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Asymmetric synthesis of a dopamine D1 agonist, dihydrexidine from D-serine

Rajesh Malhotra [a], Amit Ghosh [a,b], Rajib Ghosh [a,b], Sagar Chakrabarti [a,b], Swarup Dutta [b], Tushar K. Dey [a,b], Subho Roy [b], Sourav Basu [b,*], Saumen Hajra [c,*]

[a] *Department of Chemistry, Guru Jambheshwar University of Science and Technology, Hisar, Haryana 125 001, India*
[b] *TCG Life Sciences Ltd, Saltlake, Kolkata 700 091, India*
[c] *Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721 302, India*

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ABSTRACT

A scalable asymmetric synthesis of *trans*-2-amino-6,7-dimethoxy-1-phenyltetralin **2** and its *N*-nosyl derivative **12** have been achieved from Garner aldehyde derived from easily available D-serine using a stereoselective PhMgBr addition, Wittig reaction and TFA-mediated Friedel–Crafts cyclization as the key steps. The synthesis of dihydrexidine is accomplished from the *N*-nosyl-2-amino-1-phenyltetralin **12**.

1. Introduction

Dihydrexidine **1** is one of the important hexahydrobezophenanthredine compounds. It has been developed and designed as the first high affinity bioavailable full dopamine D1 agonist.[1,2] This is examined for the treatment of Parkinson's disease[1,2] and schizophrenia.[3] In early clinical trials, it was administered intravenously and led to intense hypotension and therefore, the development was halted. Nevertheless, further investigation on this drug is currently under progress in clinics to review its efficacy in improving the cognitive and working memory deficits in schizophrenia.[4] Interestingly, this compound shows a high level of enantiospecificity in its interaction with the D1 receptor. Hence, the development of efficient and scalable method for the asymmetric synthesis of dihydrexidine **1** is highly demanding.

There are few methods available in the literature for a racemic synthesis of dihydrexidine. The first synthesis of (±)-**1** was carried out by starting from β-tetralone,[1a] but involved a low yielding photochemical cyclization and hence was non-viable for large scale production. Two alternative strategies for the racemic synthesis of dihydrexidine were reported by Nichols et al.[5] The more recent one involves intramolecular Henry cyclization of a (nitropropyl)benzophenone followed by selective reduction of the resulting tricyclic nitroalkene. This is a safe and simple method for the synthesis of a nitrotetralin.[5a] The resolution from the mixture of isomers was also reported with the use of (*R*)-*O*-methylmandelic acid.[1d]

Several attempts have been made for the asymmetric synthesis of dihydrexidine. Ehrlich et al. have developed a general approach for the asymmetric synthesis of hexahydrobenzophenanthridine compounds starting from costly *N*-(trifluoroacetyl)-D-aspartic acid anhydride, focusing on double Friedel–Crafts reactions of two aryl units with poor to moderate stereoselectivity.[6] Tomioka et al. reported a high yielding elegant and enantioselective synthesis of dihydrexidine via a 1,4-addition of an aryllithium to dimethoxynitrotetralin at −90 °C.[7] Use of more than a stoichiometric amount of costly chiral ligand (2.5 equiv) and tetranitromethane, which is a potential carcinogen, are a serious bottleneck for large scale handling. Hajra et al. developed an efficient general method for the catalytic enantioselective synthesis of 2-amino-1-aryltetralins and then to hexahydrobenzophenanthrene via asymmetric aziridination and one-pot Friedel–Crafts cyclization of the aziridine generated in situ.[8] However, scale up of the asymmetric aziridination using nitrenoid reagent (PhINNs) is another problem.

From the above reports, it is found that aminotetralin **2** is the key precursor for the synthesis of dihydrexidine and that the development of a scalable asymmetric route towards its synthesis, and in turn dihydrexidine **1** is still a major challenge. We herein report an efficient and scalable synthesis of 2-amino-1-phenyltetralin **2** (R = H) and its *N*-nosyl derivative **12** (R = Ns) starting from Garner's aldehyde, derived from inexpensive and easily available D-serine and the synthesis of dihydrexidine from the aminotetralin **12**.

2. Results and discussion

Retrosynthetic analysis of aminotetralin **2** reveals that it can be obtained by a Friedel–Crafts type cyclization of 1,2-aminoalcohol **3**. This intermediate can in turn be prepared by the proper synthetic exploitation of Garner aldehyde **4**, derived from D-serine (Scheme 1).

Garner's aldehyde **4** was synthesized from D-serine **5** in five steps by following literature procedures.[9] The enantiomeric purity of Garner's aldehyde **4** was verified by comparing its specific rota-

* Corresponding authors. Tel.: +91 33 4000 7000; fax: +91 33 23673058 (S.B.); tel.: +91 3222 283340; fax: +91 3222 255303 (S.H.).
E-mail addresses: sourav@chembiotek.com (S. Basu), shajra@chem.iitkgp.ernet.in (S. Hajra).

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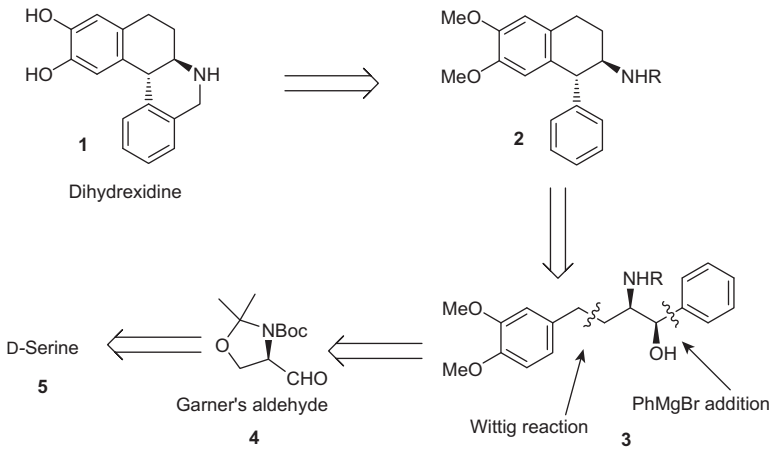
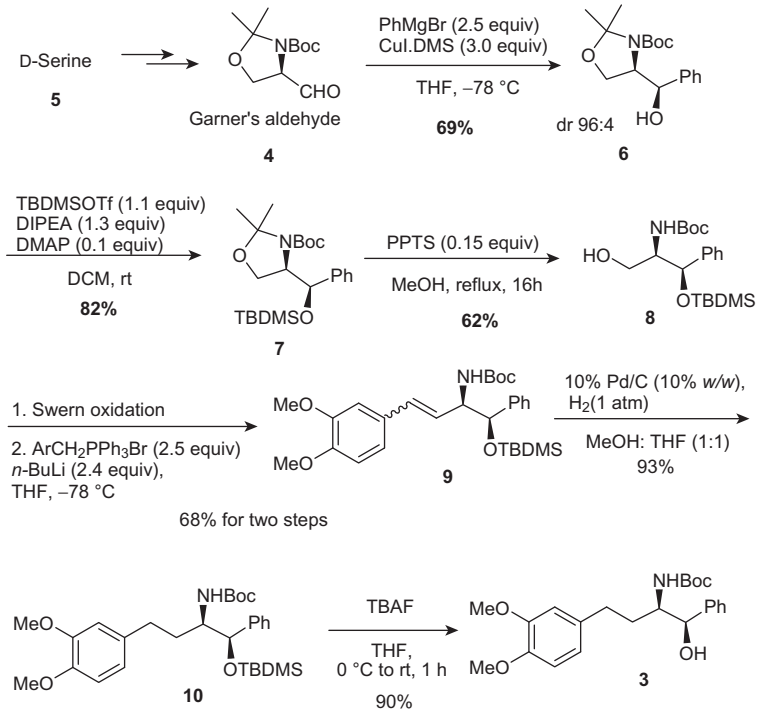


Scheme 1. Retrosynthesis of dihydrexidine **1**.

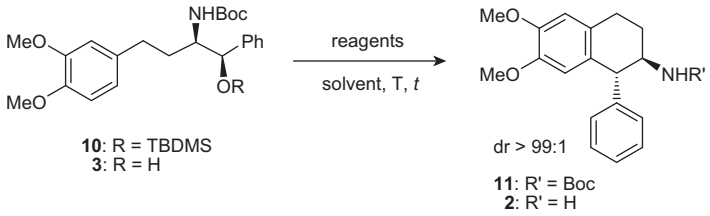
tion with the literature value.[9] Aldehyde **4** was reacted with phenyl magnesium bromide that provided a mixture of diastereomers of compound **6** with moderate selectivity (2.5:1) having the *anti*-isomer as the major one. This step was optimized further by using CuI·DMS additive[10] that afforded the desired *syn*-isomer **6** with excellent diastereoselectivity (dr 96:4) and in 69% yield (Scheme 2). The free hydroxyl group of **6** was then protected as its TBDMS ether. TBDMS was the group of choice since we have anticipated that this group will remain stable during acidic removal of the acetonide functionality. The hydroxyl functionality was protected by reaction with TBDMSOTf and gave TBDMS-protected compound **7** in 82% yield. Refluxing a methanolic solution of compound **7** in the presence of PPTS afforded the *syn*-(1*R*,2*R*)-N,O-protected-2-amino-1-phenylpropane-1,3-diol **8** in 62% yield. Swern oxidation of the primary alcohol **8** afforded the aldehyde and without purification it was reacted with the ylide generated from 3,4-dimethoxybenzyl bromide. This reaction, under standard Wittig conditions gave a mixture of *E* and *Z* olefinic product **9**. Pd/C-catalysed hydrogenation of compound **9** under atmospheric pressure led to the formation of TBDMS-protected 1,2-hydroxyamine **10** in almost quantitative yield. This reaction needs proper monitoring; longer reaction time results in 10–15% of TBDMS deprotection. For the planned Friedel–Crafts cyclization to occur, *N*-Boc-protected aminoalcohol **3** was prepared by desilylation of compound **10** with TBAF in THF.

Having constructed the basic framework, the intramolecular Friedel–Crafts cyclization of **3** was carried under different reaction conditions (Table 1). A TsCl, pyridine combination did not yield any desired product. Other reagents such as NsCl/py, TFA and methane sulfonic acid were found to be effective for cyclization (entries 2–5). The NsCl/Py combination provided a moderate yield (55%) of *N*-Boc-protected 2-amino-1-phenyltetralin **11**. Whereas TFA and MsOH mediated cyclization afforded 2-amino-1-phenyltetralin **2**. Among these reagents, TFA was found to be very efficient and showed consistent results. Later it was found that TBDMS deprotection was not necessary. Compound **10** on heating directly in TFA, furnished aminotetralin **2** in 62% yield with high diastereoselectivity (dr >99:1) (entry 6). The overall yield of aminotetralin **2**



Scheme 2. Synthesis of *syn*-aminoalcohol **3** from Garner aldehyde, derived from D-serine.

Table 1
Synthesis of aminotetralin **2** and **12** by Friedel–Crafts cyclization of aminoalcohols **3** and **10**



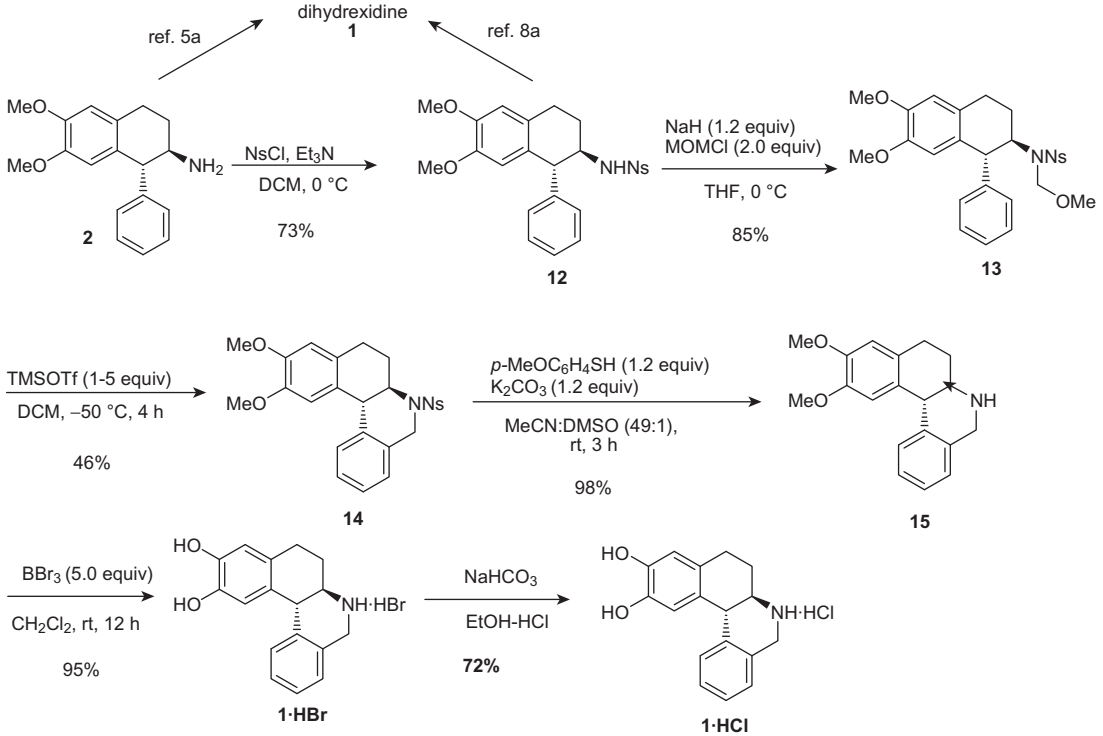
Entry	Aminoalcohol	Reagents	Solvent	Temp (°C)	Product	Yield[a] (%)
1	**3**	TsCl, Py	DCM	rt to 45	—	—
2	**3**	NsCl, Py	DCM	rt	**11**	25[b]
3	**3**	NsCl	Py	rt	**11**	55
4	**3**	$MeSO_3H$	DCM	5–10	**2**	60
5	**3**	TFA	Neat	80	**2**	70
6	**10**	TFA	Neat	80	**2**	62

[a] Isolated yield after column chromatography.
[b] Incomplete conversion.

from Garner's aldehyde **4** was found to be 13.8%. Further study reveals that the *syn*-stereochemistry of the hydroxyl functionality of aminoalcohol **10** is not so important. Friedel–Crafts cyclization of a diastereomeric mixture of compound **10** at the benzylic-OH also provided the aminotetralin **2** with excellent diastereoselectivity (dr >99:1). It is to be noted that the specific rotation of the free aminotetralin **2** in $CHCl_3$ was found to be inconsistent when compared with the reported value.[7b] However, HPLC analysis of **2** on a chiral column showed high enantioselectivity (ee 95%).

Compound **2** was transformed to *N*-nosyl protected aminotetralin **12** on treatment with nosyl chloride (4-$NO_2C_6H_4SO_2Cl$) and Et_3N. Now the specific rotation of the *N*-nosyl aminotetralin **12** {$[\alpha]_D^{25} = -64.2$ (*c* 1.0, $CHCl_3$)} is comparable with the literature data {Lit. $[\alpha]_D^{25} = -51.25$ (*c* 1.00, $CHCl_3$)}.[8a]

The synthesis of dihydrexidine **1** from both the aminotetralins **2** and **12** are known in the literature.[5a,8a] Here *N*-nosyl aminotetralin **12** was transformed to dihydrexidine hydrochloride salt **1·HCl** in five steps by following a known procedure (Scheme 3). Reaction of the sodium salt of compound **12** with MOMCl provided compound **13** in excellent yield.[8b] Then the TMSOTf mediated cyclization of *N*-MOM aminotetralin **13** at −50 °C gave the desired product **14**. This cyclization was found to be sensitive to reagent quality and also temperature. The yield varies between 40% and 52%, and depends on the TMSOTf obtained from different sources. Deprotection of the nosyl group of compound **14** with 4-methoxythiophenol and K_2CO_3 in mixed solvent (DMSO/CH_3CN = 1:49) afforded *O*-methyl dihydrexidine **15** in good yield. The spectral data and specific rotation of the synthesized compound **15**, as its hydrochloride salt, {$[\alpha]_D^{25} = +110$ (*c* 0.15, EtOH} was consistent with the literature data {$[\alpha]_D$ = +106 (*c* 0.75), EtOH}.[1d] Demethylation of hexahydrobenzophenanthridine **15** using BBr_3 accomplished the synthesis of dihydrexidine as a hydrobromide salt



Scheme 3. Synthesis of (+)-dihydrexidine hydrochloride **1·HCl** from aminotetralin **12**.

1·HBr with a specific rotation of $[\alpha]_D^{25} = +59$ (*c* 0.21, EtOH).[11] Finally successive treatment with $NaHCO_3$ and HCl in ethanol provided dihydrexidine hydrochloride **1·HCl**. It showed >99% ee by chiral HPLC analysis and with a specific rotation of $[\alpha]_D^{26} = +85$ (*c* 0.25, EtOH) {[Lit.[1d] $[\alpha]_D^{25} = +83$ (*c* 0.25, EtOH); Lit.[7b] $[\alpha]_D^{25} = +85.5$ (*c* 0.24, EtOH)]}.

3. Conclusion

In conclusion, we have accomplished an asymmetric synthesis of 2-amino-1-phenyltetralin **2** and its *N*-nosyl derivative **12**. The highly efficient diastereoselective synthesis (dr >99:1) was achieved starting from commercially available D-serine. The process is also scalable. The synthesis of dihydrexidine as a hydrobromide salt **1·HBr** and also as a hydrochloride salt **1·HCl** has been completed with high enantiomeric purity (ee >99%) from the *N*-nosyl-2-amino-1-phenyltetralin **12** in five steps.

4. Experimental

All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar). Commercial grade reagents were used without further purification. Solvents were dried and distilled following the usual protocols. Column chromatography was carried out using silica gel (100–200 mesh). TLC was performed on aluminium-backed plates coated with Silica Gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded with a 400 MHz and ^{13}C NMR spectra were recorded with a 100 MHz using $CDCl_3$, DMSO-d_6 and CD_3OD. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ ($\delta = 7.26$), DMSO-d_6 ($\delta = 2.49$) and CD_3OD ($\delta = 3.31$); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ ($\delta = 77.0$), DMSO-d_6 ($\delta = 39.7$) and CD_3OD ($\delta = 49.0$). High resolution mass spectra (HRMS) were obtained under positive electron spray ionization (*m/z* values are given). HPLC analyses were carried out by Chiralpak AD-H, Chiralcel OD-RH and Chiralcel OJ-RH columns (0.46 cm × 25 cm) 5μ.

4.1. (*R*)-4-Formyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester 4 (Garner's aldehyde)

This was prepared in 73.5% yield as a colourless liquid by following literature procedure.[9] ^{1}H NMR ($CDCl_3$, 400 MHz) (two rotamers): δ 9.55 (s. 0.5H, –C*H*O), 9.50 (s, 0.5H, –C*H*O), 4.28 (m, 0.5H, –NC*H*–), 4.15 (m, 0.5H, –NC*H*–), 4.07–4.01 (m, 2H, –CH_2O–), 1.59 [s, 3H, –C(CH_3)$_2$–], 1.5 [s, 3H, –C(CH_3)$_2$–], 1.46 [s, 4.5H, –OC(CH_3)$_3$], 1.38 [s, 4.5H, –O(CH_3)$_3$]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (rotamers) 199.3/199.2 (–*C*HO), 152.5/151.2 (–O*C*=O), 95.0/94.2 [*C*(CH$_3$)$_2$], 81.2/80.9 [-OC(CH$_3$)$_3$], 64.69/64.63 (–*C*H$_2$O), 63.8/63.3 (–NCH–), 28.1 [3C, –OC(*C*H$_3$)$_3$], 26.6/25.6 [C(*C*H$_3$)$_2$], 24.6/23.7 [C(*C*H$_3$)$_2$]. $[\alpha]_D^{25} = +93.5$ (*c* 1.00, $CHCl_3$); Lit.[9a] $[\alpha]_D^{20} = +95.0$ (*c* 1.34, $CHCl_3$); Lit.[9b] $[\alpha]_D^{20} = +83.8$ (*c* 1.00, $CHCl_3$).

4.2. (*R*)-4-[(*R*)-Hydroxyphenylmethyl]-2,2-dimethyloxazolidine -3-carboxylic acid *tert*-butyl ester 6

To a slurry of copper(I) iodide (36.6 g, 192.3 mmol, 3.0 equiv) in anhydrous tetrahydrofuran (383 ml) maintained at −78 °C was added dimethylsulphide (76.2 ml) under a nitrogen atmosphere and stirred for 5 min. A solution of phenyl magnesium bromide in THF (1.0 M; 160 mL, 160.2 mmol, 2.5 equiv) was slowly added at the same temperature over 20 min. The temperature was allowed to rise to −35 to −40 °C and stirred for 30 min. It was then re-cooled to −78 °C and a solution of Garner's aldehyde **4** (14.7 g, 64.1 mmol, 1.0 equiv) in anhydrous THF (114 mL) was added over 45 min and the reaction mixture was allowed to attain room temperature and stirred for 12 h. The reaction mass was quenched by the slow addition of saturated aqueous ammonium chloride solution (500 mL) at −10 to −5 °C and stirred at ambient temperature for 1 h. It was filtered through a Celite bed and the filtrate was extracted with ethyl acetate (3 × 750 mL). The combined organic extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography using 20% ethyl acetate in hexanes as eluent to provide the pure compound **6** (13.6 g, 69%) as a white solid. Mp 76–77 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.4–7.26 (m, 5H, –C$_6$*H*$_5$), 5.28 (s, 1H, O*H*), 4.72 (d, *J* = 6.5 Hz, 1H, PhC*H*OH), 4.19 (m, 1H, –C*H*N–), 3.68 (m, 1H, –CH_2O–), 3.6 (m, 1H, –CH_2O–), 1.59 [s, 3H, C(CH_3)$_2$], 1.53 [s, 9H, –C(CH_3)$_3$], 1.48 [s, 3H, C(CH_3)$_2$]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8 (–O*C*=O), 141.8 (*C* of Ph), 128.4 (2*C*H of Ph), 128.0 (*C*H of Ph), 127.3 (2*C*H of Ph), 94.5 [*C*(CH$_3$)$_2$], 81.7 [-O*C*(CH$_3$)$_3$], 78.1 (PhCHOH), 64.7 (*C*H$_2$O), 63.6 (–*C*HN), 28.3 [3CH$_3$ of –OC(*C*H$_3$)$_3$], 27.1 [*C*H$_3$CCH$_3$], 24.2 [CH$_3$C*C*H$_3$]. LC–MS (ESI) *m/z*: 308.2 (MH^+). HPLC analysis: chiralpak AD-H, 50% *n*-hexane, 30% ethanol and 20% *i*-PrOH, 0.2 mL/min, 210 nm, t_R (major) 18.57, t_R (minor) 20.41, ee 97.8%. $[\alpha]_D^{25} = -19.0$ (*c* 1.0, $CHCl_3$).

4.3. (*R*)-4-[(*R*)-(*tert*-Butyldimethylsilanyloxy)phenylmethyl]-2, 2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 7

To a stirred solution of the alcohol **6** (24.0 g, 78 mmol, 1.0 equiv) in anhydrous dichloromethane (240 mL) was added 2,4-dimethylaminopyridine (0.952 g, 7.8 mmol, 0.1 equiv) and diisopropylethylamine (16.3 mL, 93.6 mmol, 1.2 equiv) followed by TBDMS-triflate (17.9 mL, 78 mmol, 1.0 equiv) dropwise over 25 min at room temperature. The reaction mixture was stirred for 1 h at ambient temperature and then diluted with dichloromethane (500 mL). The reaction mass was successively washed with water (150 mL), a saturated solution of aqueous sodium bicarbonate (2 × 150 mL) and the organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using 10% ethyl acetate in hexanes as an eluent to afford the pure product **7** (27.0 g, 82%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) (two rotamers): δ 7.26 (m, 5H, –C$_6$*H*$_5$), 5.24 (d, *J* = 5.7 Hz, 0.5 H, PhC*H*O–), 5.11 (d, *J* = 4.7 Hz, 0.5 H, PhC*H*O–), 4.28 (dd, *J* = 9.7 Hz, *J* = 17.9 1H, –CH_2O–), 4.17 (m, 0.5 H, –C*H*N–), 4.04 (m, 0.5 H, –C*H*N–), 3.88 (quasi t, *J* = 8.2 Hz, 1H, –CH_2O–), 1.57 [s, 4.5H, –OC(CH_3)$_3$], 1.50 [s, 4.5H, –OC(CH_3)$_3$], 1.33 [s, 1.5H, C(CH_3)$_2$], 1.31 [s, 1.5H, C(CH_3)$_2$], 0.88 [s, 9H, –SiC(CH_3)$_3$], 0.76 [s, 1.5 H, C(CH_3)$_2$], 0.71 [s, 1.5 H, C(CH_3)$_2$], 0.065 [s, 1.5 H, –Si(CH_3)$_2$], 0.038 [s, 1.5 H, –Si(CH_3)$_2$], −0.084 [s, 1.5 H, –Si(CH_3)$_2$], −0.10 [s, 1.5 H, –Si(CH_3)$_2$]. ^{1}H NMR at 80 °C (DMSO-d_6, 400 MHz): δ 7.32–7.24 (m, 5H, –C$_6$*H*$_5$), 5.15 (d, *J* = 4.4 Hz, 1H, PhC*H*O–), 4.14–4.07 (m, 2H, –HC*H*O– and –C*H*N–), 3.89 (dd, *J* = 9.3, 6.9 Hz, 1H, –*H*CHO–), 1.51 [s, 9H, –OC(CH_3)$_3$], 1.29 [s, 3H, C(CH_3)$_2$], 0.87 [s, 9H, –SiC(CH_3)$_3$], 0.75 [s, 3H, C(CH_3)$_2$], 0.05 [s, 3H, –Si(CH_3)$_2$], 0.07 [s, 3H, –Si(CH_3)$_2$]. ^{13}C NMR ($CDCl_3$, 100 MHz) (two rotamers): δ 152.7 (0.5C, –O*C*=O), 152.1 (0.5C, –O*C*=O), 140.9 (0.5*C* of Ph), 140.4 (0.5*C* of Ph), 127.6 (*C*H of Ph), 127.5 (*C*H of Ph), 127.3 (*C*H of Ph), 127.2 (*C*H of Ph), 94.7/94.1 [*C*(CH$_3$)$_2$], 79.9 [-O*C*(CH$_3$)$_3$], 72.1/71.6 (PhCHO–), 62.6/62.5 (CH$_2$O), 62.1/61.9 (–*C*HN), 28.7/28.4 [-OC(*C*H$_3$)$_3$], 25.7 [SiC(*C*H$_3$)$_3$], 25.2/24.5 [CH$_3$C*C*H$_3$], 24.4/23.0 [CH$_3$C*C*H$_3$], 18.0 [Si*C*(CH$_3$)$_3$], −4.7/−4.8/−4.9 [Si(CH$_3$)$_2$]. LC–MS (ESI) *m/z*: 422.0 (MH^+). HPLC analysis: (chiralcel OD-RH, 10 mM ammonium bicarbonate/acetonitrile (35:65), 1.0 mL/min, 215 nm, t_R (major) 9.48; t_R (minor) 10.74 min); 93.8% ee. $[\alpha]_D^{25} = +62.2$ (*c* 1.01,

$CHCl_3$). HRMS (ESI): calcd for $C_{23}H_{39}NO_4SiNa$, 444.2546, *m/z* $[M+Na]^+$; found 444.2546.

4.4. [(1*R*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxymethyl-2-phenyl-ethyl]-carbamic acid tert-butyl ester 8

To a solution of the dimethyloxazolidine derivative **7** (7.0 g, 16.6 mmol, 1.0 equiv) in methanol (133 mL, 8 mL/mmol) was added PPTS (0.625 g, 2.5 mmol, 0.15 equiv) and the mass was stirred at 80 °C for 16 h. The reaction mixture was then concentrated under vacuum and diluted with ethyl acetate (300 mL). The ethyl acetate layer was washed with water (50 mL), brine, dried over sodium sulphate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography using 25% ethyl acetate in hexanes as eluent to provide the pure compound **8** (3.9 g, 62%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.25 (m, 5H, –C_6H_5), 4.89 (d, *J* = 3.3 Hz, 1H, PhC*H*O–), 3.73 (m, 1H, –NC*H*–), 3.69–3.60 (m, 2H, –CH_2O–), 2.37 (br s, 1H, O*H*), 1.35 [s, 9H, –OC(CH_3)$_3$], 0.89 [s, 9H, –SiC(CH_3)$_3$], 0.05 [s, 3H, –SiC(CH_3)$_2$], −0.17 [s, 3H, –SiC(CH_3)$_2$]. ^{13}C NMR ($CDCl_3$, 100 MHz); δ 156.1 (–O*C*=O), 141.5 (*C* of Ph), 128.1(2*C*H of Ph), 127.5 (*C*H of Ph) 126.3 (2*C*H of Ph), 79.5 [-O*C*(CH_3)$_3$], 73.6 (PhCHO), 63.0 (–CH_2O), 58.4 (*C*HN), 28.2 [3*C*H$_3$ of –OC(CH_3)$_3$], 25.78 [3*C*H$_3$ of –SiC(CH_3)$_3$], 18.1 [-Si*C*(CH_3)$_3$], −4.6 [-SiC(CH_3)$_2$], −5.2 [-SiC(CH_3)$_2$]. LC–MS (ESI) *m/z*: 382.4 (MH^+). HPLC analysis: (chiralpak-AD-H, *n*-hexane containing 0.05% TFA/*i*-PrOH (98:2), 1.0 mL/min, 210 nm, t_R (major) 5.96 min, t_R (minor) 6.82 min) 93.7% ee. $[\alpha]_D^{25} = -31.3$ (*c* 1.0, $CHCl_3$). HRMS (ESI): cald for $C_{20}H_{35}NOSiNa$, 404.2233 *m/z* $[M+Na]^+$; found 404.2233.

4.5. [(*R*)-1-[(*R*)-(*tert*-Butyldimethylsilanyloxy)-phenylmethyl]-3-(3,4-dimethoxyphenyl)-allyl]-carbamic acid *tert*-butyl ester 9

To a solution of oxalylchloride (2.9 mL, 33.4 mmol, 1.3 equiv) in anhydrous dichloromethane (34 mL) at −60 °C was added dimethylsulfoxide (4.7 mL, 66.8 mmol, 2.6 equiv) dropwise over 15 min and stirred for 30 min. A solution of the alcohol **8** (9.8 g, 25.7 mmol, 1.0 equiv) in anhydrous DCM (26 mL) was added dropwise over 15 min and stirred at −60 °C for 1 h. Diisopropylethylamine (13.4 mL, 77.1 mmol, 3.0 equiv) was added dropwise at the same temperature. After 20 min, the reaction mixture was brought to 0–5 °C and, 1 M aqueous hydrochloric acid solution was added until the pH reached 3–4. It was finally extracted with DCM (3 × 150 mL) and the combined organic parts were washed with 1 M aqueous hydrochloric acid solution (50 mL), water (25 mL), aqueous 5% sodium carbonate solution (3 × 25 mL) and then with brine. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide the aldehyde which was used immediately in the subsequent step.

To a slurry of the 3,4-dimethoxybenzyl phosphonium salt (44.6 g, 90.4 mmol, 2.4 equiv) in anhydrous tetrahydrofuran (110 mL, 3 mL/mmol) at −15 °C was added *n*-BuLi (1.8 M; 49.2 mL, 88.6 mmol, 2.3 equiv) dropwise over 15 min. After 15 min of stirring at the same temperature, the reaction mixture was cooled to −60 °C followed by the slow addition of a solution of the aldehyde (14.3 g, 37.6 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (180 mL, 2 mL/mmol) over 45 min. The reaction mixture was then warmed to −15 °C and stirred for 1 h. The reaction mass was allowed to warm to −5 °C and a saturated aqueous ammonium chloride solution (250 ml) was added cautiously. It was then filtered through a Celite bed and extracted with ethyl acetate (3 × 500 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes as eluent to provide a colourless liquid of pure compound **9** as a mixture of *E*/*Z* isomers (17.8 g, 67.6%). ^{1}H NMR ($CDCl_3$, 400 MHz) (major *trans*-isomer): {Ar = 3,4-MeOC_6H_3) δ 7.3–7.2 (m, 5H, C_6H_5), 6.88 (s, 1H, 3,4-MeOC_6H_3) 6.87 (d, *J* = 8.3 Hz, 1H, , 3,4-MeOC_6H_3), 6.80 (d, *J* = 8.3 Hz, 1H, 3,4-MeOC_6H_3), 6.44 (d, *J* = 16.0 Hz, 1H, ArC*H*=), 6.08 (dd, *J* = 16.0, 6.1 Hz, 1H, ACH=C*H*–), 4.90–4.78 (br s, 1H, N*H*), 4.82 (s, 1H, PhC*H*O), 4.43 (br s, 1H, C*H*N), 3.87 [s, 6H, Ar(OCH_3)$_2$], 1.32 [s, 9H, –C(CH_3)$_3$], 0.89 [s, 9H, –SiC(CH_3)$_3$], −0.01 [s, 3H, SiC(CH_3)$_2$], −0.13 [s, 3H, SiC(CH_3)$_2$]. ^{13}C NMR ($CDCl_3$,100 MHz) (major *trans*-isomer): δ 155.2 (–O*C*=O), 148.8 (MeO*C* of Ar), 148.5 ((MeO*C* of Ar), 141.4 (*C*, Ph), 130.4 (*C*, Ar), 130.0 (ACH=), 127.9 (*C*H, Ph), 127.8 (=*C*H), 127.3 (*C*H, Ph), 126.4 (*C*H, Ph), 119.3 (*C*H, Ar), 111.0 (*C*H, Ar), 108.7 (*C*H, Ar), 79.2 [O*C*(CH_3)$_3$], 76.7 (PhCHO), 55.9 (*C*HN), 55.8 (OCH_3), 55.6 (OCH_3), 28.2 [3*C*H$_3$ of –OC(CH_3)$_3$], 25.7 [3*C*H$_3$ of –SiC(CH_3)$_3$], 18.1 [-Si*C*(CH_3)$_3$], −5.0 [-SiC(CH_3)$_2$], −5.1 [-SiC(CH_3)$_2$]. LC–MS (ESI) *m/z*: 514.2 (MH^+). HPLC analysis: (chiralpak AD-H, *n*-hexane containing 0.1% diethyl amine/*i*-PrOH (98:2), 0.8 mL/min, 260 nm, t_R (major) 11.48 and 4.79 min, t_R (minor) 13.99 and 6.41 min), 96.9% ee. HRMS (ESI): calcd for $C_{29}H_{43}NO_5SiNa$, 536.2808 *m/z* $[M+Na]^+$, found 536.2808.

4.6. [(*R*)-1-[(*R*)-(*tert*-Butyldimethylsilanyloxy)-phenylmethyl]-3-(3,4-dimethoxyphenyl)-propyl]-carbamic acid *tert*-butyl ester 10

To a solution of the alkene **9** (7.0 g, 15.2 mmol, 1.0 equiv) in a mixture of methanol and THF (1:1, 150 mL) was added 10% Pd–C catalyst (0.7 g, 10% *w*/*w*) and stirred at rt for 1.5 h under hydrogen (1 atm.; balloon pressure). The reaction mixture was then filtered through a Celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and purified by flash column chromatography using 20% ethyl acetate in hexanes to give the pure product **10** (6.5 g, 93%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): (Ar = 3,4-MeOC_6H_3) δ 7.27–7.2 (m, 5H, C_6H_5), 6.78 (d, *J* = 8.0 Hz, 1H, 3,4-MeOC_6H_3), 6.70 (d, *J* = 8.0 Hz, 1H, 3,4-MeOC_6H_3), 6.69 (s, 1H, 3,4-MeOC_6H_3), 4.72 (br s, 1H, N*H*), 4.54 (d, *J* = 9.6 Hz, 1H, PhC*H*O–), 3.84 [s, 6H, Ar(OCH_3)$_2$], 3.74 (m, 1H, –C*H*N), 2.66 (m, 1H, ArCH_2), 2.57 (m, 1H, ArCH_2), 1.88 (m, 1H, –CH_2–), 1.58 (m, 1H, –CH_2–), 1.36 [s, 9H, –C(CH_3)$_3$], 0.88 [s, 9H, –SiC(CH_3)$_3$], 0.02 [s, 3H, –Si(CH_3)$_2$], −0.16 [s, 3H, –Si(CH_3)$_2$]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4 (–O*C*=O), 148.7 (MeO*C* of Ar), 147.0 (MeO*C* of Ar), 141.7 (*C*, Ph), 134.5 (*C*, Ar), 127.8 (2*C*H, Ph), 127.1 (*C*H, Ph), 126.4 (2*C*H, Ph), 120.1 (*C*H, Ar), 111.8 (*C*H, Ar), 111.2 (*C*H, Ar), 78.8 [O*C*(CH_3)$_3$], 75.7 (PhC*H*O–), 56.2 (*C*HN), 55.9 (OCH_3), 55.8 (OCH_3), 33.7 (CH_2), 32.1(CH_2), 28.3 [3*C*H$_3$ of –OC(CH_3)$_3$], 25.8 [3*C*H$_3$ of –SiC(CH_3)$_3$], 18.1 [-Si*C*(CH_3)$_3$], −4.6 [-SiC(CH_3)$_2$], −5.1 [–SiC(CH_3)$_2$]. LC–MS (ESI) *m/z*: 515.8 (MH^+); 533.0 (M+NH_4^+). HPLC analysis: (chiralcel OJ-RH, acetonitrile/10 mM ammonium acetate (1:1), 1.0 mL/min, 202 nm, t_R (major) 20.19, t_R (minor) 17.84 min), 96.4%ee. $[\alpha]_D^{25} = -5.7$ (*c* 0.85, $CHCl_3$). HRMS (ESI): calcd for $C_{29}H_{45}NO_5SiNa$, 538.2964 *m/z* $[M+Na]^+$, found 538.2964.

4.7. [(*R*)-3-(3,4-Dimethoxyphenyl)-1-(*R*)-hydroxyphenylmethyl)-propyl]-carbamic acid *tert*-butyl ester 3

To a solution of the TBDMS protected alcohol **10** (14.0 g, 27.1 mmol, 1.0 equiv) in anhydrous THF (135 mL) at 0–5 °C was added TBAF in THF (1 M; 81.5 mL, 81.5 mmol, 3.0 equiv) dropwise over 15 min. The reaction mixture was then allowed to warm to ambient temperature and stirred for 1 h. It was then concentrated under reduced pressure and purified by flash chromatography using 30% ethyl acetate in hexanes top provide the pure compound **3** (9.8 g, 90%) as a white solid. Mp 104–105 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): (Ar = 3,4-MeOC_6H_3) δ 7.33–7.25 (m, 5H. C_6H_5), 6.76 (d, *J* = 8.0 Hz, 1H, 3,4-MeOC_6H_3), 6.66 ((d, *J* = 8.0 Hz,

1H, 3,4-MeOC$_6H_3$), 6.64 (s, 1H, 3,4-MeOC$_6H_3$), 4.67 (d, J = 4.3 Hz, 1H, PhC*H*OH), 4.66 (s, 1H, N*H*), 3.83 (s, 6H, 3,4-Ar(OCH_3)$_2$), 3.73 (m, 1H, NC*H*), 2.92 (br s, 1H, O*H*), 2.66 (m, 1H, ArCH_2), 2.55 (m, 1H, ArCH_2), 1.85 (m, 1H, ArCH$_2$CH_2), 1.71 (m, 1H, ArCH$_2$CH_2), 1.38 [s, 9H, –C(CH_3)$_3$]. ^{13}C NMR (CDCl$_3$, 100 MHz): δ 156.4 (–O*C*=O), 148.7 (MeO*C*, Ar), 147.0 (MeO*C*, Ar), 141.6 (*C*, Ph), 134.1 (*C*, Ar), 128.1 (2*C*H, Ph), 127.5 (*C*H, Ph), 126.2 (2*C*H, Ph), 120.1 (*C*H, Ar), 111.6 (*C*H, Ar), 111.1 (*C*H, Ar), 79.4 [O*C*(CH$_3$)$_3$], 76.1 (PhCHO–), 56.1 (*C*HN), 55.8 (OCH$_3$), 55.6 (OCH$_3$), 33.4 (CH$_2$), 31.9 (CH$_2$), 28.2 [3CH$_3$ of –OC(*C*H$_3$)$_3$]. LC–MS (ESI): 402.2 (MH$^+$); 419.2 (M+NH$_4^+$). HPLC analysis: (chiralpak AD-H, *n*-hexane/i-PrOH (8:2), 1.0 mL/min, 220 nm, t_R (major) 13,99, t_R (minor) 8.85 min): 92.6% ee. $[\alpha]_D^{25} = -5.5$ (c 1.04, CHCl$_3$). HRMS (ESI): calcd for $C_{23}H_{31}NO_5Na$, 424.2100 m/z [M+Na]$^+$, found 424.2100.

4.8. (1*S*,2*R*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-naphthalen-2-ylamine 2

The protected amino alcohol **10** (3.1 g, 6.0 mmol) was heated with freshly distilled trifluoroaceticacid (15 mL) at 80 °C for 5 h and concentrated under reduced pressure. It was diluted with methanol (15 mL) and solid sodium bicarbonate powder was added under stirring until the effervescence ceased. It was concentrated and purified by filter column chromatography using 10% methanol in dichloromethane to provide aminotetralin **2** as a yellow sticky solid which was used immediately for the subsequent step. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31–7.13 (m, 5H, C$_6H_5$), 6.59 [s, 1H, 3,4-(MeO)$_2$C$_6H_3$], 6.15 [s, 1H, 3,4-(MeO)$_2$C$_6H_3$], 3.83 [s, 3H, Ar(OCH_3)$_2$], 3.69 (d, J = 8.1 Hz, 1H, PhC*H*Ar), 3.55 [s, 3H, Ar(OCH_3)$_2$], 3.16 (m, 1H, C*H*N), 2.99–2.91 (m, 1H, ArCH_2), 2.86–2.81 (m, 1H, ArCH_2), 2.02 (br m, 3H, 1H of CH_2 and NH_2), 1.72 (m, 1H, CH_2). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 147.3 (MeO*C*, Ar), 147.1 (MeO*C*, Ar), 144.2 (*C*, Ph), 130.0 (*C*, Ar), 129.3 (2*C*H, Ph), 128.4 (2*C*H, Ph), 128.3 (*C*, Ar), 126.6 (*C*H, Ph), 112.9 (*C*H, Ar), 110.8 (*C*H, Ar), 55.7 (2CH$_3$O), 55.0 (*C*H, ArCHPh or *C*HN), 54.4 (*C*H, C*H*N or ArCHPh), 30.2 (CH$_2$), 27.5 (*C*H$_2$). HPLC Analysis: (Chiralpak AD-H, *n*-hexane containing 0.1% Et$_2$NH/*i*-PrOH (8:2), 1.0 mL/min, 288 nm, t_R (major) 6.33 min, t_R (minor) 7.27 min), 94.6% ee. LC–MS (ESI) m/z: 284.2 (MH$^+$).

4.9. (1*S*,2*R*)-*N*-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-nitro-benzenesulfonamide 12

To a solution of aminotetralin **2** (1.05 g, 3.7 mmol, 1.0 equiv) in anhydrous DCM (20 mL) was added *p*-nitrobenzenesulphonyl chloride (0.862 g, 3.89 mmol, 1.05 equiv) and triethylamine (1.28 mL, 9.25 mmol, 2.5 equiv) at 0–5 °C. The reaction mass was allowed to attain room temperature and stirred for 3 h, concentrated under reduced pressure, diluted with water (20 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and evaporated under vacuum. The crude product was purified by flash chromatography using 30% ethyl acetate in hexanes. The yellow solid obtained was dissolved in methanol and kept at 0 °C for 12 h. It was filtered and the filtrate evaporated to obtain the enantiomerically pure *N*-nosylaminotetralin **12** (1.25 g, 44%) as a yellow solid. Mp 64–65 °C (Lit.[8a] Mp 63–64 °C). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.15 (d, J = 8.4 Hz, 2H, 4-NO$_2$C$_6H_4$SO$_2$–), 7.73 (d, J = 8.4 Hz, 2H, 4-NO$_2$C$_6H_4$SO$_2$–), 7.15–7.09 (m, 3H, C$_6H_5$), 6.83 (d, J = 7.2 Hz, 2H, C$_6H_5$), 6.59 [s, 1H, (MeO)$_2$C$_6H_2$], 6.07 [s, 1H, (MeO)$_2$C$_6H_2$], 4.75 (d, J = 7.6 Hz, 1H, N*H*), 3.84 (s, 3H, OCH_3), 3.81 (d, J = 7.1 Hz, 1H, ArC*H*Ph), 3.61 (m, 1H, C*H*N), 3.55 (s, 3H, OCH_3), 2.95–2.87 (m, 1H, ArCH_2), 2.84–2.75 (m, 1H, ArCH_2), 2.26–2.21 (m, 1H, CH_2), 1.77–1.70 (m, 1H, CH_2). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 149.6 (*C*, 4-NO$_2$C$_6$H$_4$SO$_2$), 147.9 [MeO*C*, (MeO)$_2$C$_6$H$_2$], 147.5 [MeO*C*, (MeO)$_2$C$_6$H$_2$], 146.0 (*C*, 4-NO$_2$C$_6$H$_4$SO$_2$), 142.8 (*C*, C$_6$H$_5$), 128.8 (2*C*H), 128.5 (2*C*H), 127.8 (2*C*H), 127.5 [*C*, (MeO)$_2$C$_6$H$_2$], 127.3 [*C*, (MeO)$_2$C$_6$H$_2$], 126.9 (*C*H, C$_6$H$_5$), 124.1 (2*C*H), 112.8 [*C*H, (MeO)$_2$C$_6$H$_2$], 110.7 [*C*H, (MeO)$_2$C$_6$H$_2$], 57.1 (*C*H, Ar*C*HPh or *C*HN), 55.8 (OCH$_3$), 55.7 (OCH$_3$), 51.5 (*C*H, *C*HN or Ar*C*HPh), 27.6 (CH$_2$), 26.1 (*C*H$_2$). LC–MS (ESI) m/z: 467.2 (MH$^+$). HPLC analysis: (chiralpak AD-H, *n*-hexane/*i*-PrOH (9:1), 1.0 mL/min, 220 nm, t_R (major) 25.47, t_R (minor) 33.41 min), 98.4% ee. $[\alpha]_D^{25} = -64.2$ (c 1.0, CHCl$_3$); Lit.[8a] $[\alpha]_D^{25} = -51.25$ (c 1.00, CHCl$_3$).

4.10. (1*S*,2*R*)-*N*-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-naphthalen-2-yl)-*N*-methoxymethyl-4-nitro-benzenesulfonamide 13

To a well stirred solution of **12** (5.3 g, 11.3 mmol, 1.0 equiv) in anhydrous THF (110 mL) at 0–5 °C was added sodium hydride (50% dispersion in mineral oil; 0.81 g, 16.9 mmol, 1.5 equiv) and the reaction mixture was stirred for 1 h min at 0–5 °C under a nitrogen atmosphere. Methoxymethylenechloride (MOMCl) (2.7 g, 33.9 mmol, 3.0 equiv) was added slowly to the reaction mixture and stirred for 0.5 h at the same temperature and then allowed to attain room temperature and stirred. After 2 h, the reaction was quenched by the addition of an aqueous solution of saturated ammonium chloride (50 mL). It was then extracted with ethyl acetate (3 × 150 mL) and the combined organic part was dried over anhydrous sodium sulphate and evaporated under vacuum. The crude product was purified by flash chromatography using 30% ethyl acetate in hexanes to provide the pure compound **13** (4.9 g, 85%) as a yellow solid. Mp 60–61 °C (Lit.[8b] Mp 56–57 °C). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.02 (d, J = 9.2 Hz, 2H, 4-NO$_2$C$_6H_4$SO$_2$–), 7.61 (d, J = 9.2 Hz, 2H, 4-NO$_2$C$_6H_4$SO$_2$–), 7.08–7.05 (m, 1H, C$_6H_5$), 6.99 (t, J = 7.2 Hz, 2H, C$_6H_5$), 6.88 (m, 2H, C$_6H_5$), 6.54 [s, 1H, (MeO)$_2$C$_6H_2$], 5.97 [s, 1H, (MeO)$_2$C$_6H_2$], 5.03 (d, J = 10.9 Hz, 1H, MeOCH_2N), 4.68 (d, J = 10.9 Hz, 1H, MeOCH_2N), 4.21 (d, J = 10.3 Hz, 1H, PhC*H*Ar), 4.09 (m, 1H, C*H*N), 3.82 (s, 3H, ArOCH_3), 3.47 (s, 3H, ArOCH_3), 3.34 (s, 3H, –CH$_2$OCH_3), 3.02–2.98 (m, 1H, ArCH_2), 2.84–2.78 (m, 1H, ArCH_2), 2.19–2.1 (m, 2H, CH_2). ^{13}C NMR (CDCl$_3$): δ 149.3 (*C*, 4-NO$_2$C$_6$H$_4$SO$_2$), 147.4 [MeO*C*, (MeO)$_2$C$_6$H$_2$], 147.2 [MeO*C*, (MeO)$_2$C$_6$H$_2$], 146.2 (*C*, 4-NO$_2$C$_6$H$_4$SO$_2$), 143.6 (*C*, C$_6$H$_5$), 130.2 [*C*, (MeO)$_2$C$_6$H$_2$] , 129.2 (2*C*H), 128.2 (2*C*H), 128.1 (2*C*H), 127.6 [*C*, (MeO)$_2$C$_6$H$_2$], 126.6 (*C*H), 123.7 (2*C*H), 112.8 [*C*H, (MeO)$_2$C$_6$H$_2$], 110.4 [*C*H, (MeO)$_2$C$_6$H$_2$], 76.9 (MeOCH$_2$N), 62.8 (*C*H, Ar*C*HPh or *C*HN), 55.7 (–OCH$_3$), 55.6 [2(–OCH$_3$)], 48.6 (*C*H, *C*HN or Ar*C*HPh), 30.1 (CH$_2$), 29.4 (*C*H$_2$). HPLC analysis: (chiralpak AD-H, *n*-hexane/*i*-PrOH (9:1), 1.0 mL/min, 210 nm, t_R (major) 23.71, t_R (minor) 26.17 min); 99.7% ee. $[\alpha]_D^{25} = -52.2$ (c 0.99, CHCl$_3$); {Lit.[8b] $[\alpha]_D^{28} = -36.0$ (c 1.00, CHCl$_3$)}. HRMS (ESI): calcd for $C_{26}H_{28}N_2O_7SNa$, 535.1515 m/z [M+Na]$^+$, found 535.1515.

4.11. (6a*R*,12b*S*)-10,11-Dimethoxy-6-(4-nitro-benzenesulfonyl)-5,6,6a,7,8,12a-hexahydrobenzo[*a*]-phenanthridine 14

To a well stirred solution of **13** (0.3 g, 0.585 mmol, 1.0 equiv) in dichloromethane (12 mL) at −50 °C was added TMS-triflate (0.27 mL, 1.46 mmol, 2.5 equiv) dropwise over 5 min. The reaction mixture was then slowly allowed to come to −10 °C over 4 h and an aqueous solution of saturated sodium bicarbonate (10 mL) was added. The reaction mass was extracted with DCM (3 × 40 mL) and the combined organic part was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography using 70% dicloromethane in hexanes (0.13 g, 46%) as a yellow solid. Mp 89–90 °C [Lit.[8b] Mp 88–89 °C].

^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.02 (d, J = 8.5 Hz, 2H, 4-NO$_2$C$_6H_4$-SO$_2$–), 7.7 (d, J = 8.5 Hz, 2H, 4-NO$_2$C$_6H_4$SO$_2$–), 7.27 (m, 1H, C$_6H_4$), 7.1 (t, J = 7.5 Hz, 1H, C$_6H_4$), 6.91 (t, J = 7.5 Hz, 1H, C$_6H_4$), 6.85 [s, 1H, (MeO)$_2$C$_6H_2$], 6.76 (d, J = 7.4 Hz, 1H, C$_6H_4$), 6.69 [s, 1H,

$(MeO)_2C_6H_2$], 4.68 (d, J = 16.0 Hz, 1H, PhCH_2N), 4.53 (d, J = 16.0 Hz, 1H, PhCH_2N), 4.12 (d, J = 11.6 Hz, 1H, ArCHPh), 3.89 (s, 3H, ArOCH_3), 3.78 (s, 3H, ArOCH_3), 3.17 (quasi t, J = 11.5 Hz, 1H, CHN), 3.02 (t, J = 14.0 Hz, 1H, CH_2), 2.89–2.8 (m, 2H, CH_2), 2.09–2.0 (m, 1H, CH_2). ^{13}C NMR ($CDCl_3$,100 MHz): δ 149.6 (*C*), 147.9 (*C*) 146.8 (*C*), 143.9 (*C*), 138.5 (*C*), 135.0 (*C*), 129.6 (*C*), 128.6 (2*C*H, 4-$NO_2C_6H_4SO_2$–), 127.7 (*C*H, C_6H_4), 126.1 (*C*H, C_6H_4), 125.7 (*C*H, C_6H_4), 123.9 (*C*), 123.76 (*C*H, C_6H_4) , 123.70 (2*C*H, 4-$NO_2C_6H_4SO_2$–), 112.4 [*C*H, $(MeO)_2C_6H_2$], 111.9 [*C*H, $(MeO)_2C_6H_2$], 61.5 (*C*H, Ar*C*HPh or *C*HN), 56.0 (–OCH_3), 55.8 (–OCH_3), 47.6 (PhCH_2N), 43.8 (*C*H, *C*HN or Ar*C*HPh), 31.2 (CH_2), 29.4 (*C*H_2). LC–MS (ESI) *m/z*: 481.2 (MH^+). HPLC analysis: (chiralpak AD-H, 80% *n*-hexane containing 0.1% diethyl amine/EtOH (8:2), 1.0 mL/min, 234 nm, t_R (major) 15.37, t_R (minor) 19.19 min); ee >99%. $[\alpha]_D^{25} = +38.8$ (*c* 0.37, $CHCl_3$) [Lit.[8a] $[\alpha]_D^{28} = +30.2$ (*c* 1.00, $CHCl_3$)]. HRMS (ESI): calcd for $C_{25}H_{24}N_2O_6Sna$, 503.1252 *m/z* [M+Na]$^+$, found 503.1253.

4.12. (6a*R*,12b*S*)-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine 15

To a well stirred solution of **14** (1.0 g, 2.08 mmol, 1.0 equiv) in 20 mL of CH_3CN/DMSO (49:1) at rt, were added 4-methoxythiophenol (0.58 g, 4.16 mmol, 2.0 equiv) and K_2CO_3 (0.86 g, 6.24 mmol, 3.0 equiv). The reaction mixture was then allowed to stir for 3 h. The solvent was concentrated under reduced pressure and the crude reaction mass was subjected to flash column purification using 0–10% MeOH in DCM as an eluent to obtain **15** (0.6 g, 98%) as a pale yellow sold. The solid was converted into its hydrochloride salt using an ethanolic solution of HCl, which was triturated with ethyl acetate to obtain the greenish-white solid **15·HCl** (0.65 g, 94%). Mp >200 °C [Lit.[7b] Mp >236 (dec)]. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.27 (br s, 1H, N*H*), 10.05 (br s, 1H, N*H*), 7.42–7.31 (m, 4H, C_6H_4), 6.88 [s, 1H, $(MeO)_2C_6H_2$], 6.85 [s, 1H, $(MeO)_2C_6H_2$], 4.37 (s, 2H, PhCH_2N), 4.28 (d, J = 10.9 Hz, 1H, ArCHPh), 3.76 (s, 3H, ArOCH_3), 3.7 (s, 3H, ArOCH_3), 2.94 (m, 1H, CHN), 2.90–2.72 (m, 2H, ArCH_2), 2.24–2.19 (m, 1H, CH_2), 2.05–1.95 (m, 1H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 147.5 [MeO*C*, $(MeO)_2C_6H_2$], 146.5 [MeO*C*, $(MeO)_2C_6H_2$], 137.3 (*C*), 130.4(*C*), 129.4 (*C*), 127.7 (*C*H, C_6H_4) 127.5 (*C*H, C_6H_4), 126.7 (*C*H, C_6H_4), 125.0 (*C*H, C_6H_4), 124.7 (*C*), 112.5 [*C*H, $(MeO)_2C_6H_2$], 111.9 [*C*H, $(MeO)_2C_6H_2$], 56.5 (*C*H, Ar*C*HPh or *C*HN), 55.5 (–OCH_3), 55.4 (–OCH_3), 43.3 (CH_2N), 40.5 (*C*H, *C*HN or Ar*C*HPh), 26.9 (CH_2), 25.1 (CH_2). LC–MS (ESI) *m/z*: 296.2 (MH^+). HPLC analysis: (chiralcel OD-H, *n*-hexane containing 0.1% diethyl amine/EtOH (9:1), 1.0 mL/min, 234 nm, t_R (major) 8.84, t_R (minor) 9.95 min; ee >99%. $[\alpha]_D^{25} = +110.0$ (*c* 0.15, EtOH) {Lit.[7b] $[\alpha]_D^{25} = +123.0$ (*c* 0.3, EtOH); Lit.[1d] $[\alpha]_D^{25} = +106.0$ (*c* 0.75, EtOH)}.

4.13. (6a*R*,1b*S*)-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenan-thridine hydrobromide 1·HBr (dihydrexidine hydrobromide)

To a solution of compound **15** (0.04 g, 0.135 mmol, 1.0 equiv) in DCM (6 mL) was added BBr_3 solution in DCM (1.0 M; 0.67 mL, 0.675 mmol, 5.0 equiv) over 10 min at 0 °C, and the mixture was stirred at rt. After 12 h, the mixture was quenched with MeOH (6.0 mL), stirred for 0.5 h, and then concentrated under reduced pressure to obtain a brown solid. This was triturated with ether to obtain dihydrexidine hydrobromide **1·HBr** (0.047 g) as a light brown solid in quantitative yield. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.52 (d, J = 8.0 Hz, 1H, C_6H_4), 7.44–7.36 (m, 3H, C_6H_4), 6.80 [s, 1H, $(MeO)_2C_6H_2$], 6.67 [s, 1H, $(MeO)_2C_6H_2$], 4.45 (s, 2H, PhCH_2N), 4.21 (d, J = 11.2 Hz, 1H, ArCHPh), 3.06–3.02 (dt, J = 11.2, 6.0 Hz, 1H, CHN), 2.95–2.86 (m, 1H, ArCH_2), 2.84–2.65 (m, 1H, ArCH_2), 2.35–2.25 (m, 1H, CH_2), 2.0–1.94 (m, 1H, CH_2). ^{13}C NMR (CD_3OD, 100 MHz): δ 144.6 [HO*C*, $(HO)_2C_6H_2$], 143.7 [HO*C*, $(HO)_2C_6H_2$], 136.5 (*C*), 129.9 (*C*), 128.6 (*C*), 128.4 (*C*H, C_6H_4), 127.9 (*C*H, C_6H_4), 127.5 (*C*H, C_6H_4), 127.1 (*C*H, C_6H_4), 125.0 (*C*), 115.8 [*C*H, $(HO)_2C_6H_2$], 114.5 [*C*H, $(HO)_2C_6H_2$], 58.3 (*C*H, ArCHPh or *C*HN), 45.2 (CH_2), 41.3 (*C*H, *C*HN or Ar*C*HPh), 26.8 (CH_2), 26.0 (*C*H_2). $[\alpha]_D^{25} = +59$ (*c* 0.21, EtOH).

4.14. (6a*R*,1b*S*)-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenan-thridine hydrochloride 1·HCl (dihydrexidine hydrochloride)

The residue was dissolved in water (2 mL), and the pH was adjusted to 9–10 with aqueous $NaHCO_3$ under an N_2 atmosphere. It was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers were dried over sodium sulphate and concentrated to give a crude solid. This was purified by flash column chromatography using 15% MeOH in ethyl acetate. A solution of the powder in EtOH (1 mL) and EtOH–HCl (3 mL) was stirred at rt for 0.5 h and then concentrated to obtain a light yellow powder (0.029 g, 70.7%). Mp >120 °C (dec) [Lit.[7b] Mp >122 °C (dec)]. ^{1}H NMR (CD_3OD, 200 MHz): δ 7.49–7.34 (m, 4H, C_6H_4), 6.76 [s, 1H, $(MeO)_2C_6H_2$], 6.62 [s, 1H, $(MeO)_2C_6H_2$], 4.40 (s, 2H, PhCH_2N), 4.16 (d, J = 11.0 Hz, 1H, ArCHPh), 3.03 (dt, J = 11.2, 6.0 Hz, 1H, CHN), 2.95–2.86 (m, 1H, ArCH_2), 2.84–2.65 (m, 1H, ArCH_2), 2.35–2.25 (m, 1H, CH_2), 2.0–1.94 (m, 1H, CH_2). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.86 (s, 1H, N*H*/O*H*), 9.58 (s, 1H, N*H*/O*H*), 8.87 (s, 1H, O*H*/N*H*), 8.85 (s, 1H, O*H*/N*H*), 7.45–7.30 (m, 4H, C_6H_4), 6.71 [s, 1H, $(MeO)_2C_6H_2$], 6.62 [s, 1H, $(MeO)_2C_6H_2$], 4.36 (s, 2H, PhCH_2N), 4.14 (d, J = 11.0 Hz, 1H, ArCHPh), 2.93 (m. 1H, CHN), 2.79–2.68 (m, 2H, ArCH_2), 2.17 (m, 1H, CH_2), 1.92 (m, 1H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.9 [HO*C*, $(HO)_2C_6H_2$], 143.0 [HO*C*, $(HO)_2C_6H_2$], 136.0 (*C*), 130.3 (*C*), 127.7 (*C*H, C_6H_4), 127.6 (C), 127.4 (*C*H, C_6H_4), 126.7(*C*H, C_6H_4), 126.3 (*C*H, C_6H_4), 115.8 [*C*H, $(HO)_2C_6H_2$], 114.3[*C*H, $(HO)_2C_6H_2$], 56.5 (*C*H, Ar*C*HPh or *C*HN), 43.9 (CH_2), 40.2 (*C*H, *C*HN or Ar*C*HPh), 26.1 (CH_2), 25.1 (CH_2). LC–MS (ESI) *m/z*: 268.2 (MH^+). HPLC analysis: (chiralpak AD-H (4.6 × 250 mm) 5μ, *n*-hexane containing 0.1% diethylamine)/EtOH, 1.0 mL/min, 288 nm, t_R (major) 7.06); ee >99.9%. $[\alpha]_D^{26} = +85$ (*c* 0.25, EtOH); {Lit.[1d] $[\alpha]_D^{25} = +83$ (*c* 0.25, EtOH); Lit.[7b] $[\alpha]_D^{25} = +85.5$ (*c* 0.24, EtOH)}.

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