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Enantioselective Palladium-Catalyzed Heck–Heck Cascade Reactions: Ready Access to the Tetracyclic Core of Lycorane Alkaloids

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Abstract: A rapid and efficient access to a wide variety of enantiomerically enriched C-11b substituted lycorane analogues can be achieved *via* a catalytic asymmetric Heck–Heck 6-*exo*/6-*endo* cascade reaction in the presence of (*R*)-BINAP.

Keywords: alkaloids; asymmetric catalysis; domino reactions; Heck reaction; palladium

Introduction

Catalytic asymmetric transition metal-catalyzed cascade reactions represent one of the most powerful and efficient methods for the rapid assembly of biologically active and complex chiral molecules from simple substrates.[1] Particularly, the enantioselective intramolecular Heck reaction[2] has emerged as an excellent tool for the construction of polycyclic frameworks generating tertiary and quaternary stereocenters[3] through palladium-catalyzed polyene cyclizations.[4] In this strategy, the σ-arylpalladium intermediate resulting from the migratory insertion of the arylpalladium to the alkene, would be trapped by an adequately positioned internal alkene, allowing the sequential formation of two or more rings in one step. Related cascade reactions have also been developed, where β-hydride elimination is avoided by an anion capture event.[5] In this context, Overman reported in 1989 the first example of an enantioselective palladium-catalyzed polyene cyclization of trienyl triflates for the construction of spirocyclic trienones.[6] The potential of this type of asymmetric cascade reactions for the construction of polycyclic frameworks has been shown by Keay in his total synthesis of the marine natural product, (+)-Xestoquinone.[7] Although the cyclization of dialkenylfurans with a naphthoyl triflate using (*S*)-BINAP as the chiral ligand led to moderate enantiomeric excesses, the procedure was later improved either by tuning the experimental conditions (base, solvent) in order to inhibit the hydride transfer, thus favoring the second ring closure,[8] or by changing the chiral ligands.[9] Naphthoyl halides can also be used in this process instead of the corresponding triflates.[10]

On the other hand, we had previously reported[11] that the intramolecular palladium-catalyzed reaction of 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles can be directed to the alkene (Heck reaction), avoiding the direct arylation on the pyrrole nucleus by choosing the appropriate catalytic system, regardless of the nature of the substituent on the alkene, obtaining excellent yields of pyrrolo[1,2-*b*]isoquinolines. The procedure has also been applied to the selective synthesis of medium-sized rings and to (hetero)fused indolizine systems.[12] With these precedents in mind, we decided to apply the enantioselective palladium-catalyzed polyene cyclization to the construction of the structural core of the Lycorine class of *Amaryllidaceae* alkaloids (Figure 1).[13]

These naturally occurring natural products and their derivatives exhibit a broad spectrum of pharmacological properties,[14] including anticancer,[15] antiviral,[16] antiparasitic,[17] and anti-inflammatory activities,[18] as well as being phytotoxic in herbicide bioassays.[19] Because of their unique tetracyclic structure and their bioactive properties, Lycorane-type alkaloids have attracted numerous synthetic studies.[20] However, relatively few approaches to the asymmetric synthesis of these alkaloids have been reported so far.[21]

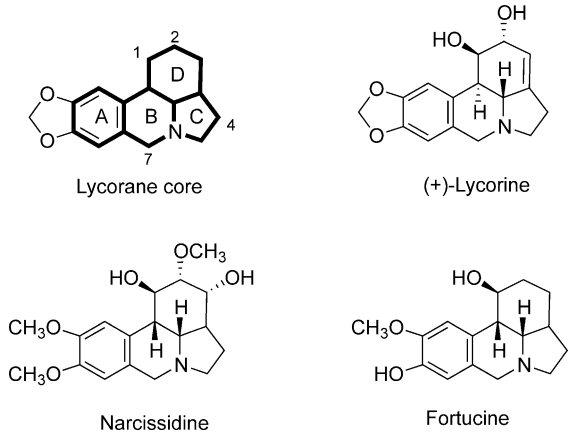


Figure 1. Lycorine class of *Amaryllidaceae* alkaloids.

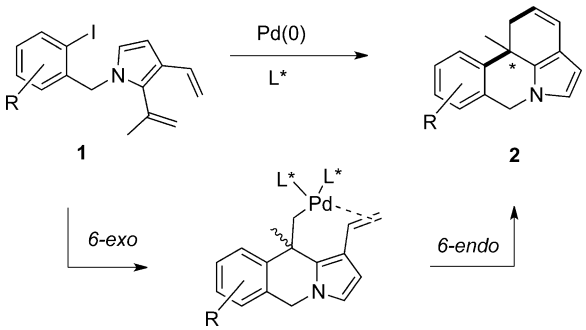
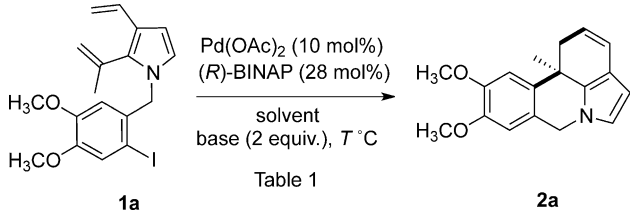


Figure 2. A 6-*exo* Mizoroki–Heck reaction to generate the quaternary stereocenter.

For this work, 2,3-dialkenylpyrroles **1** were selected to attempt the catalytic asymmetric polyene cyclization. A shown on Figure 2, a 6-*exo* Mizoroki–Heck reaction would generate the quaternary stereocenter, giving rise to the σ-alkylpalladium intermediate that would undergo a 6-*endo* insertion to give the tetracyclic framework of Lycorane alkaloids.[22]

Results and Discussion

We started studying the cascade reaction with **1a**[23] (Scheme 1). We first performed the reaction in a racemic fashion employing $Pd(OAc)_2$ (5 mol%) as catalyst, PPh_3 (14 mol%) as ligand in DMF at 80 °C. A mixture of products was obtained from which we



Scheme 1. Polyene cyclization of **1a**.

Table 1. Optimization of the cascade cyclization of **1a** with (*R*)-BINAP.

Entry	Base	*T*	Time [h]	Solvent	Yield [%]	*ee*[a] [%]
1	Et_3N	80 °C	72	DMF	17	63
2	Et_3N	110 °C	72	DMF	3	29
3	PMP	80 °C	72	DMF	7	<5
4	Cy_2NMe	80 °C	72	DMF	8	30
5	Et_3N	reflux	72	THF	13	nd
6	Et_3N	80 °C	72	dioxane	19	62
7	Et_3N	reflux	72	CH_3CN	33	67
8	**PMP**	**reflux**	**24**	**CH_3CN**	**75**	**67**
9	PMP	40 °C	72	CH_3CN	10	nd
10	PMP[b]	reflux	48	CH_3CN	43	63
11	PMP[c]	reflux	24	CH_3CN	46	58
12	PMP[d]	reflux	48	CH_3CN	76	63
13	$CyNMe_2$	reflux	30	CH_3CN	65	63
14	PMP	reflux	48	EtOH	11	68
15[e]	PMP	reflux	48	CH_3CN	82	66

[a] Determined by chiral stationary phase HPLC (Chiralcel OZ3 2% hexane/*i*-PrOH).
[b] 3 equiv.
[c] Ag_3PO_4 (2 equiv.) was added.
[d] 1 equiv.
[e] $Pd(dba)_2$ was used.

could isolate only small amounts (8%) of **2a**. We decided to optimize the reaction conditions in the asymmetric version, and we chose (*R*)-BINAP as ligand (Table 1, Scheme 1). Although only a low yield of **2a** could be obtained, the enantioselectivity of the reaction was promising, obtaining 63% *ee* using Et_3N as base. The use of different bases, such as PMP, has been shown to minimize competing hydride transfer, increasing the yield of the cyclized product.[8] However, an increase of the temperature (entry 2) or the use of different bases (entries 3 and 4) resulted in a loss of enantioselection. Different solvents were tested, and acetonitrile and dioxane increased the enantioselectivity to 67% and 62%, respectively, although the yields continued to be poor (entries 6 and 7). The best results were achieved when PMP was used as base in acetonitrile, obtaining a good yield of **2a** (72%) in 24 h, with moderate *ee* (66%) (entry 8). A decrease of the temperature to 40 °C caused a complete loss of the yield and the enantioselectivity (entry 9). An increase of the amount of the base or the addition of silver salts[10] did not improve the results (entries 10 and 11). The use of less PMP (entry 11) or Cy_2NMe resulted in longer reaction times to obtain similar levels of enantioselection and yield. The change of the solvent to ethanol[9c] resulted in a loss of yield (11%), although with the same level of enantioselection (entry 14). Finally, the change of the catalyst to $Pd(dba)_2$ (entry 15) did not improve significantly the results, requiring a longer reaction time.

We have previously demonstrated the need to use catalytic systems that follow the "classical" neutral Pd(0)/Pd(II) mechanism to promote the intramolecular alkenylation of iodinated *N*-(arylalkyl)pyrroles, as the electrophilic palladium(II) species favor the direct arylation reaction.[11,12] However, in this case, although conditions that may direct the reaction towards a cationic type of mechanism have been used, it is noteworthy that in all cases the Heck–Heck reaction was the only process observed, we did not detect the formation of any product from a direct arylation on the pyrrole nucleus.

We next carried out a further optimization of the reaction using different phosphane ligands **L1–L6** (Table 2, Scheme 2). We selected both bidentate and monodentate phosphanes, which would show different electronic and steric properties. However, under the previously optimized conditions [$Pd(OAc)_2$, PMP, CH_3CN, reflux] the use of a modified BINAP, such as Xyl-BINAP (**L1**)[9b] did not improve the results obtained with BINAP (entry 1), neither did the rest of the ligands (entries 2–4, 8, 17).

A further optimization of the reaction conditions (solvent, base) was carried out also with SEGPHOS (**L4**) and phosphoramidite **L5**, but lower yields were obtained with solvents such as toluene, ethanol or dioxane, with no improvement of the enantioselectivity. Thus, (*R*)-BINAP was selected as the most efficient phosphane ligand.

Once the best reaction conditions had been selected, we studied the scope of the reaction using different substitution patterns in the arene. As can be seen from the examples depicted on Scheme 3, the reaction tolerates different substitution patterns on the benzene ring.

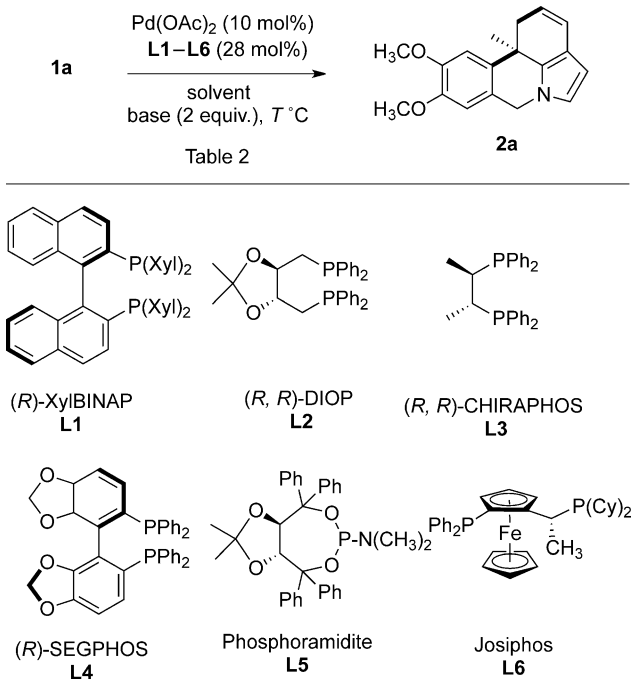
Thus, 9,10-dioxygenated compounds (Scheme 3, **2c**, **2i–k**) were obtained with consistently good yield, and maintaining the level of enantioselection. The nature of the oxygen substituent (Me, Bn or substituted benzyl derivatives) had no relevant impact in the reaction performance. Mono-alkoxylated (**2d**, **2h**) or 8,9-dimethoxylated (**2e**) derivatives were also successfully obtained. Substitution *ortho* to the iodine atom, however, resulted in a complete loss of both yield and enantioselectivity (**2f**, **2g**), in contrast with previously reported results.[7b] On the other hand, it has also been reported that, in this type of reactions, substitution on the alkene may have an important impact on the enantioselectivity. Thus, the presence of a substituent on the furan double bond or a group *ortho* to the triflate results in a significant increase in the *ee* in the palladium-catalyzed polyene cyclizations of 3,4-dialkenylfurans with benzoyl triflates.[7b] Unfortunately, in our case substitution in the α or β-positions of the pyrrole C-3 alkene completely precluded cyclization.[24]

Table 2. Cyclization of **1a** using ligands **L1–6**.

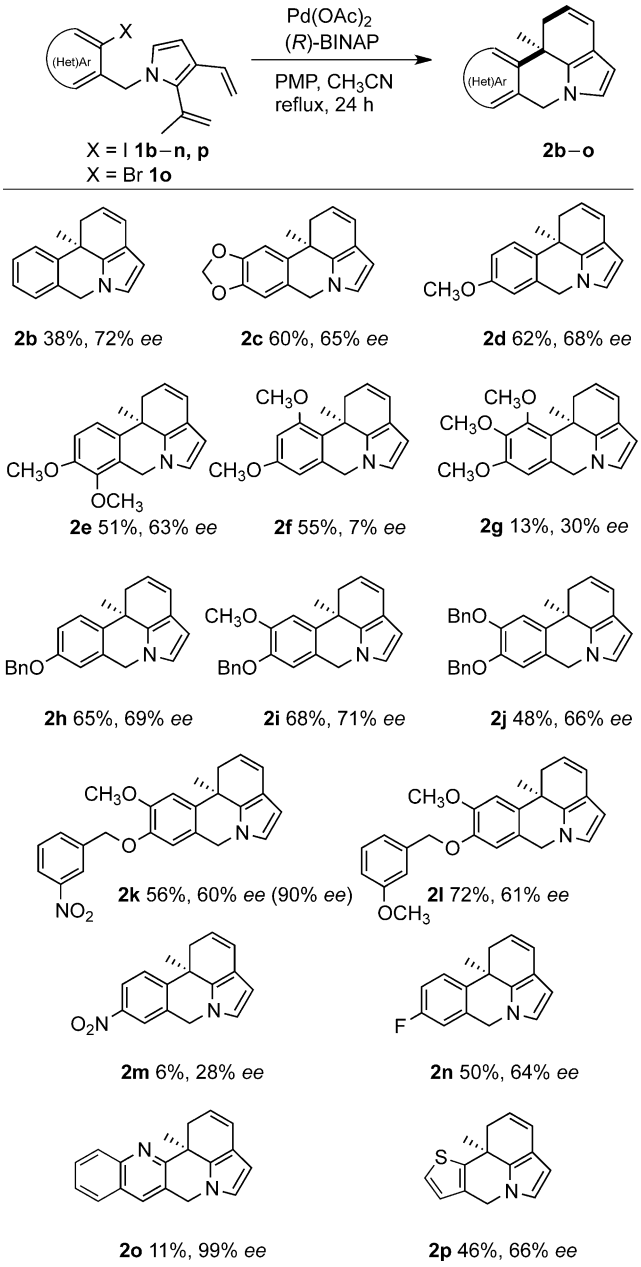
Entry	L	Base	Time [h]	Solvent	Yield [%]	*ee*[a] [%]
1	**L1**	PMP	31[d]	CH_3CN	54	55
2	**L2**	PMP	24[d]	CH_3CN	70	11
3	**L3**	PMP	31[d]	CH_3CN	18	34
4	**L4**	PMP	31[d]	CH_3CN	75	49
5	**L4**	PMP	48[d]	toluene	5	40
6	**L4**	PMP	24[d]	EtOH	33	57
7	**L5**	PMP	72[d]	THF	43	55
8	**L5**	Et_3N	24[d]	CH_3CN	44	28
9	**L5**	Et_3N	48[e]	DMF	73	41
10	**L5**	Et_3N	72[f]	DMF	59	53
11	**L5**	Et_3N	72[e]	dioxane	18	56
12	**L5**	Et_3N	72[d]	THF	69	57
13	**L5**	Et_3N	72[f]	THF	24	46
14	**L5**[b]	Cy_2NMe	9[e]	DMF	34	37
15	**L5**[b]	Cy_2NMe[c]	48[e]	DMF	75	30
16	**L5**[b]	Cy_2NMe[c]	72[d]	$CHCl_3$	8	54
17	**L6**	PMP	24[d]	CH_3CN	65	11

[a] Determined by chiral stationary phase HPLC (Chiralcel OZ3 2% hexane/*i*-PrOH).
[b] 20 mol%.
[c] 3 equiv.
[d] Reflux.
[e] 80 °C.
[f] 40 °C.

The reaction could also be applied to the non-substituted benzene ring (**2b**), or to a fluoro-substituted derivative (**2n**), but a low yield and enantioselectivity were obtained when a strong acceptor, such as a nitro



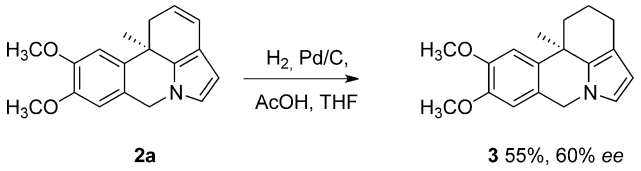
Scheme 2. Ligand optimization for the cyclization of **1a**.



Scheme 3. Extension of the methodology. Synthesis of (*R*)-pyrrolophenanthridines **2b–n** and (*S*)-heterofused analogues **2o–p**. The *ee*s were determined by chiral stationary phase HPLC (Chiralcel OD3).

group, is present (**2m**). In this case, only a 28% yield could be obtained, using an additional 10% mol of the catalyst and an extended reaction time.[25]

The procedure could also be extended to heteroaromatic analogues. In these cases the corresponding bromide **1o** and iodide **1p** were prepared,[23] and submitted to the same reaction conditions. It is noteworthy that the quinoline-fused derivative **2o** was obtained in low yield, using 20% catalyst and under an extended reaction time, but with an excellent *ee* (99%). In this case, the reaction was also carried out



Scheme 4. Catalytic hydrogenation of **2a**.

with (*S*)-BINAP, obtaining the same level of enantioselection for the opposite enantiomer (see the Supporting Information). Although the enantioselectivities obtained were in most cases moderate, the optical purity could be significantly improved after a single crystallization, as shown for **2k** (90% *ee* after crystallization from Et_2O). The absolute configuration was unambiguously assigned by single crystal X-ray analysis of **2k** as *R* (see the Supporting Information).[26] The configurations of **2a–p** were assigned assuming a uniform mechanism.

Finally, it has been shown that the double bond can be reduced by catalytic hydrogenation (Scheme 4). Thus, **2a** was hydrogenated at 30 psi affording **3a** in moderate yield (55%).

Conclusions

The Lycorane tetracyclic framework of the *Amaryllidaceae* alkaloids can be efficiently accessed through a palladium-catalyzed Heck–Heck cascade reaction. Thus, *N*-benzyl-2,3-dialkenylpyrroles undergo sequential 6-*exo*/6-*endo* cyclizations to yield enantiomerically enriched (11b*R*)-substituted pyrrolophenanthridines. The choice of the base and solvent (PMP; CH_3CN) is crucial to lead the sequence to completion, avoiding hydride transfer. (*R*)-BINAP has been shown to be the most efficient chiral phosphane ligand. The reaction can be extended to various substitution patterns on the aromatic ring, and also to heteroaromatic rings. This procedure allows a rapid and efficient access to a wide variety of enantiomerically enriched C-11b substituted lycorane analogues.

Experimental Section

Pd(0)-Catalyzed Cyclization of 1a–p. Synthesis of Pyrrolophenanthridines and Heterofused Analogues 2a–p; General Procedure

To a solution of the corresponding 2,3-dialkenylpyrrole **1a–p** (1 mmol) in anhydrous CH_3CN (15 mL) under an argon atmosphere, (*R*)-BINAP (0.28 mmol), PMP (2 mmol) and $Pd(OAc)_2$ (0.10 mmol) were added. The mixture was heated under reflux for 24 h.[27] Then the reaction mixture was diluted with AcOEt (50 mL), washed with saturated NH_4Cl (1× 30 mL) and H_2O (2×30 mL). The combined organic extracts

were dried (Na_2SO_4), and concentrated under vacuum. Flash column chromatography (silica gel, hexane/AcOEt) afforded the pyrrolophenanthridines **2a–n** and analogues **2o–p**.

(*R*)-9,10-Dimethoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2a) (Table 1, entry 8): Prepared from pyrrole **1a** (160 mg, 0.38 mmol), (*R*)-BINAP (68 mg, 0.11 mmol), PMP (0.14 mL, 0.76 mmol) and $Pd(OAc)_2$ (9.0 mg, 0.04 mmol). The reaction mixture was heated under reflux for 24 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 8:2) afforded **2a** as an oil; yield: 80 mg (75%). IR (ATR): $\nu = 1511\ cm^{-1}$ (C=C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3H, CH_3), 2.56–2.82 (m, 2H, 2×H-1), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.01 (d, $J = 15.4$ Hz, 1H, H-7a), 5.04 (d, $J = 15.4$ Hz, 1H, H-7b), 5.52–5.70 (m, 1H, H-2), 6.10 (d, $J = 2.6$ Hz, 1H, H-4), 6.49 (dd, $J = 9.4$, 3.1 Hz, 1H, H-3), 6.61 (d, $J = 2.6$ Hz, 1H, H-5), 6.72 (s, 1H, H-11), 6.86 (s, 1H, H-8); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 27.4$ (CH_3), 34.1 (C-11b), 37.1 (C-1), 47.0 (C-7), 56.4 (2×OCH_3), 105.7 (C-4), 107.8 (C-11), 109.9 (C-8), 113.4 (C-3a), 117.0 (C-5), 117.8 (C-2), 122.9 (C-11a), 123.1 (C-3), 132.0 (C-3a^1), 135.6 (C-7a), 147.3 (C-9), 148.8 (C-10); MS (CI): *m/z* (rel. intensity) = 282 (MH^+, 100), 281 (M^+, 67), 267 (22), 266 (78); HR-MS (CI): *m/z* = 282.1489, calcd. for $C_{18}H_{20}NO_2$ $[MH]^+$: 282.1494. $[\alpha]_D^{20}$: +22.7 (*c* = 0.32, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 67%, [Chiralcel OZ3, hexane/isopropyl alcohol 98:2, 0.8 mL min^{-1}, t_r (minor) = 15.3 min (16.66%), t_r (major) = 15.9 min (83.34%)].

(*R*)-11b-Methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2b): Prepared from pyrrole **1b** (66.4 mg, 0.19 mmol), (*R*)-BINAP (33.2 mg, 0.053 mmol), PMP (0.07 mL, 0.38 mmol) and $Pd(OAc)_2$ (4.3 mg, 0.019 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9.8:0.2) afforded **2b** as an oil; yield: 16 mg (38%). IR (ATR): $\nu = 1562\ cm^{-1}$ (C=C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (s, 3H, CH_3), 2.64–2.77 (m, 2H, 2×H-1), 5.07 (d, $J = 15.7$ Hz, 1H, H-7a), 5.14 (d, $J = 15.7$ Hz, 1H, H-7b), 5.53–5.67 (m, 1H, H-2), 6.13 (d, $J = 2.7$ Hz, 1H, H-4), 6.50 (dd, $J = 9.4$, 3.3 Hz, 1H, H-3), 6.63 (d, $J = 2.7$ Hz, 1H, H-5),7.15–7.48 (m, 4H, H-8, H-9, H-10, H-11; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 27.0$ (CH_3), 33.9 (C-11b), 37.2 (C-1), 47.1 (C-7), 105.3 (C-4), 113.8 (C-3a), 117.1 (C-5), 118.0 (C-2), 123.1 (C-3), 124.7 (C-11), 126.1 (C-10), 126.3 (C-9), 128.0 (C-8), 130.1 (C-3a^1), 131.9 (C-7a), 143.5 (C-11a); MS (CI): *m/z* (rel. intensity) = 222 (MH^+, 99), 221 (M^+, 79) 207 (20), 206 (100), 204 (17). HR-MS (CI): *m/z* = 222.1287, calcd. for $C_{16}H_{16}N$ $[MH]^+$: 222.1283. $[\alpha]_D^{20}$: +84.4 (*c* = 0.8, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 72%, [Chiralcel OD3, hexane/isopropyl alcohol 98:08, 0.8 mL min^{-1}, t_r (major) = 9.33 min (86.09%), t_r (minor) = 10.18 min (13.91%)].

(*R*)-9,10-Methylenedioxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2c): Prepared from pyrrole **1c** (81 mg, 0.20 mmol), (*R*)-BINAP (35.9 mg, 0.057 mmol), PMP (0.07 mL, 0.40 mmol) and $Pd(OAc)_2$ (4.7 mg, 0.02 mmol). The reaction mixture was heated under reflux for 48 h. After work up, flash column chromatography (silica gel, hexane/AcOEt 9.5:0.5) afforded **2c** as an oil; yield: 31.7 mg (60%). IR (ATR): $\nu = 1482\ cm^{-1}$ (C=C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (s, 3H, CH_3), 2.57–2.82 (m, 2H, 2×H-1), 4.98 (d, $J = 15.5$ Hz, 1H, H-7a), 5.01 (d, $J = 15.5$ Hz, 1H, H-7b), 5.54–5.68 (m, 1H, H-2), 5.97 (s, 2H, OCH_2O), 6.12 (d, $J = 2.6$ Hz, 1H, H-4), 6.49 (dd, $J = 9.4$, 3.0 Hz, 1H, H-3), 6.61 (d, $J = 2.6$ Hz, 1H, H-5), 6.69 (s, 1H, H-8), 6.86 (s, 1H, H-11); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 26.9$ (CH_3), 33.9 (C-11b), 37.4 (C-1), 47.1 (C-7), 101.2 (OCH_2O), 105.0 (C-11), 105.3 (C-4), 106.4 (C-8), 113.5 (C-3a), 117.0 (C-5), 117.9 (C-2), 123.1 (C-3), 124.0 (C-11a), 131.1 (C-3a^1), 137.1 (C-7a), 145.8 (C-10), 147.3 (C-9); MS (CI): *m/z* (%) = 266 (MH^+, 99), 265 (M^+, 90), 251 (23), 250 (100), 220 (11); HR-MS (CI): *m/z* = 266.1150, calcd. for $C_{17}H_{16}NO_2$ $[MH]^+$: 266.1181; $[\alpha]_D^{20}$: +47.3 (*c* = 1.39, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 65% [Chiralcel OD3, hexane/isopropyl alcohol 98:2, 0.8 mL min^{-1}, t_r (major) = 15.2 min (82.74%), t_r (minor) = 19.0 min (17.26%)].

(*R*)-9-Methoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2d): Prepared from pyrrole **1d** (62.0 mg, 0.16 mmol), (*R*)-BINAP (28.5 mg, 0.045 mmol), PMP (0.06 mL, 0.32 mmol) and $Pd(OAc)_2$ (3.7 mg, 0.016 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2d** as an oil; yield: 25 mg (62%). IR (ATR): $\nu = 1497\ cm^{-1}$ (C=C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3H, CH_3), 2.58–2.93 (m, 2H, 2×H-1), 3.83 (s, 3H, OCH_3), 5.02 (d, $J = 15.7$ Hz, 1H, H-7a), 5.11 (d, $J = 15.7$ Hz, 1H, H-7b), 5.53–5.67 (m, 1H, H-2), 6.11 (d, $J = 2.6$ Hz, 1H, H-4), 6.49 (dd, $J = 9.4$, 3.1 Hz, 1H, H-3), 6.61 (d, $J = 2.6$ Hz, 1H, H-5), 6.77 (d, $J = 2.3$ Hz, 1H, H-8), 6.90 (dd, $J = 8.6$, 2.3 Hz, 1H, H-10), 7.30 (d, $J = 8.6$ Hz, 1H, H-11); ^{13}C NMR (75.5 MHz, CDCl3): $\delta = 27.2$ (CH_3), 33.3 (C-11b), 37.4 (C-1), 47.3 (C-7), 55.3 (OCH_3), 105.3 (C-4), 111.6 (C-10), 113.5 (C-8), 113.6 (C-3a), 117.0 (C-5), 118.0 (C-2), 123.1 (C-3), 125.7 (C-11) 132.1 (C-11a), 132.7 (C-3a^1), 135.7 (C-7a), 157.6 (C-9); MS (CI): *m/z* (rel. intensity) = 252 (MH^+, 74), 251 (M^+, 61), 237 (21), 236 (100); HR-MS (CI): *m/z* = 252.1376, calcd. for $C_{17}H_{18}NO$ $[MH]^+$: 252.1388; $[\alpha]_D^{20}$: +54.8 (*c* = 0.79, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 68%, [Chiralcel OD3, hexane/isopropyl alcohol 90:10, 0.8 mL min^{-1}, t_r (major) = 7.04 min (83.94%), t_r (minor) = 8.03 min (16.06%)].

(*R*)-8,9-Dimethoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2e): Prepared from pyrrole **1e** (75.4 mg, 0.18 mmol), (*R*)-BINAP (34.4 mg, 0.055 mmol), PMP (0.07 mL, 0.36 mmol) and $Pd(OAc)_2$ (4.2 mg, 0.018 mmol). The reaction mixture was heated under reflux for 30 h. After work up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2e** as an oil; yield: 25.9 mg (51%). IR (ATR): $\nu = 1490\ cm^{-1}$ (C=C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3H, CH_3), 2.52–2.91 (m, 2H, 2×H-1), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.88 (d, $J = 16.6$ Hz, 1H, H-7a), 5.38 (d, $J = 16.6$ Hz, 1H, H-7b), 5.59 (ddd, $J = 9.4$, 6.0, 2.5 Hz, 1H, H-2), 6.12 (d, $J = 2.7$ Hz, 1H, H-4), 6.43–6.53 (m, 1H, H-3), 6.65 11 (d, $J = 2.7$ Hz, 1H, H-5), 6.93 (d, $J = 8.5$ Hz, 1H, H-10), 7.07 (d, $J = 8.5$ Hz, 1H, H-11); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 24.5$ (CH_3), 33.4 (C-11b), 37.4 (C-1), 42.1 (C-7), 55.9 (OCH_3), 60.4 (OCH_3), 105.3 (C-4), 111.9 (C-10), 113.5 (C-3a), 117.4 (C-11), 117.9 (C-3), 119.8 (C-5), 123.0 (C-2), 125.2 (C-7a), 132.0 (C-3a^1), 136.7 (C-11a), 145.1 (C-9), 150.4 (C-8); MS (CI): *m/z* (rel. intensity) = 282 (MH^+, 79), 266 (100), 250 (5), 235 (8); HR-MS (CI): *m/z* = 282.1482, calcd. for $C_{18}H_{20}NO_2$ $[MH]^+$: 282.1494; $[\alpha]_D^{20}$: −51.67 (*c* = 0.95, CH_2Cl_2). The enantiomeric

excess was determined by HPLC to be 63%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (major) = 10.1 min (81.28%), t_r (minor) = 10.9 min (18.72%)].

(*R*)-9,11-Dimethoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2f): Prepared from pyrrole **1f** (61.7 mg, 0.15 mmol), (*R*)-BINAP (26.3 mg, 0.042 mmol), PMP (0.06 mL, 0.30 mmol) and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2e** as an oil; yield: 23.3 mg (55%). IR (ATR): ν = 1457 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3H, CH_3), 2.43–2.63 (m, 1H, H-1a), 3.44 (dd, J = 17.0, 6.3 Hz, 1H, H-1b), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.05 (s, 2H, 2×H-7), 5.52–5.68 (m, 1H, H-2), 6.12 (d, J = 2.6 Hz, 1H, H-4), 6.35 (d, J = 2.4 Hz, 1H, H-10), 6.42–6.54 (m, 2H, H-3, H-5), 6.60 (d, J = 2.4 Hz, 1H, H-8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.3 (CH_3), 34.2 (C-11b), 37.0 (C-1), 47.3 (C-7), 55.2 (OCH_3), 55.3 (OCH_3), 98.4 (C-10), 102.4 (C-4), 105.3 (C-8), 114.0 (C-3a), 116.5 (C-5), 119.9 (C-2), 122.5 (C-3), 123.4 (C-11a), 132.7 (C-3a^1), 135.3 (C-7a), 158.8 (C-11), 159.6 (C-9). MS (CI): (rel. intensity) = 282 (MH^+, 73), 281 (M^+, 55), 267 (22), 266 (100). HR-MS (CI): m/z = 282.1481, calcd. for $C_{18}H_{20}NO_2$ $[MH]^+$: 282.1494; found:. $[\alpha]_D^{20}$: + 7.29 (c = 0.87, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 7%, [Chiralcel OD3, hexane/isopropyl alcohol 90:10, 0.8 mL min^{-1}, t_r (major) = 7.40 min (53.52%), t_r (minor) = 8.39 min (46.48%)].

(*R*)-9,10,11-Trimethoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2g): Prepared from pyrrole **1g** (66.2 mg, 0.15 mmol), (*R*)-BINAP (27.9 mg, 0.045 mmol), PMP (0.06 mL, 0.30 mmol) and $Pd(OAc)_2$ (3.5 mg, 0.015 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2g** as an oil; yield: 6 mg (13%). IR (ATR): ν = 1451 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3H, CH_3), 2.61 (dd, J = 16.8, 6.3 Hz, 1H, H-1a), 3.38 (dd, J = 16.8, 6.3 Hz, 1H, H-1b), 3.87 (s, 6H, 2×OCH_3), 3.97 (s, 3H, OCH_3), 5.00 (s, 2H, 2×H-7), 5.58 (ddd, J = 9.1, 6.2, 2.3 Hz, 1H, H-2), 6.11 (d, J = 2.7 Hz, 1H, H-4), 6.46 (dd, J = 9.4, 3.0 Hz, 1H, H-3), 6.51 (s, 1H, H-8), 6.59 (d, J = 2.7 Hz, 1H, H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.7 (CH_3), 34.8 (C-11b), 37.3 (C-1), 47.1 (C-7), 55.9 (OCH_3), 60.6 (OCH_3), 60.7 (OCH_3), 105.0 (C-4), 105.3 (C-8), 114.0 (C-3a), 116.6 (C-5), 119.5 (C-2), 122.5 (C-11a), 126.8 (C-3), 128.4 (C-3a^1), 132.1 (C-7a), 141.9 (C-10), 151.9 (C-11), 153.1 (C-9); MS (CI): m/z (rel. intensity) = 312 (88, MH^+), 311 (M^+, 66), 310 (9), 297 (23), 296 (100), 281 (6), 280 (7), 265 (6); HR-MS (CI): m/z = 312.1590, calcd. for $C_{19}H_{22}NO_3$ $[MH]^+$: 312.1600; $[\alpha]_D^{20}$: −5.84 (c = 0.94, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 30%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (minor) = 12.5 min (35.20%), t_r (major) = 15.6 min (64.80%)].

(*R*)-9-Benzyloxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2h): Prepared from pyrrole **1h** (38.2 mg, 0.08 mmol), (*R*)-BINAP (14.6 mg, 0.023 mmol), PMP (0.03 mL, 0.16 mmol) and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2h** as an oil; yield: 17 mg (65%). IR (ATR): ν = 1500 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3H, CH_3), 2.52–2.93 (m, 2H, 2×H-1), 5.01 (d, J = 15.8 Hz, 1H, H-7a), 5.06–5.14 (m, 3H, H-7b, CH_2Ph), 5.57–5.65 (m, 1H, H-2), 6.12 (d, J = 2.7 Hz, 1H, H-4), 6.49 (dd, J = 9.3, 3.3 Hz, 1H, H-3), 6.61 (d, J = 2.7 Hz, 1H, H-5), 6.86 (d, J = 2.7 Hz, 1H, H-8), 6.97 (dd, J = 8.6, 2.7 Hz, 1H, H-10), 7.28–7.53 (m, 6H, H-1, CH_2*Ph*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 33.3 (C-11b), 37.4 (C-1), 47.3 (C-7), 70.2 (CH_2Ph), 105.3 (C-4), 112.7 (C-10), 113.6 (C-3a), 114.4 (C-8), 117.0 (C-5), 118.0 (C-2), 123.1 (C-3), 125.8 (C-11), 127.4 (C-2′arom, C-6′arom), 128.0 (C-4′arom), 128.6 (C-3′, C-5′arom), 132.2 (C-11a), 136.0 (C-3a^1), 136.9 (C-7a, C-1′arom), 156.9 (C-9); MS (CI): m/z (rel. intensity) = 328 (MH^+, 100), 327 (M^+, 56), 314 (13), 313 (34), 312 (74), 221 (9); HR-MS (CI): m/z = 328.1693, calcd. for $C_{23}H_{22}NO$ $[MH]^+$: 328.1701; $[\alpha]_D^{20}$: +23.23 (c = 0.83, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 69%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (major) = 19.7 min (84.47%), t_r (minor) = 27.6 min (15.53%)].

(*R*)-9-Benzyloxy-10-methoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2i): Prepared from pyrrole **1i** (93.7 mg, 0.19 mmol), (*R*)-BINAP (33.6 mg, 0.053 mmol), PMP (0.07 mL, 0.38 mmol) and $Pd(OAc)_2$ (4.3 mg, 0.019 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 8:2) afforded **2i** as an oil; yield: 46 mg (68%). IR (ATR): ν = 1510 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 3H, CH_3), 2.58–2.89 (m, 2H, 2×H-1), 3.94 (s, 3H, OCH_3) 4.90 (d, J = 15.4 Hz, 1H, H-7a), 5.01 (d, J = 15.4 Hz, 1H, H-7b), 5.16 (s, 2H, CH_2Ph), 5.60 (ddd, J = 9.4, 5.9, 2.6 Hz, 1H, H-2), 6.11 (d, J = 2.7 Hz, 1H, H-4), 6.50 (dd, J = 9.4, 3.1 Hz, 1H, H-3), 6.59 (d, J = 2.7 Hz, 1H, H-5), 6.75 (s, 1H, H-11), 7.26–7.56 (m, 6H, H-8, CH_2*Ph*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.9 (CH_3), 33.7 (C-11b), 37.3 (C-1), 46.6 (C-7), 56.2 (OCH_3), 71.4 (CH_2Ph), 105.2 (C-4), 108.4 (C-11), 112.3 (C-8), 113.5 (C-3a), 117.0 (C-5), 117.8 (C-3), 121.6 (C-2), 127.3 (C-2′arom, C-6′arom), 127.9 (C-4′arom), 128.5 (C-3′arom, C-5′arom), 131.9 (C-3a^1), 135.3 (C-11a), 136.4 (C-7a), 137.0 (C-1′arom), 146.4 (C-10), 149.4 (C-9); MS (CI): m/z (rel. intensity) = 358 (MH^+, 99), 357 (M^+, 85), 343 (25), 342 (100), 286 (29), 266 (14), 251 (12); HR-MS (CI): m/z = 358.1793, calcd. for $C_{24}H_{24}NO_2$ $[MH]^+$: 358.1807; $[\alpha]_D^{20}$: +40.13 (c = 0.66, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 71%, [Chiralcel OD3, hexane/isopropyl alcohol 90:10, 0.8 mL min^{-1}, t_r (minor) = 15.19 min (85.44%), t_r (minor) = 17.47 min (14.56%)].

(*R*)-9,10-Bis(benzyloxy)-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2j): Prepared from pyrrole **1j** (75.5 mg, 0.13 mmol), (*R*)-BINAP (23.5 mg, 0.037 mmol), PMP (0.05 mL, 0.26 mmol) and $Pd(OAc)_2$ (3.1 mg, 0.014 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9.5:0.5) afforded **2j** as an oil; yield: 27 mg (48%). IR (ATR): ν = 1510 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3H, CH_3), 2.48–2.75 (m, 2H, 2×H-1), 4.91 (d, J = 15.5 Hz, 1H, H-7a), 5.01 (d, J = 15.5 Hz, 1H, H-7b), 5.17 (s, 2H, CH_2Ph), 5.20 (s, 2H, CH_2Ph), 5.52–5.63 (m, 1H, H-2), 6.10 (d, J = 2.7 Hz, 1H, H-4), 6.47 (dd, J = 9.5, 3.0 Hz, 1H, H-3), 6.58 (d, J = 2.7 Hz, 1H, H-5), 6.80 (s, 1H, H-11), 6.93 (s, 1H, H-8), 7.29–7.59

(m, 10H, 2×CH_2*Ph*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=26.9 (CH_3), 33.7 (C-11b), 37.3 (C-1), 46.7 (C-7), 77.6 (*C*H_2Ph), 77.8 (*C*H_2Ph), 105.2 (C-4), 112.3 (C-11), 113.2 (C-8), 113.5 (C-3a), 117.1 (C-5), 117.9 (C-2), 123.1 (C-3), 124.0 (C-11a), 127.3 (C-2′arom, C-6′arom), 127.5 (C-2″arom, C-6″arom), 127.9 (C-4′arom, C-4″arom), 128.4 (C-3′arom, C-5′arom), 128.5 (C-3″arom, C-5″arom), 132.1 (C-3a^1), 136.6 (C-7a), 137.2 (C-1′arom, C-1″arom), 147.3 (C-9), 148.5 (C-10); MS (CI): *m*/*z* (rel. intensity)=434 (MH^+, 100), 433 (M^+, 55), 419 (23), 418 (74), 343 (9), 342 (6), 327 (6), 208 (9); HR-MS (CI): *m*/*z*=434.2109, calcd. for $C_{30}H_{28}NO_2$ $[MH]^+$: 434.2120; $[\alpha]_D^{20}$: +17.39 (*c*=1.01, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 66%, [Chiralcel OD3, hexane/isopropyl alcohol 90:10, 0.8 mL min^{-1}, t_r (major)=14.93 min (82.80%), t_r (minor)=21.70 min (17.20%)].

(*R*)-10-Methoxy-11b-methyl-9-[(3-nitrobenzyl)oxy]-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2k): Prepared from pyrrole **1k** (45.5 mg, 0.08 mmol), (*R*)-BINAP (14.9 mg, 0.024 mmol), PMP (0.03 mL, 0.17 mmol) and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9.5:0.5) afforded **2k** as an oil; yield: 19 mg (56%). IR (ATR): ν=1530 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (s, 3H, CH_3), 2.58–2.91 (m, 2H, 2×H-1), 3.95 (s, 3H, OCH_3), 4.91 (d, *J*=15.5 Hz, 1H, H-7a), 5.02 (d, *J*=15.5 Hz, 1H, H-7b), 5.22 (s, 2H, C*H*$_2$Ph), 5.55–5.63 (m, 1H, H-2), 6.10 (d, *J*=2.7 Hz, 1H, H-4), 6.48 (dd, *J*=9.4, 3.1 Hz, 1H, H-3), 6.59 (d, *J*=2.7 Hz, 1H, H-5), 6.75 (s, 1H, H-11), 6.91 (s, 1H, H-8), 7.56–7.75 (m, 1H, H-5′arom), 7.75–7.82 (m, 1H, H-6′arom), 8.18 (dd, *J*=8.4, 2.3 Hz, 1H, H4′arom), 8.36 (broad s, 1H, H-2′arom); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=26.9 (CH_3), 33.7 (C-11b), 37.3 (C-1), 46.6 (C-7), 56.2 (OCH_3), 70.5 (*C*H_2Ph), 105.3 (C-4), 108.4 (C-11), 113.0 (C-8), 113.6 (C-3a), 117.1 (C-3), 117.8 (C-5), 122.2 (C-4′arom), 122.9 (C-2′arom), 123.1 (C-2), 123.1 (C-5′arom), 129.6 (C-6′arom), 131.8 (C-11a), 133.1 (C-3a^1), 137.5 (C-7a), 139.3 (C-1′arom), 145.7 (C-10), 148.5 (C-3′arom), 149.6 (C-9); MS (CI): *m*/*z* (rel. intensity)=403 (MH^+, 100), 402 (M^+, 27),387 (40), 373 (27), 372 (18), 357 (12) 251 (18), 250 (11); HR-MS (CI): *m*/*z*=403.1641, calcd. for $C_{24}H_{23}N_2O_4$ $[MH]^+$: 403.1658; $[\alpha]_D^{20}$: +49.6 (*c*=0.83, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 61%, [Chiralcel OD3, hexane/isopropyl alcohol 90:10, 0.8 mL min^{-1}, t_r (major)=26.4 min (80.30%), t_r (minor)=29.7 min (19.70%)].

(*R*)-10-Methoxy-9-[(3-methoxybenzyl)oxy]-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2l): Prepared from pyrrole **1l** (44.9 mg, 0.09 mmol), (*R*)-BINAP (15.2 mg, 0.024 mmol), PMP (0.03 mL, 0.18 mmol) and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2l** as an oil; yield: 23 mg (72%). IR (ATR): ν=1511 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (s, 3H, CH_3), 2.56–2.91 (m, 2H, 2×H-1), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.89 (d, *J*=15.4 Hz, 1H, H-7a), 5.01 (d, *J*=15.4 Hz, 1H, H-7b), 5.14 (s, 2H, C*H*$_2$Ph), 5.52–5.62 (m, 1H, H-2), 6.10 (d, *J*=2.7 Hz, 1H, H-4), 6.49 (dd, *J*=9.4, 3.1 Hz, 1H, H-3), 6.58 (d, *J*=2.7 Hz, 1H, H-5), 6.74 (s, 1H, H-11), 6.84–6.93 (m, 2H, H-8, H-4′arom), 6.98–7.09 (m, 2H, H-2′arom, H-6′arom), 7.30 (t, *J*=8.1 Hz, 1H, H-5′arom); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=26.9 (CH_3), 33.7 (C-11b), 37.3 (C-1), 46.6 (C-7), 55.2 (OCH_3), 56.2 (OCH_3), 71.2 (*C*H_2Ph), 105.3 (C-4), 108.4 (C-11), 112.3 (C-4′arom), 112.7 (C-2′arom), 113.4 (C-8), 113.5 (C-3a), 117.0 (C-6′arom), 117.8 (C-3), 119.4 (C-5), 123.0 (C-3a1), 123.1 (C-5′arom), 129.6 (C-2), 131.9 (C-7a), 136.5 (C-1′arom), 138.7 (C-11a), 146.4 (C-10), 149.4 (C-9), 159.9 (C-3′arom); MS (CI): *m*/*z* (rel. intensity)=388 (MH^+, 100), 387 (M^+, 60), 373 (19), 372 (63), 267 (6), 251 (9); HR-MS (CI): *m*/*z*=388.1920, calcd. for $C_{25}H_{26}NO_3$ $[MH]^+$: 388.1913; $[\alpha]_D^{20}$: +65.2 (*c*=1.14, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 61%, [Chiralcel OD3, hexane/isopropyl alcohol 90:10, 0.8 mL min^{-1}, t_r (major)=21.2 min (80.64%), t_r (minor)=23.9 min (19.36%)].

(*R*)-11b-Methyl-9-nitro-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2m): Prepared from pyrrole **1m** (65.3 mg, 0.16 mmol), (*R*)-BINAP (28.9 mg, 0.046 mmol), PMP (0.06 mL, 0.32 mmol) and $Pd(OAc)_2$ (3.8 mg, 0.016 mmol). The reaction mixture was heated under reflux for 48 h. Then, $Pd(OAc)_2$ (7.6 mg, 0.034 mmol) and (*R*)-BINAP (57.8 mg, 0.093 mmol) were added and heated to reflux for another 24 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2m** as an oil; yield: 2.4 mg (<10%). IR (ATR): ν=1522 (N=O), 1343 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (s, 3H, CH_3), 2.61–2.96 (m, 2H, 2×H-1), 5.19 (s, 2H, 2 × H-7), 5.61 (ddd, *J*=9.4, 5.9, 2.4 Hz, 1H, H-2), 6.14 (d, *J*=2.7 Hz, 1H, H-4), 6.50 (dd, *J*=9.4, 3.2 Hz, 1H, H-3), 6.66 (d, *J*=2.7 Hz, 1H, H-5), 7.56 (d, *J*=8.6 Hz, 1H, H-11), 8.15 (dd, *J*=2.4 Hz, 1H, H-8), 8.21 (m, *J*=8.6, 2.4 Hz, 1H, H-10); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=26.9 (CH_3), 34.7 (C-11b), 36.9 (C-1), 46.9 (C-7), 106.1 (C-4), 114.3 (C-3a), 117.5 (C-10, C-3), 121.7 (C-5), 123.1 (C-8), 123.2 (C-11), 125.9 (C-2), 130.2 (C-3a^1), 132.6(C-7a), 146.0 (C-9), 150.9 (C-11a); MS (CI): *m*/*z* (rel. intensity)=267 (MH^+, 36), 266 (M^+, 8), 265 (14), 251 (14), 238 (19), 237 (100), 236 (53), 222 (17), 221 (78); HR-MS (CI): *m*/*z*=267.1134, calcd. for $C_{16}H_{15}N_2O_2$ $[MH]^+$: 267.1134; The enantiomeric excess was determined by HPLC to be 28%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (major)=23.18 min (63.95%), t_r (minor)=34.64 min (36.05%)].

(*R*)-9-Fluoro-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (2n): Prepared from pyrrole **1n** (41.6 mg, 0.11 mmol), (*R*)-BINAP (19.7 mg, 0.031 mmol), PMP (0.04 mL, 0.22 mmol) and $Pd(OAc)_2$ (2.6 mg, 0.011 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9.5:0.5) afforded **2n** as an oil; yield: 13.3 mg (50%). IR (ATR): ν=1490 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$):δ=1.28 (s, 3H, CH_3), 2.91–2.60 (m, 2H, H-1), 5.03 (d, *J*=15.5 Hz, 1H, H-7a), 5.11 (d, *J*=15.5 Hz, 1H, H-7b), 5.69–5.55 (m, 1H, H-2), 6.12 (d, *J*=2.6 Hz, 1H, H-4), 6.49 (dd, *J*=9.4, 3.2 Hz, 1H, H-3), 6.62 (d, *J*=2.6 Hz, 1H, H-5), 6.94 (dd, *J*=9.2, 2.7 Hz, 1H, H-8), 7.04 (td, *J*=8.5, 2.7 Hz, 1H, H-10), 7.35 (dd, *J*=8.5, 5.6 Hz, 1H, H-11); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=27.1 (CH_3), 33.7 (C-11b), 37.4 (C-1), 46.9 (C-7), 105.6 (C-4), 113.06 (d, *J*=21.8 Hz, C-10), 113.8 (C-3a), 114.9 (d, *J*=21.2 Hz, C-8), 117.1 (C-3), 117.9 (C-5), 123.0 (C-2), 126.4 (d, *J*=8.3 Hz, C-11), 131.7 (C-11a), 132.9 (d, *J*=7.1 Hz, C-7a), 139.3 (C-3a^1), 160.7 (d, *J*=274.5 Hz, C-9); ^{19}F NMR (282.2 MHz, $CDCl_3$): δ=−116.7; MS (CI): *m*/*z* (rel. intensity)=240 (MH^+, 100), 239 (M^+, 67), 225 (13), 224 (55), 220 (17); HR-MS (CI): *m*/*z*=

240.1182, calcd. for $C_{16}H_{15}FN$ $[MH]^+$: 240.1189; $[\alpha]_D^{20}$: +37.2 ($c = 0.50$, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 64%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (major) = 8.00 min (81.76%), t_r (minor) = 9.46 min (18.24%)].

(*S*)-13b-Methyl-7,13b-dihydro-1*H*-benzo[b]indolo[1,7-*gh*][1,6]naphthyridine (2o): Prepared from pyrrole **1o** (53.1 mg, 0.15 mmol), (*R*)-BINAP (39.4 mg, 0.063 mmol), PMP (0.06 mL, 0.30 mmol) and $Pd(OAc)_2$ (5.2 mg, 0.023 mmol). The reaction mixture was heated under reflux for 6 days. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9:1) afforded **2o** as an oil; yield: 4.4 mg (11%). IR (ATR): $\nu = 1460$ cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 3H, CH_3), 2.88–3.20 (m, 2H, 2×H-1), 5.25 (d, $J = 15.7$ Hz, 1H, H-7a), 5.35 (d, $J = 15.7$ Hz, 1H, H-7b), 5.68–5.73 (m, 1H, H-2), 6.14 (d, $J = 2.7$ Hz, 1H, H-4), 6.48 (dd, $J = 9.5$, 3.4 Hz, 1H, H-3), 6.67 (d, $J = 2.7$ Hz, 1H, H5), 7.49–7.56 (m, 1H, H-10), 7.67–7.75 (m, 1H, H-11), 7.79 (d, $J = 8.1$ H, 1H, H-12), 8.00 (s, 1H, H-8), 8.11 (d, $J = 8.1$ Hz, 1H, H-9); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 25.4$ (CH_3), 35.9 (C-13b), 37.4 (C-1), 47.0 (C-7), 105.8 (C-4), 114.7 (C-3a), 117.1 (C-3), 119.1 (C-5), 122.2 (C-10), 124.1 (C-8a), 126.3 (C-9), 127.2 (C-12), 129.1 (C-11), 129.2 (C-3a^1), 129.3 (C-8), 131.8 (C-7a), 133.2 (C-2), 147.6 (C12a), 162.1 (C13a); MS (CI): *m/z* (rel. intensity) = 273 (MH^+, 100), 272 (M^+, 33), 258 (32), 257 (93); HR-MS (CI): *m/z* = 273.1374, calcd. for $C_{19}H_{17}N_2$ $[MH]^+$: 273.1392; The enantiomeric excess was determined by HPLC to be 99%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (major) = 9.51 min (99.37%), t_r (minor) = 11.90 min (0.63%)].

The reaction was repeated under the same conditions, but using (*S*)-BINAP a ligand, obtaining (*R*)-**2o**; $[\alpha]_D^{20}$: −338 (c = 0.79, CH_2Cl_2) The enantiomeric excess was determined by HPLC to be 99%, [Chiralcel OD3, hexane/isopropyl alcohol 98:02, 0.8 mL min^{-1}, t_r (major) = 9.56 min (0.44%), t_r (minor) = 11.85 min (99.56%)].

(*S*)-10b-Methyl-7,10b-dihydro-1*H*-pyrrolo[3,2,1-*ij*]thieno[3,2-*c*]quinoline (2p): Prepared from pyrrole **1o** (32.8 mg, 0.09 mmol), (*R*)-BINAP (16.1 mg, 0.026 mmol), PMP (0.03 mL, 0.18 mmol) and $Pd(OAc)_2$ (2.1 mg, 0.009 mmol). The reaction mixture was heated under reflux for 48 h. After work-up, flash column chromatography (silica gel, hexane/AcOEt 9.5:0.5) afforded **2p** as an oil; yield: 9.4 mg (46%). This compound could not be completely characterized because it decomposed. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 3H, CH_3), 2.53–2.73 (m, 2H, 2×H-1), 5.02 (d, $J = 15.7$ Hz, 1H, H-7a), 5.10 (d, $J = 15.7$ Hz, 1H, H-7b), 5.58–5.63 (m, 1H, H-2), 6.13 (d, $J = 2.7$ Hz, 1H, H-4), 6.45–6.54 (m, 1H, H-3), 6.63 (d, $J = 2.7$ Hz, 1H, H-5), 6.88 (d, $J = 5.1$ Hz, 1H, H-8), 7.22 (d, $J = 5.1$ Hz, 1H, H-9); MS (CI): *m/z* (rel. intensity) = 228 (MH^+, 100), 227 (M^+, 50), 226 (6), 213 (7), 212 (23); HR-MS (CI): *m/z* = 228.0841, calcd. for $C_{14}H_{14}NS$ $[MH]^+$: 228.0847; The enantiomeric excess was determined by HPLC to be 66%, [Chiralcel OD3, hexane/isopropyl alcohol 99.5:0.5, 0.3 mL min^{-1}, t_r (minor) = 16.08 min (16.96%), t_r (major) = 19.58 min (83.04%)].

(*R*)-9,10-Dimethoxy-11b-methyl-2,3,7,11b-tetrahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (3): A mixture of phenanthridine **2a** (61 mg, 0.22 mmol), palladium-on-charcoal (10 mol%) and acetic acid (0.05 mL) in THF (3 mL) was hydrogenated at 30 psi for 24 h. The mixture was filtered through a Celite pad and concentrated. The oil crude was purified by flash column chromatography (silica gel, hexane/AcOEt 8:2) to give **3** as an oil; yield: 34 mg (55%). IR (ATR): $\nu = 1511$ cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (s, 3H, CH_3), 1.77–1.92 (m, 1H, H-1a), 2.05–2.20 (m, 2H, 2 × H-$_2$), 2.32–2.41 (m, 1H, H-1b), 2.44–2.58 (m, 1H, H-3a), 2.66–2.74 (m, 1H, H-3b), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.91 (d, $J = 15.0$ Hz, 1H, H-7a), 5.08 (d, $J = 15.0$ Hz, 1H, H-7b), 5.99 (d, $J = 2.4$ Hz, 1H, H-4), 6.68 (d, $J = 2.5$ Hz, 1H, H-5), 6.76 (s, 1H, H-8), 6.94 (s, 1H, H-11); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.5$ (C-2), 22.4 (C-3), 28.8 (CH_3), 34.9 (C-1), 35.1 (C-11b), 47.4 (C-7), 56.1 (2×OCH_3), 106.3 (C-4), 107.4 (C-11), 109.8 (C-8), 113.6 (C-3a), 117.7 (C-5), 125.3 (C-7a), 131.7 (C-3a^1), 137.8 (C-11a), 146.8 (C-9), 148.4 (C-10); MS (CI): *m/z* (rel. intensity) = 284 (MH^+, 100), 283 (M^+, 59), 282 (23), 269 (27), 268 (96); HR-MS (CI): *m/z* = 284.1631, calcd. for $C_{18}H_{22}NO_2$ $[MH]^+$: 284.1651; $[\alpha]_D^{20}$: −55.73 ($c = 1.14$, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 60% [Chiralcel OD3, 98% hexane/isopropyl alcohol, 0.8 mL min^{-1}, t_r (minor) = 22.1 min (20%), t_r (major) = 24.8 min (80%)].

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[27] Longer reaction time and a higher catalyst loading were required for **2m** and **2o**. See details the folloiwing paragraphs.

