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Synthesis of (*S*)- and (*R*)-Harmicine from Proline: An Approach Toward Tetrahydro-β-carbolines

Christopher S. Lood[a] and Ari M. P. Koskinen*[a]

Keywords: Asymmetric synthesis / Natural products / Chiral pool / Alkaloids / Amino acids

(*S*)- and (*R*)-Harmicine were synthesized from L- and D-proline, respectively. This chiral pool synthesis constitutes a new approach towards C1 substituted tetrahydro-β-carbolines. The developed route makes use of the 9-phenyl-9-fluorenyl protecting group strategy of amino acids to prevent racemization of the vulnerable α-amino carbonyl stereocenter. Enantiopure harmicine (> 99 % *ee*) was obtained in nine steps from commercially available starting material. The synthesis was performed without the use of any silica gel flash chromatography.

Introduction

Tetrahydro-β-carbolines (TH*β*C), a subgroup of the indole alkaloid family, consist of a large number of natural products with wide structural diversity, and many of these compounds have received a lot of attention within the synthetic community for decades. The large attention can partly be attributed to the interesting structural features associated with some of these compounds and partly to the fact that, in many cases, they possess highly interesting medicinal properties.[1] For example, compounds such as vincamine, ajmalicine, and yohimbine (not shown) have found some use in modern medicine, and reserpine is still being prescribed for the treatment of hypertension. Tadalafil, a non-natural TH*β*C used for the treatment of erectile dysfunction, is currently one of the top grossing drugs on the market (Figure 1).

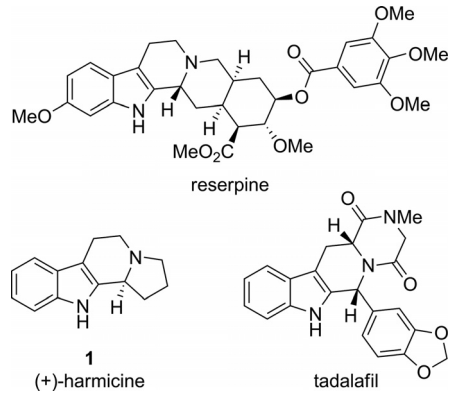

Figure 1. Examples of members of the tetrahydro-β-carboline family.

The synthesis of chiral C1 substituted TH*β*Cs has traditionally relied on a few classical approaches. Diastereoselective versions of the Pictet–Spengler reaction (PSR),[2,3] including substrate controlled reactions of tryptophan derivatives,[4] substrate controlled reactions of chiral aldehydes,[5] and the use of chiral N-auxiliaries,[6] have been developed extensively and utilized in the synthesis of a large number of these types of natural products. Asymmetric versions of the PSR have also been developed.[7] Furthermore, examples of asymmetric protocols using catalytic amounts of chiral Brønsted acids are emerging as powerful synthetic tools for the synthesis of TH*β*C derivatives.[8] Another approach that has been widely employed is the use of the Bischler–Napieralski reaction followed by asymmetric reduction of the 3,4-dihydro-β-carboline.[9–11] Other asymmetric strategies include addition of carbon nucleophiles to 3,4-dihydro-β-carbolines,[12] chiral formamide carbanion chemistry,[13] and enzymatic PSR.[14]

Harmicine **1** was first isolated from the leaf extract of the Malaysian plant *Kopsia griffithii*.[15] The leaf extract possesses antileishmanial activity, and recently antinociceptive properties have been assigned to **1**.[16] Structure elucidation revealed a new tetracyclic compound of the TH*β*C class to be part of this extract. Harmicine itself has previously been synthesized on a number of occasions.[17–19]

We have been involved in natural product synthesis starting from compounds from the chiral pool, making use of the stereochemical information embedded within amino acids. In this context, we envisioned a strategy in which the side chain of amino acid **6** would end up in the C1 position of the TH*β*C, thereby creating a new synthetic route to the TH*β*C framework (Figure 2). Performing a lateral lithiation reaction between compound **4** and Weinreb amide **5** was

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expected to generate α-amino ketone **3**.[20] Further functionalization of the benzylic position followed by indolization and ring closure would lead to the basic structure **2**, which is a C1 substituted TH*β*C, in enantiopure form.

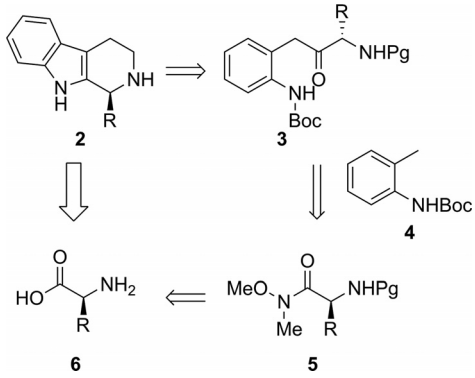
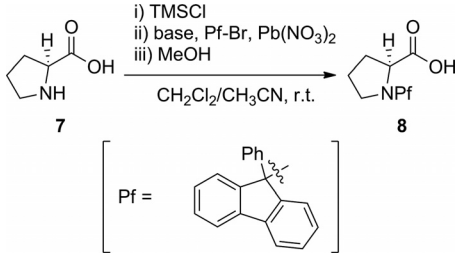


Figure 2. Synthetic strategy towards the TH*β*C framework; R = amino acid side chain, Pg = protecting group.

It is known that α-amino ketones, and also to some extent α-amino amides, are prone to racemization under strongly basic conditions. To eliminate this as a possibility, we employed the 9-phenyl-9-fluorenyl (Pf) protecting group strategy for amino acids. This strategy has been successfully used in natural product synthesis and in the synthesis of medicinally interesting compounds on a number of occasions.[21,22] To demonstrate the synthetic value of such a protocol we then embarked on the synthesis of harmicine.

Results and Discussion

The synthesis started from proline **7**, however, Pf-protection of **7** was not as trivial as first anticipated. In contrast to the Pf-protection of alanine, by using the standard literature procedure, partial racemization occurred at the labile α-stereogenic center giving rise to an *ee* of 89%.[23] This can most likely be attributed to the higher acidity of the cyclic α-proton in proline compared to that in alanine (Scheme 1). In an attempt to circumvent the problem, a more hindered base was tested. When switching from triethylamine (TEA), to diisopropylethylamine (DIPEA), the *ee* could be improved to an acceptable level of 98%. However, when starting from a chiral pool substrate such as proline, every small loss in *ee* would constitute a disappointment. In that spirit, and because the use of strong bases such as TEA or DIPEA was not necessary, we opted for a weaker base. Using *N*-



Scheme 1. Phenyl fluorenylation of proline.

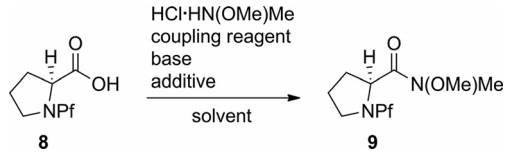
methylmorpholine (NMM; pK_{aH} 7.38, a difference of approximately 3.4 units to TEA, pK_{aH} 10.75), compound **8** was obtained in > 99% *ee* in 82% yield on a 100 mmol scale (Table 1). Acid **8** was isolated after an aqueous work up.

Table 1. Phenyl fluorenylation of proline by using different bases.

Entry	Base	*ee* [%][a]	Yield [%][b]
1	TEA	89	91
2	DIPEA	98	n.d.
3	NMM	> 99	82[c]

[a] Determined by HPLC analysis. [b] Isolated yield. [c] Scale up to 100 mmol, isolated yield.

Compound **8** was then subjected to an amide coupling reaction to obtain the corresponding Weinreb amide (Scheme 2). Initial attempts using 1,1′-carbonyldiimidazole (CDI; Table 2, entries 2–4) proved unsuccessful, and even with the addition of 4-(dimethylamino)pyridine (DMAP), no conversion was observed. By using *N*,*N*-dicyclohexylcarbodiimide (DCC), in combination with DMAP, amide **9** was obtained in a modest yield (31%) after flash chromatography (Table 2, entry 1). However, one of the aims of the described synthesis was to keep the number of chromatographic purification steps to a minimum and due to the concerns associated with side-product formation originating from this particular coupling reaction (the removal of *N*,*N*-dicyclohexylurea often requires chromatographic purification procedures), DCC was not further explored as a viable option. Instead, propylphosphonic anhydride (T3P®), being slightly less expensive than 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and also known to form water-soluble side products from the amide coupling reaction, was tested. By using a reported procedure for an α-amino acid (Table 2, entry 5), a moderate but encouraging yield of **9** of 60% was obtained.[24] Switch-



Scheme 2. Amide coupling of **8** using different coupling reagents.

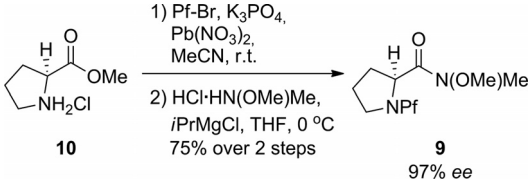
Table 2. Amide coupling reaction of **8**.[a]

Entry	Coupling reagent	Base	Additive	Solvent	Time [h]	Yield [%]
1	DCC	TEA	DMAP[b]	CH_2Cl_2	26	31[c]
2	CDI	TEA	–	THF	23	n.d.[d]
3	CDI	TEA	–	CH_2Cl_2	26	n.d [d]
4	CDI	TEA	DMAP[b]	THF	23	n.d.[d]
5[e]	T3P®	pyridine	–	EtOAc	18	60[f]
6[e]	T3P®	TEA	–	EtOAc	18	9[c]
7	T3P®	TEA	DMAP[g]	EtOAc	26	81[f], 73[h]

[a] Reactions were carried out on a 1 mmol scale with the exception of entry 1, which was carried out on a 2 mmol scale. [b] 5 mol-% used. [c] Isolated yield after flash chromatography. [d] No conversion was detected on TLC. [e] Carried out at 0 °C. [f] Isolated yield. [g] 20 mol-%. [h] Scale up to 56 mmol, isolated yield.

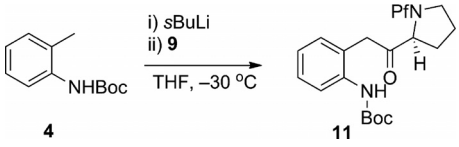
ing the base from pyridine to non-nucleophilic TEA, not surprisingly, diminished the yield substantially (Table 2, entry 6). By using an even more nucleophilic additive than pyridine, 20 mol-% DMAP, in combination with TEA (Table 2, entry 7), Weinreb amide **9** was obtained in good 81% yield. The product was obtained in satisfactory purity after simple aqueous work up.

An alternative route to the Weinreb amide **9** was also developed. The commercially available proline methyl ester HCl salt **10** was Pf-protected under conditions developed for aspartic acid, in 82% yield (Scheme 3).[23] Amide formation using *i*PrMgCl as the base gave the corresponding Weinreb amide in 92% yield. The sequence was high yielding but required at least one flash chromatographic step. Furthermore, partial racemization of the α-stereocenter, most likely in the Pf-protection step, once again proved to be an issue. The *ee* of **9** obtained from this route was 97%.



Scheme 3. Alternative route to Weinreb amide **9**.

Boc-toluidine[25] **4**, prepared from *o*-toluidine, was then coupled with Weinreb amide **9**, by using two equivalents of *s*BuLi, giving ketone **11** in good yield (85%; Scheme 4). The best results were obtained by using an excess (200 mol-%) of **4** (Table 3). The use of lower amounts led to poorer



Scheme 4. Lateral lithiation of **4**.

yields due to incomplete reactions, as shown by the presence of unreacted starting material. The product could be purified by triturating the crude material with Et_2O, giving **11** as a white solid after filtration. The reaction was scaled up to 38 mmol.

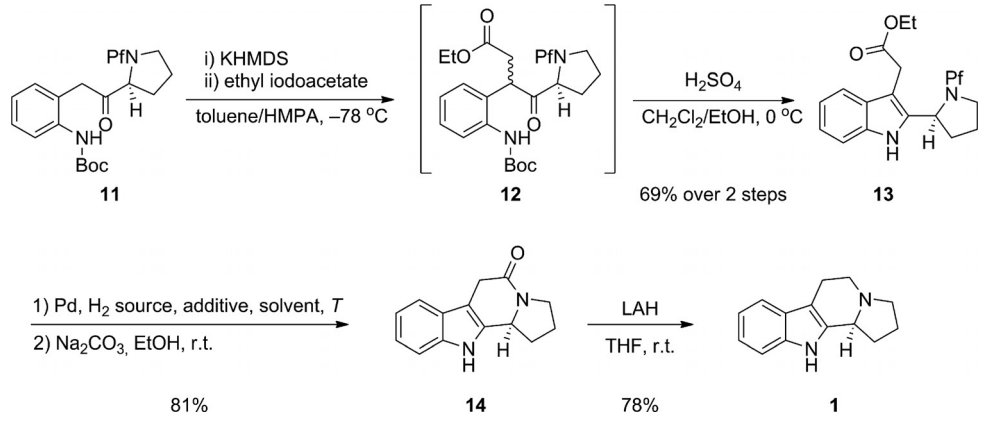
Table 3. Coupling of Boc-toludine **4** and Weinreb amide **9**.

Entry	**9** [mol-%]	**4** [mol-%]	*s*BuLi [mol-%]	Yield [%]
1	100	120	277	60[a]
2	100	150	300	70[a]
3	100	200	400	87[b], 85[c]

[a] Isolated yield after flash chromatography. [b] Isolated yield after trituration in Et_2O. [c] Scale up to 38 mmol, isolated yield.

Ketone **11** was then enolized by using 100 mol-% KHMDS in combination with hexamethylphosphoramide (HMPA; needed to facilitate the formation of the enolate), and subsequently quenched with an acetate electrophile to give intermediate **12** (Scheme 5). Ethyl iodoacetate proved to work very well in the reaction. However, because we were unable to isolate **12**, the crude material was treated directly with sulfuric acid in EtOH, using CH_2Cl_2 as a cosolvent to cleave the Boc group. Upon Boc cleavage the aniline nitrogen condensed with the ketone to give indole **13** in 69% over two steps. Compound **13** was purified by trituration from an EtOAc/hexane mixture, giving an amorphous solid after filtration.

Having installed the carbon frame work, all that remained was the removal of the Pf-group followed by lactam formation and reduction to give harmicine. The Pf-deprotection under hydrogenolysis of **13**, however, required some optimization of the reaction conditions (Table 4). Conventional hydrogenation using Pd/C under 1 atm H_2 (g) gave essentially no conversion. Using Pearlman's catalyst under conditions developed for a Pf-protected pyrroleproline also proved unsuccessful (Table 4, entry 4).[26] Preparing the Pd/C in situ from $Pd(OAc)_2$ and activated charcoal did not improve the reaction outcome (Table 4, entry 5).[27] By using Pd/C, 1 atm H_2 (g), and HCl in EtOH heated to re-



Scheme 5. Transformation of ketone **11** into harmicine **1**.

Table 4. Pf deprotection of indole **13** to give lactam **14**.

Entry	Pd source[a]	H_2 source	Additive	Solvent	*T* [°C]	Time [h]	Yield [%][b]
1[c]	Pd/C	H_2(g)	HCl	EtOH	room temp.	26	n.d.[d]
2[c]	Pd/C	H_2(g)	HCl	EtOH	reflux	4	34[e]
3[c]	Pd/C	H_2(g)	–	AcOH	room temp.	72	n.d.[d]
4[c]	$Pd(OH)_2$	H_2(g)	–	MeOH/THF	room temp.	48	n.d.[d]
5[c]	Pd/C[f]	H_2(g)	–	AcOH	room temp.	48	n.d.[g]
6[h]	Pd/C	HCOOH	–	EtOH	100	5	n.d.[g]
7[i]	Pd/C	HCOOH/ammonium formate	–	EtOH	100	4	0[j]
8[k]	Pd/C	1,4-cyclohexadiene[l]	AcCl	EtOH	reflux	5	n.d.[d]
9[k]	Pd/C	hydrazine[m]	–	EtOH	reflux	4.5	38[e]
10[k]	Pd/C	$NH_4H_2PO_2$[l]	–	EtOH	reflux	3	81[n]

[a] Pd/C: 10 wt.-% on carbon; $Pd(OH)_2$: 20 wt.-% on carbon. [b] Isolated yield. [c] Typical procedure: Indole **13** in the designated solvent (with or without HCl, 300 mol-%) together with Pd (entry 1–3: 10 mol-%; entry 4: 20 mol-%) was stirred in a hydrogen atmosphere (1 atm). [d] No conversion. [e] Isolated yield after flash chromatography. [f] Pd/C formed from $Pd(OAc)_2$ and activated charcoal.[27] [g] Low conversion, decomposition. [h] Reaction performed in a sealed tube with a 1:1 ratio of HCOOH/EtOH using 10 mol-% Pd. [i] Reaction performed in a sealed tube with a 1:1 ratio of HCOOH/EtOH using Pd (10 mol-%) and ammonium formate (2000 mol-%). [j] No product obtained. [k] Typical procedure: Indole **13** in EtOH (with or without AcCl, 200 mol-%) together with Pd (entry 8–9: 10 mol-%, entry 10: 5 mol-%) and the designated H_2 source was stirred and heated to reflux. [l] 600 mol-%. [m] 2000 mol-%. [n] Isolated yield after trituration in toluene.

flux, a yield of 34% was obtained (Table 4, entry 2). However, being concerned with the safety aspects of heating a Pd mixture under a hydrogen atmosphere we turned our attention to catalytic transfer hydrogenation (CTH) conditions.[28] By using HCOOH[29] with or without ammonium formate[30] together with Pd/C in a sealed tube at 100 °C gave low conversions and none of the desired product could be isolated (Table 4, entries 6 and 7). 1,4-Cyclohexadiene[31] proved completely inactive in EtOH at reflux (Table 4, entry 8). Hydrazine[32,33] gave full conversion but only provided **14** in a modest yield of 38% (Table 4, entry 9). Success was achieved by using ammonium hypophosphite[34] in ethanol at reflux. Full conversion was achieved in only three hours, and, after treatment of the crude mixture with Na_2CO_3, lactam **14** was obtained in good yield (81%). The product was isolated by triturating the crude mixture with toluene, once again avoiding the use of silica gel chromatography. To the best of our knowledge, this approach constitutes the first reported Pf-hydrogenolysis reaction under transfer hydrogenation conditions.

The synthesis of harmicine was then completed by reducing the lactam with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) at room temp. Harmicine was isolated after aqueous work up in 78% yield. Both (*S*)-harmicine (from L-proline) and (*R*)-harmicine (from D-proline) were synthesized and chiral HPLC analysis confirmed the *ee* to be > 99%. The nine-step sequence from commercially available starting material was performed without the use of any flash chromatographic purification and the synthesis was scaled up to give 1.16 g of (*S*)-harmicine in one batch.

Conclusions

The synthesis of (*S*)-harmicine and (*R*)-harmicine was completed from L-proline and D-proline, respectively, by using the Pf-group as an amine protecting group strategy. The synthesis was optimized to the point where no silica gel flash chromatography was required and gave the title compound in a total yield of 19% over nine steps with an *ee* of > 99%. During the course of the synthesis, some problems concerning the use of Pf as a protecting group were encountered; however, these problems were subsequently solved. Racemization of proline in the Pf-protection step was circumvented by the use of a weaker base. We also report, to the best of our knowledge, the first Pf-deprotection under transfer hydrogenation conditions. As a final conclusion, this study constitutes a new approach to the synthesis of chiral tetrahydro-β-carbolines and further work involving the synthesis of other natural products from the tetrahydro-β-carboline class by using different amino acids will be reported in due time.

Experimental Section

General Information: Dry solvents (THF, MeCN, CH_2Cl_2 and toluene) were obtained from a solvent drying system (MB SPS-800, using neutral alumina as desiccant). Other solvents used where of P.A. quality, with the exception of HPLC grade hexane for the intended use of HPLC analysis, and used as such directly from the bottles. HMPA and NMM were distilled from CaH_2 and stored over 4 Å molecular sieves. TMSCl was distilled from CaH_2. $Pb(NO_3)_2$ and K_3PO_4 were dried in an oven prior to use. Reagents were obtained from Sigma–Aldrich, TCI Europe, or Johnson Matthey Chemicals Limited. Celite used for filtration was Celite 535, purchased from Sigma–Aldrich. TLC monitoring was performed on silica gel 60 F_{254} on aluminum support obtained from Merck. Visualization of TLC plates was done using UV light (λ = 254 nm) and/or staining the plates with ninhydrin solution (1 g of ninhydrin dissolved in 100 mL of EtOH and 0.2 mL glacial AcOH) or vanillin solution (2.4 g of vanillin dissolved in 100 mL of EtOH, 2 mL of conc. H_2SO_4 and 1.2 mL glacial AcOH). NMR spectra were recorded with a Bruker Avance 400 spectrometer at ambient temperature and the peaks were calibrated to TMS (^{1}H: δ = 0.00 ppm), or residual solvent ^{13}C in $CDCl_3$ (^{13}C: δ = 77.0 ppm) or [D_6]DMSO (^{13}C: δ = 39.5 ppm). Optical rotations were measured with a Perkin–Elmer 343 Polarimeter equipped with a sodium lamp and a

10 cm quartz cuvette. HRMS spectra were recorded with a Waters Micromass LCT Premier (ESI/TOF) mass spectrometer. Elemental analysis was recorded with a Perkin–Elmer 2400 Series II CHNS/O Analyzer . IR was recorded either with a Perkin–Elmer Spectrum One FTIR spectrometer (KBr disc) or a Bruker ALPHA ECO-ATR FTIR spectrometer (film).

***tert*-Butyl *o*-Tolylcarbamate (4):** To THF (100 mL) was added *o*-toluidine (19.8 mL, 187 mmol, 100 mol-%) and Boc_2O (44.8 g, 205 mmol, 110 mol-%), and the solution was heated to reflux for 3 h, after which it was cooled to room temp. Evaporation gave an orange oil, which was crystallized from hexane (20 mL) to form white translucent needles, yield 33 g (85%); R_f = 0.36 (Hex/EtOAc, 9:1). IR (film): $\tilde{\nu}$ = 3271, 2983, 2967, 1701, 1678, 1585, 1521, 1456, 1390, 1363, 1292, 1263, 1245, 1198, 1153, 1050, 1024, 988, 948, 910, 860, 843, 777, 744, 733, 710, 635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (br. d, J = 7.8 Hz, 1 H), 7.19 (t, 7.8 Hz, 1 H), 7.14 (d, J = 7.4 Hz, 1 H), 6.99 (t, J = 7.4 Hz, 1 H), 2.25 (s, 3 H), 1.52 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 153.0, 136.3, 130.2, 127.2, 126.7, 123.6, 120.9, 80.3, 28.3, 17.6 ppm. $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 69.51, H 8.39, N 6.74.

(*S*)-1-(9-Phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylic Acid (8): To a suspension of L-proline (11.5 g, 100 mmol, 100 mol-%) in anhydrous CH_2Cl_2 (400 mL) and anhydrous MeCN (50 mL) in a flame-dried Morton flask under argon was added TMSCl (12.7 mL, 100 mmol, 100 mol-%). The resulting solution was heated to reflux for 1 h, after which it was cooled to room temp. NMM (24.2 mL, 220 mmol, 220 mol-%) was added followed by PfBr (38.5 g, 120 mmol, 120 mol-%) and $Pb(NO_3)_2$ (22.1 g, 67 mmol, 67 mol-%) as solids, giving a yellow/brown suspension, which was stirred at room temp. for 65 h. MeOH (10.1 mL, 250 mmol, 250 mol-%) was added, the reaction mixture was filtered through Celite, and the resulting filter cake was washed with CH_2Cl_2 (ca. 200 mL, or until no UV activity could be observed in the filtrate). The filtrate was evaporated to give a thick red oil, which was then partitioned between Et_2O (600 mL) and 5 wt.-% aqueous citric acid (600 mL). The organic phase was removed and the aqueous phase was extracted with Et_2O (4× 150 mL). The combined organic phases were extracted with 1 M NaOH (300 mL) and discarded. The aqueous phase was washed with Et_2O (200 mL) and AcOH was added until ca. pH 7, giving a suspension. The suspension was extracted with 20% *i*PrOH in $CHCl_3$ (3× 300 mL) and the combined organic phases were washed with brine (500 mL), dried with Na_2SO_4, filtered, and the solvents evaporated. Two portions of hexane were added (to remove remaining *i*PrOH and $CHCl_3$) and the product was evaporated to dryness giving an orange foam, yield 29.1 g (82%); R_f = 0.15 (Hex/EtOAc, 1:1); $[a]_D^{20}$ +258.7 (*S*) (c = 1.10, CH_2Cl_2); $[a]_D^{20}$ –259.8 (*R*) (c = 1.09, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3059, 2966, 2874, 1716, 1647, 1636, 1488, 1449, 1362, 1316, 1203, 1156, 907, 732, 702, 666, 644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.5 Hz, 1 H), 7.64 (d, J = 7.5 Hz, 1 H), 7.57 (d, J = 7.5 Hz, 1 H), 7.50–7.44 (m, 3 H), 7.40–7.20 (m, 7 H), 3.43 (m, 1 H), 3.21 (dd, J = 9.1, 2.2 Hz, 1 H), 3.10 (app. dt, J = 10.6, 8.3 Hz, 1 H), 1.96 (m, 1 H), 1.76 (m, 2 H), 1.63 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.0, 145.9, 144.6, 141.4, 140.6, 139.3, 129.2, 129.0, 128.6, 128.0, 127.8, 127.7, 126.8, 126.0, 125.8, 120.3, 120.0, 76.9, 62.5, 50.7, 30.9, 24.7 ppm. HRMS: calcd. for $C_{24}H_{22}NO_2$ $[M + H]^+$ 356.1651; found 356.1647.

(*S*)-*N*-Methoxy-*N*-methyl-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxamide (9): To a suspension of **8** (19.9 g, 56 mmol, 100 mol-%) and HCl·HN(OMe)Me (8.19 g, 84mmol, 150 mol-%) in EtOAc (230 mL) were added Et_3N (35.1 mL, 252 mmol, 450 mol-%) and DMAP (1.37 g, 11.2 mmol, 20 mol-%). T3P (50 mL, 84 mmol, 150 mol-%, 50 wt.-% solution in EtOAc) was then added by using an addition funnel at room temp. The suspension was stirred for 23 h, then the reaction was quenched with 0.5 M aqueous HCl (400 mL). The organic phase was separated and washed with 0.5 M aqueous HCl (2× 300 mL), then the combined aqueous phases were back-extracted once with EtOAc (300 mL). The combined organic phases were washed with 10 wt.-% K_2CO_3 (300 mL), brine (300 mL), dried with Na_2SO_4, filtered and finally evaporated to dryness to give a thick red oil. Upon addition of Et_2O (50 mL) followed by evaporation, the oil solidified into a red-orange solid (16.3 g, 73%), which was subjected to chiral HPLC analysis (Chiralpak IA; Hex/EtOH, 98:2; 1 mL/min): R_t = 9.8 (*S*), 10.6 (*R*) min; > 99% *ee* for both (*S*) and (*R*) enantiomers; R_f = 0.45 (Hex/EtOAc, 1:1); $[a]_D^{20}$ +49.8 (*S*) (c = 0.8, CH_2Cl_2); $[a]_D^{20}$ –49.1 (*R*) (c = 0.78, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3059, 2964, 2868, 1667, 1599, 1487, 1449, 1386, 1352, 1314, 1281, 1175, 1114, 1087, 1031, 1000, 909, 763, 734, 704, 641, 618 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.3 Hz, 1 H), 7.63–7.59 (m, 4 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.39 (m, 1 H), 7.30 (m, 1 H), 7.27–7.14 (m, 5 H), 3.71 (br., 1 H), 3.29 (m, 1 H), 2.91 (br. m, 7 H), 1.93 (m, 1 H), 1.74 (m, 1 H), 1.61 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 177.1, 148.7, 147.9, 144.1, 140.9, 139.7, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 126.9, 126.8, 126.4, 119.4, 119.2, 77.0, 60.2, 57.6, 50.1, 32.0, 32.0, 24.8 ppm. HRMS: calcd. for $C_{26}H_{27}N_2O_2$ $[M + H]^+$ 399.2073; found 399.2062.

(*S*)-*tert*-Butyl (2-{2-Oxo-2-[1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidin-2-yl]ethyl}phenyl)carbamate (11): Compound **4** (15.1 g, 76 mmol, 200 mol-%) was dissolved in anhydrous THF (160 mL) in a flame-dried flask under argon, and the solution was cooled to –30 °C. *s*BuLi (1.4 M in cyclohexane, 109 mL, 76 mmol, 400 mol-%) was added dropwise by using an addition funnel. After approximately half the volume of *s*BuLi had been added, the solution took on a bright-yellow color. The solution was stirred for 1 h, then **9** (15.8 g, 38 mmol, 100 mol-%), dissolved in anhydrous THF (55 mL) was added to the yellow solution by using a Teflon cannula. After 30 min, the reaction was quenched with saturated NH_4Cl (150 mL) and H_2O (20 mL) and allowed to warm to room temp. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2× 50 mL). The combined organic phases were dried with Na_2SO_4, filtered, and evaporated to give a thick oil (occasionally a solid), which was then dissolved (or suspended in case of a solid) in Et_2O (60 mL). After a few minutes a precipitate started to form, and the suspension was stored in a refrigerator overnight. Filtration with subsequent washing of the filter cake with ice-cold Et_2O (3× 15mL) and hexane (2× 15 mL) gave a white amorphous solid (17.6 g, 85%). The solid was subjected to chiral HPLC analysis (Chiralpak IB; Hex/EtOH, 95:5; 1 mL/min): R_t = 5.7 (*R*), 6.2 (*S*) min; > 99% *ee* for both (*S*) and (*R*) enantiomers. R_f = 0.55 (Hex/EtOAc, 75:25). $[a]_D^{20}$ +80.8 (*S*) (c = 0.81, CH_2Cl_2); $[a]_D^{20}$ –81.7 (*R*) (c = 0.81, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3338, 3059, 2976, 2869, 1719, 1589, 1512, 1477, 1449, 1391, 1366, 1343, 1302, 1235, 1156, 1051, 1024, 909, 733, 703, 640, 619 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.5 Hz, 1 H), 7.70 (br. d, J = 8.1 Hz, 1 H), 7.64–7.42 (m, 6 H), 7.34 (m, 1 H), 7.30–7.17 (m, 6 H), 7.10 (m, 1 H), 6.95 (m, 1 H), 6.88 (m, 1 H), 3.40 (m, 1 H), 3.35 (s, 2 H), 3.13 (m, 2 H), 1.83 (m, 1 H), 1.61 (m, 3 H), 1.54 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 212.8, 153.6, 149.1, 146.0, 143.0, 141.9, 139.3, 137.4, 130.2, 128.7, 128.6, 128.4, 127.8, 127.7, 127.5, 127.4, 126.8, 126.5, 123.9, 120.0, 119.8, 80.0, 76.8, 67.2, 51.1, 42.9, 30.7, 28.4, 25.2 ppm. HRMS: calcd. for $C_{36}H_{37}N_2O_3$ $[M + H]^+$ 545.2804; found 545.2801.

(*S*)-Ethyl 2-{2-[1-(9-Phenyl-9*H*-fluoren-9-yl)pyrrolidin-2-yl]-1*H*-indol-3-yl}acetate (13): To a flame-dried 500 mL flask was added anhydrous toluene (230 mL) and KHMDS (0.5 M in toluene, 48.3 mL, 24.1 mmol, 100 mol-%), the solution was cooled to –78 °C and HMPA (24 mL, 137.9 mmol, 600 mol-%) was added. Compound **11** (12.5 g, 23 mmol, 100 mol-%) was added as a solid in four portions, giving a pale-yellow suspension. The suspension was taken to room temp. and stirred for 1 h until an orange solution had formed. The reaction mixture was cooled to –78 °C and ethyl iodoacetate (5.44 mL, 46.0 mmol, 200 mol-%) was added. The reaction was quenched after 15 min by pouring the reaction mixture into saturated NH_4Cl (200 mL). Water (50 mL) was added and the phases were separated. The organic phase was washed with 0.5 M HCl (3× 100 mL) and the combined aqueous phases were extracted once with Et_2O (200 mL). The organic phases where pooled and subsequently washed with brine (400 mL), dried with Na_2SO_4, filtered, and finally evaporated to dryness to give a yellow oil. The yellow oil was dissolved in CH_2Cl_2 (230 mL) and cooled to 0 °C. A 6M stock solution of H_2SO_4 in EtOH (38.3 mL, 230 mmol, 1000 mol-% of H_2SO_4) was added by using a dropping funnel, initially giving a forest green solution, which grew darker with time. The reaction mixture was carefully poured into a separatory funnel containing ice-cold sat $NaHCO_3$ (500 mL); CAUTION: vigorous gas evolution. The biphasic mixture was gently shaken and the phases where separated. The organic phase was washed with additional sat $NaHCO_3$ (2× 500 mL) until the pH of the combined aqueous phases was ≥ 7. The combined aqueous phases were extracted with CH_2Cl_2 (300 mL) and the combined organic phases were washed with brine (300 mL), dried with Na_2SO_4, filtered, and evaporated to give a wet brown solid. The solid residue was suspended in Hex/EtOAc (4:1, 30 mL) and filtered. The filtrate was washed with ice-cold Hex/EtOAc (3× 5 mL, 4:1) to give a pale-brown powder (7.65 g). The mother liquid was evaporated and redissolved in Hex/EtOAc (4:1, 10 mL) and placed in a freezer overnight. Filtration and washing of the filtrate with ice-cold Hex/EtOAc (4:1, 3× 2 mL) gave an additional 0.51 g of pale-brown solid, giving a combined weight of 8.16 g (69% yield) over two steps. The solid was subjected to chiral HPLC analysis (Chiralpak IB; Hex/EtOH, 95:5; 1 mL/min): R_t = 8.0 (*R*), 9.5 (*S*) min; > 99%*ee* for both (*S*) and (*R*) enantiomers. R_f = 0.27 (toluene/isopropanol, 98:2), 0.55 (Hex/EtOAc, 75:25); $[\alpha]_D^{20}$ –20.1 (*S*) (*c* = 0.79, CH_2Cl_2); $[\alpha]_D^{20}$ +21.1 (*R*) (*c* = 0.83, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3398, 3058, 2974, 2868, 1718, 1600, 1487, 1461, 1448, 1368, 1343, 1299, 1266, 1239, 1154, 1131, 1105, 1065, 1031, 905, 725, 700, 638, 618 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 7.76 (d, *J* = 7.5 Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.49–7.45 (m, 4 H), 7.37–7.31 (m, 3 H), 7.24–7.16 (m, 3 H), 7.10 (m, 1 H), 7.01 (m, 1 H), 6.84 (dt, *J* = 7.5, 1.0 Hz, 1 H), 6.72 (d, *J* = 7.7 Hz, 1 H), 6.20 (dt, *J* = 7.5, 1.0 Hz, 1 H), 3.93 (q, *J* = 7.1 Hz, 2 H), 3.73 (m, 1 H), 3.47 (m, 1 H), 3.20 (m, 1 H), 3.11 (d, *J* = 15.2 Hz, 1 H), 2.77 (d, *J* = 15.0 Hz, 1 H), 1.93 (m, 2 H), 1.68 (m, 2 H), 1.09 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9, 148.3, 146.3, 143.5, 142.4, 141.4, 138.0, 134.5, 128.9, 128.7, 128.2, 127.5, 127.4, 127.1, 126.7, 126.6, 125.0, 120.8, 119.7, 118.9, 118.9, 118.0, 110.4, 102.9, 77.0, 60.3, 54.2, 51.1, 35.2, 30.0, 25.2, 14.1 ppm. HRMS: calcd. for $C_{35}H_{33}N_2O_2$ $[M + H]^+$ 513.2542; found 513.2551.

(*S*)-2,3,11,11b-Tetrahydro-1*H*-indolizino[8,7-*b*]indol-5(6*H*)-one (14): A one-necked flask equipped with a condenser was charged with **13** (5.13 g, 10 mmol, 100 mol-%), $NH_4H_2PO_2$ (4.98 g, 60 mmol, 600 mol-%) and EtOH (100 mL). The suspension was degassed and 10 wt.-% Pd/C (0.53 g, 0.5 mmol, 5 mol-%) was added. The reaction mixture was heated to reflux for 3 h, then cooled to room temp. The thick suspension was filtered through Celite and eluted with EtOH (100 mL). The EtOH was evaporated and the resulting solid was partitioned between CH_2Cl_2 (300 mL) and 10 wt.-% K_2CO_3 (200 mL). The aqueous phase was extracted with CH_2Cl_2 (200 mL) and the combined organic phase was washed with brine (200 mL), dried with Na_2SO_4, filtered, and evaporated to give a yellow solid. The crude product was suspended together with Na_2CO_3 (10.6 g, 100 mmol, 1000 mol-%) in EtOH (200 mL) and stirred at room temp. for 20 h. The reaction solvent was evaporated and the solid was partitioned between CH_2Cl_2 (300 mL) and H_2O (200 mL). The aqueous phase was extracted with CH_2Cl_2 (2× 200 mL) and the combined organic phases where washed with brine (400 mL), dried with Na_2SO_4, filtered, and evaporated to give a yellow solid. The solid was suspended in toluene (5 mL) and filtered. The filter cake was washed with toluene (3× 3 mL) and hexane (5 mL) to give **14** (1.83 g, 81%) as a pale-yellow powder. R_f = 0.28 (CH_2Cl_2/MeOH, 95:5); $[\alpha]_D^{20}$ –107.1 (*S*) (*c* = 0.4, DMSO); $[\alpha]_D^{20}$ +108.2 (*R*) (*c* = 0.4, DMSO). IR (KBr disk): $\tilde{\nu}$ = 3165, 3114, 3070, 2984, 2949, 2912, 2879, 2828, 2752, 1602, 1502, 1463, 1386, 1337, 1318, 1278, 1268, 1256, 1222, 1203, 1150, 1117, 1009, 962, 874, 760, 732, 666, 633, 608, 563, 500 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.18 (s, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.09 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H), 7.00 (ddd, *J* = 7.8, 7.1, 0.9 Hz, 1 H), 4.72 (m, 1 H), 3.65 (app. dt, *J* = 11.8, 8.8 Hz, 1 H), 3.55 (dd, *J* = 20.0, 4.5 Hz, 1 H), 3.48 (dd, *J* = 19.9, 2.9 Hz, 1 H), 3.34 (m, 1 H), 2.53 (m, 1 H), 1.99 (m, 2 H), 1.59 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 166.5, 136.8, 131.9, 125.4, 121.2, 118.8, 118.0, 111.3, 104.1, 60.0, 44.2, 31.3, 29.9, 22.1 ppm. HRMS: calcd. for $C_{14}H_{15}N_2O$ $[M + H]^+$ 227.1184; found 227.1193.

(*S*)-Harmicine (1): In a flame-dried flask under argon, **14** (1.58 g, 7 mmol, 100 mol-%) was suspended in anhydrous THF (70 mL). LAH (1.59 g, 42 mmol, 600 mol-%) was added to the reaction in two equally sized portions. The reaction mixture was stirred at room temp. for 5 h, then cooled to 0 °C and water (1.6 mL) was carefully added dropwise (CAUTION: vigorous gas evolution). NaOH (1.6 mL, 4 M aqueous solution) was added dropwise and the reaction was taken to room temp., then water (6.3 mL) was added and the reaction was stirred for 30 min. The resulting yellow suspension was filtered through Celite and eluted with THF (20 mL) followed by CH_2Cl_2 (20 mL). The filtrate was evaporated and then portioned between CH_2Cl_2 (70 mL) and sat aqueous NH_4Cl solution (100 mL). The aqueous phase was extracted with CH_2Cl_2 (35 mL), then the combined organic phases were washed with sat aq. $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2× 50 mL). The combined organic phases were washed with brine (100 mL), dried with Na_2SO_4, filtered, and evaporated to give harmicine as a yellow solid (1.16 g, 78%). The solid was subjected to chiral HPLC analysis (Chiralpak IB; Hex/EtOH, 93:7 with 0.1% ethylene diamine; 1 mL/min) R_t = 9.0 (*S*), 11.2 (*R*) min; > 99%*ee* for both (*S*) and (*R*) enantiomers. R_f = 0.14 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{20}$ –112.0 (*S*) (*c* = 0.77, CH_2Cl_2), (*R*) +113.4 (*c* = 0.69, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3400, 3149, 3055, 2919, 2848, 2746, 2244, 1450, 1349, 1326, 1313, 1281, 1200, 1165, 1142, 1122, 1009, 906, 727, 646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (br. s, 1 H), 7.48 (m, 1 H), 7.27 (m, 1 H), 7.10 (m, 2 H), 4.21 (m, 1 H), 3.32 (ddd, *J* = 12.8, 5.3, 2.3 Hz, 1 H), 3.07 (m, 1 H), 2.98–2.83 (m, 3 H), 2.64 (m, 1 H), 2.25 (m, 1 H), 1.87 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 136.0, 135.4, 127.3, 121.3, 119.3, 118.0, 110.7, 107.7, 56.9, 49.3, 45.9, 29.4, 23.4, 17.8 ppm. HRMS: calcd. for $C_{14}H_{17}N_2$ $[M + H]^+$ 213.1392; found 213.1389.

Supporting Information (see footnote on the first page of this article): Alternative synthesis of **9** via **15**, HPLC chromatograms for

enantiopurity determination of compounds **9**, **10**, **13**, **1**. Copies of the ^{1}H and ^{13}C NMR spectra of compounds **4**, **8**, **15**, **9**, **11**, **13**, **14**, **1**.

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