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Asymmetric synthesis of the dopamine D1 agonist, dihydrexidine

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ABSTRACT

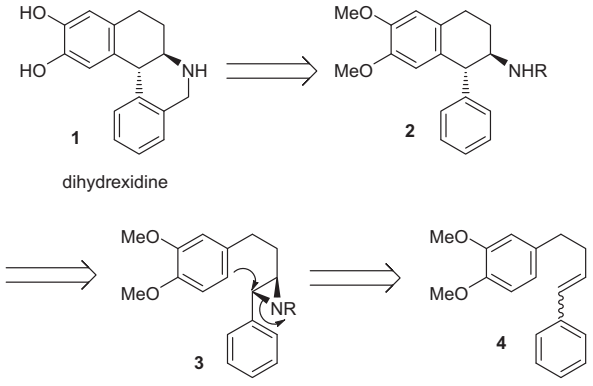
A concise asymmetric synthesis of first, high affinity domaine D1 full agonist, dihydrexidine has been accomplished via catalytic enantioselective aziridination and subsequent one-pot Friedel–Crafts cyclization of an in situ generated tethered aziridine with high diastereo- and enantioselectivities.

1. Introduction

Hexahydrobenzophenanthridine is an important structural subunit of various natural products and pharmaceuticals.[1,2] For example dihydrexidine **1** has been designed and developed as the first high affinity full efficacy agonist for dopamine D1 receptor.[2a,3] This is in clinical trial for the potential treatment of Parkinson's disease and the cognitive deficits of schizophrenia.[4] More importantly, this compound has been found to exhibit a high level of enantiospecificity in their interaction with the D1 receptor. Hence, the development of an efficient and concise method for the asymmetric synthesis of dihydrexidine **1** is highly in demand. There are several methods for the racemic[2a,5] synthesis of dihydrexidine, however, there are only three asymmetric syntheses of **1**, which are known in the literature.[6,7] A general chiral-pool approach for the asymmetric synthesis of hexahydrobenzophenanthridines was developed by Ehrlich et al. based on the Friedel–Crafts acylation of veratrole from costly *N*-(trifluoroacetyl)-D-aspartic acid anhydride.[6] Tomioka et al. developed an elegant and impressive general method for the asymmetric synthesis of dihydrexidine via the enantioselective 1,4-conjugate addition of an aryllithium to nitroalkenes at −90 °C using more than a stoichiometric amount of a chiral ligand, followed by reduction of the nitro group and cylization.[7] It was found that *trans*-2-amino-1-aryltetralins **2** is the advanced intermediate for the synthesis of dihydrexidine. A convenient strategy for this synthesis is an intramolecular Friedel–Crafts type cyclization of the tethered chiral aziridine **3** (Scheme 1).[8] Herein, we report a asymmetric synthesis of (+)-dihydrexidine **1** via catalytic enantioselective aziridination and subsequent one-pot Friedel–Crafts type cyclization with high diastereo- and enantioselectivity.

2. Results and discussion

To commence the synthesis, styrene **4** was prepared from a Wittig reaction of aldehyde **5** as a mixture of diastereomers



Scheme 1. Retrosynthesis of dihydrexidine.

(*E*:*Z* = 78:22) in good yield. Aldehyde **5** was synthesized from the corresponding dihydrocinnamyl alcohol using a literature procedure[9] (Scheme 2).

It was found that copper(II) triflate was an efficient dual catalyst for the aziridination[10] of alkenes as well as for the Friedel–Crafts cyclization of tethered and in situ generated aziridine, while [*N*-(*p*-nitrobenzenesulfonyl)imino]-phenyliodinane, PhIN-SO_2(4-$NO_2C_6H_4$) [PhINNs] was a successful nitrenoid source for this purpose.[8a] Therefore, catalytic enantioselective aziridination and Friedel–Crafts cyclization of styrene **4** was investigated in the presence of different bis-oxazoline (Box) ligands mostly derived from L-amino acids (Table 1). The reaction of **4** (5.0 equiv) with PhINNs (1.0 equiv) was carried out in the presence of bis(oxazoline)-copper complexes derived from 0.1 equiv of $Cu(OTf)_2$ and 0.12 equiv of Box ligand **6a** in dichloromethane (DCM) at rt. Within 1.5 h cyclization was observed to proceed rapidly to exclusively afford *trans*-2-amino-1-phenyltetralin **2** (dr >99:1) with 42% ee in 46% yield (Table 1, entry 1). Under the similar reaction conditions, other Box-$Cu(OTf)_2$ catalysts **6b–h** were investigated. With the sterically demanding *tert*-butyl Box ligand **6b**, there was no appreciable improvement in ee (47%), but provided a slightly lower yield (39%) (entry 2).

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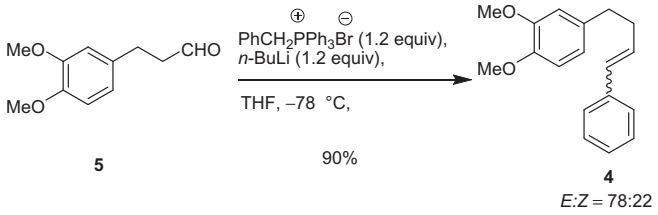
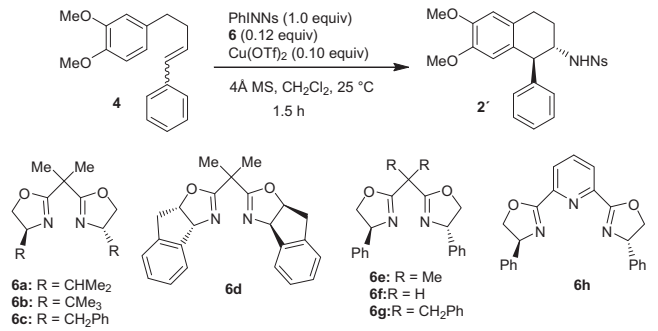


Scheme 2. Synthesis of alkene **4**.

Table 1
Screening of catalysts for the asymmetric aziridination and Friedel–Crafts cyclization



Entry	Ligand **6**	Yield[a] (%)	dr (*trans:cis*)[b]	ee[c] (%)
1	(*S*)-**6a**	46	>99:1	42
2	(*S*)-**6b**	39	>99:1	47
3	(*S*)-**6c**	50	>99:1	56
4	(*R*)-**6d**	51	>99:1	48[d]
5	(*S*)-**6e**	75	>99:1	87
6	(*S*)-**6f**	19	>99:1	11
7	(*S*)-**6g**	46	>99:1	42
8	(*S*)-**6h**	28	>99:1	21

[a] Isolated yield after column chromatography.
[b] Diastereomeric ratio was measured from the ^{1}H NMR analysis of the crude reaction mixture.
[c] Enantiomeric excess was determined by chiral HPLC.
[d] The other enantiomer was formed predominantly.

Improved enantioselectivity (ee 56%) was observed with benzyl substituted Box-ligand **6c** (entry 3). Similar selectivity was also obtained with Box-ligand **6d**, derived from indanol amine (entry 4). The Box-ligand **6e**, derived from phenylglycine, provided very good enantioselectivity and yield (87% ee and 75% yield) (entry 5). However, changing to the unsubstituted Box-ligand **6f**, caused both the yield and the ee to drop to 19% and 11%, respectively (entry 6). The corresponding *gem*-dibenzyl ligand **6g** showed little improvement in yield to ee (entry 7). Ligands containing an additional binding site, such as Py-Box **6h** derived from phenylglycine, also reduced the yield as well as the ee (entry 8). Among all the bis-oxazoline-Cu catalysts, **6e** with a *gem*-dimethyl derived from phenylglycine, was found to be the best and gave the *trans*-*N*-nosyl-2-amino-1-phenyltetralin **2′** in 75% yield with 87% ee (entry 5). The absolute stereochemistry of aminotetralin **2′** was assigned by analogy with the literature report.[11,8b,8c] It is worth noting that the *E*:*Z* mixture of styrene (78:22) on aziridination and subsequent Friedel–Crafts cyclization provided exclusively *trans*-2-amino-1-phenyltetralin **2′** (dr >99:1) and the corresponding *cis*-cyclized product was not detected. This is due to the dual chemoselectivity of the aziridination and Friedel–Crafts reactions.[8a,8b]

To commence the synthesis of active dihydrexidine, the reaction of styrene **4** was carried out under the same conditions in the presence of $Cu(OTf)_2$ (0.1 equiv) and (*R*)-Box-ligand **6e′** derived from D-phenyl glycine and it gave provided the desired *trans*-*N*-nosyl-2-amino-1-phenyltetralin **2** in 75% yield with 87% ee (Scheme 3). Recrystallization of compound **2** from methanol at 5 °C crystallized out the minor enantiomer and enhanced the ee of the mother liquor to >99%ee with 70% recovery yield. The specific rotation of pure compound **2** was found to be $[\alpha]_D^{28} = -52.0$ (*c* 1.0, $CHCl_3$).

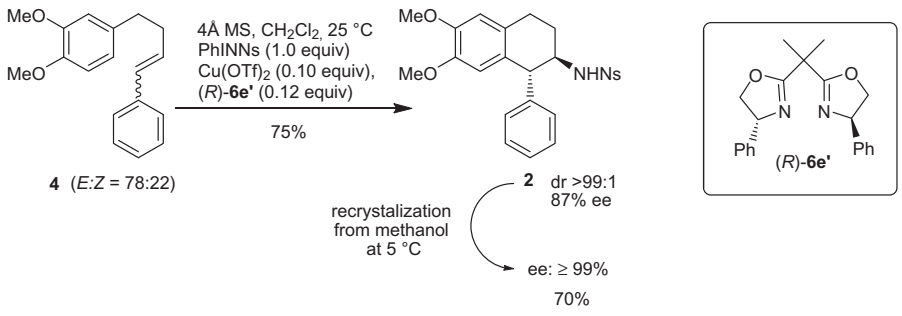
Denosylation of compound **2** with 4-methoxythiophenol and K_2CO_3 in CH_3CN/DMSO (49:1) afforded aminotetralin **7**. Pictet–Spengler cyclization of aminotetralin **7** under conventional conditions was unsuccessful in giving hexahydrobenzophenanthridine compound **8**.[7a] Therefore, an attempt was made to synthesize compound **9** from compound **2** using $CH_2(OMe)_2$ and BF_3–Et_2O. However, it afforded a non-separable mixture (1:1) of the desired compound **9** and double alkylation product **10** (Scheme 4).

However, when the sodium salt of compound **2**, generated by the reaction of NaH, was reacted with MOMCl at 0 °C and within 1 h, compound **9** was obtained in excellent yield (Scheme 5). The Pictet–Spengler type cyclization of compound **9** using TMSOTf (1.1 equiv) at −50 °C in DCM led to the formation of the desired *N*-nosyl hexahydrobenphenanthridine **11** in 55% yield after 4 h.

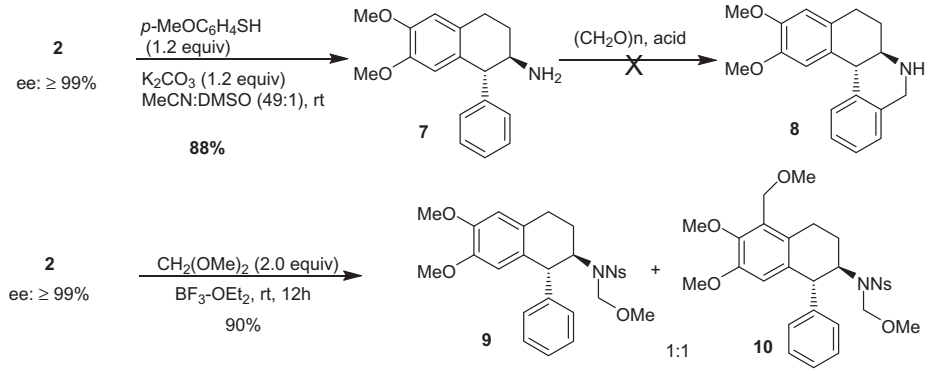
The deprotection of the *N*-nosyl group of compound **11** upon treatment with 4-methoxythiophenol and K_2CO_3 in a mixed solvent of CH_3CN/DMSO (49:1) at rt gave *O*-methyldihydrexidine **8** in 92% yield after 2.5 h. The specific rotation of compound **8** {$[\alpha]_D^{28} = -217.9$ (*c* 1.1, $CHCl_3$)} was comparable to the literature[7b] data {$[\alpha]_D^{25} = -222$ (*c* 1.1, $CHCl_3$)}. The BBr_3 mediated demethylation of compound **8** in DCM completed the synthesis of dihydrexidine as a hydrobromide salt, **1**·**HBr** in 95% yield. Finally, dihydrexidine hydrochloride **1**·**HCl** was obtained by successive treatment with $NaHCO_3$ and saturated HCl in dry ethanol. The specific rotation of dihydrexidine hydrochloride **1**·**HCl** {$[\alpha]_D^{28} = +79.9$ (*c* 0.25, EtOH) was in good agreement with the literature[2d] data {$[\alpha]_D^{25} = +83$ (*c* 0.25, EtOH)}.

3. Conclusion

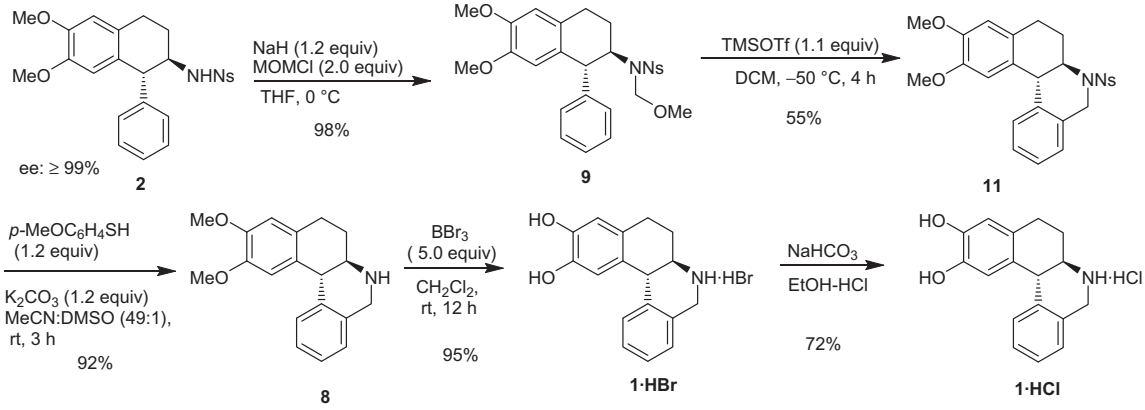
In conclusion, we have accomplished the concise asymmetric synthesis of (+)-dihydrexdine·HCl via a one-pot catalytic



Scheme 3. Synthesis of aminotetralin **2**.



Scheme 4. Attempts towards the synthesis of compounds **8** and **9**.



Scheme 5. Synthesis of dihydrexidine hydrochloride.

enantioselective aziridination and subsequent Friedel–Crafts cyclization with tethered and in situ generated aziridine with high diastereo- and enantioselectivity.

4. Experimental

4.1. General

All reactions were carried out using oven-dried glassware under an argon (Ar) atmosphere. Commercial grade reagents were used without further purification. Solvents were dried and distilled following the usual protocols. Flash chromatography was carried out using silica gel (230–400 mesh). TLC was performed on aluminum-backed plates coated with Silica Gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded at 200 and 400 MHz and ^{13}C NMR spectrum were recorded at 50 and 100 MHz using $CDCl_3$ and CD_3OD. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ ($\delta = 7.26$) and CD_3OD ($\delta = 3.31$); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance ($\delta = 77.0$) and CD_3OD resonance ($\delta = 49.1$). High resolution mass spectra (HRMS) were obtained under positive electron spray ionization (*m/z* values are given). HPLC analyses were done by Chiralpak AD-H column (0.46 cm × 15 cm). Optical rotations were measured on a polarimeter.

4.1.1. 1,2-Dimethoxy-4-(4-phenyl-but-3-enyl)-benzene 4

To a stirred suspension of benzyl triphenylphosphonium bromide (16.7 g, 38.65 mmol) in dry THF (78 mL) under a nitrogen atmosphere, *n*-BuLi in hexane (24.2 mL, 1.6 M in hexane) was injected dropwise at −78 °C via a glass syringe. The temperature was slowly raised to −30 °C and at this temperature the stirring was continued for 20 min. The reaction mixture was re-cooled to −78 °C and 3-(3,4-dimethoxyphenyl)-propionaldehyde **5** (5.0 g, 25.0 mmol) in dry THF (25 mL) was slowly added. The reaction mixture was allowed to reach room temperature. The reaction was quenched with aqueous NH_4Cl solution and extracted with ether (three times). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. Flash column chromatography (EtOAc/hexane = 1:9) of the crude mass over silica-gel yielded alkene **4** (5.9 g, 90%) as a *E*/*Z*-mixture (*E*:*Z* = 78:22). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.37–7.15 (m, 5H), 6.86–6.70 (m, 3H), 6.44 (d, *J* = 11.0 Hz, 0.22H), 6.42 (d, *J* = 16.0 Hz, 0.78H), 6.30 (m, 0.78H), 5.70 (m, 0.22H), 3.86 (s, 4.68H), 3.85 (s, 0.66H), 3.84 (s, 0.66H), 2.80–2.60 (m, 2.44H), 2.58–2.46 (m, 1.56H). ESI-MS *m/z*: 268 (M^+).

4.1.2. (1*S*,2*R*)-*N*-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-naphthalen-2-yl)-4-nitro-benzenesulfonamide 2

A 10 mL two-necked round bottomed flask was charged with (*R*)-bis-oxazoline ligand **6e′** (0.01 g, 0.03 mmol, 0.12 equiv) and $Cu(OTf)_2$ (0.009 g, 0.025 mmol, 0.1 equiv). Anhydrous DCM (1 mL) was injected and the resulting mixture was stirred for 30 min. To this solution, PhINNs (0.1 g, 0.24 mmol, 1.0 equiv), alkene **4** (0.29 g, 1.23 mmol, 5.0 equiv) and 0.2 g of powdered molecular sieves (4 Å) were added and the reaction mixture was allowed to stir at 25 °C under an argon atmosphere for 1.5 h. On dissolution of PhINNs, the reaction was quenched by diluting with ethyl acetate (10 mL) and filtering through a short plug of silica gel. The silica gel was washed with an additional 10 mL of ethyl acetate. The filtrate was concentrated by rotary evaporation under reduced pressure. The crude mass was subjected to purification by flash column chromatography using EtOAc/hexane (1:4) as an eluent,

which provided aminotetralin **2** (0.084 g, 75%). Mp 63–64 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.20–7.06 (m, 3H), 6.90–6.80 (m, 2H), 6.60 (s, 1H), 6.10 (s, 1H), 4.82 (d, J = 7.6 Hz, 1H), 3.85 (s, 3H), 3.78 (d, J = 7.8 Hz, 1H), 3.64 (m, 1H), 3.56 (s, 3H), 2.98–2.75 (m, 2H), 2.28–2.17 (m, 1H), 1.85–1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.6, 148.0, 147.6, 146.0, 142.8, 128.8 (2C), 128.4 (2C), 127.8 (2C), 127.5, 127.3, 127.0, 124.1 (2C), 112.8, 110.8, 57.1, 55.7, 55.7, 51.5, 27.6, 26.1. Before recrystallisation, HPLC analysis: (chiralcel AD-H, 10% *i*-PrOH/*n*-hexane, 1.0 mL/min, 220 nm, t_r (major) 23.3 min, t_r (minor) 34.0 min); 87% ee. After one recrystalisation from methanol at 5 °C, HPLC analysis: (chiralcel AD-H, 10% *i*-PrOH/*n*-hexane, 1.0 mL/min, 220 nm, t_r (major) 23.1 min); ee $\geqslant$ 99%. $[\alpha]_D^{28} = -52.0$ (c 1.00, $CHCl_3$). ESI-MS m/z: 469 (MH^+). HRMS (EI) calcd for $C_{24}H_{24}N_2O_6S$, 491.1253 m/z $(M+Na)^+$; found, 491.1251 m/z.

4.1.3. (1*S*,2*R*)-*N*-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-methoxymethyl-4-nitrobenzenesulfonamide 9

To a well stirred solution of **2** (0.1 g, 0.214 mmol) taken in THF (2 mL) at 0 °C, NaH (1.2 equiv) was added and allowed to stir for 30 min under an argon atmosphere. Next, MOMCl (2 equiv) was slowly added and stirred. After 1.5 h, the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate and dried over $NaSO_4$. The reaction mixture was subjected to column purification using 20% EtOAc in hexane as an eluent to obtain **9** (0.108 g, 98%) as a yellow solid. Mp 56–57 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.03 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.08–6.90 (m, 3H), 6.88–6.86 (m, 2H), 6.55 (s, 1H), 5.99 (s, 1H), 5.04 (d, J = 11.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.23 (d, J = 10.2 Hz, 1H), 4.16–4.09 (m, 1H), 3.83 (s, 3H), 3.48 (s, 3H), 3.35 (s, 3H), 3.10–2.95 (m, 1H), 2.88–2.77 (m, 1H), 2.21–2.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.7, 147.8, 147.6, 146.5, 143.8, 130.6, 129.4 (2C), 128.5 (2C), 128.4 (2C), 128.0, 126.8, 123.9 (2C), 113.3, 110.9, 76.6, 63.1, 56.03, 55.94, 55.90, 48.9, 30.4, 29.6. $[\alpha]_D^{28} = -36.0$ (c 1.00, $CHCl_3$). HRMS (EI) calcd for $C_{26}H_{28}N_2O_7S$, 535.1515 m/z $(M+Na)^+$; found, 535.1511 m/z.

4.1.4. (6a*R*,12b*S*)-10,11-Dimethoxy-6-(4-nitrobenzenesulfonyl)-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine 11

To a well stirred solution of **9** (0.1 g, 0.195 mmol) taken in 4 ml DCM at −50 °C, 1.1 equiv of TMSOTf was added slowly and the reaction mixture was allowed to stir for 4 h. Upon completion, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc and dried over Na_2SO_4. The reaction mass was subjected to column purification using 15% EtOAc in hexane as an eluent to obtain **11** (0.052 g, 55%) as a yellow solid. Mp 88–89 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 4.4 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.91(t, J = 7.6 Hz, 1H), 6.85 (s, 1H), 6.77 (d, J = 7.2 Hz, 1H), 6.71 (s, 1H), 4.69 (d, J = 16.0 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.12 (d, J = 11.6 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.20–3.14 (m, 1H), 3.06–2.99 (m, 1H), 2.90–2.81 (m, 1H), 2.10–2.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.7, 148.1, 146.9, 144.0, 138.5, 135.1, 129.7, 128.6 (2C), 127.8, 126.2, 125.8, 124.0, 123.8, 123.7 (2C), 112.6, 112.1, 61.6, 56.1, 55.9, 47.7, 43.9, 31.3, 29.4. $[\alpha]_D^{28} = +30.2$ (c 1.00, $CHCl_3$). HRMS (EI) calcd for $C_{25}H_{24}N_2O_6S$, 503.1253 m/z $(M+Na)^+$; found, 503.1250 m/z.

4.1.5. (6a*R*,12b*S*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine 8

To a well stirred solution of **11** (0.1 g, 0.208 mmol) taken in 2 mL CH_3CN/DMSO (49:1) at rt, 1.2 equiv of 4-methoxythiophenol and 1.2 equiv of K_2CO_3 were added and the reaction mixture was allowed to stir for 3 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the crude reaction mass was subjected to column purification by using 3% MeOH in DCM as an eluent to give **8** (0.056 g, 92%) as a white solid. Mp 156–157 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, J = 7.2 Hz, 1H), 7.32–7.18 (m, 2H), 7.17 (d, J = 6.8 Hz, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 4.07 (s, 2H), 3.88 (s, 3H), 3.86 (d, J = 9.0 Hz, 1H), 3.77 (s, 3H), 2.96–2.89 (m, 1H), 2.84–2.71 (m, 2H), 2.36 (br s, 1H), 2.25–2.17 (m, 1H), 1.78–1.72 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.2, 146.7, 136.7, 136.3, 130.7, 129.9, 128.1, 126.9, 126.2 (2C), 111.9, 110.2, 58.6, 56.1, 56.0, 48.4, 44.3, 28.5, 27.4. $[\alpha]_D^{28} = -217.9$ (c 1.1, $CHCl_3$) {lit[7b] $[\alpha]_D^{25} = -222$ (c 1.1, $CHCl_3$)}. ESI-MS m/z: 296 $(M+H)^+$. HRMS (EI) calcd for $C_{19}H_{21}NO_2$, 296.1651 m/z $(M+H)^+$; found, 296.1632 m/z.

4.1.6. (6a*R*,12b*S*)-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine hydrobromide 1·HBr

To a well stirred solution of **8** (0.05 g, 0.169 mmol) taken in DCM (2 mL) at rt, 5 equiv BBr_3 (1 M solution in DCM) were slowly added and reaction mixture was allowed to stir for 12 h. Upon completion of the reaction, the mixture was quenched with MeOH (2 mL) and stirred for 30 min after which the solvent was evaporated to give a crude reaction mixture. Then the crude mass was scratched and washed with dry ether to get **1·HBr** (0.56 g, 95%) as a light yellow solid. Mp 185–186 °C. ^{1}H NMR (CD_3OD, 200 MHz): δ 7.54–7.38 (m, 4H), 6.81 (s, 1H), 6.67 (s, 1H), 4.45 (s, 2H), 4.22 (d, J = 11.4 Hz, 1H), 3.12–2.72 (m. 3H), 2.42–2.22 (m, 1H), 2.06–1.99 (m, 1H). ^{13}C NMR (CD_3OD, 50 MHz): δ 145.7, 144.8, 137.7, 131.0, 129.7, 129.5, 129.0, 128.6, 128.1, 126.1, 116.9, 115.6, 59.4, 46.4, 42.4, 28.0, 27.1. $[\alpha]_D^{28} = +37.0$ (c 0.20, EtOH). ESI-MS m/z: 268 (MH^+). HRMS (EI) calcd for $C_{17}H_{17}NO_2$, 268.1338 m/z $(M+H)^+$; found, 268.1283 m/z.

4.1.7. (6a*R*,12b*S*)-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine hydrochloride 1·HCl[2d]

At first, **1·HBr** (0.05 g, 0.143 mmol) was dissolved in H_2O (5 mL) and the pH was adjusted to 9–10 with $NaHCO_3$ under an Ar atmosphere. The mixture was extracted with $CHCl_3$ and dried over Na_2SO_4 to give a pale yellow solid. A solution of this pale yellow solid in EtOH (1 mL) and EtOH–HCl (3 mL) was stirred at rt for 0.5 h and concentrated. The residue was dried azeotropically with benzene (3 mL) to afford dihydrexidine hydrochloride **1·HCl** (0.031 g, 72%) as a pale yellow solid. Mp >120 °C (dec). ^{1}H NMR (CD_3OD, 200 MHz): δ 7.49–7.34 (m, 4H), 6.76 (s, 1H), 6.62 (s, 1H), 4.40 (s, 2H), 4.16 (d, J = 11.0 Hz, 1H), 3.01–2.75 (m. 3H), 2.35–2.20 (m, 1H), 2.05–1.85 (m, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 145.5, 144.6, 137.5, 130.8, 129.5, 129.3, 128.8, 128.4, 128.0, 125.9, 116.7, 115.4, 59.2, 46.2, 42.2, 27.8, 26.9. $[\alpha]_D^{28} = +79.9$ (c 0.25, EtOH) {lit[2d] $[\alpha]_D$ = +83 (c 0.25, EtOH)}. ESI-MS m/z: 268 $(M+H)^+$. HRMS (EI) calcd for $C_{17}H_{17}NO_2$, 268.1338 m/z $(M+H)^+$; found, 268.1283 m/z.

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