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Advanced Synthesis & Catalysis

Practical Stereoselective Synthesis of C3-Spirooxindole- and C2-Spiropseudoindoxyl-Pyrrolidines *via* Organocatalyzed Pictet-Spengler Reaction/Oxidative Rearrangement Sequence

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Abstract: A stereoselective synthetic route to chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidines was accomplished by an enantioselective organocatalyzed Pictet-Spengler reaction of tryptamines and isotryptamines followed by a diastereoselective oxidative rearrangement using eco-friendly oxidants (i.e., $NaOCl \cdot 5H_2O$ and Oxone®). This sequential reaction enables rapid access to chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidines in a one-pot process. A Wnt signaling inhibitory assay of the prepared enantioenriched spiro compounds demonstrated that they exhibited moderate activities.

Keywords: Squaramide catalyst; Spiro compound; One-pot synthesis; Green oxidant; Wnt signaling inhibitory activity

Introduction

Among the large family of biologically active spirooxindoles,[1] C3-spirooxindole-pyrrolidines are found in a variety of natural compounds and pharmaceuticals, such as horsfiline,[2] elacomine,[3] and spirotryptastatin A[4] (Figure 1a). In addition, C2-spiropseudoindoxyl-pyrrolidines, which are structural analogs of C3-spirooxindole-pyrrolidines, have recently received increasing attention in the fields of organic chemistry and drug discovery because of their potent pharmacological activities, with example compounds including fluorocurine,[5] mitragynine pseudoindoxyl,[6] and rauniticine pseudoindoxyl[7] (Figure 1a). Various synthetic methods have been reported for the construction of chiral C3-spirooxindole-pyrrolidine[1c,8] and C2-spiropseudoindoxyl-pyrrolidine scaffolds[9] (Figure 1b). To date, the enantioselective syntheses of chiral spirooxindole-pyrrolidine frameworks have been mainly achieved using indole derivatives, with example routes including the cycloaddition reactions of ylideneoxindoles[8f,i] and azaaurones,[10] the Michael addition reactions of tryptamine-derived oxindoles,[11] and the Pictet-Spengler (PS) reactions[12]/oxidative rearrangements of tryptamine derivatives[13] in an asymmetric manner. While the use of oxindole derivatives as substrates is reliable, a multi-step preparation of the oxindole scaffold is inevitable. In contrast, the enantioselective PS reaction/diastereoselective oxidative rearrangement of readily available tryptamine is an attractive and rapid approach to chiral C3-spirooxindole-pyrrolidines because the oxindole moiety and the chiral spiro center can be constructed simultaneously from chiral tetrahydro-β-carbolines. For example, Jacobsen and Seidel independently contributed to the development of a highly enantioselective PS reaction of non-protected tryptamines using their unique organocatalysts.[12c,i] Furthermore, Tong and coworkers recently developed an oxidative rearrangement of tetrahydro-β-carbolines to yield C3-spirooxindole-pyrrolidines, which employed a catalytic amount of KBr, in addition to Oxone® as the terminal oxidant.[13k]

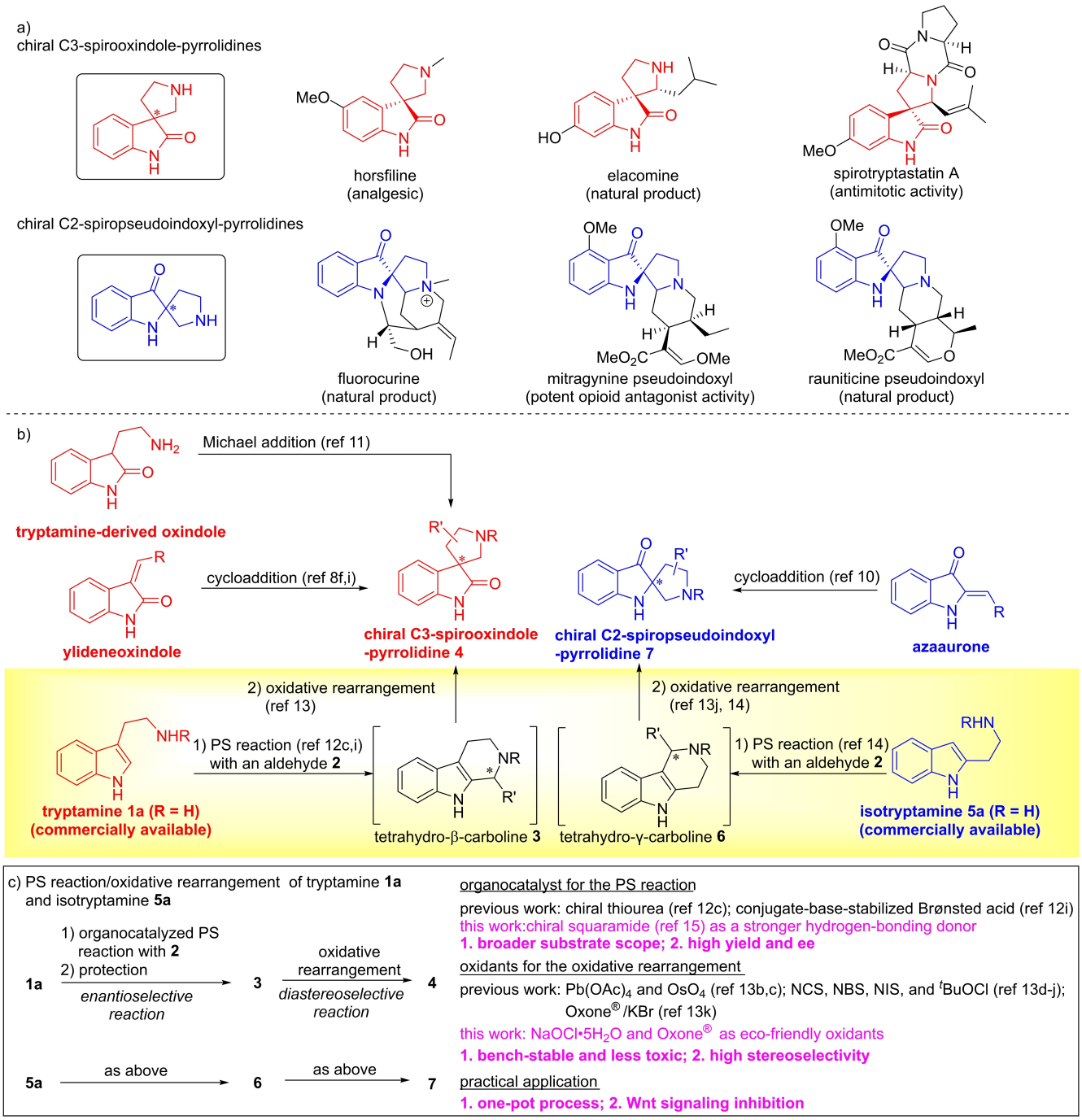


Figure 1. (a) Selected examples of natural products and biologically active compounds containing the chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidine skeletons. (b) Representative enantioselective syntheses of chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidine skeletons. (c) This work: asymmetric syntheses of chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidine frameworks *via* a squaramide-catalyzed PS reaction/green oxidant-mediated diastereoselective oxidative rearrangement sequence.

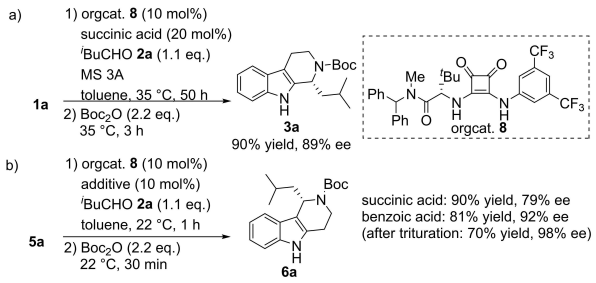
In 2011, Jacobsen and co-workers also reported that a chiral thiourea catalyzed the highly enantioselective PS reaction of isotryptamines. Subsequent NBS-mediated oxidative rearrangement of tetrahydro-γ-carboline provided the chiral C2-spiropseudoindoxyl-pyrrolidine in 48% yield without any loss in enantiopurity.[14] Although significant progress has been made in the syntheses of diverse spirooxindoles, a facile, eco-friendly, and highly stereoselective strategy is still required. Thus, we herein describe a practical synthetic

route to chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidines *via* an enantioselective PS reaction of commercially available tryptamine and isotryptamine using the chiral squaramide as a single organocatalyst, and a subsequent diastereoselective oxidative rearrangement, wherein $NaOCl \cdot 5H_2O$ and Oxone® are employed as eco-friendly oxidants (Figure 1c). In addition, we examine the feasibility of a one-pot process for this sequential reaction. Finally, the ability of the newly obtained enantioenriched spiro compounds to inhibit the Wnt signaling pathway is examined.

Result and Discussion

Organocatalyzed Enantioselective Pictet-Spengler Reactions of Tryptamine 1 and Isotryptamine 5

Initially, to obtain the enantioenriched tetrahydro-β-carbolines **3**, we tested the organocatalyzed enantioselective PS reaction of non-activated tryptamine **1a** with isovaleraldehyde **2a** based on previously reported methods.[12c] Following a comprehensive screening of the reaction conditions (see Table S1 in the Supporting Information), the *tert*-leucine-derived squaramide catalyst **8**[15] (10 mol%), which was initially utilized in the enantioconvergent catalytic S_N1 reaction by Jacobsen, allowed the reaction to proceed in toluene at 35 °C to yield the desired product **3a** in 89% yield and 90% ee following Boc protection of the PS product (Scheme 1a). Subsequently, based on the results presented in Scheme 1a, we investigated the catalytic enantioselective synthesis of the tetrahydro-γ-carbolines **6a** using isotryptamine **5a** and isovaleraldehyde **2a**. The reaction using 10 mol% of organocatalyst **8** in addition to succinic acid provided the corresponding product **6a** in 90% yield and 79% ee. Replacement of the acidic additive with benzoic acid significantly improved the enantioselectivity to 92% ee, and after trituration with *n*-hexane, **6a** was obtained in 70% yield and 98% ee (Scheme 1b).[14,16] The highly enantioselective PS reactions of both tryptamine **1a** and isotryptamine **5a** were successfully catalyzed by organocatalyst **8**, which combined the steric bulks of the *tert*-butyl and benzhydryl groups with squaramide as a strong hydrogen-bonding donor. The absence of either component had a detrimental effect on the enantioselectivity (see Tables S1 and S2 in the Supporting Information).

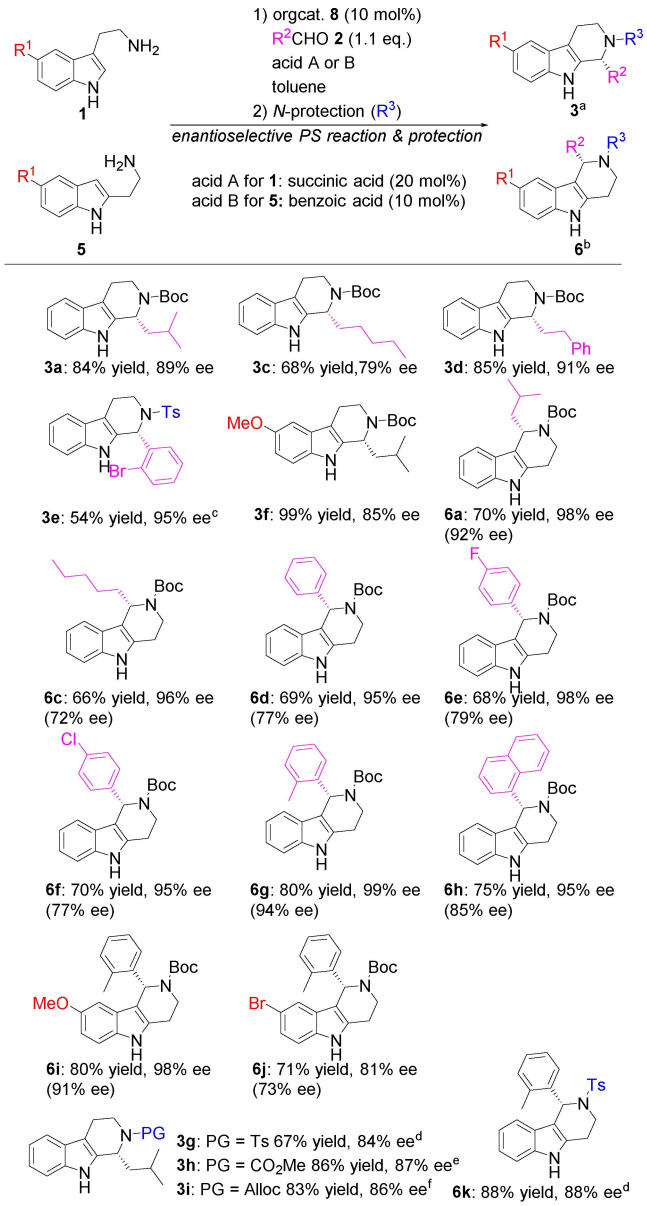


Scheme 1. Enantioselective PS reaction of tryptamine **1a** and isotryptamine **5a** with isovarelaldehyde **2a** catalyzed by chiral squaramide catalyst **8** in the presence of an acidic additive. Yields of **3a** and **6a** were determined by NMR analysis.

With the optimal reaction conditions in hand, we examined the substrate scope for the PS reactions of tryptamines **1** or isotryptamines **5** with aldehydes **2** in the presence of squaramide catalyst **8** and an appropriate acidic additive (succinic acid or benzoic acid) (Scheme 2). Aliphatic and aromatic aldehydes, including 1-hexanal, 3-phenylpropanal, and *o*-bromobenzaldehyde were suitable for this reaction, and products **3c**–**3e** were obtained in moderate to good yields and high enantioselectivities (54–85% yields, 79–95% ees). In addition, methoxy-substituted tryptamine **1b** was smoothly converted into the desired spirooxindole **3f** (99% yield, 85% ee). In the case of the enantioselective PS reaction of isotryptamine **5a**, 1-hexanal, in addition to a range of sterically and electronically different aromatic aldehydes, was applicable to the present transformation, affording the desired products **6c**–**6h** in good yields (66–80%) and high enantioselectivities (95–99% ees) after trituration with *n*-hexane. When *o*-tolualdehyde and either isotryptamine **5b** ($R^1 = OMe$) or **5c** ($R^1 = Br$), bearing electron-donating or electron-withdrawing substituents, were employed as substrates, the desired products **6i** and **6j** were obtained in yields of 80% and 71%, and ee values of 98% and 81%, respectively. A variety of *N*-protecting groups, including tosyl (Ts), allyloxycarbonyl (Alloc), and methoxycarbonyl, were successfully installed, providing the desired products **3g**–**3i** and **6k** in good yields (up to 88%) and good enantioselectivities (up to 88% ee).

Diastereoselective Oxidative Rearrangement of Tetrahydro-β- and -γ-Carbolines 3 and 6

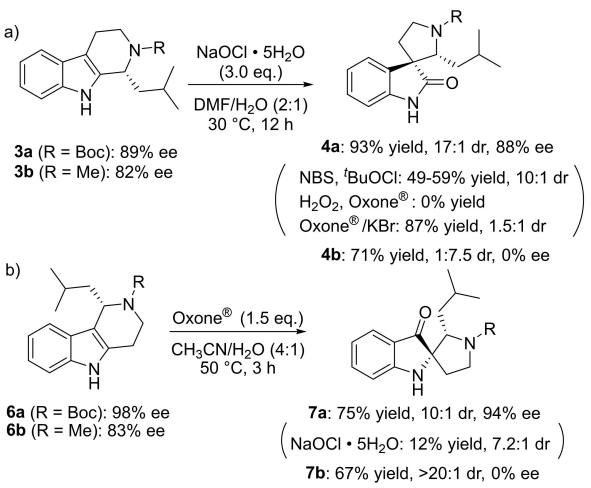
To achieve the highly diastereoselective oxidative rearrangement of tetrahydro-β-carboline **3** without any loss in enantiopurity, a range of oxidative conditions was examined (Scheme 3a). Among the various oxidants subjected to screening, $NaOCl \cdot 5H_2O$,[17] which is a bench-stable and easily removable green oxidant, efficiently promoted the oxidative rearrangement of the Boc-protected tetrahydro-β-carboline **3a**. More specifically, in a DMF/H_2O (2:1) mixed solvent system, the desired spirooxindole **4a** was obtained in 93% yield and in a highly diasetereoselective manner with no reduction in the enantiopurity being observed (17:1 dr, 88% ee). The use of other oxidants, such as NBS, ^{t}BuOCl, Oxone®, and H_2O_2, gave **4a** in moderate to low yields (up to 59%). Under Tong's reaction conditions, the desired product **4a** was obtained in a



Yields are for the isolated compounds **3** and **6**. [a]Reactions were carried out with **1** (0.1 mmol), **2** (0.11 mmol), succinic acid (20 mol%), MS3A (50 mg), and orgcat. **8**. (10 mol%) in degassed dry toluene (2 mL) at 35 °C. After 50 h, Boc_2O (0.22 mmol) was added. [b]Reactions were conducted with **5** (0.1 mmol), **2** (0.11 mmol), benzoic acid (10 mol%), and orgcat. **8** (10 mol%) in degassed dry toluene (2 mL) at 22 °C. After 1 h, Boc_2O (0.22 mmol) was added. The ee values in parentheses correspond to the ee value of **6** without trituration using *n*-hexane. [c]Orgcat. **8** (20 mol%) and malonic acid (0.1 mmol) were used instead of succinic acid. [d]TsCl (0.15 mmol) and Et_3N (0.2 mmol) were used. [e]$ClCO_2Me$ (0.15 mmol) and Et_3N (0.2 mmol) were used. [f]AllocCl (0.15 mmol) and Et_3N (0.2 mmol) were used.

Scheme 2. Substrate scope of the enantioselective PS reaction catalyzed by **8**. Yields are for the isolated compounds **3** and **6**.

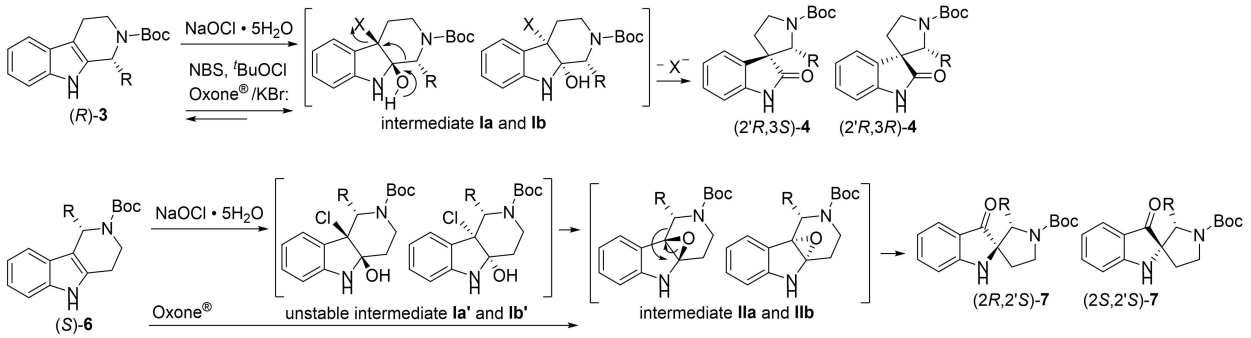
high yield but with a low diastereoselectivity (1.5:1 dr).[13k] Although the oxidative rearrangement of tetrahydro-γ-carboline **6a** with $NaOCl \cdot 5H_2O$ gave the C2-spiropseudoindoxyl-pyrrolidine **7a** with acceptable



Scheme 3. Diastereoselective oxidative rearrangement of tetrahydro-β-carbolines **3a** and **3b** and tetrahydro-γ-carbolines **6a** and **6b**.

diastereoselectivity, the yield was only 12% due to the low reactivity of **6a**, which contrasted to the use of Oxone®, wherein **7a** was obtained in 75% yield with a good diastereoselectivity (10:1), and no reduction in enantiopurity (Scheme 3b).[18] In addition, examination of the protecting groups on the nitrogen atom suggested that the electron-withdrawing Boc group was crucial for the transformation because the reactions of tetrahydro-β-carboline **3b** and tetrahydro-γ-carboline **6b** bearing electron-donating methyl group on the nitrogen atom significantly reduced the optical purity (products **4b** and **7b**, respectively), likely due to a retro-Mannich reaction of the products.[13g]

A plausible reaction mechanism for the present oxidative rearrangement is proposed in Scheme 4; in 2021, Li and Sun reported a similar oxidative rearrangement of tetrahydrocarbolines **3** and **6** to produce spiroxindoles **4** and **7** using NIS as an oxidant.[13k] Thus, the oxidative additon of water to tetrahydro-β-carboline **3** results in the formation of intermediate **I**, which is converted into C3-spirooxindole-pyrrolidine **4** through rearrangement. In our system, $NaOCl \cdot 5H_2O$ readily promotes the addition of OH^- and X^+ (Cl^+) to generate intermediate **Ia**. Under basic conditions ($NaOCl \cdot 5H_2O$, pH 11),[19] the rearrangement of **Ia** subsequently occurs to give the product (2′*R*,3*S*)-**4** as the major product. However, neutral oxidants (e.g., NBS, ^{t}BuOCl, and Oxone®/KBr) lead to intermediates **Ia** and **Ib** (X = Br for NBS and Oxone®/KBr; X = Cl for ^{t}BuOCl) via reversible epimeraization of the imine precursors[13j] to give diastereomers **4**. We also found that NBS had a detrimental effect on yield due to promoting the undesired bromination of the indole benzene ring. Oxone® and H_2O_2 are inappropriate for this transformation because these oxidants cannot generate



Scheme 4. A plausible reaction mechanism for the oxidative rearrangements of tetrahydro-β-carbolines **3** and tetrahydro-γ-carbolines **6**.

intermediates. In the case of the oxidative rearrangement of tetrahydro-γ-carboline **6** using NaOCl·5H$_2$O, unstable intermediates **Ia**′ and **Ib**′ form to produce many by-products, thereby resulting in low yields of the desired compound **7**. When Oxone® was used for the reaction, intermediates **IIa** and **IIb** were smoothly formed, and product **7a** was obtained through a semi-pinacol-type rearrangement.

The substrate scope of the diastereoselective oxidative rearrangement was then investigated using a series of tetrahydro-β-carbolines **3** and tetrahydro-γ-carbolines **6** with the desired eco-friendly oxidant (NaOCl·5H$_2$O or Oxone®), as illustrated in Scheme 5. More specifically, tetrahydro-β-carbolines **3c**–**3e** [R^2 = *n*-pentyl (**3c**); phenethyl (**3d**); *o*-bromophenyl (**3e**)] provided the corresponding products **4c**–**4e** in moderate to good yields (42–81%) and high stereoselectivities (10:1–20:1 drs, and 82–93% ees). In addition, tetrahydro-γ-carbolines **6d**–**6h**, which contain an aromatic ring, were converted into the corresponding products **7d**–**7h** with excellent diastereoselectivities, regardless of the electronic and steric properties of the substrates (58–97% yields, >20:1 drs, 93–97% ees). The use of 5-substituted substrates **6i** (R^1 = OMe) and **6j** (R^1 = Br) allowed the formation of spirocycles **7i** and **7j** in moderate yields (up to 63%) and with high stereoselectivities yield (>20:1 dr, and 93% ee), while treatment with tetrahydrocarbolines **3f** and **6c** in the presence of the appropriate oxidants furnished the corresponding products **4f** and **7c** in good yields (up to 86% yield) with acceptable diastereoselectivities (7.3:1 dr) and high enantioselectivities (90% ee). Furthermore, electron-withdrawing protecting groups, such as Ts, CO$_2$Me, and Alloc, were tolerated in the highly diastereoselective oxidative rearrangement, affording spiro compounds **4g**–**4i** and **7k** without any loss in enantiopurity (51–76% yields, 15:1–>20:1 drs, 84–90% ees). Optically pure **4** and **7** were readily obtained by recrystallization of the enantiomerically enriched products. The absolute configuration of chiral spirooxindole **4g** prepared using organocatalyst (*S*)-**8** was determined to be 2'*R*,3*S* by single X-ray crystallographic analysis (Figure 2),[20] and the absolute configuration of chiral spiropseudoindoxyl-pyrrolidine **7a** prepared using organocatalyst (*S*)-**8** was assigned as 2*S*,2'*S* by comparison of its ^{1}H NMR and optical rotation data with reported values.[14]

The Asymmetric One-Pot Syntheses of Chiral C3-Spirooxindole- and C2-Spiropseudoindoxyl-Pyrrolidines from Tryptamine and Isotryptamine

After the successful development of the organocatalyzed PS reaction/oxidative rearrangement sequence, we focused our attention on the asymmetric one-pot syntheses of chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidines from tryptamines and isotryptamines (Scheme 6). For this purpose, each two-step reaction was attempted in a single vessel. To our delight, the enantioselective PS reaction of tryptamine **1a** with isovaleraldehyde, and the subsequent NaOCl·5H$_2$O-mediated oxidative rearrangement of tetrahydro-β-carboline **3a** proceeded smoothly to afford the desired C3-spirooxindole-pyrrolidine **4a** in a moderate yield (55%) with a high stereoselectivities (15:1 dr, 88% ee) without the isolation of **3a** (Scheme 6a). In addition, the one-pot transformation of isotryptamine **5a** with *o*-tolualdehyde into C2-spiropseudoindoxyl-pyrrolidine **7g** was achieved in 47% yield, >20:1 dr, and 86% ee under the optimized

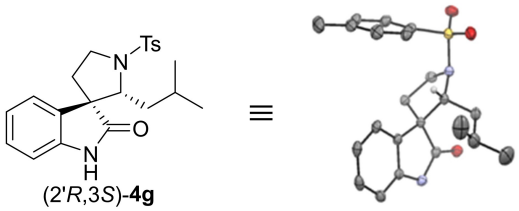
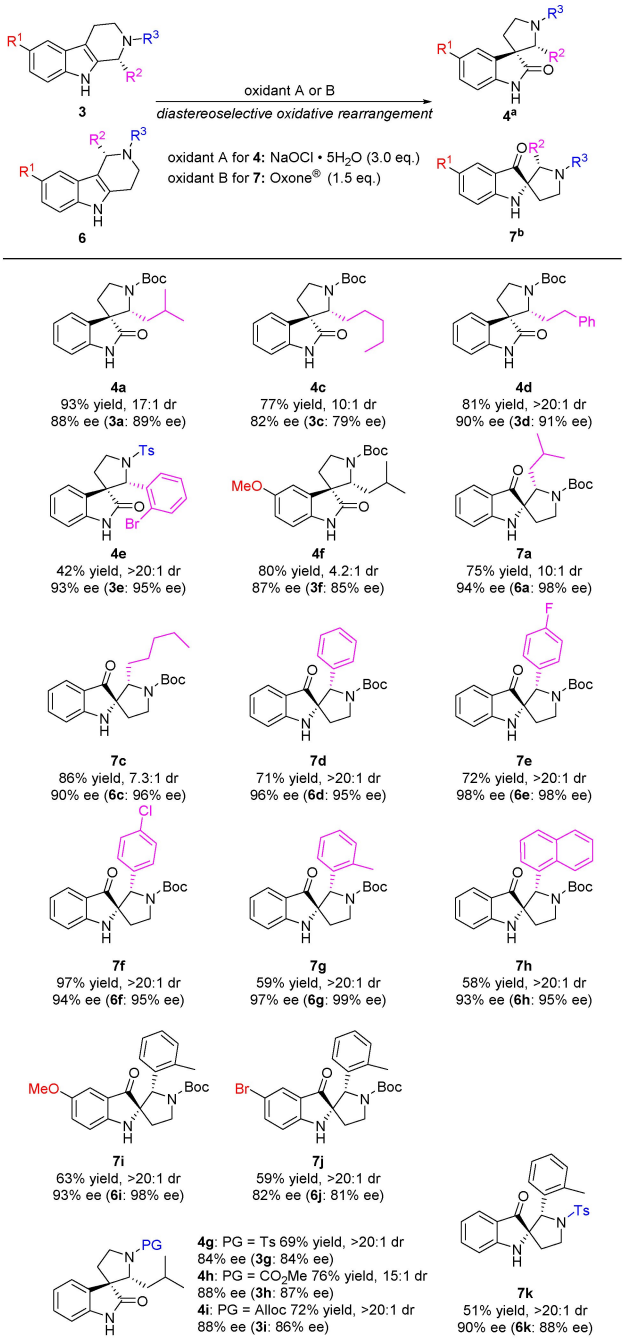


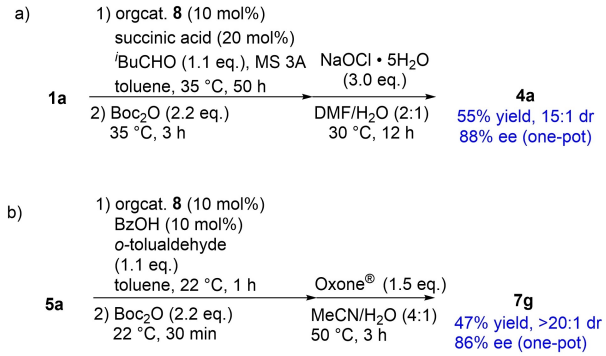
Figure 2. ORTEP drawing of compound (2'*R*,3*S*)-**4g** with ellipsoids at 50% probability (H atoms are omitted for clarity).



Yields are for the isolated compounds **4** and **7**. The ee values in parentheses correspond to the ee values of starting materials **3** and **6**. [a]Reactions were performed with **3** (0.073 mmol), and $NaOCl{\cdot}5H_2O$ (0.22 mmol) in DMF/H_2O (2:1, 1.1 mL) at 30 °C for 12 h. [b]Reactions were executed with **6** (0.05 mmol) and Oxone® (0.075 mmol) in CH_3CN/H_2O (4:1, 1 mL) at 50 °C for 3 h.

Scheme 5. Substrate scope of the diastereoselective oxidative rearrangement. Yields are for the isolated compounds **4** and **7**. The ee values in parentheses correspond to the ee values of starting materials **3** and **6**.

conditions (Scheme 6b). To the best of our knowledge, this is the first successful example of an asymmetric



Scheme 6. Asymmetric one-pot syntheses of the chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidines **4a** and **7g** from tryptamine **1a** and isotryptamine **5a**.

one-pot syntheses of chiral C3-spirooxindole- and C2-spiropseudoindoxyl-pyrrolidines from tryptamine and isotryptamine.

Evaluation of the Activities of 4 and 7 for the Inhibition of Wnt Signaling

To evaluate the biological activities of chiral spirooxindoles **4** and spiropseudoindoxyls **7**, a Wnt signaling inhibitory assay was employed, since we previously found that oxindole derivatives exhibited potential to inhibit the Wnt signaling pathway.[21a] The Wnt signaling pathway plays an important role in the motility, morphology, differentiation, and proliferation of cells. In addition, various human cancers, such as colon cancer, aberrantly activate the Wnt pathway.[21c] Therefore, compounds that inhibit the Wnt signaling could be considered potential candidates for anticancer agents.[21] Thus, to survey the abilities of spiro products **4** and **7** to inhibit the Wnt signaling pathway, we employed a TOP-Flash assay, which is a cell-based reporter luciferase assay measuring TCF/β-catenin transcription in the cell line STF/293 with LiCl as a GSK-3β inhibitor to induce β-catenin accumulation (see Supporting Information). Gratifyingly, spiro compound (2*S*,2'*S*)-**7g** (>99% ee) inhibited TCF/β-catenin transcription with an IC_{50} value of 2.2 μM, and was found to exhibit a low cytotoxicity, in addition to low inhibition of the FOP-Flash activity (Figure 3).[22,23]

Conclusion

In conclusion, a facile enantioselective synthetic route toward chiral C3-spirooxindole-pyrrolidines was developed via sequential processes involving the squaramide-catalyzed enantioselective Pictet-Spengler (PS) reaction of tryptamines followed by the $NaOCl{\cdot}5H_2O$-mediated diastereoselective oxidative rearrangement. Using Oxone® as an alternative oxidant, this protocol

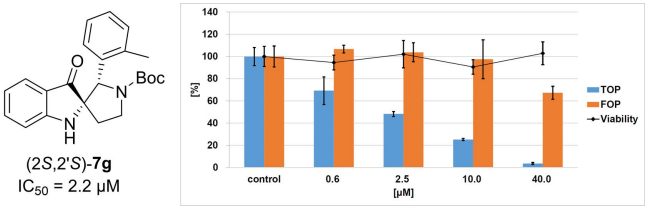


Figure 3. Synthesized spiro compound **7g** exhibiting inhibition of the TCF/β-catenin transcriptional activity.

was also applicable to isotryptamines, affording chiral C2-spiropseudoindoxyl-pyrrolidines in high diastereo- and enantioselectivities. We found that the squaramide catalyst was effective in the enantioselective PS reaction of both non-protected tryptamines and isotryptamines. Furthermore, our sequential reactions were successfully applied to a one-pot system, providing the desired spiro compounds in a highly stereoselective manner. Moreover, the newly synthesized enantioenriched spiro heterocycle was found to inhibit the Wnt signaling pathway with almost no cytotoxicity. Further application of this organocatalytic/oxidative rearrangement sequence for the stereoselective construction of complex heterocycles is ongoing in our group, and the results will be presented in due course.

Experimental Section

General information

^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were recorded with a JEOL JMN ECS400 FT NMR, JNM ECA 600 FT NMR or Bruker AVANCE II (^{1}H-NMR 400 MHz and 600 MHz, ^{13}C-NMR 100, 125, 150 MHz, ^{19}F-NMR 565 MHz). ^{1}H NMR spectra are reported as follows: chemical shift in ppm relative to the chemical shift of $CHCl_3$ (7.26 ppm) or CH_3OH (3.31 ppm), integration, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). ^{13}C-NMR spectra reported in ppm relative to the central line of triplet for $CDCl_3$ (77 ppm) or CD_3OD (49 ppm). Hexafluorobenzene was used as external standards for ^{19}F-NMR. ESI-MS spectra were obtained with JMS-T100LC (JEOL). Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector). FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Absolute configuration was determined by Rigaku R-AXIS RAPID 191R diffractometer using filtered Cu–Kα radiation. Column chromatography on SiO_2 was performed with Kanto Silica Gel 60 (40–100 μm). Commercially available organic and inorganic compounds were used without further purification.

General procedure for the organocatalyzed Pictet-Spengler reaction of tryptamine 1 with aldehyde 2

A flame dried test tube was charged with tryptamine **1** (0.1 mmol, 1 equiv.), MS 3A (50 mg). Then, toluene (2 mL), catalyst **8** (0.01 mmol, 6.2 mg, 10 mol%), and succinic acid (0.02 mmol, 2.4 mg, 20 mol%) were added. After the mixture was stirred for 2 min under a nitrogen atmosphere, aldehyde **2** (0.11 mmol, 1.1 equiv.) was added and stirred at 35 °C for 50 h. The reaction mixture was treated with Boc_2O (0.22 mmol, 48.0 mg, 2.2 equiv.) and stirred at 35 °C for 3 h. The reaction was quenched with water, and then the mixture was extracted with EtOAc three times. The combined organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the crude product was purified by flash chromatography (EtOAc/*n*-hexanes = 1:3) to give the product **3**.

General procedure for the organocatalyzed Pictet-Spengler reaction of isotryptamine 5 with aldehyde 2

To a stirred solution of isotryptamine **5** (0.1 mmol, 1 equiv.), chiral squaramide **8** (0.01 mmol, 6.2 mg, 10 mol%) in toluene (1 mL), a solution of benzoic acid (0.01 mmol, 1.2 mg, 10 mol%) in toluene (1 mL) and aldehyde **2** (0.11 mmol, 1.1 equiv.) were added. The resulting heterogeneous solution was stirred at 22 °C for 1 h. The reaction mixture was treated with Boc_2O (0.22 mmol, 48.0 mg, 2.2 equiv.) and stirred at 22 °C. After 30 min, the solvent was removed under reduced pressure, and the resulting residue was triturated with *n*-hexane (10 mL). The solid product was crashed out from the mixture in *n*-hexane solution and filtrated to provide the desired *N*-Boc-protected product **6**.

General procedure for oxidative rearrangement of tetrahydro-*β*-carboline 3 using NaOCl·5H$_2$O

To a stirred solution of tetrahydro-β-carboline **3** (0.073 mmol, 1 equiv.) in DMF (0.73 mL) and H_2O (0.36 mL), sodium hypochlorite pentahydrate (0.22 mmol, 36.2 mg, 3 equiv.) was added. After stirring for 12 h at 30 °C, the mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:2) to give the desired compound **4**.

General procedure for oxidative rearrangement of tetrahydro-*γ*-carboline 7 using Oxone®

To a stirred solution of tetrahydro-γ-carboline **6** (0.05 mmol, 1.0 equiv.), MeCN (0.8 mL) and H_2O (0.2 mL), Oxone® (0.075 mmol, 46.1 mg, 1.5 equiv.) was added. After stirring at 50 °C for 3 h, the reaction mixture was diluted with water and concentrated under reduced pressure. The mixture was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the crude residue was purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:2) to give the desired product **7**.

General procedure for the asymmetric one-pot synthesis of chiral C3-spirooxindole-pyrrolidine 4a from tryptamine 1a

A flame dried test tube was charged with tryptamine **1a** (0.1 mmol, 16.0 mg, 1 equiv.), MS 3A (50 mg). Then, toluene (2 mL), catalyst **8** (0.01 mmol, 6.2 mg, 10 mol%), and succinic acid (0.02 mmol, 2.5 mg, 20 mol%) were added. After the mixture was stirred for 2 min under a nitrogen atmosphere, isovaleraldehyde (0.11 mmol, 9.5 mg, 1.1 equiv.) was added and the solution was stirred 35 °C for 50 h. The reaction mixture was treated with Boc_2O (0.22 mmol, 48.0 mg, 2.2 equiv.) and stirred at 35 °C for 3 h. The solution was concentrated under reduced pressure, and then DMF (1 mL), H_2O (0.5 mL), and sodium hypochlorite pentahydrate (0.3 mmol, 49.4 mg, 3 equiv.) were added. After stirring at 30 °C for 12 h, the reaction mixture was diluted water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:2) to give the desired compound **4a** (18.9 mg, 55%).

General procedure for the asymmetric one-pot synthesis of chiral C2-spiropseudoindoxyl-pyrrolidine 7g from isotryptamine 5a

To a stirred solution of isotryptamine **5a** (0.05 mmol, 8.0 mg, 1 equiv.) and chiral squaramide **8** (5 μmol, 3.1 mg, 10 mol%) in toluene (0.5 mL), a solution of benzoic acid (5 μmol, 0.61 mg, 10 mol%) in toluene (0.5 mL) and *o*-tolualdehyde (0.055 mmol, 6.6 mg, 1.1 equiv.) were added. After the resulting heterogeneous solution was stirred at 22 °C for 1 h, Boc_2O (0.11 mmol, 24.0 mg, 2.2 equiv.) was added and the mixture was stirred at 22 °C for further 30 min. The organic solvent was evaporated under reduced pressure. Then, MeCN (0.8 mL), H_2O (0.2 mL), and Oxone® (0.075 mmol, 46.1 mg, 1.5 equiv.) were added to the crude residue and stirred at 50 °C. After stirring for 3 h, the mixture was diluted with water and concentrated under reduced pressure, and then extracted with EtOAc. The separated organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:2) to give the desired product **7g** (8.8 mg, 47%).

(*S*)-squaramide catalyst (8) Catalyst **8** was obtained as a white solid according to a previously reported procedure.[15] ^1H, ^{13}C NMR charts were consistent with previously reported data. This compound was observed as a 4:1 mixture of rotamers in CD_3OD. ^1H NMR (400 MHz, CD_3OD) δ 8.13 (s, 2H), 8.08 (s, minor), 7.60–7.58 (s, 1H, mixture major/minor), 7.42–7.22 (m, 11H, mixture major/minor), 7.15–7.11 (m, 2H), 7.08–7.04 (s, 1H, mixture major/minor), 6.74 (s, minor), 5.39 (s, 1H), 5.36 (s, minor), 3.03 (s, 3H), 2.77 (s, minor), 1.10 (s, 9H), 1.07 (s, minor); ^{13}C NMR (100 MHz, CD_3OD) δ 185.6, 184.9 (minor), 182.1, 181.9 (minor), 173.1 (minor), 172.7, 170.4, 170.2 (minor), 164.3, 163.8 (minor), 142.3, 140.1, 139.4, 133.8 (q, $J_{C\text{-}F}$ = 33.2 Hz), 130.5, 130.2, 129.7, 129.6, 129.2, 129.0, 128.4, 124.5 (d, $J_{C\text{-}F}$ = 272 Hz), 119.1, 116.5, 66.4 (minor), 62.6, 61.5, 61.2 (minor), 54.8 (minor), 37.6, 37.1 (minor), 34.1, 32.2 (minor), 26.6; IR (KBr) 3237, 2973, 2371, 1576, 1496, 1454, 1372, 1280, 1128 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{30}F_6N_3O_3$: *m/z* ([M + H^+]) 618.2186, found 618.2187.

tert-Butyl (*R*)-1-isobutyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3a)

White solid, 27.6 mg, 84% yield; ^1H, ^{13}C NMR charts were consistent with previously reported data.[13k] ^1H NMR (400 MHz, $CDCl_3$) δ 7.76/7.71 (brs, 1H), 7.48–7.44 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.17–7.10 (m, 2H), 5.42–5.22 (m, 1H), 4.49–4.23 (m, 1H), 3.21–3.08 (m, 2H), 2.90–2.77 (m, 1H), 2.69–2.63 (m, 1H), 1.88–1.74 (m, 1H), 1.58–1.48 (m, 1H), 1.48 (s, 9H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.28, 154.89, 135.84, 135.42, 134.84, 126.89, 121.73, 121.53, 119.52, 119.35, 118.11, 117.86, 110.71, 108.78, 108.16, 80.11, 79.66, 49.81, 49.16, 44.36, 43.82, 38.43, 37.12, 28.46, 25.17, 24.86, 23.37, 22.51, 21.47, 21.06; IR (KBr) 3292, 2952, 1660, 1415, 1170, 742 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}N_2O_2Na$: *m/z* ([M + Na^+]) 351.2043, found 351.2042; $[\alpha]_D^{25} = -33.4$ (*c* = 0.14, in $CHCl_3$ for 89% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 5.8 min (major isomer) and 11.4 min (minor isomer).

(*R*)-1-Isobutyl-2-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3b)

^1H, ^{13}C NMR charts were consistent with previously reported data.[13k] ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (brs, 1H), 7.51–7.48 (m, 1H), 7.33–7.29 (m, 1H), 7.17–7.07 (m, 2H), 3.63–3.61 (m, 1H), 3.24–3.17 (m, 1H), 2.93–2.81 (m, 2H), 2.70–2.63 (m, 1H), 2.48 (s, 3H), 1.99–1.90 (m, 1H), 1.78–1.70 (m, 1H), 1.61–1.53 (m, 1H), 1.03–0.96 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.70, 135.44, 127.29, 121.30, 119.27, 118.00, 110.60, 107.37, 57.56, 47.51, 43.20, 41.32, 25.25, 23.21, 22.68, 17.65; HRMS (ESI) calcd for $C_{16}H_{23}N_2$: *m/z* ([M + H^+]) 243.1856, found 243.1849; $[\alpha]_D^{17} = -8.4$ (*c* = 1.9, in $CHCl_3$ for 82% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 5.5 min (major isomer) and 7.6 min (minor isomer).

tert-Butyl (*R*)-1-pentyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3c)

White solid, 23.2 mg, 68% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59/7.99 (brs, 1H), 7.52–7.45 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.17–7.00 (m, 2H), 5.39–5.09 (m, 1H), 4.56–4.20 (m, 1H), 3.26–3.01 (m, 1H), 2.89–2.74 (m, 1H), 2.67 (m, 1H), 1.88–1.67 (m, 2H), 1.64–1.12 (m, 15H), 1.00–0.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.31, 154.94, 146.74, 135.94, 135.20, 134.62, 126.85, 121.67, 121.40, 119.44, 119.18, 118.10, 117.84, 110.87, 110.77, 108.72, 107.79, 85.19, 79.88, 79.78, 51.54, 50.97, 38.68, 37.41, 35.09, 34.70, 31.80, 28.47, 27.37, 26.13, 25.83, 22.63, 22.49, 21.55, 21.19, 13.98; IR (KBr) 3330, 2935, 1665, 1418, 1164, 739 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{30}N_2O_2Na$: *m/z* ([M + Na^+]) 365.2199, found 365.2190; $[\alpha]_D^{25} = -16.6$ (*c* = 0.12, in $CHCl_3$ for 79% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 7.6 min (major isomer) and 14.3 min (minor isomer).

tert-Butyl (*R*)-1-phenethyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3 d)

Colorless oil, 37.7 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74/7.60 (brs, 1H), 7.48–7.46 (m, 1H), 7.25–7.19 (m, 6H), 7.17–7.08 (m, 2H), 5.39–5.11 (m, 1H), 4.60–4.27 (m, 1H), 3.27–3.10 (m, 1H), 2.92–2.76 (m, 3H), 2.76–2.64 (m, 1H), 2.9–2.0 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.38, 154.93, 141.64, 141.51, 135.96, 134.65, 133.92, 128.51, 128.25, 126.78, 126.04, 125.77, 124.28, 123.04, 121.76, 121.54, 119.46, 119.26, 118.16, 117.89, 110.89, 110.32, 108.89, 108.03, 80.00, 51.42, 50.76, 38.77, 37.71, 36.74, 36.40, 32.80, 32.45, 28.47, 21.47, 21.11; IR (KBr) 3363, 2917, 1664, 1423, 1233, 1166, 1002 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}N_2O_2Na$: *m/z* ([M+Na$^+$]) 399.2048, found 399.2041; $[\alpha]_D^{26} = -42.9$ (*c* = 0.14, in $CHCl_3$ for 91% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 10.7 min (major isomer) and 25.0 min (minor isomer).

(*R*)-1-(2-Bromophenyl)-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3 e)

White solid, 26.1 mg, 54% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[24] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (brs, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.65–7.61 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.25–7.21 (m, 2H), 7.17–7.11 (m, 5H), 7.09–7.05 (m, 1H), 6.56 (s, 1H), 4.07–4.01 (m, 1H), 3.76–3.69 (m, 1H), 2.88–2.71 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.35, 140.05, 136.48, 136.10, 133.24, 130.98, 129.66, 129.54, 129.40, 127.86, 127.25, 126.23, 122.53, 122.37, 119.64, 118.23, 111.02, 108.67, 55.39, 42.30, 21.38, 20.55; IR (KBr) 3398, 1468, 1336, 1162, 768, 740, 658 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}BrN_2O_2SNa$: *m/z* ([M+Na$^+$]) 503.0394, found 503.0396; $[\alpha]_D^{20} = -138.7$ (*c* = 0.12, in $CHCl_3$ for 95% ee); HPLC Daicel ChiralPak IF column, *n*-Hexane/*i*-PrOH = 7/1, 1.0 mL/min, λ = 280 nm, tR = 19.0 min (minor isomer) and 30.4 min (major isomer).

tert-Butyl (*R*)-1-isobutyl-5-methoxy-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3 f)

Colorless oil, 35.5 mg, 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60/7.57 (brs, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.92–6.91 (m, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 5.40–5.19 (m, 1H), 4.48–4.23 (m, 1H), 3.85 (s, 3H), 3.20–3.07 (m, 1H), 2.86–2.73 (m, 1H), 2.64–2.60 (m, 1H), 1.81–1.76 (m, 2H), 1.53–1.42 (m, 10H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.20, 154.87, 154.09, 136.37, 135.74, 130.89, 127.29, 111.57, 111.41, 111.19, 108.94, 108.66, 108.00, 100.36, 80.10, 79.64, 55.94, 55.73, 55.48, 49.86, 49.18, 44.37, 43.85, 38.42, 37.11, 28.44, 25.16, 24.84, 23.35, 22.51, 21.51, 21.11; IR (KBr) 3319, 2954, 1668, 1459, 1416, 1218, 1165 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{30}N_2O_3Na$: *m/z* ([M+Na$^+$]) 381.2154, found 381.2159; $[\alpha]_D^{27} = -25.1$ (*c* = 0.11, in $CHCl_3$ for 85% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 6.4 min (major isomer) and 12.0 min (minor isomer).

(*R*)-1-Isobutyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3 g)

White solid, 25.6 mg, 67% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (brs, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.31–7.24 (m, 2H), 7.16–7.12 (m, 1H), 7.07–7.02 (m, 3H), 5.19 (m, 1H), 4.10 (dd, *J* = 15.6 Hz, 7.2 Hz, 1H), 3.45–3.37 (m, 1H), 2.48–2.27 (m, 2H), 2.26 (s, 3H), 2.02–1.94 (m, 1H), 1.86–1.79 (m, 1H), 1.55–1.50 (m, 1H), 1.08(d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.16, 137.95, 135.73, 133.55, 129.32, 126.75, 126.66, 121.81, 119.30, 117.98, 110.77, 107.33, 51.48, 44.94, 39.01, 24.65, 23.38, 21.99, 21.31, 19.51; IR (KBr) 3359, 1327, 1160, 734, 653, 583 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_2SNa$: *m/z* ([M+Na$^+$]) 405.1607, found 405.1598; $[\alpha]_D^{23} = -79.3$ (*c* = 0.19, in $CHCl_3$ for 84% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 7/1, 1.0 mL/min, λ = 280 nm, tR = 13.2 min (major isomer) and 16.2 min (minor isomer).

Methyl (*R*)-1-isobutyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3 h)

Colorless oil, 24.5 mg, 86% yield; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75/7.71 (brs, 1H), 7.48–7.45 (m, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.18–7.14 (m, 1H), 7.12–7.08 (m, 1H), 5.43–5.25 (m, 1H), 4.50–4.28 (m, 1H), 3.74 (s, 3H), 3.25–3.15 (m, 1H), 2.91–2.79 (m, 1H), 2.72–2.66 (m, 1H), 1.85–1.74 (m, 2H), 1.57–1.51 (m, 1H), 1.10–0.97 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.68, 156.32, 135.86, 134.97, 134.48, 126.83, 121.73, 121.57, 119.48, 119.34, 118.10, 117.88, 110.77, 108.51, 107.87, 52.77, 52.61, 49.94, 49.88, 44.20, 43.81, 38.10, 37.87, 25.04, 24.91, 23.39, 22.33, 22.01, 21.40, 20.96; IR (KBr) 3329, 2956, 2871, 1683, 1530, 1469, 1315, 1387, 1232, 1195, 751 cm^{-1};; HRMS (ESI) calcd for $C_{17}H_{23}N_2O_2$: *m/z* ([M+H$^+$]) 287.1754, found 287.1750; $[\alpha]_D^{26} = -55.3$ (*c* = 0.19, in $CHCl_3$ for 87% ee): HPLC Daicel ChiralPak IBN-5 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 23.9 min (major isomer) and 32.4 min (minor isomer).

Allyl (*R*)-1-isobutyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3 i)

White solid, 26.0 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.48 (t, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.18–7.07 (m, 2H), 6.03–5.93 (m, 1H), 5.30–5.46 (m, 2H), 5.24 (d, *J* = 10.5 Hz, 1H), 4.71–4.59 (m, 2H), 4.54–4.32 (m, 1H), 3.28–3.16 (m, 1H), 2.94–2.82 (m, 1H), 2.73–2.67 (m, 1H), 1.90–1.76 (m, 2H), 1.60–1.52 (m, 1H), 1.10–0.99 (m. 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.81, 155.47, 135.84, 134.93, 134.42, 133.03, 132.81, 126.85, 121.86, 121.70, 119.59, 119.46, 118.16, 117.95, 117.21, 110.79, 108.68, 108.07, 66.36, 66.08, 49.95, 49.86, 44.32, 43.89, 38.17, 37.88, 25.10, 24.90, 23.39, 22.39, 22.29, 21.50, 20.99; IR (KBr) 3323, 2955, 1679, 1602, 1417, 1229, 1196, 1129 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}N_2O_2Na$: *m/z* ([M+Na$^+$]) 335.1730, found 335.1732; $[\alpha]_D^{23} = -49.1$ (*c* = 0.23, in $CHCl_3$ for 86% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 27.4 min (minor isomer) and 29.4 min (major isomer).

(S)-tert-Butyl 1-isobutyl-3,4-dihydro-1H-pyrido [4,3-b]indole-2(5H)-carboxylate (6 a)

White solid, 22.9 mg, 70% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] The compound exits as a 3:1 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (brs, 1H), 7.91 (brs, 0.3H), 7.47 (d, J = 7.8 Hz, 1.3H), 7.31 (d, J = 7.3 Hz, 1.3H), 7.17–7.07 (m, 3H), 5.57 (m, 0.3H), 5.39 (d, J = 8.7 Hz, 1H), 4.48 (dd, J = 6.4 Hz, 1H), 4.27 (dd, J = 13.5, 5.3 Hz, 0.3H), 3.31–3.18 (m, 1.3H), 3.00–2.88 (m, 1.3H), 2.58 (dd, J = 15.8, 3.4 Hz, 1.3H), 1.88–1.78 (m, 1.3H), 1.76–1.63 (m, 2.6H), 1.52–1.46 (m, 11.7H), 1.20 (d, J = 6.4 Hz, 3.9H), 1.00–0.94 (d, J = 6.9 Hz, 3.9H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 155.35, 135.79, 131.98, 125.34, 121.39, 119.41, 117.70, 112.49, 110.86, 110.66, 80.01, 49.36, 44.40, 36.05, 28.48, 25.03, 23.89, 23.19, 22.22; selected minor rotamer peaks: 37.31, 25.38; HRMS (ESI) calcd for $C_{20}H_{28}N_2O_2Na^+$: m/z ([M + Na^+]) 351.2043, found 351.2031; $[\alpha]_D^{22}$ = + 103.1 (c = 0.12, in $CHCl_3$ for 98% ee); HPLC Daicel ChiralPak IBN-5 column, n-Hexane/i-PrOH = 50/1, 1.0 mL/min, λ = 280 nm, tR = 25.7 min (major isomer) and 35.1 min (minor isomer).

(*S*)-1-Isobutyl-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (6 b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (brs, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.14 (m, 2H), 3.82 (dd, J = 9.2, 4.4 Hz, 1H), 3.34–3.26 (m, 1H), 3.02–2.91 (m, 2H), 2.52–2.46 (m, 4H), 2.03–1.93 (m, 1H), 1.74–1.67 (m, 1H), 1.63–1.57 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.53, 130.78, 126.70, 121.06, 119.14, 118.11, 111.76, 110.60, 56.82, 44.81, 44.28, 41.61, 25.38, 23.76, 22.25, 18.39; IR (KBr) 3284, 2955, 1503, 1382, 1272, 1120 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}N_2Na$: m/z ([M + Na^+]) 415.2000, found 415.1996; $[\alpha]_D^{18}$ = −32.9 (c = 0.12, in $CHCl_3$ for 83% ee); HPLC Daicel ChiralPak AD-3 column, n-Hexane/i-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 5.6 min (major isomer) and 10.6 min (minor isomer).

(*S*)-*tert*-Butyl 1-pentyl-3,4-dihydro-1H-pyrido[4,3-b] indole-2(5H)-carboxylate (6 c)

White solid, 22.7 mg, 66% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] The compound exists as a 5:2 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (brs, 1H), 7.48 (d, J = 7.3 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.16–7.09 (m, 2H), 5.39–5.49 (m, 0.3H), 5.28 (d, J = 8.2 Hz, 0.7H, major rotamer), 4.50 (dd, J = 13.5, 5.3 Hz, 0.7H, major rotamer), 4.23–4.38 (m, 0.3H, minor rotamer), 3.23–3.16 (m, 1H), 3.00–2.92 (m, 1H), 2.62–2.58 (m, 1H), 2.02–1.90 (m, 1H), 1.80–1.67 (m, 1H), 1.59–1.40 (m, 2H), 1.48 (s, 9H), 1.38–1.29 (m, 3H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz), major rotamer: δ 155.33, 135.83, 131.97, 125.44, 121.34, 119.36, 117.87, 112.26, 110.84, 79.80, 51.18, 36.17, 35.01, 31.84, 28.47, 26.46, 23.29, 22.78, 14.05; selected minor rotamer peaks: 50.38, 37.47; HRMS (ESI) calcd for $C_{21}H_{30}N_2O_2Na$: m/z ([M + Na^+]) 365.2199, found 365.2188; $[\alpha]_D^{22}$ = + 78.1 (c = 0.16, in $CHCl_3$ for 96% ee); HPLC Daicel ChiralPak AD-3 column, n-Hexane/i-PrOH = 20/1, 1.0 mL/min, λ = 280 nm, tR = 10.4 min (major isomer) and 11.5 min (minor isomer).

(*S*)-*tert*-Butyl 1-phenyl-3,4-dihydro-1H-pyrido [4,3-b]indole-2(5H)-carboxylate (6 d)

White solid, 24.1 mg, 69% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] The compound exists as a 3:2 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.41–7.36 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H,), 7.31–7.24 (m, 3H), 7.16–7.12 (2H, m), 7.00 (t, J = 7.6 Hz, 1H), 6.65 (brs, minor rotamer, 0.4H), 6.43 (brs, major rotamer, 0.6H), 4.39 (brs, major rotamer, 0.6H), 4.20 (brs, minor rotamer, 0.4H), 3.15–3.04 (m, 2H), 2.70 (m, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) major totamer: δ 154.68, 141.42, 135.86, 133.51, 128.17, 127.42, 126.16, 121.59, 119.64, 118.61, 110.64, 109.53, 80.27, 54.05, 36.53, 28.58, 23.48; selected minor rotamer peaks: 52.87, 37.59; IR (KBr) 3292, 2937, 1654, 1462, 1419, 1366, 1295, 1253, 1234, 1164, 1147 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}N_2O_2Na$: m/z ([M + Na^+]) 371.1730, found 371.1721; $[\alpha]_D^{20}$ = + 89.1 (c = 0.16, in $CHCl_3$ for 95% ee); HPLC Daicel ChiralPak AD-3 column, n-Hexane/i-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 7.5 min (minor isomer) and 8.5 min (major isomer).

(*S*)-*tert*-Butyl 1-(4-fluorophenyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (6 e)

White solid, 24.9 mg, 68% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] The compound exists as a 3:2 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (brs, 1H), 7.37–7.33 (m, 3H), 7.14 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02–6.94 (m, 3H), 6.58 (brs, minor rotamer, 0.4H), 6.40 (brs, major rotamer, 0.6H), 4.38 (brs, major rotamer, 0.6H), 4.23 (brs, minor rotamer, 0.4H), 3.11–3.00 (m, 2H), 2.77–2.69 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 162.14 ($J_{C\text{-}F}$ = 203 Hz), 154.59, 137.26, 135.89, 133.61, 129.90, 125.96, 121.68, 119.68, 118.41, 114.94 ($J_{C\text{-}F}$ = 16.8 Hz), 110.73, 109.32, 80.51, 53.39, 36.41, 28.57, 23.47; selected minor rotamer peaks: 52.27, 37.51; ^{19}F NMR (565 MHz, $CDCl_3$) δ −118.30; HRMS (ESI) calcd for $C_{22}H_{23}FN_2O_2Na$: m/z ([M + Na^+]) 389.1636, found 389.1633; $[\alpha]_D^{21}$ = + 205.2 (c = 0.2, in $CHCl_3$ for 98% ee); HPLC Daicel ChiralPak AD-3 column, n-Hexane/i-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 6.7 min (minor isomer) and 8.8 min (major isomer).

(*S*)-*tert*-Butyl 1-(4-chlorophenyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (6 f)

White solid, 26.9 mg, 70% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] The compound exists as a 2:1 mixture of rotamers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (brs, 1H), 7.35–7.25 (m, 3H), 7.25–7.19 (m, 2H), 7.11–7.06 (m, 2H), 6.97 (t, J = 8.0 Hz, 1H), 6.72–6.50 (brs, minor rotamer, 0.3H), 6.50–6.28 (brs, major rotamer, 0.6H), 4.51–4.31 (brs, major rotamer, 0.6H), 4.30–4.08 (brs, minor rotamer, 0.3H), 3.07–2.93 (m, 2H), 2.65–2.61 (m, 1H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz), major rotamer: δ 154.67, 139.97, 135.92, 133.20, 129.62, 128.30, 125.87, 121.60,

119.61, 118.30, 110.78, 108.74, 80.49, 53.48, 36.70, 28.54, 23.40; selected minor rotamer peaks: δ 52.53, 37.49; HRMS (ESI) calcd for $C_{22}H_{23}ClN_2O_2Na$: *m/z* ([M+Na$^+$]) 405.1340, found 405.1336; $[\alpha]_D^{18} = +152.4$ ($c = 0.17$, in $CHCl_3$ for 95% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 7.6 min (minor isomer) and 8.7 min (major isomer).

(*S*)-*tert*-Butyl 1-o–tolyl-3,4-dihydro-1H-pyrido [4,3-b]indole-2(5H)-carboxylate (6 g)

White solid, 29.0 mg, 80% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (brs, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 6.4 Hz, 1H), 7.19–7.08 (m, 3H), 6.99–6.94 (m, 2H), 6.87 (d, J = 7.2 Hz, 1H), 6.67 (brs, 1H), 4.13 (brs, 1H), 3.17–3.11 (m, 2H), 2.71–2.64 (m, 1H), 2.64 (s, 3H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.06, 138.66, 137.61, 135.72, 133.40, 130.71, 129.32, 127.49, 126.08, 125.27, 121.51, 119.55, 118.50, 110.58, 80.14, 51.51, 37.45, 28.40, 22.99, 20.04; IR (KBr) 3330, 1677, 1487, 1388, 1290, 1217, 1186, 1136, 1108 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_2Na$: *m/z* ([M+Na$^+$]) 385.1886, found 385.1882; $[\alpha]_D^{20} = +89.1$ ($c = 0.16$, in $CHCl_3$ for 99% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 5.5 min (minor isomer) and 6.1 min (major isomer).

(*S*)-*tert*-Butyl 1-(naphthalen-1-yl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (6 h)

White solid, 30.0 mg, 75% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] The compound exists as a 2:1 mixture of rotamers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, J = 8.4 Hz, 1H), 8.04 (brs, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.32 (m, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 6.8 Hz, 1H), 7.09–7.05 (m, 2H), 6.95 (t, J = 8.0 Hz, 1H), 4.14–4.01 (m, 1H), 3.14–3.09 (m, 2H), 2.68 (d, J = 12.4 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): major rotamer: δ 154.99, 136.45, 135.84, 133.99, 132.27, 128.49, 127.66, 126.37, 125.67, 124.95, 121.56, 119.59, 118.72, 110.68, 110.19, 80.06, 51.10, 37.89, 28.48, 23.49; selected minor rotamer peaks: δ 37.20, 22.64; IR (KBr) 3381, 2925, 1665, 1601, 1448, 1409, 1366, 1292, 1160, 1140, 1099 cm^{-1};HRMS (ESI) calcd for $C_{26}H_{26}N_2O_2Na$: *m/z* ([M+Na$^+$]) 421.1886, found 421.1882; $[\alpha]_D^{17} = +87.8$ ($c = 0.2$, in $CHCl_3$ for 95% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 5.3 min (minor isomer) and 7.4 min (major isomer).

(*S*)-*tert*-Butyl 8-methoxy-1-o–tolyl-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (6 i)

White solid, 31.4 mg, 80% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (brs, 1H), 7.14–7.25 (m, 3H), 6.97 (t, J = 7.3 Hz, 1H), 6.89–6.87 (m, 1H), 6.78 (dd, J = 8.7, 2.3 Hz, 1H), 6.71–6.60 (m, 1H), 6.52 (brs, 1H), 4.14–4.10 (m, 1H), 3.68 (s, 3H), 3.14–3.03 (m, 2H), 2.69–2.56 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.05, 154.00, 138.61, 137.63, 134.21, 130.86, 130.71, 129.31, 127.46, 126.67, 125.33, 111.16, 110.98, 110.44, 101.11, 80.05, 55.88, 51.74, 37.51, 28.41, 23.13, 19.99; IR (KBr) 3352, 2942, 1663, 1628, 1457, 1308, 1243, 1212, 1170,1141, 1114 cm^{-1};HRMS (ESI) calcd for $C_{24}H_{28}N_2O_3Na$: *m/z* ([M+Na$^+$]) 415.1992, found 415.1988; $[\alpha]_D^{23} = +216.7$ ($c = 0.15$, in $CHCl_3$ for 98% ee); HPLC Daicel ChiralPak IF-3 column, *n*-Hexane/*i*-PrOH = 97/3, 1.0 mL/min, λ = 280 nm, tR = 23.1 min (minor isomer) and 34.6 min (major isomer).

(*S*)-*tert*-Butyl 8-bromo-1-o–tolyl-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (6 j)

White solid, 31.4 mg, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (brs, 1H), 7.24 (s, 1H), 7.20–7.15 (m, 4H), 6.97 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.60 (s, 1H), 4.22–4.18 (m, 1H), 3.23–3.04 (m, 2H), 2.65–2.55 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.99, 138.18, 137.78, 134.87, 134.45, 130.90, 129.14, 127.85, 127.69, 125.34, 124.41, 121.02, 112.90, 112.02, 110.41, 80.22, 51.71, 37.31, 28.40, 23.04, 19.98; IR (KBr) 3342, 2943, 1659, 1487, 1460, 1403, 1371, 1308, 1245, 1213, 1168, 1141, 1115 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}BrN_2O_2Na$: *m/z* ([M+Na$^+$]) 463.0992, found 463.0987; $[\alpha]_D^{17} = +118.4$ ($c = 0.15$, in $CHCl_3$ for 81% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 280 nm, tR = 7.7 min (mionor isomer) and 8.6 min (major isomer).

(*S*)-1-(*o*-Tolyl)-2-tosyl-2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indole (6 k)

White solid, 36.6 mg, 88% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (brs, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.27–7.24 (m, 2H), 7.18–7.07 (m, 3H), 7.00–6.90 (m, 4H), 6.84 (dd, J = 7.6, 0.8 Hz, 1H), 6.70 (s, 1H), 3.89 (dd, J = 14.8, 6.0 Hz, 1H), 3.47–3.39 (m, 1H), 2.80 (s, 3H), 2.59–2.44 (m, 2H), 2.29 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.92, 137.71, 137.66, 137.55, 135.69, 131.57, 131.09, 129.18, 128.92, 127.91, 127.07, 125.59, 125.42, 121.76, 119.66, 118.06, 110.52, 109.49, 53.47, 38.43, 21.36, 21.26, 20.13; IR (KBr) 3398, 1459, 1325, 1155, 741 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_2SNa$: *m/z* ([M+Na$^+$]) 439.1451, found 439.1444; $[\alpha]_D^{22} = +43.2$ ($c = 1.35$, in $CHCl_3$ for 88% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 30.2 min (minor isomer) and 33.0 min (major isomer).

tert-Butyl (2′*R*,3*S*)-2′-isobutyl-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (4 a)

White solid, 23.3 mg, 93% yield (17:1 dr); ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[13k] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (brs, 1H), 7.25–7.20 (m, 1H), 7.07–7.00 (m, 2H), 6.88 (d, J = 7.6 Hz, 1H), 4.13–3.68 (m, 3H), 2.54–2.43 (m, 1H), 2.07–2.00 (m, 1H), 1.90–1.70 (m, 1H), 1.52–1.28 (m, 11H), 0.88–0.73 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.55, 154.67, 139.45, 134.66, 128.06, 122.86, 122.44, 109.84, 80.16, 63.48, 55.71, 43.78, 40.08, 35.41, 33.84, 28.49, 25.03, 22.95, 22.63; IR (KBr) 3247, 2957, 1704, 1620, 1473, 1369, 1331, 1232, 1119, 747 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}N_2O_3Na$: *m/z* ([M+Na$^+$]) 367.1992, found 367.1997;

$[\alpha]_D^{25} = -19.7$ ($c = 0.21$, in $CHCl_3$ for 88% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 280 nm, tR = 11.4 min (minor isomer) and 18.9 min (major isomer).

(2′*R**,3*S**)-2′-Isobutyl-1′-methyl-spiro[indoline-3,3′-pyrrolidin]-2-one (4 b)

Colorless oil, 13.4 mg, 71% yield and 0% ee (7.5:1 dr); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (brs, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 3.31 (t, J = 7.6 Hz, 1H), 2.73–2.70 (m, 1H), 2.63–2.57 (m, 1H), 2.41 (s, 3H), 2.35–2.29 (m, 1H), 2.07–2.02 (m, 1H), 1.22–1.18 (m, 1H), 1.25–1.14 (m, 2H), 0.98–0.94 (m, 1H), 0.75 (d, J = 6.4 Hz, 3H), 0.52 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ182.72, 140.13, 133.38, 127.64, 125.40, 122.42, 109.42,71.52, 57.22, 56.01, 40.49, 38.70, 36.64, 24.79, 23.85, 21.89; HRMS (ESI) calcd for $C_{16}H_{23}N_2O$: *m/z* ([M + H$^+$]) 259.1805, found 259.1797

tert-Butyl (2′*R*,3*S*)-2-oxo-2′-pentylspiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (4 c)

Colorless oil, 20.1 mg, 77% yield (10:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (brs, 1H), 7.26–7.20 (m, 1H), 7.11–6.99 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 4.10–3.69 (m, 3H), 2.60–2.32 (m, 1H), 2.07–2.00 (m, 1H), 1.96–1.63 (m, 2H), 1.45 (s, 9H), 1.33–0.95 (m, 6H), 0.89–0.71 (m, 3H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 179,34 178.56, 154.74, 139.48, 134.70, 133.88, 128.02, 122.84, 122.38, 109.79, 79.88, 65.29, 55.80, 44.89, 43.85, 35.42, 33.84, 31.67, 31.29, 28.43, 26.29, 22.50, 13.85; IR (KBr) 3250, 2957, 1732, 1695, 1620, 1472, 1393, 1334, 1174, 1125, 747 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{30}N_2O_3Na$: *m/z* ([M + Na$^+$]) 381.2149, found 381.2141; $[\alpha]_D^{25} = -14.8$ ($c = 0.12$, in $CHCl_3$ for 82% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR = 5.4 min (minor isomer) and 6.7 min (major isomer).

tert-Butyl (2′*R*,3*S*)-2-oxo-2′-phenethylspiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (4 d)

White solid, 23.0 mg, 81% yield (>20:1 dr); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.94 (brs, 1H), 7.25–7.14 (m, 3H), 7.05–7.01 (m, 2H), 6.92 (d, J = 6.8 Hz, 1H), 4.14–3.78 (m, 3H), 2.64–2.38 (m, 3H), 2.33–2.15 (m, 2H), 2.11–2.04 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.35, 154.66, 141.87, 139.34, 134.52, 133.76, 128.30, 125.72, 123.03, 125.72, 123.03, 122.52, 109.91, 80.14, 79.76, 65.50, 64.71, 55.78, 44.93, 44.06, 35.55, 34.09, 33.54, 33.16, 32.80, 28.47 cm^{-1}; IR (KBr) 3275, 2970, 1716, 1671, 1412, 1168, 1124, 887 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}N_2O_3Na$: *m/z* ([M + Na$^+$]) 415.1992, found 415.1996. $[\alpha]_D^{20} = +22.1$ ($c = 0.17$, in $CHCl_3$ for 90% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 7/1, 1.0 mL/min, λ = 280 nm, tR = 6.3 min (minor isomer) and 8.5 min (major isomer).

(2′*R*,3*S*)-2′-(2-Bromophenyl)-1′-tosylspiro[indoline-3,3′-pyrrolidin]-2-one (4 e)

White solid, 15.3 mg, 42% yield (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (brs, 1H), 7.66–7.64 (m, 1H), 7.59 (m, 3H), 7.46–7.40 (m, 2H), 7.38–7.35 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 7.16–7.12 (m, 1H), 4.50 (s, 1H), 3.12 (t, J = 7.0 Hz, 2H), 2.87 (t, J = 7.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 143.2, 140.6, 136.8, 136.7, 133.4, 131.7, 131.0, 129.5, 128.4, 128.0, 127.8, 127.4, 126.9, 122.2, 121.3, 121.1, 119.3, 112.2, 43.7, 25.2, 21.5; IR (KBr) 3324, 3060, 2925, 1622, 1469, 1326, 1279, 1156, 746 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}BrN_2O_3SNa$: *m/z* ([M + Na$^+$]) 519.0348, found 519.0341; $[\alpha]_D^{20} = -58.9$ ($c = 0.14$, in $CHCl_3$ for 93% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 7/1, 1.0 mL/min, λ = 265 nm, tR = 34.2 min (minor isomer) and 47.2 min (major isomer).

tert-Butyl (2′*R*,3*R*)-2′-isobutyl-5-methoxy-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (4 f)

Colorless oil, 21.9 mg, 80% yield (4.2:1 dr); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (brs, 1H), 6.83–6.74 (m, 2H), 6.71–6.61 (m, 1H), 4.11–3.85 (m, 2H), 3.76 (s, 3H), 3.73–3.64 (m, 1H), 2.60–2.32 (m, 1H), 2.11–1.97 (m, 1H), 1.97–1.74 (m, 1H), 1.75–1.60 (m, 2H), 1.47 (s, 9H), 1.41–1.29 (m, 1H), 0.93–0.70 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) 177.9, 157.1, 136.0, 132.4, 125.5, 125.0, 112.8, 109.9, 80.2, 63.5, 56.1, 55.8, 43.7, 40.2, 34.0, 28.5, 25.0, 23.0, 22.6 ; IR (KBr) 3205, 2955, 1705, 1659, 1501, 1412, 1367, 1339, 1209, 1111, 1038, 747 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{30}N_2O_4Na$: *m/z* ([M + Na$^+$]) 397.2098, found 397.2088; $[\alpha]_D^{27} = +38.2$ ($c = 0.13$, in $CHCl_3$ for 87% ee); HPLC (Chiral AD-3 column), *n*-Hexane/*i*-PrOH = 7/1, 1.0 mL/min, λ = 280 nm, tR = 7.1 min (major isomer) and 16.8 min (major isomer).

(2′*R*,3*S*)-2′-Isobutyl-1′-tosylspiro[indoline-3,3′-pyrrolidin]-2-one (4 g)

White solid, 20.1 mg, 69% yield; ^{1}H, ^{13}C NMR charts were consistent with previously reported data. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.46–7.39 (m, 3H), 7.19–7.14 (m, 1H), 6.90–6.86 (m, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 4.03–3.93 (m, 2H), 3.80–3.75 (m, 1H), 2.49 (s, 3H), 2.10–1.97 (m, 2H), 1.85–1.78 (m, 1H), 1.70–1.62 (m, 1H), 1.11–1.01 (m, 1H), 0.75 (d, J = 6.4 Hz, 3H), 0.64 (d, J = 6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.81, 143.80, 139.60, 135.41, 131.77, 129.88, 128.41, 127.69, 122.77, 122.36, 109.81, 65.44, 56.85, 48.04, 42.00, 37.40, 24.89, 23.59, 21.60, 21.17; IR (KBr) 3172, 2956, 1700, 1473, 1351, 1163, 670, 661, 570 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_3SNa$: *m/z* ([M + Na$^+$]) 421.1564, found 421.1557. $[\alpha]_D^{23} = -46.8$ ($c = 0.17$, in $CHCl_3$ for 84% ee); HPLC (Chiral AD-3 column), *n*-Hexane/*i*-PrOH = 7/1, 1.0 mL/min, λ = 280 nm, tR = 24.2 min (major isomer) and 35.9 min (minor isomer).

Methyl (2′*R*,3*S*)-2′-isobutyl-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (4 h)

Colorless oil, 16.7 mg, 76% yield (15:1 dr); ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[13k] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (brs, 1H), 7.22 (t, J = 8.2 Hz, 1H), 7.13–7.01 (m, 2H), 6.92 (d, J = 7.8 Hz, 1H), 4.20–3.95 (m, 1H), 3.94–3.79 (m, 2H), 3.74 (s, 3H), 2.61–2.36 (m, 1H), 2.10–2.03 (m, 1H), 1.94–1.62 (m, 2H), 1.40–1.28 (m, 1H), 0.80 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.96, 178.23, 155.62, 139.54, 134.35, 133.38, 128.21, 123.00, 122.47, 109.84, 63.60, 55.69, 52.46, 44.54, 40.17, 39.69, 35.56, 33.89, 25.15, 23.15, 22.55, 21.96; IR (KBr) 3250, 2956, 1703, 1677, 1620, 1454, 1387, 1335, 1119, 750 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_2O_3Na$: *m/z* ([M + Na^+]) 325.1530, found 325.1526; $[\alpha]_D^{25}$ = −10.4 (*c* = 0.12, in $CHCl_3$ for 88% ee); HPLC (Chiral AD-3 column), *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 280 nm, tR*t* (minor isomer) = 8.3 min, *t* (major isomer) = 10.0 min.

Allyl (2′*R*,3*S*)-2′-isobutyl-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (4 i)

Colorless oil, 17.2 mg, 72% yield (> 20:1 dr); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.63 (brs, 1H), 7.25–7.21 (m, 1H), 7.14–7.01 (m, 2H), 6.91 (d, J = 7.6 Hz, 1H), 6.09–5.77 (m, 1H), 5.50–5.01 (m, 2H), 4.72–4.50 (m, 2H), 4.23–3.68 (m, 3H), 2.64–2.37 (m, 1H), 2.14–1.99 (m, 1H), 1.97–1.65 (m, 2H), 1.60–1.19 (m, 1H), 0.81 (d, J = 5.6 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.90, 178.16, 154.91, 154.64, 139.53, 139.28, 134.35, 133.39, 133.08, 132.76, 128.22, 123.01, 122.50, 117.98, 117.37, 109.82, 66.16, 65.82, 63.61, 55.69, 55.54, 44.58, 44.37, 40.17, 39.64, 35.55, 33.89, 29.65, 25.14, 23.17, 22.74, 22.45, 21.96; IR (KBr) 3159, 3082, 2960, 1700, 1620, 1474, 1108, 999, 929, 753 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}N_2O_3Na$: *m/z* ([M + Na^+]) 351.1687, found 351.1684 $[\alpha]_D^{2}$ = −11.8 (*c* = 0.13, in $CHCl_3$); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 280 nm, tR = 7.2 min (minor isomer) and = 9.1 min (major isomer).

(2*S*,2′*S*)-*tert*-Butyl 2′-isobutyl-3-oxospiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 a)

Yellow solid, 12.9 mg, 75% yield (10:1 dr); ^{1}H, ^{13}C NMR charts were consistent with previously reported data.[14] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 6.88–6.80 (m, 2H), 4.97 (brs, 1H), 4.02 (t, J = 6.4 Hz, 1H), 3.93 (m, 1H), 3.41–3.34 (m, 1H), 2.23–2.12 (m, 1H), 1.92–1.86 (m, 1H), 1.63–1.59 (m, 1H), 1.51–1.39 (m, 10H), 1.32–1.23 (m, 1H), 0.82 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.58, 159.91, 155.07, 137.20, 124.86, 119.63, 119.09, 112.10, 79.83, 73.54, 60.10, 44.57, 44.50, 40.71, 35.27, 28.48, 24.86, 23.41, 22.20; HRMS (ESI) calcd for $C_{20}H_{28}N_2O_3Na$: *m/z* ([M + Na^+]) 367.1998, found 367.1996; $[\alpha]_D^{17}$ = −7.0 (*c* = 0.32, in $CHCl_3$ for 94% ee); HPLC Daicel ChiralPak OD–H column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 390 nm, tR = 10.9 min (major isomer), 15.7 min (minor isomer).

(2*S**,2′*S**)-2′-Isobutyl-1′-methyl-spiro[indoline-2,3′-pyrrolidin]-3-one (7 b)

Yellow solid, 8.6 mg, 67% yield and 0% ee (> 20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 6.82–6.74 (m, 2H), 5.22 (brs, 1H), 3.21 (td, J = 8.9, 2.7 Hz, 1H), 2.52–2.42 (m, 2H), 2.39–2.28 (m, 5H), 1.93–1.85 (m, 1H), 1.32–1.18 (m, 2H), 1.08 (m, 1H), 0.80–0.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 160.3, 137.2, 124.6, 120.1, 118.3, 111.6, 74.9, 71.7, 54.7, 40.2, 37.4, 36.2, 25.7, 23.7, 22.2; IR (KBr) 3210, 2954, 1620, 1492, 1469, 1320, 1241, 1097, 1037 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}N_2O$: *m/z* ([M + H^+]) 259.1805, found 259.1799.

(2*S*,2′*S*)-*tert*-Butyl 2′-pentyl-3-oxospiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 c)

Yellow solid, 15.4 mg, 86% yield (7.3:1 dr); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J = 8.0 Hz, 1H), 7.44–7.48 (m, 1H), 6.88–6.83 (m, 2H), 4.63 (brs, 1H), 3.92 (t, J = 6.8 Hz, 2H), 3.43–3.36 (m, 1H), 2.21–2.14 (m, 1H), 1.93–1.61 (m, 2H), 1.48 (s, 9H), 1.20–1.18 (m, 6H), 1.07–1.01 (m, 1H), 0.77 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.58, 159.91, 155.07, 137.20, 124.86, 119.63, 119.09, 112.10, 79.83, 73.54, 60.10, 44.57, 44.50, 40.71, 35.27, 28.48, 24.86, 23.41, 22.20. IR (KBr) 3287, 2929, 1690, 1672, 1621, 1470, 1403, 1366, 1172, 1146 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{30}N_2O_3Na$: *m/z* ([M + Na^+]) 381.2149, found 381.2138; $[\alpha]_D^{17}$ = −6.9 (*c* = 0.30, in $CHCl_3$ for 90% ee); HPLC Daicel ChiralPak OD–H column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 390 nm, tR = 11.8 min (major isomer) and 21.5 min (minor isomer).

(2*S*,2′*S*)-*tert*-Butyl 2′-phenyl-3-oxospiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 d)

Yellow solid, 12.9 mg, 71% yield (> 20:1 dr); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.31–7.24 (m, 3H), 7.07–7.05 (m, 2H), 6.81 (t, J = 7.2 Hz, 1H), 6.59 (d, J = 7.2 Hz, 1H), 4.90 (brs, 1H), 4.03–4.15 (m, 2H), 3.83–3.73 (m, 1H), 2.35–2.17 (m, 1H), 2.16–2.04 (m, 1H), 1.43–1.14 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.76, 159.85, 154.43, 139.25, 137.30, 128.34, 127.61, 126.19, 124.76, 119.87, 119.27, 111.97, 73.73, 65.70, 64.10, 44.73, 32.97, 28.03; IR (KBr) 3342, 2979, 1693, 1681, 1621, 1393, 1168, 1134, 754 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}N_2O_3Na$: *m/z* ([M + Na^+]) 387.1679, found 387.1669; $[\alpha]_D^{17}$ = −12.0 (*c* = 0.28, in $CHCl_3$ for 96% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 390 nm, tR = 29.6 min (minor isomer) and 33.4 min (major isomer).

(2*S*,2′*S*)-*tert*-Butyl 2′-(*p*–fluorophenyl)-3-oxospiro [indoline-2,3′-pyrrolidine]-1′-carboxylate (7 e)

Yellow solid, 13.7 mg, 72% yield (> 20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.39–7.35 (m, 1H), 7.09–7.03 (m, 2H), 6.97 (m, 2H), 6.82 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 4.90 (s, 1H), 4.15–4.03 (m, 2H), 3.79–3.73 (m, 1H), 2.37–2.30 (m, 1H), 2.10–2.03 (m, 1H), 1.48–1.18 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.37, 162.21 ($J_{C\text{-}F}$ = 245 Hz), 159.74, 154.44, 137.46, 134.96, 127.78 ($J_{C\text{-}F}$ = 7.7 Hz),

124.77, 119.80, 119.38, 115.21 ($J_{C\text{-}F}$ = 20.9 Hz), 111.97, 80.03, 73.87, 72.63, 65.57, 65.36, 44.81, 33.07, 28.09; ^{19}F NMR (565 MHz, $CDCl_3$) δ −118.33, −118.70; IR (KBr) 3341, 2972, 1693, 1672, 1619, 1382, 1173, 1157, 1098, 755 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{23}FN_2O_3Na$: *m/z* ([M + Na$^+$]) 415.2000, found 415.1996; $[\alpha]_D^{20}$ = −12.2 (*c* = 0.14, in $CHCl_3$ for 98% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 390 nm, tR = 8.8 min (minor isomer) and 10.4 min (major isomer).

(2*S*,2′*S*)-*tert*-Butyl 2′-(*p*–chlorophenyl)-3-oxospiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 f)

Yellow solid, 19.4 mg, 97% yield (> 20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.39–7.35 (m, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.88 (s, 1H), 4.22–4.02 (m, 2H), 3.78–3.72 (m, 1H), 2.27 (s, 1H), 2.09–2.02 (m, 1H), 1.55–0.88 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.25, 159.67, 154.36, 137.91, 137.54, 133.20, 128.42, 127.57, 124.81, 119.73, 119.45, 112.01, 80.12, 73.79, 72.15, 65.44, 63.83, 44.77, 33.27, 28.03; IR (KBr) 3337, 1697, 1664, 1620, 1405, 1170, 1146, 756 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{23}ClN_2O_3Na$: *m/z* ([M + Na$^+$]) 421.1289, found 421.1280; $[\alpha]_D^{20}$ = −11.4 (*c* = 0.13, in $CHCl_3$ for 94% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 390 nm, tR = 8.7 min (minor isomer) and 13.6 min (major isomer).

(2*S*,2′*S*)-*tert*-Butyl 2′-*o*–tolyl-3-oxospiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 g)

Yellow solid, 11.2 mg, 59% yield (> 20:1 dr); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.95–6.93 (m, 2H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.84 (brs, 1H), 4.17–4.00 (m, 2H), 3.83–3.71 (m, 1H), 2.33 (s, 3H), 2.23–2.11 (m, 2H), 1.16–1.45 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.6, 160.1, 154.0, 138.5, 137.4, 136.0, 130.1, 127.3, 126.2, 125.1, 124.8, 119.1, 119.0, 111.7, 79.5, 73.0, 60.5, 43.9, 32.4, 27.9, 19.3.; IR (KBr) 3320, 2976, 1690, 1670, 1620, 1471, 1408, 1363, 1168, 1133, 751 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_3Na$: *m/z* ([M + Na$^+$]) 401.1836, found 401.1824; $[\alpha]_D^{17}$ = −50.7 (*c* = 0.14, in $CHCl_3$ for 97% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 390 nm, tR = 16.9 min (major isomer) and = 20.0 min (minor isomer).

(2*S*,2′*S*)-*tert*-Butyl 2′-(1-naphtyl)-3-oxospiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 h)

Yellow solid, 12.1 mg, 58% yield (> 20:1 dr); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83–7.80 (2H, m), 7.67–7.60 (1H, m), 7.50 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 6.6 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.23–7.15 (m, 2H), 6.85–6.76 (m, 1H), 6.34–6.28 (m, 1H), 5.84–5.76 (brs, 1H), 4.16–4.11 (m, 1H), 3.93–3.76 (m, 2H), 2.29–2.25 (m, 2H), 1.49–0.99 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.53, 160.18, 159.11, 154.66, 154.26, 137.35, 136.16, 135.13, 133.62, 133.34, 131.32, 128.53, 128.26, 126.01, 125.81, 125.29, 125.15, 124.77, 123.10, 122.80, 119.22, 111.93, 80.14, 79.67, 73.29, 71.91, 60.14, 59.14, 44.08, 32.75, 32.01, 28.46, 27.87; IR (KBr) 3331, 2976, 1696, 1670, 1620, 1393, 1135, 754 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{26}N_2O_3Na$: *m/z* ([M + Na$^+$]) 437.1836, found 437.1823; $[\alpha]_D^{19}$ = +13.1 (*c* = 0.26, in $CHCl_3$ for 93% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 10/1, 1.0 mL/min, λ = 390 nm, tR = 12.1 min (major isomer) and 15.7 min (minor isomer).

tert-Butyl (2*S*,2′*S*)-5-methoxy-3-oxo-2′-(o–tolyl)spiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 i)

Yellow solid, 12.8 mg, 63% yield (> 20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.14 (m, 3H), 7.04–7.07 (m, 3H), 6.58 (d, *J* = 8.7 Hz, 1H), 5.17 (brs, 1H), 4.03 (m, 1H), 3.92–3.80 (m, 2H), 3.77 (s, 3H), 1.99 (s, 3H), 1.47–1.12 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.80, 156.00, 154.12, 153.59, 138.36, 136.07, 130.26, 127.93, 127.36, 126.24, 125.18, 119.64, 113.57, 104.63, 79.57, 74.21, 61.04, 60.01, 55.74, 44.30, 33.20, 28.45, 27.95, 19.37; IR (KBr) 3347, 2972, 1690, 1494, 1394, 1224, 1131, 734 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}N_2O_4Na$: *m/z* ([M + Na$^+$]) 431.1941, found 431.1929; $[\alpha]_D^{24}$ = −19.0 (*c* = 0.11, in $CHCl_3$ for 93% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 390 nm, tR = 18.7 min (major isomer) and 29.0 min (minor isomer).

tert-Butyl (2*S*,2′*S*)-5-bromo-3-oxo-2′-(o–tolyl)spiro[indoline-2,3′-pyrrolidine]-1′-carboxylate (7 j)

Yellow solid, 13.4 mg, 59% yield (> 20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.4 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.23–7.14 (m, 3H), 7.09 (d, *J* = 6.9 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.25–5.09 (br, 1H), 3.97–4.11 (m, 2H), 3.89–3.71 (m, 1H), 2.29–2.09 (m, 2H), 1.99 (s, 3H), 1.46–1.13 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.11, 158.53, 154.02, 139.93, 138.29, 135.99, 130.76, 130.35, 127.55, 127.37, 126.39, 125.16, 120.70, 113.36, 111.33, 79.71, 73.67, 72.29, 60.58, 59.64, 43.93, 32.54, 28.44, 27.94, 19.43; IR (KBr) 3330, 2970, 1690, 1619, 1474, 1390, 1175, 725 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}BrN_2O_3Na$: *m/z* ([M + Na$^+$]) 479.0946, found 479.0929; $[\alpha]_D^{17}$ = +51.0 (*c* = 0.11, in $CHCl_3$ for 82% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/*i*-PrOH = 20/1, 1.0 mL/min, λ = 390 nm, tR = 11.4 min (major isomer) and 28.2 min (minor isomer).

(2*S*,2′*S*)-2′-(o-Tolyl)-1′-tosylspiro[indoline-2,3′-pyrrolidin]-3-one (7 k)

Yellow solid, 11.0 mg, 51% yield (> 20:1 dr); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.37 (m, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.27–7.23 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.01 (s, 1H), 3.97 (s, 1H), 3.76–3.87 (m, 2H), 2.48 (s, 3H), 2.20–2.15 (m, 1H), 2.07–1.93 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.86, 159.89, 143.72, 137.56, 137.16, 135.65, 134.06, 130.44, 129.58, 128.00, 127.77, 126.74, 126.40, 124.88, 119.36, 118.70, 111.78, 72.86, 62.51, 45.93, 33.65, 21.70, 19.43; IR (KBr) 3387, 2925, 1690, 1619, 1492, 1469, 1341, 1163, 754 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_3SNa$: *m/z* ([M + Na$^+$]) 455.1408, found 455.1385; $[\alpha]_D^{24}$ = +101.2 (*c* = 0.11, in $CHCl_3$ for 90% ee); HPLC Daicel ChiralPak AD-3 column, *n*-Hexane/

i-PrOH = 7/1, 1.0 mL/min, λ = 390 nm, tR = 17.0 min (minor isomer) and 26.8 min (major isomer).

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[16] Due to the higher reactivity of isotryptamine **5a** than tryptamine **1a** on the PS reaction, an additive of dicarboxylic acid (without chiral catalyst) readily promoted background reaction to afford the racemic product **6a** in 46% yield, led to decreasing ee values of **6a**. Thus, to suppress the undesired racemic pathway, monocarboxtlic acid was used for **5a**.

[17] $NaOCl \cdot 5H_2O$ was supplied from Nippon Light Metal Company, Ltd (https://www.nikkeikin.com/SHC5/index.html).

[18] Decreasing yield (51%) and diastereoselectivity (6.7:1) of **7a** were confirmed when Oxone® with KBr conditions[13k] was applied to oxidative rearrangement of **6a**.

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[22] Initially, our synthesized compounds **4** and **7** were employed for the TOP-Flash assay as an initial screening. Most of the compounds did not exhibit the high cytotoxicity. However, except for **7g**, the sufficient inhibitory activity cannot be detected. Therefore, the spiro compound **7g** was applied to the FOP-Flash assay to double check for the exact activity.

[23] The compound (2*R*,2'*R*)-**7g** also indicated the Wnt-signaling inhibitory activity with IC_{50} value of 3.8 μM.

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UPDATES

Practical Stereoselective Synthesis of C3-Spirooxindole- and C2-Spiropseudoindoxyl-Pyrrolidines *via* Organocatalyzed Pictet-Spengler Reaction/Oxidative Rearrangement Sequence

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Dr. M. Kondo, N. Matsuyama, T. Z. Aye, Dr. I. Mattan, T. Sato, Y. Makita, Prof. M. Ishibashi, Prof. M. A. Arai, Dr. S. Takizawa*, Prof. H. Sasai*