedure to obtain equilibrated mixtures of diastereomers through a nitrile-stabilized carbanion, with the 3*R**,8*R** diastereomers being the thermodynamic products for three- and five-membered rings, and the 3*R**,8*S** diastereomer in the case of six-membered rings, as predicted by DFT calculations. The diastereoselectivity of the reactions was dependent on ring size, and systematically diminished with ring size increase. In spirocyclopentyloxindoles **8** and **9** pseudorotation is largely hindered by high barriers. In these compounds, envelope conformations with the cyano group disposed equatorial and the spiranic carbon atom at the flap in **8**, and C9 at the flap in **9**, were identified by NMR measurements, DFT calculations, and by single-crystal X-ray analysis of **8**. In spirocyclohexyloxindole **11** the conformational ring interconversion is frozen in a chair conformation with the cyano group in an equatorial position, whereas for **10** inverted chair conformations could exist in solution, with one of them being highly populated. It is clear that in these compounds the general conformation of the backbone revealed by NMR studies in solution is retained in the solid. X-ray diffraction studies finally served as an ultimate proof of relative configuration assignments.

## 4. Experimental

### 4.1. General

DMF was dried by standard method from $MgSO_4$ and NaOH, successively, and stored over molecular sieves. All commercial grade reagents were used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 $F_{254}$ coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was performed using silica gel 60 (230–400 mesh). IR spectra were obtained using a Perkin–Elmer 16 FPC FT spectrophotometer. NMR spectra were recorded on Varian Mercury spectrometers working at 300 and 75.4 MHz for $^1H$ and $^{13}C$, respectively. NMR data are reported in parts per million ($\delta$) downfield from tetramethylsilane, using the formulae numbering given in Scheme 1 with the normal abbreviations (s, singlet; d, doublet; t, triplet; br, broad; m, multiplet) and *c* and *t* to denote cis and trans to CN, respectively. All structural assignments were supported by gHMBC, gHSQC, and NOESY. GC/MS analyses were conducted on a Varian CP 3800 GC equipped with a selective mass Varian Saturn 2000 detector and a 30 m, 0.25 mm i.d., 0.25 μm CP-SIL capillary column, using helium as carrier gas (1 mL/min), programmed from 70 °C, to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. Relative percentage amounts were calculated from total ion chromatograms by the computer. MS analyses were obtained in the electron impact (EI) mode at an ionizing voltage of 70 eV. High-resolution (HR) mass spectra were measured at the UCR Mass Spectrometry Facility, University of California, Riverside, CA.

**4.1.1. General procedure for spirocyclization of oxindole 1.** To a solution of oxindole **1** (200 mg, 1.07 mmol) in DMF (4 mL) was added NaH (64.5 mg, 2.68 mmol), and the suspension was stirred at room temperature for 5 min before addition of the corresponding alkyl dibromide (1.3 mmol). The resulting mixture was stirred for 5 h at the same temperature, quenched with water (5 mL) and 5% aqueous HCl (1.5 mL), extracted with EtOAc (3×25 mL), washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo to give a mixture containing mainly isomers **4/5**, **8/9** or **10/11**.

**4.1.1.1. (1*R**,2*R**)- and (1*S**,2*R**)-1′-Methyl-2′-oxo-1′,2′-dihydrospiro[cyclopropane-1,3′-indole]-2-carbonitrile 4 and 5.**[10] Following the general procedure, **1** was reacted with dibromomethane (226.0 mg, 1.3 mmol) to give a 2:1 mixture of **4** and **5** that was separated by flash chromatography (acetone/hexane 1:19) to afford successively **4** (130.0 mg, 60.7%) and **5** (64.9 mg, 30.3%). The spectral and analytical data were consistent with those reported.[10]

**4.1.1.2. (1′-Methyl-2′-oxo-3-vinyl-2,3-dihydro-3-indolyl)acetonitrile (3b).** Following the general procedure, **1** was reacted with 1,2-dibromoethane (244.2 mg, 1.3 mmol) to give alkene **3b** (74.3 mg, 33%) as colorless oil, after flash chromatography (EtOAc/hexane 1:19). $R_f$ 0.42 (EtOAc/hexane 2:3). IR ($CHCl_3$, $cm^{-1}$): 3012, 2254, 1716, 1614. $^1H$ NMR ($CDCl_3$): $\delta$ 7.50 (1H, ddd, $J$=7.4, 1.1, 0.5 Hz, H4), 7.40 (1H, td, $J$=7.7, 1.2 Hz, H6), 7.17 (1H, td, $J$=7.6, 1.2 Hz, H5), 6.93 (1H, br d, $J$=8.0 Hz, H7), 6.00 (1H, dd, $J$=17.3, 10.4 Hz, H9), 5.35 (1H, d, $J$=10.4 Hz, H10), 5.23 (1H, d, $J$=17.3 Hz, H10′), 3.23 (3H, s, Me), 3.02 (1H, d, $J$=16.5 Hz, H8), 2.71 (1H, d, $J$=16.5 Hz, H8′). $^{13}C$ NMR ($CDCl_3$): $\delta$ 174.9 (C2), 143.1 (C7a), 134.0 (C9), 129.6 (C6), 127.7 (C3a), 124.7 (C4), 123.2 (C5), 118.9 (C10), 116.3 (CN), 108.9 (C7), 51.6 (C3), 26.6 (Me), 25.4 (C8). EIMS *m*/*z* (relative intensity) 212 ($M^+$, 38.7), 172 (100), 144 (52.2). HRMS calcd for $C_{13}H_{12}N_2O$ $[M+H]^+$ 213.1028, found 213.1028.

**4.1.1.3. (1*R**,2*R**)- and (1*S**,2*R**)-1′-Methyl-2′-oxo-1′,2′-dihydrospiro[cyclopentane-1,3′-indole]-2-carbonitrile 8 and 9.** Following the general procedure, **1** was reacted with 1,3-dibromopropane (262.5 mg, 1.3 mmol) to give a mixture of **3c**, **8**, and **9** in a 1:3:2 ratio, respectively. The GC retention times (min) for the three compounds are: **3c**, 5.26; **8**, 5.84; **9**, 5.86. Pure **8** and **9** were obtained by fractional crystallization (acetone/hexane) after flash chromatography (EtOAc/hexane 1:4) of the crude mixture. Data for **8**: (76.7 mg, 31.6%) as colorless crystals (acetone/hexane), mp 135–137 °C. $R_f$ 0.26 (EtOAc/hexane 3:7). IR ($CHCl_3$, $cm^{-1}$): 3016, 2244, 1710, 1614. $^1H$ NMR ($CDCl_3$): $\delta$ 7.34 (1H, br d, $J$=7.4 Hz, H4), 7.33 (1H, td, $J$=7.7, 1.4 Hz, H6), 7.11 (1H, td, $J$=7.7, 1.1 Hz, H5), 6.84 (1H, br d, $J$=7.7 Hz, H7), 3.30 (1H, dd, $J$=9.3, 8.5 Hz, H8), 3.25 (3H, s, Me), 2.58 (1H, m, H9*t*), 2.30 (1H, m, H9*c*), 2.25 (1H, m, H11*t*), 2.15 (1H, m, H10*t*), 2.15 (1H, m, H10*c*), 1.98 (1H, m, H11*c*). $^{13}C$ NMR ($CDCl_3$): $\delta$ 178.1 (C2), 143.0 (C7a), 130.7 (C3a), 129.0 (C6), 123.8 (C4), 123.1 (C5), 119.1 (CN), 108.5 (C7), 56.0 (C3), 38.3 (C8), 37.4 (C11), 31.7 (C9), 26.6 (Me), 24.6 (C10). EIMS *m*/*z* (relative intensity) 226 ($M^+$, 100), 185 (75), 160 (70). HRMS calcd for $C_{14}H_{14}N_2O$ $[M+H]^+$ 227.1184, found 227.1184. Data for **9**: (51.2 mg, 21.0%) as white solid (acetone/hexane), mp 123–126 °C. $R_f$ 0.28 (EtOAc/hexane 3:7). IR ($CHCl_3$, $cm^{-1}$): 3014, 2244, 1712, 1614. $^1H$ NMR ($CDCl_3$): $\delta$ 7.29 (1H, td, $J$=7.7, 1.4 Hz, H6), 7.14 (1H, dd, $J$=7.4, 1.1 Hz, H4), 7.06 (1H, td, $J$=7.4, 1.1 Hz, H5), 6.84 (1H, br d, $J$=7.7 Hz, H7), 3.24 (3H, s, Me), 3.04 (1H, dd, $J$=11.0, 7.7 Hz, H8), 2.56 (1H, m, H9*t*), 2.35 (1H, m, H9*c*), 2.31 (1H, m, H10*c*), 2.25 (1H, m, H11*c*), 2.00 (1H, m, H11*t*), 1.98 (1H, m, H10*t*). $^{13}C$ NMR ($CDCl_3$): $\delta$ 177.2 (C2), 143.5 (C7a), 130.3 (C3a), 128.8 (C6), 122.8 (C5), 121.7 (C4), 118.7 (CN), 108.3 (C7), 56.4 (C3), 39.7 (C8), 36.5 (C11), 30.7 (C9), 26.5 (Me), 24.7 (C10). EIMS *m*/*z* (relative intensity) 226 ($M^+$, 63), 185 (100), 160 (70). HRMS calcd for $C_{14}H_{14}N_2O$ $[M+H]^+$ 227.1184, found 227.1183.

**4.1.1.4. (1*R**,2*R**)- and (1*S**,2*R**)-1′-Methyl-2′-oxo-1′,2′-dihydrospiro[cyclohexane-1,3′-indole]-2-carbonitrile 10 and 11.** To a solution of oxindole **1** (200 mg, 1.07 mmol) in DMF (4 mL) was added NaH (64.5 mg, 2.68 mmol), and the mixture was stirred at room temperature for 5 min before addition of 1,4-dibromobutane (280.7 mg, 1.3 mmol). The mixture was stirred for 3 h at the same temperature and then an additional portion of NaH (25.8 mg, 1.07 mmol) was added. After 7 h at room temperature, the reaction was quenched with water (5 mL) and 5% aqueous HCl (1.5 mL), extracted with EtOAc (3×25 mL), washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo to give a mixture of diastereomers **10** and **11** together with alkene **3d** in a 3:4:1 ratio, respectively. The mixture was purified by flash chromatography (EtOAc/hexane 1:19) to afford successively **11**, **10**, and **3d**. The GC retention times (min) for the three compounds are: **3d**, 5.57; **10**, 6.21; **11**, 6.04. Data for **10**: (57.7 mg, 22.4%) as colorless crystals (acetone/hexane), mp 154–156 °C. $R_f$ 0.41 (EtOAc/hexane 3:7). IR ($CHCl_3$, $cm^{-1}$): 3014, 2244, 1712, 1614, 1472. $^1H$ NMR ($CDCl_3$): $\delta$ 7.61 (1H, br d, $J$=7.4 Hz, H4), 7.38 (1H, td, $J$=7.7, 1.1 Hz, H6), 7.12 (1H, td, $J$=7.7, 1.1 Hz, H5), 6.94 (1H, br d, $J$=7.7 Hz, H7), 3.26 (3H, s, Me), 3.08 (1H, dd, $J$=11.3, 4.1 Hz, H8), 2.28 (1H, m, H9*t*), 2.06 (1H, m, H9*c*), 2.00 (1H, m, H10*c*), 1.86 (1H, m, H11*t*), 1.86 (1H, m, H11*c*), 1.83 (1H, m, 12*t*), 1.72 (1H, m, 12*c*), 1.60 (1H, m, H10*t*). $^{13}C$ NMR ($CDCl_3$): $\delta$ 177.4 (C2), 143.4 (C7a), 130.0 (C3a), 129.0 (C6), 125.0 (C4), 122.6 (C5), 119.1 (CN), 108.7 (C7), 49.0 (C3), 34.2 (C8), 32.1 (C12), 26.5 (Me), 25.3 (C9), 23.4 (C10), 20.0 (C11). EIMS *m*/*z* (relative intensity) 240 ($M^+$, 100), 186 (46), 160 (85). HRMS calcd for $C_{15}H_{16}N_2O$ $[M+H]^+$ 241.1341, found 241.1343. Data for **11**: (76.9 mg, 29.8%) as colorless crystals (acetone/hexane), mp 149–151 °C. $R_f$ 0.44 (EtOAc/hexane 3:7). IR ($CHCl_3$, $cm^{-1}$): 3014, 2244, 1706, 1614, 1472. $^1H$ NMR ($CDCl_3$): $\delta$ 7.32 (1H, dd, $J$=7.7, 1.5 Hz, H6), 7.16 (1H, ddd, $J$=7.4, 1.6, 0.6 Hz, H4), 7.10 (1H, dd, $J$=7.4, 1.0 Hz, H5), 6.88 (1H, br d, $J$=7.7 Hz, H7), 3.24 (3H, s, Me), 2.86 (1H, dd, $J$=12.6, 3.6 Hz, H8), 2.62 (1H, m, H9*c*), 2.24 (1H, m, H11*c*), 2.00 (1H, m, H10*c*), 2.01 (1H, m, H9*t*), 1.85 (1H, m, 12*c*), 1.70 (1H, m, 12*t*), 1.63 (1H, m, H11*t*), 1.41 (1H, m, H10*t*). $^{13}C$ NMR ($CDCl_3$): $\delta$ 176.4 (C2), 143.1 (C7a), 131.5 (C3a), 129.0 (C6), 122.8 (C5), 121.8 (C4), 119.2 (CN), 108.4 (C7), 47.7 (C3), 35.9 (C8), 33.5 (C12), 26.1 (Me), 24.8 (C9), 24.3 (C10), 19.4 (C11). EIMS *m*/*z* (relative intensity) 240 ($M^+$, 100), 186 (35), 160 (70). HRMS calcd for $C_{15}H_{16}N_2O$ $[M+H]^+$ 241.1341, found 241.1342. Data for **3d**: (6.0 mg, 2.3%) as colorless oil $R_f$ 0.40 (EtOAc/hexane 3:7). IR ($CHCl_3$, $cm^{-1}$): 3014, 2252, 1712, 1640, 1470. $^1H$ NMR ($CDCl_3$): $\delta$ 7.44 (1H, br d, $J$=7.4 Hz, H4), 7.37 (1H, td, $J$=7.7, 1.1 Hz, H6), 7.16 (1H, td, $J$=7.7, 1.1 Hz, H5), 6.90 (1H, br d, $J$=7.7 Hz, H7), 5.62 (1H, ddt, $J$=12.1, 5.2, 6.6 Hz, CH═), 4.87 (1H, dq, $J$=5.2, 1.6 Hz, $CH_2$═), 4.83 (1H, dq, $J$=12.3, 1.6 Hz, $CH_2$═), 3.23 (3H, s, Me), 2.86 and 2.58 (2H, d, $J$=16.7 Hz, H8,8′), 2.10 (2H, t, $J$=8 Hz, $CH_2$-9), 1.69 (2H, m, $CH_2$-10). $^{13}C$ NMR ($CDCl_3$): $\delta$ 176.7 (C2), 143.5 (C7a), 136.6 (CH═), 129.3 (C6), 128.8 (C3a), 123.3 (C4, C5), 116.5 (CN), 115.4 ($CH_2$═), 108.6 (C7), 48.7 (C3), 35.2 (C9), 28.5 (C10), 26.4 (Me), 26.1 (C8). EIMS *m*/*z* (relative intensity) 240 ($M^+$, 6), 186 (65), 159 (100). HRMS calcd for $C_{15}H_{16}N_2O$ $[M+H]^+$ 241.1341, found 241.1338.

### 4.2. X-ray diffraction analysis of 8, 10, and 11

Single crystals of **8**, **10**, and **11** were grown by slow crystallization from acetone/hexane. The X-ray data of **8** were measured on a Bruker Smart 6000 CCD diffractometer using Mo Kα radiation ($\lambda$=0.71073 Å). A total of 1321 frames

were collected with a scan width of 0.3° and exposure time of 10 s/frame. The frames were processed with the SAINT software package, provided by the diffractometer manufacturer. The X-ray data of **10** and **11** were collected on a Bruker-Nonius CAD4 diffractometer using Cu Kα radiation ($\lambda$=1.54184 Å). The data were collected in the $\omega-2\theta$ scan mode. Unit cell refinements were done using the CAD4 Express v 2.0 software. All structures were solved by direct methods using the SHELXS-97 program included in the WinGX v 1.64.05 crystallographic software package. For the structural refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. The idealized disordered *N*-methyl groups in **8**, **10**, and **11** were assumed with two positions rotated by 60° and with a half occupancy for hydrogen atoms.[19] Compound **8** crystallized as colorless blocks in the monoclinic space group $P2_1/n$ with cell dimensions $a$=7.4840(3) Å, $b$=16.8650(7) Å, $c$=9.5910(4) Å, $\beta$=102.75(2)° and was refined to final $R$ indices (all data) $R$ (%)=5.5, $R$w (%)=12.3. Compound **10** crystallized as colorless blocks in the triclinic space group $P$-1 with cell dimensions $a$=7.995(1) Å, $b$=8.911(1) Å, $c$=10.321(2) Å, $\alpha$=65.67(1)°, $\beta$=80.04(1)°, $\gamma$=89.59(1)° and was refined to final $R$ indices (all data) $R$ (%)=4.4, $R$w (%)=11.8. Compound **11** crystallized as colorless blocks in the orthorhombic space group *Pcab* with cell dimensions $a$=10.925(3) Å, $b$=11.069(1) Å, $c$=21.435(3) Å and was refined to final $R$ indices (all data) $R$ (%)=3.8, $R$w (%)=10.9. Data collection and refinement parameters, atom coordinates, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre. The CCDC deposition number for **8** is 645052, that for **10** is 645053, and that for **11** is 645054.

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