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# Asymmetric Synthesis of Congested Spiro-cyclopentaneoxindoles via an Organocatalytic Cascade Reaction

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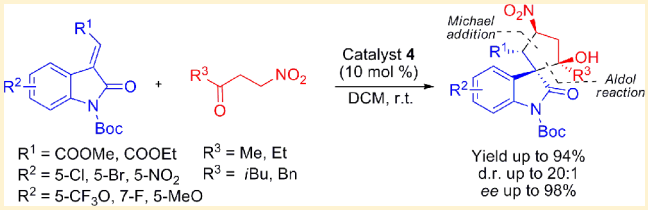
Supporting Information

**ABSTRACT:** Starting from simple alkylidene oxindoles and nitroketones, a highly stereoselective methodology was developed for the synthesis of spiro-cyclopentaneoxindoles with four consecutive stereogenic centers. Using an organocatalytic cascade of Michael and aldol reactions in the presence of a chiral thiourea catalyst products were obtained in moderate to high yields and excellent enantioselectivities. Nitro, ester, and hydroxyl groups were introduced to the spiro ring, which could be used to facilitate further functionalization of the products.




A spirooxindole scaffold makes up the core of many natural and synthetic bioactive compound[1−4] exhibiting a broad range of activities, including antitumor[5] and antimalarial activity[6] (Figure 1). For those reasons, the asymmetric synthesis of spirooxindoles has received considerable attention (for recent reviews, see refs 7 and 8). However, the formation of spiro rings with multiple consecutive stereocenters still remains an inspiring and difficult task.[9−11]

The main challenges en route to chiral spirooxindoles are the formation of a quaternary spiro center and the need to exhibit a stringent control over the stereochemical outcome of the reaction, as in most cases multiple stereocenters are formed.

Many strategies have been devised for spirooxindole core formation, with the ones employing alkylidene oxindoles as precursors being most prominent.[12−15] Alkylidene indolinones are activated via the carbonyl group for the initial Michael addition, effectively delaying the formation of the quaternary center that takes place during the cyclization step to form the spiro ring. This tactic allows us to overcome the high energy barrier associated with quaternary center formation, as well as delivering the chiral induction for the later stages of the cascade by the initial chirality generated by a Michael addition step.

Among the other spirooxindoles, the synthesis of functionalized all-carbon spiro-cyclopentane derivatives is still a challenge.[16−20] More important than the size of the cycle is its substitution pattern enabling constructing various derivatives of spiro-cyclopentaneoxindoles with promising medicinal properties. In a recent paper,[21] we described a new methodology for the asymmetric synthesis of spiro-cyclopropyloxindoles[22] starting from alkylidene indolinones. Inspired by this work, as well as recent literature examples and success in our own laboratory in organocatalytic Michael[23−27] and aldol reactions,[28] we set out to develop a new methodology for the formation of highly substituted spiro-cyclopentaneoxindoles (the structural core of many natural products) employing alkylidene oxindoles and nitroketones as precursors. β-Nitroketones **2** with an ethylene bridge between functional groups, which both can be activated by hydrogen bonding, can act as versatile substrates for organocatalysis.[29] Although the nucleophilic and electrophilic sites are present in the same molecule, a sufficiently short linker ensures a suppressed intramolecular reaction making them ideal building blocks for cascade reactions. With these considerations, we envisioned a new Michael−aldol cascade using alkylidene oxindoles and nitroketones leading to the formation of highly functionalized spiro-cyclopentaneoxindoles (Scheme 1). Nitro, ester, and hydroxyl groups in the target compound are reactive sites for further transformations making obtained spiro-cyclopentaneoxindoles highly valuable building blocks.

This two-step cascade reaction involves an initial Michael addition of nitronate to alkylidene oxindole **1**, followed by intramolecular cyclization via an aldol reaction. In the course of the cascade, four consecutive stereogenic centers are formed, two of which are quaternary. From the outset, it was envisioned, that the reaction could be catalyzed by bifunctional thiourea or a squaramide catalyst (Figure 2),[30−32] as both alkylidene indolinones **1** and nitroketones **2** can by activated by hydrogen bonding. It was deemed necessary for the alkylidene oxindole to bear a protecting group, as this could provide an additional hydrogen bond acceptor group, as well as increasing the solubility of the substrate. It is known that the protective group at nitrogen of the oxindole influences the stereoselectivity of the aldol reaction.[33,34] From the synthetic point of view it was reasonable to use easily removable Boc-group. For the generation of a nitronate, however, the presence of a tertiary amine subunit within the catalyst was considered to be crucial (deprotonation during nitronate formation).

To investigate the proposed cascade, a model reaction between alkylidene oxindole **1a** and nitroketone **2a** was chosen (Table 1). Initial optimization experiments were conducted in

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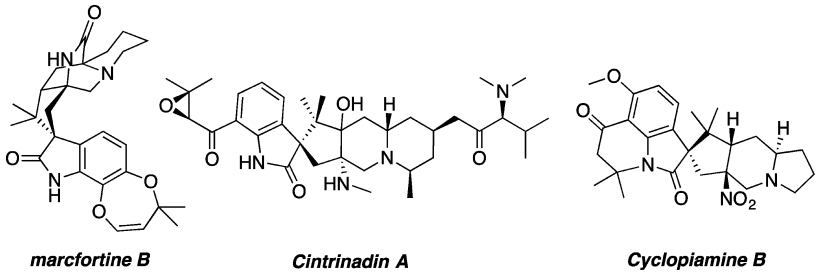
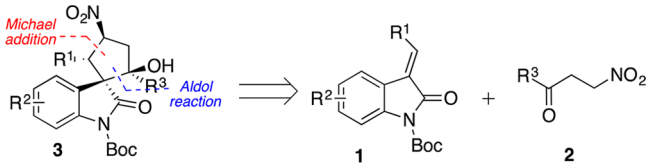



**Figure 1.** Spirooxindole-containing natural products.

**Scheme 1. Retrosynthetic Analysis for Spirocyclopentaneoxindole Formation**



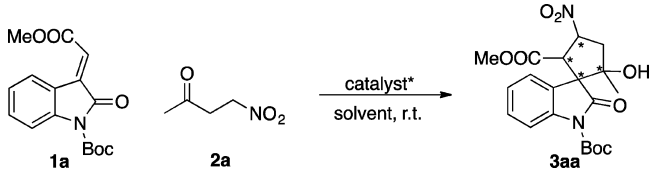

toluene at ambient temperature. To our delight, when 10 mol % of thiourea **4** catalyst was used, in the presence of 2 equiv of nitroketone **2a**, product was isolated in 86% yield with a 10:1 diastereomeric ratio and 96% ee (Table 1, entry 1). Lowering the catalyst loading and excess of nitroketone had a detrimental effect on the reaction rate and yield (Table 1, entry 2). Squaramide **5** as well as thioureas **6** and **7** provided inferior results in respect to catalyst **4** (Table 1, entries 3–6). When solvent was switched from toluene to DCM, however, the reaction rate was slightly increased with only a minor influence on the stereoselective outcome of the reaction (Table 1, entry 7).

With the optimal conditions in hand (1 equiv of **1**, 2 equiv of **2**, 10 mol % of thiourea **4** in DCM), next we set out to determine the full substrate scope for the reaction (Scheme 2). Different alkylidene oxindoles **1** were subjected to the reaction conditions, both with electron-withdrawing and -donating groups at the aromatic ring.

The electronic nature of an alkylidene oxindole **1** had little to no effect on the reactivity and selectivity of the reaction. All products were obtained in high yield (79–94%) and good to excellent diastereoselectivities (from 10:1 to 20:1) and high enantioselectivities (Scheme 2). Although it should be noted that the ester moiety was essential for the successful reaction outcome, as with phenyl, cyano, or 4-nitrobenzoyl groups either no reaction occurred or a complex mixture of products was detected by TLC.

The absolute stereochemistry of the product was unambiguously assigned by a single-crystal X-ray diffraction of spirocyclopentanoxindole **3ea** after the Boc-group had been cleaved (Figure 3). Other compounds in the series were assigned on the basis of analogy. Taking into account the structural information gained from the X-ray structure, we propose that after the initial Michael addition of the nitronate to alkylidene oxindole has occurred ester and nitro groups are in *trans* orientation. The carbonyl group of the ketone and nitro group are hydrogen-bonded to the catalyst, efficiently fixing their orientation for the cyclization to proceed stereospecifically. This ensures a preferred *cis*-configuration of the nitro and hydroxyl groups in the final product.

**Table 1. Screening Results**[a]




| entry | 2 (equiv) | catalyst (mol %) | solvent | time (h) | yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 4 (10 mol %) | toluene | 3 | 86 | 10:1 | 96 |
| 2 | 1.2 | 4 (5 mol %) | toluene | 20 | 57 | 10:1 | 96 |
| 3 | 1.2 | 5 (5 mol %) | toluene | 46 | 29 | 3:1 | 82 |
| 4 | 1.2 | 6 (5 mol %) | toluene | 24 | 49 | 7:1 | −94 |
| 5 | 2 | 6 (10 mol %) | toluene | 3 | 75 | 7:1 | −99 |
| 6 | 2 | 7 (10 mol %) | toluene | 2 | 71 | 5:1 | −99 |
| 7 | 2 | 4 (10 mol %) | DCM | 2 | 87 | 10:1 | 95 |

[a]Reaction conditions: alkylidene oxindole, nitroketone, and catalyst were mixed and stirred at rt until TLC showed full conversion. [b]Isolated yield. [c]Determined by $^1$H NMR; [d]Determined by chiral HPLC.

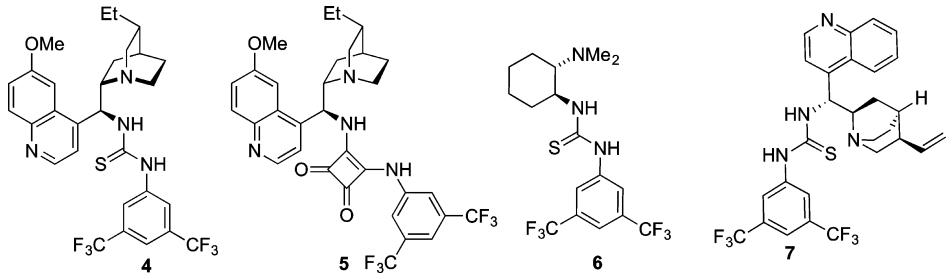



**Figure 2.** Catalysts used.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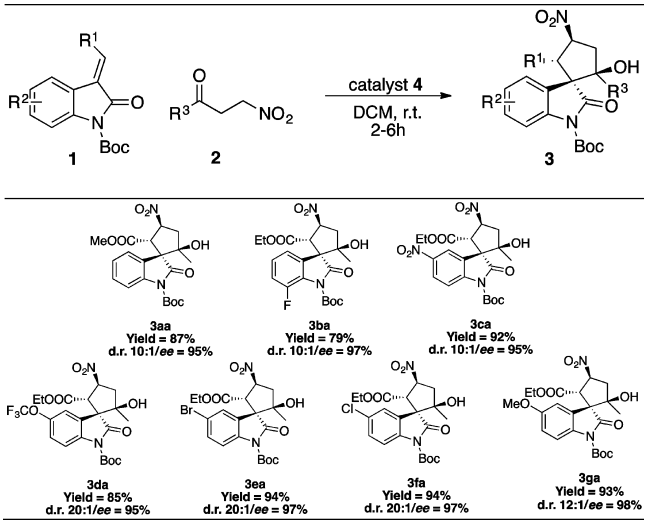
**Scheme 2. Substrate Scope Experiments**[a]




[a]Reaction conditions: 1 equiv of alkylidene oxindole **1** (0.15 mmol), 2 equiv of nitroketone **2** (0.3 mmol), and 10 mol % of catalyst **4** (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).

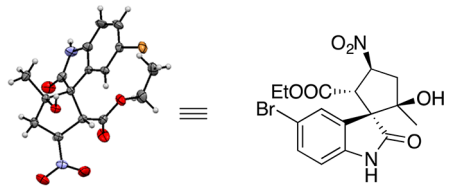
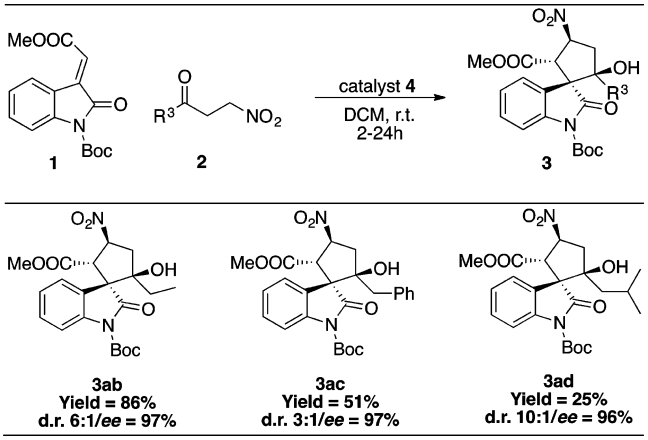


**Figure 3.** X-ray structure of spirooxindole **3ea′** (one of two similar molecules in the asymmetric unit).

To further expand the substrate scope of our methodology, different nitroketones **2** were synthesized and subjected to the reaction conditions (Scheme 3). A clear correlation between the size of the substituent $R^3$ and reaction rate, as well as selectivity, emerged. With the ethyl group as $R^3$, only a slight drop in diastereoselectivity was observed (dr 6:1) as the product was obtained in high yield and 97% ee for the major isomer. The benzyl substituent proved more challenging as only moderate selectivity (dr 2:1) and yield (51%) were achieved (Scheme 3). The sterically bulkiest isobutyl group produced product with high dr 10:1 but with low yield (25%). Finally, phenyl-substituted nitroketone was prepared, but under optimal cascade reaction conditions no product was obtained. It is noteworthy, however, that in all cases high enantioselectivity was retained.

**Scheme 3. Substrate Scope Experiments**[a]




[a]Reaction conditions: 1equiv of alkylidene oxindole **1** (0.15 mmol), 2 equiv of nitroketone **2a** (0.3 mmol) and 10 mol % of catalyst **4** (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).

In conclusion, we have developed a new organocatalytic, highly enantioselective methodology for the synthesis of spirocyclopentaneoxindoles via a Michael−aldol cascade reaction. During the cascade reaction, four consecutive stereogenic centers were formed, two of which were quaternary. In most cases, high diastereoselectivities were observed (up to 20:1) which were only diminished when sterically more demanding nitroketones were employed as reaction substrates. The final product can be easily unprotected to obtain free spirooxindoles, and versatile functional groups (nitro, hydroxyl, and ester) were introduced to the spiro ring, which could easily be transformed to other functionalities. This represents a novel strategy for the synthesis of highly functionalized spirooxindoles with an all-carbon spiro ring.

## EXPERIMENTAL SECTION

**General Methods.** Full assignment of $^1$H and $^{13}$C chemical shifts is based on the 1D and 2D FT NMR spectra on a 400 MHz instrument. Solvent peaks ($CHCl_3/CDCl_3$ $\delta$ = 7.26/77.16) were used as chemical shift references. Chiral HPLC was performed using Chiralcel OD-H, Chiralpak AD-H, and Chiralpak AS-H columns. Mass spectra were recorded by using Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Precoated silica gel 60 $F_{254}$ plates were used for TLC, whereas for column chromatography Merck silica gel was used. Commercial reagents were generally used as received. DCM and EtOAc were distilled from $P_2O_5$.

**Synthesis of Catalysts.** Thiourea **6** was commercially available from Strem and used as received. Thioureas **4** and **7** and squaramide **5** were prepared according to literature procedures.[35−37]

**Synthesis of Starting Materials.** Methylene indolinones **1a−g** were prepared according to literature procedures from commercially available isatines using a Boc protection−Wittig sequence.[38] Nitroketones **2** were prepared as described by Miyakoshi et al.[39]

**5-Methyl-1-nitrohexan-3-one 2d.** Synthesis was based on the literature procedure.[39] 5-Methylhex-1-en-3-one (0.6 g, 5.4 mmol) and sodium nitrite (0.74 g, 10.7 mmol) were dissolved in THF (2.7 mL). Acetic acid (0.6 mL, 10.7 mmol) was added dropwise and the mixture stirred at ambient temperature for overnight. The reaction mixture was extracted with water/DCM, and the organics were back-extracted with satd $NaHCO_3$ and dried over $MgSO_4$. The mixture was filtered, concentrated, and purifed by silica gel column chromatography (eluent petroleum ether/acetone 20:1) to yield 337 mg (40%) of product as yellow oil: IR $\nu$ 2961, 1717, 1557 cm$^{-1}$; $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 4.67−4.62 (m, 2H), 3.04 (t, *J* = 6.0 Hz, 2H), 2.40 (d, *J* = 7.0 Hz, 2H), 2.26−2.12 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 205.7, 69.0, 51.9, 38.9, 24.7, 22.6; HRMS (ESI) calcd for $[M + Na]^+$ $(C_7H_{13}NO_3Na)^+$ requires *m*/*z* 182.0788, found 182.0788.

**General Procedure for the Synthesis of Spiro-cyclopentaneoxindoles.** Methylene oxindole **1** (0.15 mmol, 1 equiv), nitroketone **2** (0.3 mmol, 2 equiv), and thiourea **4** (10 mol %, 0.015 mmol) were dissolved in DCM (0.5 mL) and stirred at ambient temperature until TLC showed complete disappearance of the limiting starting material. The mixture was directly purified by silica gel column chromatography using a mixture of heptane/EtOAc as eluent. The diastereomeric ratio was determined by $^1$H NMR and enantioselectivity by chiral HPLC analysis.

**1′-*tert*-Butyl 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxy-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**late 3aa.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane:EtOAc as an eluent in 87% yield (55 mg) with dr 10/1 and ee 99% that was determined after the cleavage of the Boc-group [Chiralcel AD-H, Hex/*i*-PrOH 80:20, 1 mL/min, 230 nm; *major* ($t_R$ = 9.44 min) and *minor* ($t_R$ = 8.04 min)]: IR $\nu$ 3497, 2981, 2258, 1783, 1739, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 7.87 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.47 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.42−7.36 (m, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 5.55 (ddd, *J* = 10.4, 6.3, 1.9 Hz, 1H), 4.70 (d, *J* = 6.3 Hz, 1H), 3.56 (s, 3H), 3.18 (dd, *J* = 15.3, 10.4 Hz, 1H), 2.61 (dd, *J* = 15.1, 1.9 Hz, 1H), 2.20 (s, 1H), 1.63 (s, 9H), 1.03 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.9, 169.9, 148.8, 140.8, 129.6, 125.2, 124.7, 124.5, 115.2, 85.2, 85.0, 82.4, 65.8, 54.8, 52.9, 43.2, 28.2, 21.6; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{20}H_{24}N_2O_8Na)^+$ requires *m*/*z* 443.1425, found 443.1423.

**1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-7′-Fluoro-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ba.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-7-fluoro-2-oxoindoline-1-carboxylate **1b** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 79% yield (54 mg) with dr 10/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* ($t_R$ = 10.01 min) and *minor* ($t_R$ = 11.02 min)]: IR $\nu$ 3503, 2983, 2259, 1783, 1743, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 7.31 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.25−7.12 (m, 2H), 5.56 (ddd, *J* = 10.3, 6.0, 1.7 Hz, 1H), 4.66 (d, *J* = 5.9 Hz, 1H), 4.12−3.93 (m, 2H), 3.22−3.10 (m, 1H), 2.69−2.60 (m, 1H), 2.25−2.20 (m, 1H), 1.59 (s, 9H), 1.09−1.01 (m, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.1, 169.1, 148.5 (d, *J* = 251.0 Hz), 147.1, 128.9 (d, *J* = 2.2 Hz), 127.5 (d, *J* = 9.5 Hz), 125.5 (d, *J* = 7.0 Hz), 120.6 (d, *J* = 3.5 Hz), 117.7 (d, *J* = 20.3 Hz), 85.2 (d, *J* = 32.7 Hz), 82.6, 66.2 (d, *J* = 1.7 Hz), 62.1, 54.8, 42.9, 27.7, 21.4, 13.6; HRMS (ESI) calcd for $[M + H]^+$ $(C_{21}H_{26}FN_2O_8)^+$ requires *m*/*z* 453.1668, found 453.1660.

**1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4,5′-dinitro-2′-oxospiro-[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ca.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-5-nitro-2-oxoindoline-1-carboxylate **1c** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 92% yield (66 mg) with dr 10/1 and ee 95% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* ($t_R$ = 12.73 min) and *minor* ($t_R$ = 8.13 min)]: IR $\nu$ 3502, 2983, 1791, 1765, 1740, 1557, 1526 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 8.34 (d, *J* = 2.5 Hz, 1H), 8.26 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 5.51 (ddd, *J* = 10.5, 6.4, 1.8 Hz, 1H), 4.72−4.58 (m, 1H), 4.04 (qd, *J* = 7.1, 3.4 Hz, 1H), 3.89 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.16 (dd, *J* = 15.5, 10.3 Hz, 1H), 2.57 (dd, *J* = 15.5, 1.8 Hz, 1H), 2.39 (s, 1H), 1.57 (s, 9H), 1.04−0.91 (m, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 174.9, 168.9, 148.3, 146.0, 144.7, 127.1, 125.7, 121.2, 115.0, 86.3, 85.1, 82.8, 65.4, 62.4, 55.7, 43.8, 28.2, 21.6, 13.8; HRMS (ESI) calcd for $[M + K]^+$ $(C_{21}H_{25}N_3O_{10}K)^+$ requires *m*/*z* 518.1172, found 518.1169.

**1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4-nitro-2′-oxo-5′-(trifluoromethoxy)spiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3da.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxo-5-(trifluoromethoxy)indoline-1-carboxylate **1d** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 85% yield (66 mg) with dr 20/1 and ee 95% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* ($t_R$ = 5.41 min) and *minor* ($t_R$ = 4.77 min)]: IR $\nu$ 3496, 2983, 1787, 1739, 1557 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 7.90 (d, *J* = 8.9 Hz, 1H), 7.41−7.38 (m, 1H), 7.29−7.21 (m, 1H), 5.56 (ddd, *J* = 10.3, 6.2, 1.8 Hz, 1H), 4.60 (d, *J* = 6.2 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.94 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.20 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.61 (dd, *J* = 15.3, 1.8 Hz, 1H), 2.26 (s, 1H), 1.62 (s, 9H), 1.06 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.2, 169.1, 148.6, 145.9 (d, *J* = 2.2 Hz), 139.2, 127.4, 122.1, 120.58 (d, *J* = 257.4 Hz), 118.7, 115.9, 85.4, 85.1, 82.7, 65.8, 62.1, 55.3, 43.5, 28.2, 21.6, 13.7; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{22}H_{25}F_3N_2O_9Na)^+$ requires *m*/*z* 541.1402, found 541.1408.

**1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-5′-Bromo-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ea.** Synthesized according to the general procedure from *tert*-butyl (*E*)-5-bromo-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1e** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 94% yield (72 mg) with dr 20/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* ($t_R$ = 8.39 min) and *minor* ($t_R$ = 5.85 min)]: IR $\nu$ 3496, 2981, 1785, 1738, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, Chloroform-d) $\delta$ 7.70 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.7, 2.1 Hz, 1H), 5.48 (ddd, *J* = 10.3, 6.2, 1.8 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.12 (ddd, *J* = 15.4, 10.3, 1.3 Hz, 1H), 2.55 (dd, *J* = 15.3, 1.7 Hz, 1H), 2.16 (d, *J* = 1.1 Hz, 1H), 1.55 (s, 9H), 1.01−0.93 (m, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 174.9, 169.0, 148.5, 139.7, 132.3, 128.0, 127.6, 117.6, 116.5, 85.2, 85.1, 82.6, 65.6, 62.0, 55.1, 43.2, 28.1, 21.5, 13.6; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{21}H_{25}BrN_2O_8Na)^+$ requires *m*/*z* 535.0686, found 535.0687.

**1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-5′-Chloro-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3fa.** Synthesized according to the general procedure from 1′-*tert*-butyl 5-ethyl (1*S*,2*R*,4*S*,5*S*)-5′-bromo-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate **1f** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane:EtOAc as an eluent in 94% yield (66 mg) with dr 20/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* ($t_R$ = 7.67 min) and *minor* ($t_R$ = 5.69 min)]: IR $\nu$ 3499, 2982, 1786, 1738, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 7.76 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.49 (ddd, *J* = 10.3, 6.1, 1.8 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 4.05 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.12 (ddd, *J* = 15.3, 10.3, 1.2 Hz, 1H), 2.55 (dd, *J* = 15.4, 1.6 Hz, 1H), 2.15 (d, *J* = 1.2 Hz, 1H), 1.55 (s, 9H), 1.04−0.89 (m, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.1, 169.1, 148.7, 139.3, 130.2, 129.5, 127.4, 125.3, 116.2, 85.3, 85.2, 82.7, 65.7, 62.1, 55.3, 43.4, 28.2, 28.2, 21.6, 13.7; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{21}H_{25}ClN_2O_8Na)^+$ requires *m*/*z* 491.1191, found 491.1193.

**1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-5′-methoxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ga.** Synthesized according to the general procedure from (*E*)-ethyl 2-(5-methoxy-2-oxoindolin-3-ylidene)acetate **1g** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 93% yield (65 mg) with dr 12/1 and ee 98% [Chiralcel OD-H, Hex/*i*-PrOH 95:5, 1 mL/min, 230 nm; *major* ($t_R$ = 15.57 min) and *minor* ($t_R$ = 20.66 min)]: IR $\nu$ 2984, 2254, 1789, 1739, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 7.78 (d, *J* = 8.9 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.55 (ddd, *J* = 10.4, 6.1, 1.8 Hz, 1H), 4.61 (d, *J* = 6.1 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.90 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.82 (s, 3H), 3.16 (ddd, *J* = 15.3, 10.4, 1.6 Hz, 1H), 2.61 (dd, *J* = 15.2, 1.8 Hz, 1H), 2.23 (d, *J* = 1.6 Hz, 1H), 1.61 (s, 9H), 1.05−0.97 (m, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 175.8, 169.4, 156.9, 148.9, 134.0, 126.9, 116.0, 114.0, 111.1, 85.3, 84.7, 82.6, 66.1, 61.9, 55.8, 54.9, 43.1, 28.2, 21.6, 13.7; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{22}H_{28}N_2O_9Na)^+$ requires *m*/*z* 487.1687, found 487.1692.

**1′-*tert*-Butyl 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Ethyl-2-hydroxy-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ab.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 1-nitropentan-3-one **2b**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 86% yield (56 mg) with dr 6/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* ($t_R$ = 11.87 min) and *minor* ($t_R$ = 7.41 min)]: IR $\nu$ 3502, 2980, 1784, 1739, 1556 $cm^{-1}$; $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ 7.86 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.48 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.42−7.35 (m, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 5.58 (ddd, *J* = 10.5, 6.6, 2.0 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H),


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3.57 (s, 3H), 3.13−3.04 (m, 1H), 2.58 (dd, $J$ = 15.3, 1.9 Hz, 1H), 2.06 (d, $J$ = 1.6 Hz, 1H), 1.63 (s, 9H), 1.54−1.42 (m, 1H), 1.12−0.99 (m, 1H), 0.81 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 176.0, 169.9, 148.8, 140.9, 129.6, 125.6, 124.7, 124.4, 115.3, 85.2, 85.1, 85.0, 66.0, 55.1, 52.9, 41.0, 28.2, 28.2, 27.66, 7.7; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{21}H_{26}N_2O_8Na)^+$ requires $m/z$ 457.1581, found 457.1587.

**1′-*tert*-Butyl 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Benzyl-2-hydroxy-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ac.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 4-nitro-1-phenylbutan-2-one **2c**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 51% yield (38 mg) with dr 3/1 and ee 97% for major isomer [Chiralcel OD-H, Hex/*i*-PrOH 95:5, 1 mL/min, 230 nm; *major* ($t_R$ = 15.72 min) and *minor* ($t_R$ = 17.51 min)]: IR $\nu$ 3494, 2982, 2258, 1785, 1742, 1555 cm$^{-1}$; for the *major* isomer: $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 7.80−7.75 (m, 1H), 7.51 (dd, $J$ = 7.5, 1.3 Hz, 1H), 7.33 (td, $J$ = 7.9, 1.4 Hz, 1H), 7.20−7.13 (m, 5H), 7.09−7.03 (m, 1H), 6.97−6.92 (m, 2H), 5.49 (ddd, $J$ = 10.4, 6.4, 1.7 Hz, 1H), 4.68 (d, $J$ = 6.4 Hz, 1H), 3.51 (s, 3H), 3.34−3.24 (m, 1H), 2.69−2.63 (m, 1H), 2.24−2.17 (m, 1H), 2.01 (s, 1H), 1.59 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 176.0, 169.8, 148.8, 140.8, 134.4, 130.1, 129.5, 128.9, 128.2, 127.6, 125.8, 125.3, 115.0, 85.1, 84.9, 83.9, 65.3, 55.5, 52.9, 42.4, 40.5, 28.3; HRMS (ESI) calcd for $[M + Na]^+$ $(C_{26}H_{28}N_2O_8Na)^+$ requires $m/z$ 519.1738, found 519.1740.

**1′-*tert*-Butyl) 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-isobutyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ad.** Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 5-methyl-1-nitrohexan-3-one **2d**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 25% yield (17 mg) with dr 10/1 and ee 96% for major isomer [Chiralcel OD-H, Hex/*i*-PrOH 95:5, 1 mL/min, 230 nm; *major* ($t_R$ = 12.35 min) and *minor* ($t_R$ = 6.80 min)]: IR $\nu$ 3512, 2958, 2873, 2258, 1786, 1739, 1556 cm$^{-1}$; $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 7.90−7.83 (m, 1H), 7.47 (dd, $J$ = 7.5, 1.3 Hz, 1H), 7.41 (td, $J$ = 7.9, 1.4 Hz, 1H), 7.23 (td, $J$ = 7.6, 1.0 Hz, 1H), 5.58 (ddd, $J$ = 10.5, 6.6, 1.9 Hz, 1H), 4.66 (d, $J$ = 6.6 Hz, 1H), 3.56 (s, 3H), 3.17 (ddd, $J$ = 15.3, 10.5, 1.6 Hz, 1H), 2.67 (dd, $J$ = 15.2, 2.0 Hz, 1H), 2.05 (d, $J$ = 1.8 Hz, 1H), 1.64 (s, 9H), 1.34−1.24 (m, 2H), 0.92−0.89 (m, 1H), 0.83 (dd, $J$ = 15.1, 6.6 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 176.0, 169.9, 148.8, 140.9, 129.6, 125.6, 124.8, 124.3, 115.4, 85.4, 85.3, 85.0, 66.7, 54.6, 52.9, 43.0, 41.8, 28.2, 24.4, 24.3, 24.1; HRMS (ESI) calcd for $[M + K]^+$ $(C_{23}H_{30}N_2O_8K)^+$ requires $m/z$ 501.1634, found 501.1630.

**Methyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-5-carboxylate 3aa′.** Title compound was prepared for the determination of enantiomeric purity of spiro-oxindole **3aa** by treatment with TFA at ambient temperature. Ee 99% [Chiralcel AD-H, Hex/*i*-PrOH 80:20, 1 mL/min, 230 nm; *major* ($t_R$ = 9.44 min) and *minor* ($t_R$ = 8.04 min)]: IR $\nu$ 3421, 2989, 1730, 1699, 1546 cm$^{-1}$; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 7.48 (ddd, $J$ = 7.6, 1.3, 0.6 Hz, 1H), 7.28 (td, $J$ = 7.7, 1.3 Hz, 1H), 7.07 (td, $J$ = 7.6, 1.1 Hz, 1H), 6.92 (dt, $J$ = 7.8, 0.8 Hz, 1H), 5.54 (ddd, $J$ = 10.5, 6.3, 1.9 Hz, 1H), 4.73 (d, $J$ = 6.2 Hz, 1H), 3.52 (s, 3H), 3.13 (dd, $J$ = 14.9, 10.5 Hz, 1H), 2.61−2.51 (m, 1H), 1.00 (s, 3H); $^{13}$C NMR (101 MHz, MeOD) $\delta$ 180.8, 172.1, 144.0, 129.7, 129.1, 127.2, 123.1, 110.4, 86.3, 82.3, 67.3, 55.1, 52.8, 44.7, 21.2. Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.12; H, 5.06; N, 8.72.

**Ethyl (1*S*,2*R*,4*S*,5*S*)-5′-Bromo-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-5-carboxylate 3ea′.** Title compound was prepared by treatment of oxindole **3ea** (0.13 mmol, 66 mg) with TFA (50 equiv, 6.4 mmol, 0.5 mL) in DCM (5 mL) at ambient temperature (reaction monitored by TLC). Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent to afford 52 mg (yield = 98%) of product as white solid (mp = 168−170 °C). Product was used to grow a single crystal for X-ray diffraction. Optical rotation for the enantipure compound (single crystal): $[\alpha]$ = −142.3 ($c$ = 0.07, MeOH); IR $\nu$ 3419, 2990, 1733, 1698, 1544 cm$^{-1}$; $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 8.11 (s, 1H), 7.61 (d, $J$ = 2.0 Hz, 1H), 7.43 (dd, $J$ = 8.3, 2.1 Hz, 1H), 6.81 (d, $J$ = 8.2 Hz, 1H), 5.56 (ddd, $J$ = 10.2, 6.3, 1.8 Hz, 1H), 4.62 (d, $J$ = 6.3 Hz, 1H), 4.14−3.95 (m, 2H), 3.19 (dd, $J$ = 15.3, 10.4 Hz, 1H), 2.59 (dd, $J$ = 15.4, 1.9 Hz, 1H), 2.35 (s, 1H), 1.12−1.03 (m, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 178.3, 169.5, 140.8, 132.2, 129.3, 128.8, 115.6, 111.3, 85.1, 82.2, 65.8, 62.1, 54.6, 43.4, 21.6, 13.8; HRMS (ESI) calcd for $[M + H]^+$ $(C_{16}H_{18}BrN_2O_6)^+$ requires $m/z$ 413.0343, found 413.0341.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1$H and $^{13}$C NMR spectra, HPLC chromatograms, and crystallographic data of compound **3ea**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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