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Pd-Catalyzed Assembly of Spirooxindole Natural Products: A Short Synthesis of Horsfiline

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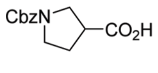

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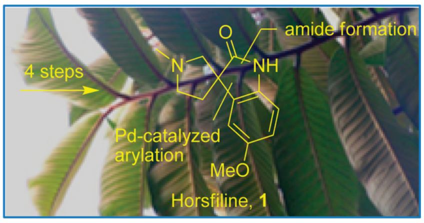

The Pd-catalyzed intramolecular α-arylation of amides is applied to the synthesis of functionalized spirooxindoles. The substrate scope is evaluated, and the reaction is demonstrated to be useful for the assembly of spirooxindole natural products and derivatives thereof. As an application, a new synthesis of horsfiline **1** is presented, giving the natural product in only 4 steps from commercially available amino acid **12**.

Introduction

Spirocyclic structures are abundant in many natural products and have always been a challenge for synthetic organic chemists.[1] In particular the 3,3′-pyrrolidinyl-spirooxindoles (some prominent examples are depicted in Figure 1) constitute a pharmaceutically valuable class of biologically active compounds, which can be isolated from plants and fungi.[2] These natural products have a fascinating architecture, and various biological activities such as anticancer properties,[3] contraceptive action,[4] and antimigraine activity[5] have been reported. The 3,3′-pyrrolidinyl-spirooxindole scaffold is therefore a privileged structural element with respect to pharmaceutical applications. In our efforts toward targeted anticancer agents,[6] we have been attracted by these natural products because some members of the spirooxindole family show pronounced and cell-type-specific anticancer properties.[3]

A large number of synthetic methodologies have been developed for the preparation of spirooxindole natural products, and the reader is referred to some recent reviews to get an overview.[7] A key point in each synthesis is the construction of the spirocyclic scaffold with its quarternary carbon center. Most strategies rely on indole precursors for the construction of the key structural element, and only a limited number of procedures construct the indole itself. Elegant examples of the latter approach are Overman's Heck cyclizations of unsaturated anilides.[8] This approach allows the synthesis of many derivatives with high structural diversity

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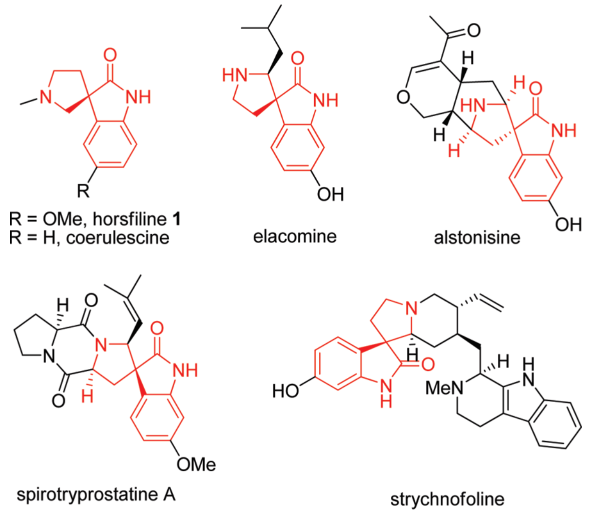


FIGURE 1. Some examples for bioactive natural products containing the 3,3′-pyrrolidinyl-spirooxindole scaffold (highlighted in red).

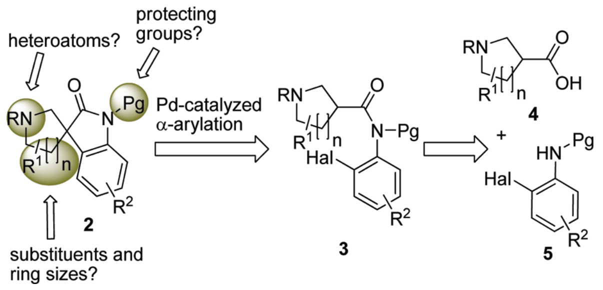


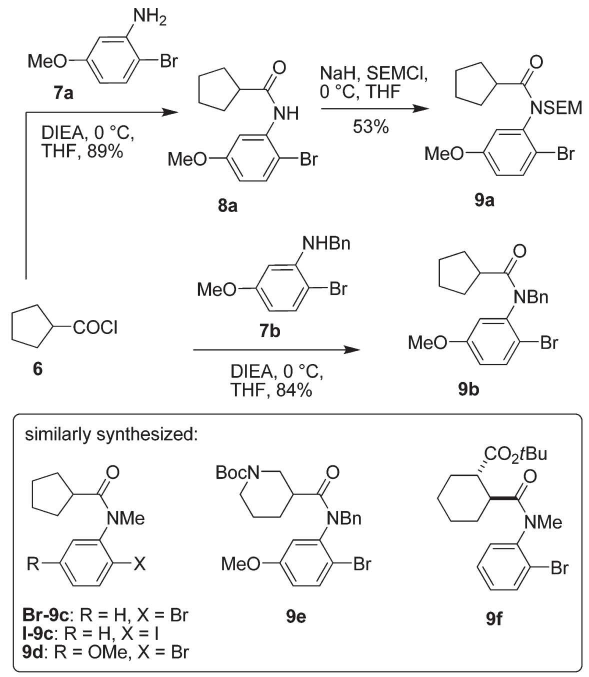
FIGURE 2. Retrosynthesis of the spirooxindole scaffold **2**.

in the indole moiety, making it particularly attractive for the preparation of compound libraries for biological screenings.[9]

Results and Discussion

Our approach is depicted in Figure 2. We planned to construct the spirooxindole **2** by an intramolecular α-arylation of the intermediate *o*-haloanilide **3**. This intermediate would be prepared from carboxylic acids **4** and anilines **5** by amide formation. This method is particularly attractive, because many derivatives of both educts (anilines **5** and carboxylic acids **4**) are commercially available or can be synthesized with limited efforts for more complex derivatives.[10]

SCHEME 1. **Synthesis of Cyclization Precursors**



The key step of this concept is the Pd-catalyzed α-arylation of an appropriate amide precursor **3**. This reaction has first been reported by Hartwig for inter- and intramolecular variants.[11]

However, the method has rarely been used for the synthesis of spiro compounds, nor has it been applied to the synthesis of densely functionalized natural products.

In consequence, we first focused on some model reactions to evaluate the substrate scope and optimal conditions for the attempted α-arylation. The key questions to be addressed were (1) What are the right conditions for the arylation of carboxamides **3** containing nitrogen heterocycles? (2) What kind of protecting groups (particularly for the anilide nitrogen) are compatible? (3) Are sterically hindered and functionalized (particularly "competing" carboxyl derivatives) anilides suitable substrates?

The synthesis of the required cyclization precursors is shown for two examples, **9a** and **9b** (Scheme 1). All other anilides **9c**−**9f** were synthesized similarly in one or two steps (see Supporting Information for details).

The first cyclizations of anilides **9a**, **9c**, and **9d** using conditions reported by Hartwig ($Pd(PCy_3)_2$ in dioxane, 55 °C)[11] proceeded smoothly and gave the desired spirooxindoles **10a**, **10c**, and **10d** in reasonable yields (Table 1). The conversion of educts **9a**, **9c**, and **9d** was quantitative, and the only detectable byproducts are the dehalogenated anilides

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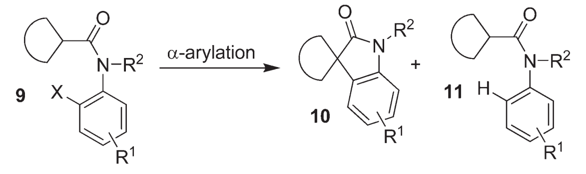
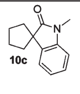
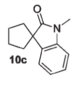
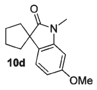
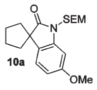
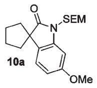
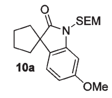
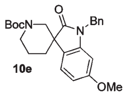
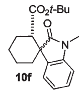
TABLE 1. Evaluation of Reaction Scope and Conditions



anilide	conditions	oxindole **10**	yield **10**	yield **11**
I-9c	$Pd(PCy_3)_2$, NaO*t*-Bu, dioxane, 55 °C		66%	30%
Br-9c	$Pd(PCy_3)_2$, NaO*t*-Bu, dioxane, 55 °C		77%	17%
9d	$Pd(PCy_3)_2$, NaO*t*-Bu, dioxane, 55 °C		80%	20%[a]
9a	$Pd(PCy_3)_2$, NaO*t*-Bu, dioxane, 55 °C		0%	77%
9a	$Pd(PCy_3)_2$, NaO*t*-Bu, toluene, 110 °C		83%	9%
9a	*i*-Pr-PEPPSI, NaO*t*-Bu, toluene, 110 °C		89%	3%
9e	*i*-Pr-PEPPSI, NaO*t*-Bu, toluene, 110 °C		71%	19%
9f	*i*-Pr-PEPPSI, NaO*t*-Bu, toluene, 110 °C		75%[b]	-

[a] Estimated amount, determined from the ^{1}H NMR of the crude product. [b] 1:1 mixture of two diastereomers.

11. The reaction works for aryliodides like **I-9c** and arylbromides like **Br-9c** or **9d**, the latter giving less debromination as a side reaction. In consequence, we have used arylbromides for following conversions.

The nature of the second nitrogen substituent of the anilide is of crucial importance, because for most natural products this position is unsubstituted, and it would thus be necessary to introduce suitable protecting groups (instead of methyl in **9c**, **9d**, and **9f**) here. *N*-Alkyl and *N*-benzyl groups are generally well tolerated, but the conversion of the SEM-protected anilide **9a** using the above-mentioned conditions ($Pd(PCy_3)_2$ in dioxane, 55 °C) did not give the desired spirooxindole **10a**.[12] The same is true for conversions of nipecotic acid derivatives like **9e** or cyclohexyl carboxamides like **9f** under the same conditions.

However, switching the solvent to toluene and increasing the temperature improves the situation, and a good yield of spirooxindole **10a** was obtained upon conversion of anilide **9a** with $Pd(PCy_3)_2$. The best results gave the [Pd]-PEPPSI-catalyst[13] in toluene at 110 °C. This catalytic system has been reported previously to give excellent results for the α-arylation of sterically hindered substrates by Hartwig and Lee.[11a] Using these improved conditions, even SEM-protected anilides like **9a**, sterically hindered and functionalized derivatives of cyclohexane carboxamides like **9f**, or heterocycles like **9e** gave the corresponding spirooxindoles **10** in good yields.

According to the retrosynthesis in Figure 2, the α-arylation of anilides was applied to a short total synthesis of (±)-horsfiline **1**. This spirooxindole was first isolated from the malaysian tree *Horsfieldia superba* in 1991 by Bodo and coworkers.[14] It has been used frequently as a model compound to demonstrate the power of novel methodology in natural product synthesis, and a number of syntheses have been reported.[15]

We started with the commercially available Cbz-protected pyrollidine-2-carboxylic acid **12**, which was coupled to the anilide **7c** with PCl_5 to give **13** in good yield (Scheme 2).[16] The α-arylation of **13** with the [Pd]-PEPPSI-catalyst system at 110 °C gave spirooxindole **14** in excellent yield. Conversion of the starting material was complete, and no dehalogenation was observed. Spirooxindole **14** is a known precursor for horsfiline.[15] With a slight modification of a known procedure[15e] we have been able to convert Cbz-protected **14** to

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[12] The reason for the slow and sluggish reactions with SEM-protected anilides like **9a** under these conditions is unclear. In contrast to methyl- and benzyl-substituted anilides (nearly exclusively *syn*), we noticed a high percentage of the *anti*-anilide rotamer (~30%) for compound **9a**. This rotamer is unproductive for the cyclization. In addition, a number of side products were observed for the conversions of SEM-protected substrates. This might be due to a high reactivity of the aminal CH_2 group in the SEM protecting group.

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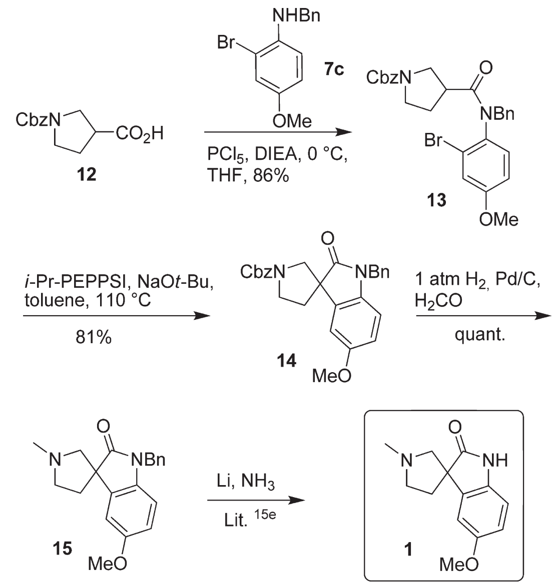
[16] It is remarkable that anilide **13** shows a double set of signals in ^{1}H and ^{13}C NMR spectra due to the presence of two diastereomers. The barrier to rotation around the aryl-*N*-bond is unusually high for an *o*-bromoanilide. No coalescence was observed in DMSO up to 120 °C by NMR. For comparison to similar substances, see: (a) Siddall, T. H.; Stewart, W. E. *J. Org. Chem.* **1968**, *34*, 2927. (b) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955. (c) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.

SCHEME 2. Total Synthesis of Horsfiline 1



N-Bn-horsfiline **15** by Cbz-deprotection and reductive amination with paraformaldehyde in one step. We have not been able to deprotect Cbz and Bn in **14** simultaneously as suggested by Kung.[15l] Even increasing the hydrogen pressure up to 20 bar does not permit the cleavage of the *N*-benzyl amide. Instead, unwanted side reactions such as ring opening of the spirocycle **14** were observed.

However, a two-step procedure with a final deprotection of **15** with Li/NH_3 following a protocol of Fuji[15e] gave horsfiline **1**. The overall yield for the four-step total synthesis of the natural product **1** is 58%. To the best of our knowledge this is the shortest synthesis of horsfiline **1** reported.

Conclusion

In summary, we have applied the intramolecular Pd-catalyzed α-arylation of anilides to the synthesis of 3,3′-pyrrolidinyl-spirooxindoles. The [Pd]-PEPPSI-catalyst system was found to be the best choice for conversion of functionalized heterocyclic derivatives. The methodology is valuable for the synthesis of spirooxindole natural products as has been demonstrated with the synthesis of (±)-horsfiline **1**. More complex spirooxindoles should also be accessible, and these applications are under investigation in our group. In addition, we are currently using this approach for the construction of solid-supported spirooxindole libraries for screening purposes.

Experimental Section

General Procedure A: Amide Formation with PCl_5. To a cooled solution of 1 equiv of the carboxylic acid in abs THF was added 0.9−1.0 equiv of PCl_5 under nitrogen atmosphere. After 1 h the solvent was distilled off, and the residue was coevaporated twice with abs THF. Solvent was added again, and first 1.0−1.2 equiv of DIEA or TEA followed by a solution of 1.0−1.2 equiv of the aniline derivative in abs THF was added dropwise. The mixture was stirred at rt while the reaction was monitored *via* TLC. After completion, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combined organic phases were washed with aqueous 1 M HCl or satd $NaHSO_4$ solution, satd Na_2CO_3 or $NaHCO_3$ solution, and brine, dried over Na_2SO_4 ,and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography.

General Procedure B: Amide Formation from Acid Chlorides. To a cooled solution of 1 equiv of the carboxylic acid chloride in abs THF was added dropwise 1 equiv of DIEA followed by a solution of 1 equiv of the aniline derivative in abs THF. The mixture was stirred at rt while the reaction was monitored *via* TLC. After completion, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine, then dried over Na_2SO_4, and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography.

General Procedure C: Preparation of *N*-Methyl-anilides. To a cooled solution of 1 equiv of the anilide in abs THF was added 1.5 equiv of NaH (60% in mineral oil) under nitrogen atmosphere. After 1 h approximately 10 equiv of MeI was added dropwise. The mixture was stirred at rt while the reaction was monitored *via* TLC. After completion, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine, then dried over Na_2SO_4, and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography.

General Procedure D: Preparation of *N*-SEM Protected Anilides. To a cooled solution of 1 equiv of the anilide in abs THF was added 1.5 equiv of NaH (60% in mineral oil) under nitrogen atmosphere. After 1 h approximately 1.5−3.0 equiv of SEM-chloride was added dropwise. The mixture was stirred at rt while the reaction was monitored *via* TLC. After completion, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine, then dried over Na_2SO_4, and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography.

General Procedure E: Pd-Catalyzed α-Arylation. Catalyst (10 mol %) and 3 equiv freshly prepared NaO*t*-Bu were dissolved in freshly dried solvent under argon in a Schlenck flask. The *o*-haloanilide was dissolved in a second flask in dry solvent and was added to the catalyst solution through a syringe. The flask was sealed carefully, and the solution was stirred at the denoted temperature and time. It was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine, then dried over Na_2SO_4, and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography.

***o*-Bromoanilide 8a.** According to general procedure B, 0.33 g (2.49 mmol) of cyclopentane carboxylic acid chloride **6** was treated with 0.43 mL of DIEA and 0.50 g of *o*-bromoaniline **7a** (2.49 mmol) in 10 mL of abs THF. The title compound was obtained as a colorless oil after flash chromatography (EtOAc/Cyclohexane 1:15) in 0.66 g (89%) yield. ^1H NMR ($CDCl_3$, 400 MHz, δ) 8.13 (d, J = 2.8 Hz, 1H), 7.68 (broad, 1H), 7.37 (d, J = 8.9 Hz, 1H), 6.54 (dd, J = 8.8 Hz, 4.0 Hz, 1H), 3.80 (s, 3H), 2.78 (quin., J = 8.1 Hz, 1H), 1.95−2.04 (m, 2H), 1.84−1.94 (m, 2H), 1.74−1.84 (m, 2H), 1.60−1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 174.9, 159.8, 136.8, 132.3, 112.0, 106.4, 103.4, 55.7, 47.4, 30.6, 26.1 ppm; mp 95 °C; HRMS-EI (m/z) $[M]^+$ calcd for $C_{13}H_{16}BrNO_2$ 297.0359, found 297.0367.

***o*-Iodoanilide I-8c.** To a cooled solution of 0.40 g (3.50 mmol) of cyclopentane carboxylic acid in abs Et_2O was added 0.73 g (3.50 mmol) of PCl_5 under nitrogen atmosphere. After 1 h the solvent was distilled off, and the residue was dissolved in benzene. A solution of 0.77 g (3.50 mmol) of *o*-iodoaniline in abs Et_2O was added dropwise. The mixture was stirred at rt while the reaction was monitored *via* TLC. After completion, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent gave 0.56 g of *o*-iodoanilide **I-8c** (1.78 mmol) as a colorless foam. The crude product was used in the next step without further purification.

***o*-Bromoanilide Br-8c.** According to general procedure A, 0.39 g (1.46 mmol) of *o*-bromoanilide **Br-8c** was obtained from 0.73 g (6.40 mmol) of cyclopentane carboxylic acid, 0.74 mL of TEA (6.73 mmol), and 1.16 g (6.74 mmol) of *o*-bromoaniline in 23% yield as a colorless wax that was purified by flash chromatography (EtOAc/Cyclohexane 1:15). ^{1}H NMR ($CDCl_3$, 600 MHz, δ) 8.38 (d, J = 8.0 Hz, 1H), 7.68 (broad, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 6.96 (t, J = 7.7 Hz, 1H), 2.78 (quin., J = 8.1 Hz, 1H), 1.97−2.03 (m, 2H), 1.89−1.95 (m, 2H), 1.77−1.83 (m, 2H), 1.62−1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 174.4, 136.1, 132.4, 128.5, 125.0, 122.0, 113.4, 47.4, 30.7, 26.2 ppm; HRMS-EI (m/z) $[M]^+$ calcd for $C_{12}H_{14}BrNO$ 267.0259 found 267.0256.

***o*-Bromoanilide 8f.** In a round-bottom flask, 0.50 g (9.23 mmol) of cyclohexane dicarboxylic acid anhydride and 1.60 g (9.23 mmol) of *o*-bromoaniline were stirred in 20 mL of toluene for 48 h. The reaction mixture was filtered, and the precipitated product was washed with toluene and dried *in vacuo*. *o*-Bromoanilide **8f** was obtained in 71% yield (0.75 g, 2.30 mmol) as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz, δ) 12.1 (s, 1H), 9.31 (broad, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 3.12 (broad, 1H), 2.78 (broad, 1H), 2.12−2.24 (m, 2H), 1.45−1.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 175.1, 172.6, 136.4, 132.5, 127.8, 126.9, 126.7, 117.9, 42.9, 41.9, 27.3, 25.4, 23.8, 22.6 ppm; mp 172 °C; HRMS-ES (m/z) $[M]^-$ calcd for $C_{14}H_{15}BrNO_2$, 324.0241, found 324.0248.

***N*-SEM-Protected *o*-Bromoanilide 9a.** According to general procedure D, 0.25 g (0.57 mmol) of *o*-bromoanilide **9a** was obtained from 0.32 g (1.07 mmol) of *o*-bromoanilide **8a** in 53% yield as a colorless oil that was purified by flash chromatography (EtOAc/Cyclohexane 1:10). ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.52−7.54 (m, 1H), 6.81−6.83 (m, 2H), 5.62 (d, J = 10.4 Hz, 1H), 4.41 (d, J = 10.4 Hz, 1H), 3.80 (s, 3H), 3.60−3.69 (m, 2H), 2.37−2.41 (m, 1H), 1.89−1.96 (m, 1H), 1.60−1.73 (m, 5H), 1.37−1.43 (m, 2H), 0.90−0.99 (m, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 177.8, 159.6, 141.3, 133.7, 117.7, 115.3, 114.3, 76.0, 66.2, 55.8, 42.7, 32.0, 30.4, 26.4, 18.3, −1.4 ppm; HRMS-EI (m/z) $[M]^+$ calcd for $C_{19}H_{30}BrNO_3Si$ 427.1178, found 427.1177.

***N*-Benzyl-*o*-bromoanilide 9b.** According to general procedure B, 0.33 g (2.49 mmol) of cyclopentane carboxylic acid chloride **6** was treated with 0.43 mL of DIEA and 0.72 g of *o*-bromoaniline **7b** (2.49 mmol) in 10 mL of abs THF. The title compound was obtained as a colorless oil after flash chromatography (EtOAc/PE 1:8) in 0.81 g (84%) yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.52 (d, J = 8.3 Hz, ^1J = 9.1 Hz, 3.3 Hz, J = 14.0 Hz, J = 14.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 176.8, 159.2, 141.7 ppm; HRMS-ES (m/z) $[M + Na]^+$ calcd for $C_{20}H_{22}BrNO_2Na$ 410.0726, found 410.0727.

***N*-Methyl-*o*-bromoanilide Br-9c.** According to general procedure B, 0.18 g (0.64 mmol) of *N*-methyl-*o*-bromoanilide **9c** was obtained from 0.24 g (0.90 mmol) of *o*-bromoanilide **Br-8c**, 0.04 g of NaH (1.80 mmol, dispersion in mineral oil), and 0.13 mL of MeI (2.08 mmol) in 71% yield as a colorless solid that was purified by flash chromatography (EtOAc/Cyclohexane 1:10). ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.67 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 7.37 (dt, J = 7.5 Hz, 1.4 Hz, 1H), 7.21−7.27 (m, 2H), 3.18 (s, 3H), 2.33 (quin., J = 8.2 Hz, 1H), 1.85−1.91 (m, 1H), 1.61−1.75 (m, 4H), 1.53−1.60 (m, 1H), 1.34−1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 176.9, 143.2, 133.9, 130.3, 129.7, 128.9, 123.9, 42.4, 36.1, 31.5, 30.7, 26.3, 26.2 ppm; mp 71 °C; HRMS-ES (m/z) $[M + Na]^+$ calcd for $C_{13}H_{16}BrNONa$ 304.0307, found 304.0309.

***N*-Methyl-*o*-iodoanilide I-9c.** According to general procedure A, 0.20 g (0.68 mmol) of the title compound was obtained from 0.48 g (1.51 mmol) of *o*-iodoanilide **I-8c**, 0.06 g of NaH (1.50 mmol, dispersion in mineral oil), and 0.14 mL of MeI (2.24 mmol) in 40% yield as a colorless solid that was purified by flash chromatography ($MeOH/CH_2Cl_2$ 1:15). ^{1}H NMR ($CDCl_3$, 400 MHz, δ)7.93 (dd, J = 1.5 Hz, 1.5 Hz, 1H), 7.41 (dddd, J = 7.9 Hz, 7.6 Hz, 1.5 Hz, 1.2 Hz, 1H), 7.24 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.07 (ddd, J = 7,0 Hz, 7.6 Hz, 1.5 Hz, 1H), 3.17 (s, 3H), 2.30 (quin., J = 8.4 Hz, 1H), 1.91−1.99 (m, 1H), 1.63−1.75 (m, 4H), 1.52−1.59 (m, 1H) 1.36−1.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 176.8, 146.6, 140.2, 129.9, 129.7, 129.4, 100.3, 42.7, 36.2, 31.8, 30.9, 26.3 ppm; mp 108 °C; HRMS-ES (m/z) $[M + Na]^+$ calcd for $C_{13}H_{16}INONa$ 352.0169, found 352.0165. Elemental analysis: calcd C 47.43%, H 4.90%, N 4.26%, found C 47.48%, H 4.99%, N 4.32%.

***N*-Methyl-*o*-bromoanilide 9d.** According to general procedure B, 0.30 g (0.95 mmol) of *N*-methyl-*o*-bromoanilide **9d** was obtained from 0.41 g (1.38 mmol) of *o*-bromoanilide **8a**, 0.08 g of NaH (2.8 mmol, dispersion in mineral oil), and 2.0 g of MeI (13.8 mmol) in 69% yield as a colorless solid that was purified by flash chromatography (EtOAc/Cyclohexane 1:10). Mp 57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.52−7.55 (m, 1, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 176.9, 159.9, 143.8, 134.1, 115.8, 115.4, 113.9, 55.8, 42.4, 36.0, 31.6, 30.8, 26.3 ppm; HRMS-EI (m/z) $[M + Na]^+$ calcd for $C_{14}H_{18}BrNO_2Na$ 334.0413, found 334.0406.

***N*-Benzyl-*o*-bromoanilide 9e.** The title compound was prepared according to general procedure A from 0.30 g of Boc-nipecotic acid (1.31 mmol) and 0.46 g of aniline **7b**. The crude product was purified by column chromatography (PE/EtOAc 3:1) to give 0.30 g of **9e** (45% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.56 (d, J = 6.8 Hz, 1H), 7.17−7.23 (m, 5H), 6.79 (dd, J = 3.0 Hz, 9.2 Hz, 1H), 6.24 (d, J = 3.4 Hz, 1H), 5.64 (d, J = 13.9 Hz, 1H), 4.01−4.12 (m, 2H), 3.96 (d, J = 15.0 Hz 1H), 3.58 (s, 3H), 2.54 (dt, J = 2.8 Hz, 13.2 Hz, 1H), 2.43 (dt, J = 3.0 Hz, 13.6 Hz, 1H), 2.13 (tt, J = 3.0 Hz, 11.2 Hz, 1H), 1.82−1.93 (m, 2H), 1.63−1.78 (m, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 174.6, 159.3, 154.8, 141.2, 137.2, 34.1, 129.4, 128.5, 127.7, 116.7, 115.9, 114.3, 79.6, 55.6, 51.5, 43.1, 40.4, 29.2, 28.6, 28.0 ppm; HRMS-EI (m/z) $[M + Na]^+$ calcd for $C_{25}H_{31}BrN_2O_4$ 525.1365, found 525.1366.

***N*-Methyl-*o*-bromoanilide 9f.** According to general procedure B, 0.67 g (2.05 mmol) of *o*-bromoanilide **8f** was treated with 180 mg of NaH (14.5 mmol, 60% dispersion in mineral oil) and 1.3 mL (20.8 mmol) of MeI. The resulting crude product was stirred in 20 mL of 2 N aqueous NaOH/THF at rt for 2 h, and the solution was acidified to pH 1 and extracted three times with CH_2Cl_2. The combined organics were washed with H_2O and dried, and the solvent was distilled off *in vacuo* to give a crude product that was crystallized from EtOAc/PE to give 0.59 g (1.73 mmol) of the carboxylic acid (84% yield). ^{1}H NMR (DMSO-d_6, 400 MHz, mixture of rotamers and conformers, δ) 7.27−7.92 (m, 4H), 2.61−2.62 (m, 3H), 2.04−2.51 (m, 2H), 1.07−1.89 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 175.2, 173.2, 172.8, 142.5, 142.1, 133.8, 132.8, 130.6, 129.9, 129.3, 129.1, 122.3, 42.5, 37.8, 37.7, 35.8, 26.0, 24.2, 21.2 ppm; mp 120 °C; HRMS-ES (m/z) $[M]^-$ calcd for $C_{15}H_{18}BrNO_3$ 338.0397, found 338.0395.

Under nitrogen atmosphere, 0.42 g (1.23 mmol) of this carboxylic acid was stirred with 0.35 g (1.62 mmol) of Boc_2O and 46 mg (0.37 mmol) of DMAP in 30 mL of *t*-BuOH at rt. After 12 h the mixture was diluted with EtOAc and washed with 1 M NaOH and 1 M HCl each three times. After flash chromatography with EtOAc/PE 1:5, 150 mg (0.38 mmol) of the title compound **9f** was obtained as a colorless wax in 31% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of isomers, δ) 7.00−7.70 (m, 4H), 2.14−3.37 (m, 5H), 0.75−2.00 (m, 17H); HRMS-ES (*m*/*z*) [M + Na]$^+$ calcd for $C_{19}H_{26}BrNO_3Na$ 418.0994, found 418.0985.

N**-Benzyl-*****o*****-bromoanilide 9g.** According to general procedure B, 0.59 g (1.47 mmol) of *o*-bromoanilide **9g** was obtained from 0.30 g (2.05 mmol) of cyclohexane carboxylic acid chloride, 0.60 g (2.05 mmol) of *N*-benzyl-*o*-bromo-aniline **7b**, and 0.36 mL of DIEA (2.12 mmol) in 72% yield as a colorless solid that was purified by flash chromatography (EtOAc/PE 1:10). ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.54 (d, *J* = 8.8 Hz, 1H), 7.16−7.27 (m, 5H), 6.76 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 6.23 (d, *J* = 2.8 Hz, 1H), 5.65 (d, *J* = 14.4 Hz, 1H), 3.91 (d, *J* = 14.4 Hz, 1H), 3.56 (s, 3H), 1.94−2.00 (m, 1H), 1.42−1.85 (m, 6H), 0.89−1.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 176.4, 159.4, 141.5, 137.8, 133.9, 129.5, 128.5, 127.5, 116.7, 115.7, 114.3, 55.5, 51.1, 42.4, 30.5, 28.9, 25.9, 25.3 ppm; mp 119 °C; HRMS-ES (*m*/*z*) [M + Na]$^+$ calcd for $C_{21}H_{24}BrNO_2Na$ 424.0883, found 424.0880. Elemental analysis: calcd C 62.69%, H 6.01%, N 3.48%, found C 62.33%, H 5.86%, N 3.41%.

Spirooxindole 10c. According to general procedure E, 45 mg (0.14 mmol) of *N*-methyl-*o*-iodoanilide **I-9c** was treated with $Pd(PCy_3)_2$ and NaO*t*-Bu in dioxane for 4 d at 55 °C; 66% of spirooxindole **10c** and 34% dehalogenated side product **11c** were isolated. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.24 (dt, *J* = 7.5 Hz, 1.2 Hz, 1; ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 182.1, 143.1, 137.0 ppm; HRMS-EI (*m*/*z*) [M]$^+$ calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1152.

Dehalogenated Side Product 11c. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.36−7.43 (m, 2H), 7.31−7.33 (m, 1H), 7.17−7.20 (m, 2H), 3.26 (s, 3H), 2.54 (quin, *J* = 8.1 Hz, 1H), 1.55−1.83 (m, 7H), 1.34−1.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 144.6, 129.8, 127.7, 127.6, 42.0, 37.7, 31.3, 26.3 ppm.

Spirocyclization of *****N***-Methyl-*****o*****-bromoanilide Br-9c.** According to general procedure E, 45 mg (0.16 mmol) of *N*-methyl-*o*-bromoanilide **Br-9c** was treated with $Pd(PCy_3)_2$ and NaO*t*-Bu in dioxane for 4 d at 55 °C; 77% of the spirooxindole **10c** and 23% of the dehalogenated product **11c** were isolated.

Spirooxindole 10d. According to general procedure E, 70 mg (0.22 mmol) of *N*-methyl-*o*-bromoanilide **9d** was treated with $Pd(PCy_3)_2$ and NaO*t*-Bu in dioxane for 4 d at 55 °C; 80% of spirooxindole **10d** was isolated after column chromatography. The crude product contained ~20% dehalogenated side product **11d**, which was not isolated in pure form. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.08 (d, *J* = 8.4 Hz, ^1J = 2.4 Hz, 8.4 Hz, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 3.18 (s, 3H), 2.01−2.17 (m, 4H), 1.91−1.99 (m, 2H), 1.76−1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz, δ) 182.7, 159.8, 144.2, 128.9, 123.2, 106.2, 96.1, 55.7, 53.6, 38.7, 26.6, 26.4 ppm; HRMS-EI (*m*/*z*) [M + Na]$^+$ calcd for $C_{14}H_{17}NO_4$ 321.1259, found 321.1243.

Spirooxindole 10a. According to general procedure E, 23 mg (54 μmol) *N*-SEM-protected *o*-bromo-anilide **9a** was reacted with *i*-Pr-PEPPSI and NaO*t*-Bu in toluene for 12 h at 110 °C; 83% of spirooxindole **10a** and 17% dehalogenated product **11a** were isolated. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.09 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 5.13 (s, 2H), 3.81 (s, 3H), 3.53−3.57 (m, 2H), 2.09−2.16 (m, 2H), 2.01−2.08 (m, 2H), 1.93−2.00 (m, 2H), 1.79−1.85 (m, 2H), 0.89−0.97 (m, 2H), −0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 183.3, 159.8, 142.5, 128.4, 123.0, 107.7, 96.9, 69.5, 66.0, 55.5, 53.8, 38.9, 26.5, 17.9, −1.3 ppm; HRMS-EI (*m*/*z*) [M]$^+$ calcd for $C_{19}H_{29}NO_3Si$ 347.1917, found 347.1925.

Dehalogenated Side Product 11a. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.30 (t, *J* = 8.0 Hz, 1H), 6.89 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 6.79−6.83 (m, 1H), 6.75−6.76 (m, 1H), 5.06 (s, 2H), 3.82 (s, 3H), 3.63 (t, *J* = 8.8 Hz, 2H), 2.59 (quint, *J* = 7.6 Hz, 1H), 1.62−1.85 (m, 8H), 0.92−0.97 (m, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 178.0, 160.4, 143.4, 130.2, 120.9, 114.6, 113.4, 77.5, 65.8, 55.5, 42.4, 31.5, 26.5, 18.3, −1.3 ppm; HRMS-EI (*m*/*z*) [M]$^+$ calcd for $C_{19}H_{31}NO_3Si$ 349.2073, found 349.2049.

Spirooxindole 10e. The title compound was prepared according to general procedure E, from 50 mg (0.10 mmol) of *o*-bromoanilide **9e**; 71% of the spirooxindole **10e** and 17% of the dehalogenated side product **11e** were obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.18−7.32 (m, 6H), 6.51 (dd, *J* = 2.4 Hz, 8.2 Hz, 1H), 6.33 (d, *J* = 2.4, 1H), 4.87 (s, 2H), 3.86−3.93 (m, 2H), 3.72 (s, 3H), 1.72−1.79 (m, 4H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz, δ) 180.4, 160.1, 155.2, 143.3, 135.9, 129.0, 127.8, 127.3, 126.0, 124.0, 106.1, 97.6, 79.8, 55.5, 43.6, 39.5, 38.8, 33.1, 28.6 ppm; HRMS-EI (*m*/*z*) [M + Na]$^+$ calcd for $C_{25}H_{30}N_2O_4$ 445.2098, found 445.2091.

Dehalogenated Side Product 11e. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.15−7.27 (m, 6H), 6.85 (dd, *J* = 2.3 Hz, 8.4 Hz, 1H), 6.55 (d, *J* = 6.9 Hz, 1H), 6.46 (t, *J* = 2.3 Hz, 1H), 4.84 (s, 2H), 4.03 (d, *J* = 13.5 Hz, 2H), 3.71 (s, 3H), 2.45 (t, *J* = 12.7 Hz, 2H), 2.35 (tt, *J* = 3.6 Hz, 1H), 1.76 (dddd, *J* = 6.5 Hz, 12.7 Hz, 2H), 1.57−1.61 (m, 2H), 1.43 (s, 9H).; ^{13}C NMR ($CDCl_3$, 101 MHz, δ) 174.6, 160.5, 154.8, 143.4, 137.8, 130.4, 128.9, 128.5, 127.5, 120.6, 114.3, 113.7, 79.6, 55.5, 53.1, 43.1, 39.8, 28.7, 28.5 ppm; HRMS-EI (*m*/*z*) [M + Na]$^+$ calcd for $C_{25}H_{32}N_2O_4$ 447.2254, found 447.2232.

Spirooxindole 10f. According to general procedure E, 40 mg (0.10 mmol) of *N*-methyl-*o*-bromoanilide **9f** was reacted with *i*-Pr-PEPPSI and NaO*t*-Bu in toluene for 12 h at 77 °C. The crude product was purified by HPLC (chromolith RP18, 3 mm × 100 mm, MeCN 20% to 60% in H_2O over 30 min). A fast and a slow fraction corresponding to the two diastereomers of **10f** were collected. Fast fraction (19.3 min, 34% yield): ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.22 (dt, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.12 (dd, *J* = 7.2 Hz, 1.3 Hz, 1H), 7.02 (dt, *J* = 7.5 Hz, 0.9 Hz, 1H), 6.78 (d, *J* = 6.7 Hz, 1H), 3.19 (s, 3H), 2.77 (dd, *J* = 13.0 Hz, 3.6 Hz, 1H), 2.47−2.58 (m, 1H), 2.20−2.30 (m, 1H), 1.85−2.20 (m, 2H), 1.53−1.70 (m, 4H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 178.9, 172.3, 143.5, 134.0, 127.8, 122.2, 121.8, 107.6, 80.4, 51.9, 47.5, 35.8, 28.2, 27.7, 26.1, 25.6, 24.4, 19.9, 18.6 ppm; HRMS-ES (*m*/*z*) [M + Na]$^+$ calcd for $C_{19}H_{25}NO_3Na$ 338.1727, found 338.1729. Slow fraction (19.8 min, 41% yield): ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.71 (dd, *J* = 7.9 Hz, 1.6 Hz, 1H), 7.65 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 7.42 (dt, *J* = 7.7 Hz, 1.5 Hz, 1H), 7.21−7.25 (m, 1H), 3.16 (s, 3H), 2.69−2.74 (m, 1H), 2.35−2.42 (m, 1H), 1.78−1.83 (m, 1H), 1.58−1.64 (m, 1H), 1.44 (s, 9H), 1.21−1.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 175.2, 142.8, 133.8,131.6, 129.6, 128.9, 122.8, 80.0, 46.4, 43.1, 36.4, 29.2, 28.4, 28.2, 25.5 ppm; HRMS-ES (*m*/*z*) [M + Na]$^+$ calcd for $C_{19}H_{25}NO_3Na$ 338.1727, found 338.1731.

N**-Benzyl-*****o*****-bromoanilide 13.** To a cooled solution of 0.30 g (1.20 mmol) of carboxylic acid **12** in 10 mL of abs THF was added 0.25 g (1.20 mmol) of PCl_5 under nitrogen atmosphere. After 1 h the solvent was distilled off, and the residue coevaporated twice with 10 mL of abs THF. The resulting solid was dissolved in 10 mL of abs THF, and first 0.16 g (1.20 mmol) of DIEA followed by a solution of 0.34 g (1.20 mmol) of *o*-bromoaniline **7c** in 10 mL of abs THF was added dropwise. The mixture was stirred at rt while the reaction was monitored *via* TLC. After completion, the reaction was quenched with water and extracted with CH_2Cl_2 three times. The combined organic layers were washed with each 10 mL of aqueous 1 M HCl, satd Na_2CO_3 solution, and brine, dried over Na_2SO_4, and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography (hexane/EtOAc 6:4) to give 0.54 g (1 mmol) of *o*-bromoanilide **13** in 86% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 7.06−7.28 (m, 11H), 6.52−6.638 (m, 2H), 5.39 (dd, *J* = 15.5 Hz, 1H), 5.00 (m, 2H), 3.89 (dd, *J* = 12.4 Hz, 1H), 3.72 (s, 3H), 3.50−3.67 (m, 2H), 3.31−3.59 (m, 1H), 3.10−3.20 (m, 1H), 2.62−2.69 (m, 1H), 1.87−1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 172.7, 159.9, 154.5, 136.9, 136.8, 136.7, 131.4, 129.3, 128.4, 127.9, 127.6, 124.4, 119.0, 114.1, 66.7, 55.8, 51.9, 49.9, 45.7, 41.9, 29.2 ppm; HRMS-ES (*m*/*z*) $[M + H]^+$ calcd for $C_{27}H_{26}BrN_2O_4$ 523.1232, found 523.1233.

***N*-Bn-*N*-Cbz-Horsfiline 14.** *i*-Pr-PEPPSI (2.6 mg, 0.004 mmol) and 9.2 mg of freshly prepared NaO*t*-Bu (0.1 mmol) were dissolved in 2 mL of abs toluene under argon in a Schlenck flask. Next, 20 mg (0.04 mmol) of anilide **13** was dissolved in a second flask in 2 mL of abs toluene and was added to the catalyst solution through a syringe. The flask was sealed carefully, and the solution was stirred for 12 h at reflux. After cooling, the reaction was treated with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 three times. The combined organic layers were washed with 10 mL of brine, then dried over Na_2SO_4, and filtered. The solvent was distilled off, and the crude product was purified by flash chromatography (hexane/EtOAc 6:4) to give 13 mg (0.03 mmol, 81%) of the title compound **14**. ^1H NMR ($CDCl_3$, 400 MHz, δ) 7.24−7.44 (m, 10H), 6.79 (d, J = 6.2 Hz, 1H), 6.69 (dd, J = 2.5 Hz, 2.3 Hz, 1H), 6.63 (d, J = 8.6 Hz, 1H), 5.18 (d, J = 16.1 Hz, 2H), 4.90 (s, 2H), 3.78−4.01 (m, 4H), 3.73 (s, 3H), 2.45−2.54 (m, 1H), 2.04−2.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ); 177.2, 156.4, 154.8, 135.8, 135.4, 128.9, 128.6, 128.1, 128.0, 127.8, 127.3, 112.5, 110.3, 109.8, 67.1, 55.9, 54.7, 54.3, 45.9, 45.4, 44.0, 36.4, 35.8 ppm; HRMS-ES (*m*/*z*) $[M + Na]^+$ calcd for $C_{27}H_{26}N_2O_4Na$ 465.1785, found 465.1773.

***N*-Bn-Horsfiline 15.** Spirooxindole **14** (13 mg, 0.03 mmol) and 9 mg (0.30 mmol) of paraformaldehyde were treated with a catalytic amount of 10% Pd/C and stirred under a hydrogen atmosphere (1 atm). After filtration through Celite and purification of the crude product by flash chromatography (CH_2Cl_2/MeOH 20:1), 10 mg (0.03 mmol, quant.) of the title compound **15** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz, δ) 7.24−7.38 (m, 5H), 7.08 (d, J = 2.7 Hz, 1H), 6.65 (dd, J = 2.6 Hz, 6.1 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 4.88 (s, 2H), 3.76 (s, 3H), 3.06−3.11 (m, 1H), 2.86−2.96 (m, 2H), 2.76 (dd, J = 7.7 Hz, 8.8 Hz 1H), 2.47 (s, 3H), 2.39−2.44 (m, 1H), 2.08−2.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ); 180.3, 156.5, 137.4, 136.2, 135.5, 128.9, 127.7, 127.4, 112.3, 110.5, 109.2, 66.5, 56.8, 56.1, 53.9, 44.0, 42.0, 38.4 ppm; HRMS-ES (*m*/*z*) $[MH]^+$ calcd for $C_{20}H_{23}N_2O_2$, 323.1754, found 323.1751.

(±)-Horsfiline 1. According to a literature procedure[5] 17 mg (0.05 mmol) of the spirooxindole **15** was added to a solution of lithium in liquid ammonia at −70 °C. The title compound was characterized by ^1H NMR and ^{13}C NMR and the spectra were found to be in accordance to the literature data. The molecular formula was proven by HRMS (ES).

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Supporting Information Available: General experimental data and NMR spectra for compounds **8**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.