Stereoselective Synthesis of Aporphine Alkaloids Using a Hypervalent Iodine(III) Reagent-Promoted Oxidative Nonphenolic Biaryl Coupling Reaction. Total Synthesis of (*S*)-(+)-Glaucine

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Abstract: The aporphine alkaloid (+)-glaucine (**8a**) and two other analogues **8b**,**c** have been synthesized in good yield and high ee from the appropriate 1,2-diarylethylamine derivatives, which were in turn prepared using (*S*)-(+)-phenylglycinol as chiral support. Next, a sequence of simple transformations: N-alkylation with bromoacetaldehyde diethyl acetal, N-methylation, Pommeranz–Fritsch cyclization, and ionic hydrogenation led to the key intermediate, optically active, 1-benzyltetrahydroisoquinolines **7a**–**c**. The final C-ring closure step was performed by C–C biaryl bond formation by an hypervalent iodine(III) reagent promoted oxidative coupling, affording the target heterocycles **8a**–**c** in good yields and with no racemization at the formerly created stereogenic center.

Key words: alkaloids, amino alcohols, asymmetric synthesis, chiral auxiliaries, iodine

Aporphines are a small group of alkaloids characterized by the tetracyclic skeleton shown in Figure 1, in which relevant features are the presence of an isoquinoline core, together with a biaryl subunit, and one stereogenic center at C-6a. Interest in natural and non-natural aporphines arises from the diverse array of biological properties displayed.[1] In fact, plant sources of aporphines have been used for many years in the treatment of asthma, whooping cough, and different types of tumors like pharynx tumor and uterine bleeding.[2] Relevant examples include (+)-boldine and its non-phenolic dimethyl ether (+)-glaucine, which display antioxidative and cytoprotective properties[3] and act as dopamine antagonist in vivo.[4](+)-Isoteoline has shown antagonist activity at 5-HT_{2c} serotonergic receptors;[5] nantenine derivatives cause an inhibitory effect on the α-adrenoceptors in the rat aorta;[6] apomorphine, a non-natural aporphine, acts as a dopaminergic agent in the central nervous system dysfuntions,[7] and several others have potential uses in cancer treatment.[8] Interestingly, some of the above mentioned activities are structurally related to the presence of the biphenyl system, the nature of the substituent at C-2 and a benzylic hydrogen neighboring a nitrogen lone electron pair,[9] but more detailed studies on structure-activity relationships have also shown that the configuration of the C-6a stereogenic center is of essential importance for the dopaminergic action.[10] With all these circumtances in mind, the development of new and efficient synthetic procedures for the preparation of these alkaloids in a stereocontrolled way turns out to be a challenging field for the synthetic organic chemist.

The strategies that have been commonly employed for the synthesis of aporphines can be classified according to the last ring built up during the synthesis (Figure 1). In this context, reports have appeared in which the B ring is the last one to be assembled by some kind of heterocyclization process,[11] but the most frequently employed strategy relies upon formation of the C ring at the final stage of the synthetic route by connecting both aromatic A and D rings via biaryl C–C bond formation. These routes utilize an appropriately functionalized 1-benzylisoquinoline as the penultimate intermediate.

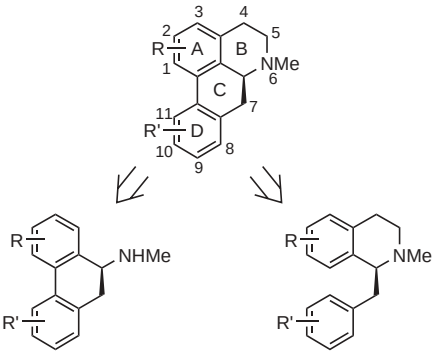

Figure 1 The aporphine skeleton with the adopted numbering scheme and the commonly employed retrosynthetic approaches to it.

Related to the last topic mentioned, some syntheses of aporphines have appeared in which this biaryl C–C bond formation has been attained either by cyclization of aminophenols,[12] by benzyne-mediated cyclization,[13]or by radical- or lead tetraacetate-mediated coupling of 1-benzylisoquinolines bearing a bromo subtituent at the appropriate position of one of the two aromatic rings to be coupled.[14,15] However, these methodologies suffer from many drawbacks, such as large amounts of side-products often isolated together with the desired tetracycles. Another frequently employed method in this context is the oxidative biaryl phenolic or non-phenolic coupling. Among these two approaches, the former suffers from the limitation that a 1-benzylisoquinoline bearing one hy-

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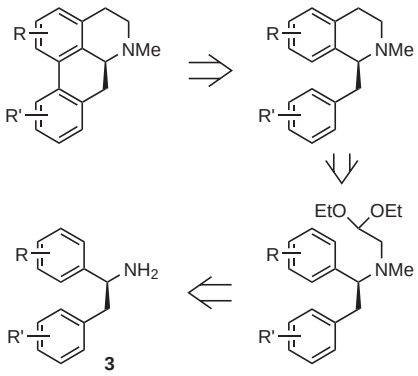
droxy group at C-6 is required while in the later a hydroxyl group is necessary at either the C-3′ or C-4′ position of the starting material. As a consequence, the non-phenolic coupling normally affords better yields of the desired product.[16] Finally, another strategy which has to be mentioned is the direct preparation of aporphines by acid-promoted rearrangement of morphinanes,[10a,17] however this methodology requires the previous preparation of synthetically more complex precursors.

As already mentioned, the stereochemistry at C-6a has a major influence on the biological activity presented by most of the aporphines described. Surprisingly, only a few reports have succeeded in establishing general stereoselective methods for the preparation of these alkaloids. In this sense, Comins et al. have reported the synthesis of (+)-glaucine in which the key synthetic intermediate, a chiral non-racemic *N*-acyl-1-(2′-bromobenzyl)tetrahydroisoquinoline was prepared by means of a diastereoselective Pictet–Spengler reaction using cyclohexyl-based chiral auxiliaries.[18] Unfortunately the final radical-mediated biaryl bond formation step gave a very low yield of the desired product. Alternatively, the enantioselective synthesis of ()-glaucine has been reported in which the preparation of enantioenriched 1-benzylisoquinolines via Bischler–Napieralski cyclization/reduction of phenethylamides derived from a modified form of L-(+)-ascorbic acid or D-()-tartaric acid was implicated.[19] The final transformation into the aporphine alkaloid was achieved using chromium(III) oxide or thallium trifluoroacetate. However, either low yields or separation of diastereomeric mixtures at intermediate steps of the synthesis was often required.

The well-known chiral formamidine method established by Meyers, has been used by himself as a tool for reaching a great number of chiral non-racemic isoquinoline alkaloids, including some natural aporphines, in high enantiomeric excess. Application of this methodology allowed the authors to prepare the required 1-benzyltetrahydroisoquinolines which were transformed into the final compounds by C-C biaryl bond formation using a non-phenolic metal-mediated oxidative coupling, thus obtaining (+)-glaucine and (+)-ocoteine with optical purities of 87% and 93%, respectively, although in moderate yields (40–50%).[20] Finally, another conceptually different approach for the stereocontrolled preparation of these tetracycles has been reported by Hara et al. in which a lead tetraacetate-mediated oxidation of racemic 1-benzyltetrahydroisoquinolines in the presence of a chiral acid was performed.[21] The oxidation process furnished a diastereomeric mixture of two *p*-quinol acylates in a nearly 1:1 ratio, which had to be separated, each of them being further applied to the synthesis of the corresponding aporphines enantiomer. Finally, it has to be mentioned that an enzymatic lipase-catalyzed resolution of the acetates of racemic phenolic aporphines has also been described,[22] although the final compounds were obtained in moderate chemical and optical yields.

With all these circumstances in mind, and continuing our ongoing interest in the development of general routes for the asymmetric synthesis of isoquinoline alkaloids,[23] we wish to present herein a highly effective and general approach for the asymmetric synthesis of aporphines. In this context, we decided to explore the possibilities of enantiopure 1,2-diarylethylamines of type **3** as useful chiral starting materials for the preparation of conveniently functionalized 1-benzyltetrahydrosoquinolines, which afterwards would afford the desired heterocycles after final build-up of the C ring by connecting the A and D rings. Consequently, according to the retrosynthetic analysis depicted in Scheme 1, N-alkylation of 1,2-diarylethylamines **3** with bromoacetaldehyde diethylacetal (BADA), followed by Pommeranz–Fritsch cyclization should afford the corresponding 1-benzyltetrahydroisoquinolin-4-ols, which, after removal of the 4-OH substituent should provide the key 1-benzyltetrahydroisoquinolines, ready for the last C–C biaryl coupling step. At this point, as we have previously shown that the existent methodologies normally afford poor results, we have explored new ways for performing this coupling, which includes the use of recently developed hypervalent iodine(III) reagents.[24]



Scheme 1

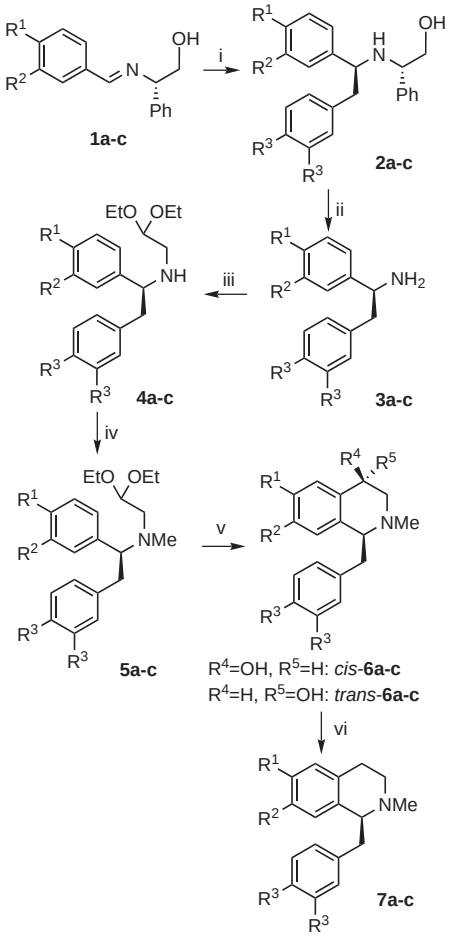
The synthesis of the chiral starting compounds, the 1,2-diarylethylamines **3a**–**c**, was performed under conditions previously reported by our group,[23g] using the reaction between freshly prepared Grignard benzylic reagents and imines **1a**–**c**, followed by removal of the chiral appendage by catalytic hydrogenation. In this way, chiral non-racemic amines **3a**–**c** were obtained as highly enantioenriched materials (>92% ee by chiral HPLC analysis under conditions optimized for a racemic standard). Next, we proceeded to perform a sequential N-alkylation reaction with bromoacetaldehyde diethylacetal (BADA) and subsequent N-methylation under standard conditions (HCHO, $NaBH_3CN$), thus obtaining the tertiary amines **5a**–**c** in good yields. At this point, it has to be mentioned that when we inverted the order of introduction of the alkyl chains at the nitrogen atom of the amines **3a**–**c**, that is, when we carried out the N-methylation step first, we observed a significant decrease in the obtained yields. In addition, considerably longer reaction times were needed in

the reaction in which the acetaldehyde chain was introduced.

Continuing with the synthesis, we focused on the formation of the future B ring of the final aporphines, which was planned to be accomplished via standard Pommeranz–Fritsch cyclization. Indeed, 1-benzyltetrahydroisoquinolin-4-ols **6a**–**c** were cleanly obtained when amines **5a**–**c** were stirred in HCl–acetone. These isoquinolinols were obtained as a 1:1 mixture of epimers, which could be separated by flash column chromatography in the case of **6a**, and were therefore completely characterized as pure isomers. Anyway, the fact that the stereocenter at the 4-position of the isoquinoline core had to be removed in the next step, made this separation unnecessary and the derivatives *cis*- and *trans*-**6a**–**c** were used in the next step as a mixture of epimers.

Next, we proceeded to carry out the reduction of these isoquinolinols **6a**–**c** to the key 1-benzyltetrahydroisoquinolines **7a**–**c**. In this context, the so-called ionic hydrogenation reaction[25] is a widely employed reductive transformation that allows the deoxygenation of alcohols that can form stable carbocations (e.g. benzylic alcohols), which are then transformed into the corresponding alkanes, as happens in our case. Among the different reported carboxylic acid/$NaBH_4$ combination of reagents developed for this reaction,[26] we choose TFA as the proton source, due to its high ionizing power together with its low nucleophilic character. In fact, we have previously applied this methodology for the reduction of other structurally related 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols with excellent results.[23a] Consequently, compounds **6a**–**c** were treated with a solution of $NaBH_4$ in TFA, affording, after 2–3 hours, the reduced heterocycles **7a**–**c** in excellent yields after flash column chromatography purification (Scheme 2). Remarkably, chiral HPLC analysis of the crude reaction mixture indicated that the reaction proceeded with no racemization, at the remaining stereogenic center at the 1-position, thus, 1-benzyl-1,2,3,4-tetrahydroisoquinolines **7a**–**c** were obtained as almost enantiomerically pure compounds (see Table 1).

Once the key 1-benzyltetrahydroisoquinolines were prepared, we turned our attention to the final C–C biaryl coupling that should build up the tetracyclic skeleton and



Scheme 2 Reagents and conditions (i) $ArCH_2MgCl$, THF, 40 °C. (ii) H_2, Pd/C, HCl, MeOH, r.t. (iii) BADA, K_2CO_3, MeCN, reflux. (iv) $HCHO_{aq.}$, $NaBH_3CN$, MeCN, r.t. (v) concd HCl/acetone 1:1, r.t. (vi) $NaBH_4$, TFA, CH_2Cl_2, r.t.

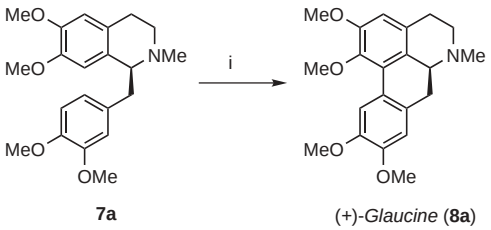
therefore should allow us to complete the synthesis of the desired aporphines. As previously mentioned, among the methods reported for this transformation,[27] one of the most promising is the non-phenolic oxidative coupling between both aromatic rings. In this context, most of the methodologies reported in the literature involve the use of transition metal trifluoroacetates as oxidants,[28] which are very often prepared in situ by treatment of the correspond-

Table 1 Yields and Stereoselectivities Obtained in the Asymmetric Synthesis of the 1-Benzyltetrahydroisoquinolines **7a**–**c**

R^1	R^2	R^3	Prod	Yield (%)[a]	Prod	Yield (%)[a]	ee (%)[b]	Prod	Yield (%)[a]	Prod	Yield (%)[a]	Prod	Yield (%)[c]	Prod	Yield (%)[a]	ee (%)[d]
OMe	OMe	OMe	**2a**	80[e]	**3a**	92[e]	95	**4a**	93	**5a**	85	**6a**	85	**7a**	85	94
H	OMe	OCH_2O	**2b**	78	**3b**	80	92	**4b**	78	**5b**	75	**6b**	-	**7b**	82[f]	91
H	OMe	OMe	**2c**	75	**3c**	82	94	**4c**	75	**5c**	78	**6c**	-	**7c**	86[f]	93

[a] Yield of pure product after purification by flash column chromatography.
[b] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes–*i*-PrOH, 50:50 as eluent. Flow rate 0.90 mL/min.).
[c] Global yield for both diastereoisomers *cis*- and *trans*-**7**.
[d] Determined by chiral HPLC (Chiracel OD, UV detector, hexanes–*i*-PrOH, 75:25 as eluent. Flow rate 0.60 mL/min.).
[e] See ref.[23g]
[f] Yield calculated from product **5** (2 steps).

ing metal oxides with trifluoroacetic anhydride/trifluoroacetic acid (TFAA/TFA). We proceeded then to test some of these oxidation systems, using (*S*)-laudanosine **7a** as the model compound (Scheme 3), with the results shown in Table 2.

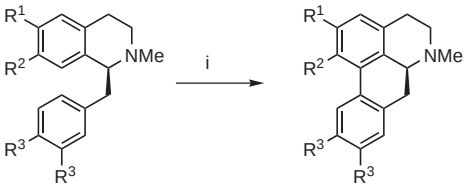


7a (+)-*Glaucine* (**8a**)

Scheme 3 Reagents and conditions: (i) see Table 2.

As can be seen in Table 2, the use of the Cr_2O_3 afforded no coupling product, and the starting material was recovered unchanged even after prolonged reaction times (entry 1). On the other side, when we used the $Ce(OH)_4$/TFAA/TFA or the RuO_2/TFAA/TFA combination of reagents (entries 2–5), in the presence of a Lewis acid like $BF_3{\cdot}OEt_2$, the desired aporphine, the natural product (*S*)-(+)-glaucine (**8a**), was obtained in variable yields, the best results obtained were with the RuO_2/TFAA/TFA/$BF_3{\cdot}OEt_2$ system (entries 4 and 5). Remarkably, we also noticed that the order of the addition of reagents was crucial to the yield of the coupling reaction. We observed that the yield significantly improved when the Lewis acid was the last reagent to be added (entry 5) compared to the reaction in which the $BF_3{\cdot}OEt_2$ was added together with the metal oxide (entry 4), before the addition of TFAA and TFA (see experimental part). Although the role of this Lewis acid has not already been completely established, it is thought that it activates the *para*-alkoxy substituent on one of the aromatic rings, therefore favoring the oxidative coupling by stabilization of the intermediate aromatic radical cationic species.[28a,29] Finally, we also tested the radical-mediated coupling (entry 6) but in this case we could only detect starting material even after 48 hours reaction time and reflux temperature.

Although this ruthenium-mediated oxidative coupling procedure afforded the desired tetracycles in good yields, we also observed slight racemization of the stereogenic center. This fact prompted us to find alternative procedures to perform this reaction. In this context, the hypervalent iodine(III) reagent phenyliodine bis(trifluoroacetates) (PIFA) has been shown to be an alternative reagent for oxidative coupling of phenols and phenol ethers,[30] and therefore this prompted us to test this reagent in our particular case. To our delight, the PIFA-promoted oxidative coupling of substrate **7a** proceeded cleanly, in good yield and with no noticeable racemization at the stereogenic center present in the starting compound (Table 3). Additional advantages of this reaction are the considerably shorter reaction times (30 min vs 24–48 h) and the lower temperatures used. These optimized conditions were further extended to the two other 1-benzyltetrahydroisoquinolines **7b**–**c**, affording the final aporphines **8b**–**c** in good yields and as almost enantiomerically pure compounds (Scheme 4).



7a-c **8a-c**

Scheme 4 Reagents and conditions: (i) PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 ºC.

Table 2 Oxidative Coupling of 1-Benzyltetrahydroisoquinoline **7a**

Entry	Reagents	T (ºC)	Yield (%)[a]	ee (%)[b]
1	Cr_2O_3/TFAA/TFA	reflux	–[c]	–
2	$Ce(OH)_4$/TFAA/TFA/$BF_3.OEt_2$	0ºC	60	93
3	$Ce(OH)_4$/TFAA/TFA/$BF_3.OEt_2$	r.t.	10[d]	–
4	RuO_2/$BF_3.OEt_2$/TFAA/TFA	–10 ºC	60	91
5	RuO_2/TFAA/TFA/$BF_3{\cdot}OEt_2$[e]	–10 ºC	75	91
6	Bu_3SnH/AIBN	reflux	–	–

[a] Yield of **7a** after flash column chromatography purification.
[b] Determined by HPLC (Chiralcel OD column, UV detector, hexanes–*i*-PrOH 95:5, flow rate 0.9 mL/min.).
[c] Starting material was recovered unchanged.
[d] Over-oxidation products were obtained.
[e] $BF_3{\cdot}OEt_2$ was the last reagent added.

Table 3 Synthesis of Aporphines **8a**–**c** by PIFA-Mediated Oxidative Coupling

Prod.	R^1	R^2	R^3	Yield (%)[a]	ee (%)[b]
8a	OMe	OMe	OMe	75	94
8b	H	OMe	OCH_2O	75	91
8c	H	OMe	OMe	78	93

[a] Yield of **8a**–**c** after purification by flash column chromatography.
[b] Determined by HPLC (Chiralcel OD column, UV detector, hexanes–*i*-PrOH 95:5 flow rate 0.9 mL/min.).

In summary, a very simple and efficient synthetic route to obtain optically pure aporphine alkaloids has been developed starting from chiral 1,2-diarylethylamines, which in turn, were obtained enantiomerically pure by using phenylglycinol as the source of chirality. Then, a sequence of transformations (N-alkylations, Pommeranz–Fritsch cyclization, ionic hydrogenation, and oxidative C–C biaryl coupling) was performed to reach to the aporphine core. Besides, this last C–C biaryl coupling has been performed by means of a hypervalent iodine(III)-mediated reaction, under a completely different protocol which supersedes

other reported methodologies, both in terms of the yields obtained and the absence of racemization at the stereogenic center present in the starting compounds. The usefulness of this methodology has been exemplified with the synthesis of the natural aporphine (+)-glaucine (**8a**), but it has to be mentioned that the described protocol is interesting from a synthetic point of view taking into account the large number of diarylethylamines of type **3** available by this method and thus should lead to the synthesis of a wide range of naturally and unnaturally occurring aporphine derivatives.

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25 ºC, and were recorded at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and resonances are reported in ppm relative to TMS unless otherwise stated. Assignment of individual ^{13}C resonances is supported by DEPT experiments. Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm. thick silica gel plates (Merck Kiesegel GF254). Visualization was accomplished by UV light or by spraying with Dragendorff´s reagent.[31] Flash column chromatography on silica gel was performed with Merck Kiesegel 60 (230–400 mesh).[32] Enantiomeric excesses was determined by chiral HPLC analysis of non-crystallized samples using a Chiracel OD column with a UV detector with the eluents and flow rates as indicated in each case. All solvents used in reactions were dried and purified according to standard procedures.[33] Imines **1a**–**c**, amine **2a**, and 1,2-diarylethylamine **3a** were prepared according to reported procedures.[23g] All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 ºC) overnight and purged with argon.

Synthesis of Amines 2b,c; Typical Procedure

A solution of imine **1b** (2.27 g, 8.9 mmol) in THF (35 mL) was added to a freshly prepared solution of (3,4-methylendioxybenzyl)magnesium chloride (5 equiv) in the same solvent (60 mL), and the mixture was heated at 45–50 ºC for 5 h. After cooling, the reaction was quenched with a sat. solution of NH_4Cl (20 mL), the organic layer was decanted, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was distilled under vacuum. The residue was purified by flash column chromatography (hexanes–EtOAc, 1:1) to afford **2b** (2.72 g, 6.91 mmol).

(+)-(2*S*,1′*S*)-2-(3,4-Methylendioxyphenyl)-1-(3-methoxyphenyl)-*N*-(2-hydroxy-1-phenylethyl)ethylamine (2b)

Yield: 78%; $[\alpha]_D^{20}$ +65.2 (*c* 0.2, EtOH).

IR (KBr): 3540–3250 (NH, OH) cm^{-1}.

^1H NMR: δ = 2.11 (br s, 2 H), 2.81 (dd, *J* = 13.5, 7.1 Hz, 1 H), 2.97 (dd, *J* = 13.5, 6.7 Hz, 1 H), 3.50 (dd, *J* = 10.7, 7.0 Hz, 1 H), 3.65–3.86 (m, 6 H), 5.83 (s, 2 H), 6.42–6.80 (m, 7 H), 7.15–7.30 (m, 5 H).

^{13}C NMR: δ = 43.5, 55.6, 61.7, 62.0, 65.5, 100.6, 107.9, 109.6, 110.0, 110.6, 119.2, 122.2, 127.0, 127.1, 127.3, 128.4, 132.4, 135.2, 141.3, 145.7, 147.8, 148.5.

MS (EI): *m*/*z* (%) = 270 (100), 255 (20), 77 (9).

(+)-(2*S*,1′*S*)-2-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-*N*-(2-hydroxy-1-phenylethyl)ethylamine (2c)

Amine **2c** (2.39 g, 5.90 mmol) was obtained following the typical procedure starting from imine **1c** (2.00 g, 7.80 mmol).

Yield: 75%; $[\alpha]_D^{20}$ +61.2 (*c* 0.1, EtOH).

IR (KBr): 3550–3250 (NH, OH) cm^{-1}.

^1H NMR: δ = 2.19 (br s, 2 H), 2.90 (dd, *J* = 13.6, 6.7 Hz, 1 H), 2.92 (dd, *J* = 13.6, 6.7 Hz, 1 H), 3.50 (dd, *J* = 10.6, 7.0 Hz, 1 H), 3.66–3.89 (m, 12 H), 6.40–6.91 (m, 6 H), 7.11–7.27 (m, 5 H).

^{13}C NMR: δ = 43.2, 55.0, 55.5, 55.7, 55.8, 61.4, 62.0, 65.1, 110.3, 110.9, 112.4, 112.7, 119.5, 121.3, 127.1, 127.3, 128.4, 129.2, 130.9, 133.5, 141.0, 145.2, 148.3, 159.4.

MS (EI): *m*/*z* (%) = 286 (100), 271 (20), 77 (9).

Cleavage of the Chiral Appendage; Typical Procedure

A solution of the amine **2b** (0.39 g, 1.0 mmol) in EtOH (10 mL) was hydrogenated (2 atm) in the presence of 10% Pd/C (0.8 g) and of 10% HCl (8 mL). After absorption of hydrogen was complete (45–60 h), the catalyst was filtered off and the filtrate was basified with a sat. solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (EtOAc) to afford amine **3b** (0.21 g, 0.82 mmol).

(+)-(1*S*)-1-(3-Methoxyphenyl)-2-(3,4-methylendioxyphenyl)ethylamine (3b)

Yield: 80%; $[\alpha]_D^{20}$ +35.5 (*c* 0.2, CH_2Cl_2).

IR (KBr): 3210–3200 (NH_2) cm^{-1}.

^1H NMR: δ = 1.66 (br s, 2 H), 2.71 (dd, *J* = 13.5, 8.7 Hz, 1 H), 2.91 (dd, *J* = 13.5, 5.0 Hz, 1 H), 3.80 (s, 3 H), 4.10 (dd, *J* = 8.7, 5.0 Hz, 1 H), 5.90 (s, 2 H), 6.61–6.81 (m, 4 H), 6.91–6.93 (m, 2 H), 7.20–7.27 (m, 1 H).

^{13}C NMR: δ = 45.9, 55.0, 57.4, 100.7, 109.4, 111.7, 112.3, 118.6, 122.1, 129.3, 132.6, 145.9, 147.2, 147.4, 159.5.

MS (EI): *m*/*z* (%) = 254 (28), 207 (100), 135 (97).

(+)-(1*S*)-2-(3,4-Dimethoxyphenyl)-1-(3-methoxyphenyl)ethylamine (3c)

Amine **3c** (1.39 g, 5.93 mmol) was obtained following the typical procedure starting from amine **2c** (2.39 g, 5.91 mmol).

Yield: 82%; $[\alpha]_D^{20}$ +21.0 (*c* 0.4, CH_2Cl_2).

IR (KBr): 3560–3360 (NH_2) cm^{-1}.

^1H NMR: δ = 1.69 (br s, 2 H), 2.76 (dd, *J* = 13.5, 8.7 Hz, 1 H), 2.95 (dd, *J* = 13.5, 5.0 Hz, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.14 (dd, *J* = 8.7, 5.0 Hz, 1 H), 6.60–6.94 (m, 6 H).

^{13}C NMR: δ = 45.8, 55.2, 55.7, 55.8, 111.0, 112.1, 112.4, 112.4, 118.8, 121.2, 129.3, 131.3, 136.9, 147.2, 147.5; 148.6.

MS (EI): *m*/*z* (%) =136 (100), 109 (15), 94 (6).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.07; H, 7.57; N, 4.87.

Synthesis of N-Alkylated Amines 4a–c; Typical Procedure

To a stirred suspension of K_2CO_3 (0.97 g, 8.2 mmol) in anhyd MeCN (25 mL) was added a solution of amine **3a** (0.80 g, 2.52 mmol) in the same solvent (15 mL) and the mixture was refluxed for 2 h. Then, bromoacetaldehyde diethylacetal (1.52 mL, 10.1 mmol) was added in one portion and the reflux was continued until the conversion was complete (3 d). After cooling, the mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to afford, after crystallization from hexanes, pure amine **4a** as a white solid (1.02 g, 2.34 mmol).

(+)-(1*S*)-1,2-Bis(3,4-dimethoxyphenyl)-*N*-(2,2-diethoxyethyl)ethylamine (4a)
Yield: 93%; mp 73–75 ºC; $[\alpha]_D^{20}$ +20.5 (*c* 0.4, CH_2Cl_2).

IR (KBr): 3310 (NH), 1260 (COC) cm^{-1}.

^1H NMR: δ = 0.98 (t, *J* = 7.0 Hz, 6 H), 1.67 (br s, 1 H), 2.39–2.44 (m, 2 H), 2.69–2.74 (m, 2 H), 3.25–3.40 (m, 2 H), 3.42–3.48 (m, 2 H), 3.60–3.66 (m, 1 H), 3.68 (s, 3 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 4.39 (t, *J* = 5.1 Hz, 1 H), 6.49–6.78 (m, 6 H).

^{13}C NMR: δ = 14.9, 44.7, 49.5, 55.4, 55.5, 61.4, 61.5, 64.2, 101.5, 109.9, 110.7, 111.0, 112.4, 119.3, 120.9, 131.2, 136.0, 147.3, 147.8, 148.5, 148.8.

MS (EI): *m*/*z* (%) = 301 (15), 282 (53), 236 (100), 190 (32), 151 (30).

Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.13; N, 3.23. Found: C, 66.67; H, 8.29; N, 3.14.

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-1-(3-methoxyphenyl)-2-(3,4-methylendioxyphenyl)ethylamine (4b)
Amine **4b** (0.24 g, 0.66 mmol) was obtained following the typical procedure starting from amine **3b** (0.20 g, 0.83 mmol).

Yield: 78%; $[\alpha]_D^{20}$ +10.2 (*c* 0.2, CH_2Cl_2).

IR (neat): 3300 (NH), 1260 (COC) cm^{-1}.

^1H NMR: δ = 1.06 (t, *J* = 7.1 Hz, 3 H), 1.08 (t, *J* = 7.1 Hz, 3 H), 1.78 (br s, 1 H), 2.42–2.58 (m, 2 H), 2.70–2.89 (m, 2 H), 3.34–3.58 (m, 2 H), 3.70–3.73 (m, 1 H), 3.78 (s, 3 H), 4.50 (t, *J* = 5.2 Hz, 1 H), 5.88 (s, 2 H), 6.57–6.89 (m, 6 H), 7.17–7.23 (m, 1 H).

^{13}C NMR: δ = 15.1, 44.8, 49.7, 55.0, 61.9, 64.7, 100.7, 101.7, 108.0, 109.3, 112.3, 112.5, 119.6, 122.1, 129.1, 132.4, 145.2, 145.9, 147.5, 159.6.

MS (EI): *m*/*z* (%) = 254 (33), 206 (100), 160 (64), 135 (76).

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-2-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-ethylamine (4c)
Amine **4c** (1.34 g, 3.62 mmol) was obtained following the typical procedure starting from amine **3c** (1.39 g, 4.86 mmol).

Yield: 75%; $[\alpha]_D^{20}$ +18.5 (*c* 0.5, CH_2Cl_2).

IR (neat): 3300 (NH), 1250 (COC) cm^{-1}.

^1H NMR: δ = 1.06 (t, *J* = 7.0 Hz, 3 H), 1.10 (t, *J* = 7.0 Hz, 3 H), 1.78 (br s, 1 H), 2.43–2.59 (m, 2 H), 2.74–2.87 (m, 2 H), 3.34–3.43 (m, 2 H), 3.46–3.54 (m, 2 H), 3.68–3.74 (m, 1 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.50 (t, *J* = 5.3, 1 H), 6.57–6.88 (m, 6 H), 7.17–7.26 (m, 1 H).

^{13}C NMR: δ = 15.1, 44.6, 49.6, 55.0, 55.5, 55.6, 61.7, 61.8, 64.7, 101.6, 110.8, 112.1, 112.1, 119.6, 121.0, 129.1, 131.0, 145.1, 147.0, 147.3, 148.5, 148.4, 159.5.

MS (EI): *m*/*z* (%) = 281 (12), 270 (54), 207 (100), 151 (49).

N-Methylation of Aminoacetals 4a–c; Typical Procedure
Aminoacetal **4a** (0.25 g, 0.58 mmol) was dissolved in anhyd MeCN (25 mL), 35% aq HCHO (0.25 mL, 2.9 mmol), and $NaBH_3CN$ (0.18 g, 2.9 mmol) was added in one portion. The solution was stirred at r.t. until TLC analysis showed complete conversion (typically 12 h). Then, the mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure. The resulting residue was purified by flash column chromatography (hexanes–EtOAc, 2:8) to afford **5a** (0.24 g, 0.54 mmol) as a colorless oil.

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-1,2-bis(3,4-dimethoxyphenyl)-*N*-methylethylamine (5a)
Yield: 85%; $[\alpha]_D^{20}$ +38.5 (*c* 0.8, CH_2Cl_2).

IR (neat): 1130 (COC) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.16 (t, *J* = 7.1 Hz, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H), 2.34 (s, 3 H), 2.48 (dd, *J* = 13.5, 5.1 Hz, 1 H), 2.68 (dd, *J* = 13.5, 5.2 Hz, 1 H), 2.86 (dd, *J* = 13.4, 9.3 Hz, 1 H), 3.20 (dd, *J* = 13.4, 5.2 Hz, 1 H), 3.41–3.62 (m, 4 H), 3.69 (s, 3 H), 3.78 (s, 3 H), 3.81–3.84 (m, 7 H), 4.52 (t, *J* = 5.1 Hz, 1 H), 6.46 (d, *J* = 1.8 Hz, 1 H), 6.54 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.63–6.86 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 15.2, 38.7, 39.8, 55.6, 55.7, 55.8, 56.8, 61.6, 61.7, 70.7, 101.9, 110.3, 110.7, 111.9, 112.5, 121.1, 132.2, 132.4, 146.9, 147.8, 148.2, 148.4.

MS (EI): *m*/*z* (%) = 402 (3), 300 (90), 296 (100), 285 (47), 195 (52), 151 (40).

Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 67.22; H, 8.51; N, 3.24.

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-1-(3-methoxyphenyl)-*N*-methyl-2-(3,4-methylendioxyphenyl)ethylamine (5b)
Amine **5b** (0.18 g, 0.45 mmol) was obtained following the typical procedure starting from amine **4b** (0.24 g, 0.60 mmol).

Yield: 75%; $[\alpha]_D^{20}$ +30.9 (*c* 0.1, CH_2Cl_2).

IR (neat): 1160 (COC) cm^{-1}.

^1H NMR: δ = 1.16 (t, *J* = 7.1 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 2.30 (s, 3 H), 2.46 (dd, *J* = 13.5, 5.2 Hz, 1 H), 2.65 (dd, *J* = 13.5, 5.2 Hz, 1 H), 2.88 (dd, *J* = 13.5, 8.3 Hz, 1 H), 3.12 (dd, *J* = 13.5, 6.0 Hz, 1 H), 3.42–3.64 (m, 4 H), 3.76 (s, 3 H), 3.71–3.80 (m, 1 H) 4.52 (t, *J* = 5.1 Hz, 1 H), 5.84 (s, 2 H), 6.48–6.78 (m, 6 H), 7.13–7.20 (m, 1 H)

^{13}C NMR: δ = 15.2, 38.2, 39.4, 55.0, 56.7, 61.7, 61.8, 70.5, 100.5, 107.7, 109.6, 112.0, 114.6, 121.2, 122.0, 128.7, 133.4, 140.7, 145.4, 147.5, 159.1.

MS (EI): *m*/*z* (%) = 220 (100), 207 (86), 150 (64), 121 (35).

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-2-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-*N*-methylethylamine (5c)
Amine **5c** (1.16 g, 2.80 mmol) was obtained following the typical procedure starting from amine **4c** (1.34 g, 3.60 mmol).

Yield: 78%; $[\alpha]_D^{20}$ +14.4 (*c* 0.7, CH_2Cl_2).

IR (neat): 1120 (COC) cm^{-1}.

^1H NMR: δ = 1.16 (t, *J* = 7.0 Hz, 3 H), 1.17 (t, *J* = 7.0 Hz, 3 H), 2.33 (s, 3 H), 2.49 (dd, *J* = 13.5, 5.0 Hz, 1 H), 2.70 (dd, *J* = 13.5, 5.1 Hz, 1 H), 3.20 (dd, *J* = 13.5, 5.1 Hz, 1 H), 3.42–3.69 (m, 4 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 3.79 (s, 3 H), 3.63–3.84 (m, 2 H), 4.53 (t, *J* = 5.0 Hz, 1 H), 6.46–6.78 (m, 6 H), 7.12–7.19 (m, 1 H).

^{13}C NMR: δ = 15.3, 38.6, 39.7, 55.1, 55.5, 55.7, 56.8, 61.6, 61.8, 70.9, 101.9, 110.6, 112.0, 119.6, 112.5, 114.7, 121.1, 121.3, 128.6, 132.1, 141.2, 146.9, 148.1, 159.1.

MS (EI): *m*/*z* (%) = 266 (48), 149 (100).

Synthesis of 1-Benzyltetrahydroisoquinolin-4-ols *cis*-6a–c and *trans*-6a–c; Typical Procedure
A solution of aminoacetal **5a** (0.71 g, 1.6 mmol) in acetone (10 mL) and concd HCl (5 mL) was stirred overnight at r.t. The mixture was cooled on an ice bath, basified with 1 M NaOH and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford tetrahydroisoquinolin-4-ols **6a** as a mixture of two diastereoisomers (0.50 g, 1.40 mmol; global yield: 85%). Both diastereoisomers were separated by flash column chromatography

(CH_2Cl_2–MeOH, 0–2%) to afford pure oily samples of tetrahydroisoquinolinols *cis*- and *trans*-**6a**.

(+)-(1*S*,4*S*)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (*cis*-6a)
$[\alpha]_D^{20}$ +25.0 (*c* 1.0, CH_2Cl_2).

IR (neat): 3500–3300 (OH) cm^{-1}.

^1H NMR: δ = 1.70–1.90 (br s, 1 H, OH), 2.55 (dd, *J* = 13.1, 9.1 Hz, 1 H), 2.66 (s, 3 H), 2.77 (dd, *J* = 12.5, 2.8 Hz, 1 H), 3.13–3.22 (m, 2 H), 3.48 (s, 3 H), 3.77 (s, 3 H), 3.77–3.81 (m, 1 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.47 (br s, 1 H), 5.80 (s, 1 H), 6.48 (d, *J* = 1.7 Hz, 1 H), 6.54 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.89 (s, 1 H).

^{13}C NMR: δ = 34.7, 42.8, 54.3, 55.2, 55.7, 55.8, 55.9, 64.0, 65.9, 110.1, 111.0, 111.2, 113.0, 122.0, 127.5, 129.5, 131.1, 147.2, 147.5, 147.9, 148.6.

MS (EI): *m*/*z* (%) = 371 (12), 222 (100), 208 (36), 190 (25), 151(61).

()-(1*S*,4*R*)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (*trans*-6a)
$[\alpha]_D^{20}$ –70.4 (*c* 1.0, CH_2Cl_2).

IR (neat): 3450–3200 (OH) cm^{-1}.

^1H NMR: δ = 2.66 (s, 3 H), 2.84–2.98 (m, 1 H), 3.02 (dd, *J* = 11.6, 4.0 Hz, 1 H), 3.13–3.15 (m, 2 H), 3.63 (s, 3 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.77–3.82 (m, 1 H), 4.39 (br s, 1 H), 6.32 (d, *J* = 1.8 Hz, 1 H), 6.50 (s, 1 H), 6.49–6.54 (m, 1 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 6.77 (s, 1 H).

^{13}C NMR: δ = 39.3, 43.1, 55.6, 55.7, 55.8, 55.9, 57.4, 64.6, 65.9, 109.5, 110.5, 110.9, 113.1, 122.1, 128.3, 129.5, 129.9, 147.5, 147.7, 148.2, 148.4.

(1*S*,4*R*)- and (1*S*,4*S*)-1-(3,4-Methylenedioxybenzyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (*cis*-6b and *trans*-6b) and (1*S*,4*R*)- and (1*S*,4*S*)-1-(3,4-dimethoxybenzyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (*cis*-6c and *trans*-6c)
They were prepared according to the general procedure and used directly as a mixture of diastereoisomers without further purification in the next step of the synthesis.

Reduction of 1-Benzyltetrahydroisoquinolinols 6a–c; Typical Procedure
A solution of diastereomeric tetrahydroisoquinolinols *cis*-**6a** and *trans*-**6a** (0.36 g, 1.00 mmol) in CH_2Cl_2 (10 mL) was dropwise added over a cooled (0 ºC) suspension of $NaBH_4$ pellets (0.38 g, 10 mmol) in TFA (4.6 mL, 60 mmol). The reaction mixture was stirred at r.t. until complete conversion of starting materials had occured (typically 2–3 h) and then the volatiles were removed under reduced pressure. The resulting slurry was basified with 1 M NaOH (10 mL) and extracted with CH_2Cl_2. The combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (CH_2Cl_2–MeOH, 99:1) to afford 1-benzyltetrahydroisoquinoline **7a** (0.30 g, 0.85 mmol).

(+)-(1*S*)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline [(+)-Laudanosine, 7a]
Yield: 85%; $[\alpha]_D^{20}$ +90.0 (*c* 0.2, EtOH) [Lit.[20a] +96.6 (*c* 0.41, EtOH].

^1H NMR: δ = 2.53 (s, 3 H), 2.58–2.61 (m, 1 H), 2.72–2.86 (m, 3 H), 3.10–3.20 (m, 2 H), 3.56 (s, 3 H), 3.68 (dd, *J* = 7.7, 4.7 Hz, 1 H), 3.78 (s, 3 H), 3.83(s, 3 H), 3.84 (s, 3 H), 6.1 (s, 1 H), 6.55–6.78 (m, 4 H).

^{13}C NMR: δ = 25.4, 40.8, 42.6, 46.9, 55.5, 55.6, 55.7, 55.8, 64.8, 110.8, 110.9, 111.0, 112.8, 121.8, 125.9, 129.1, 132.4, 146.1, 147.1, 147.2, 148.4.

MS (EI): *m*/*z* (%) = 206 (M^+ – 15, 100).

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.32; H, 7.77; N, 3.47.

(+)-(1*S*)-7-Methoxy-2-methyl-1-(3,4-methylendioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (7b)
Isoquinoline **7b** (0.25 g, 0.83 mmol) was obtained following the typical procedure starting from amine **5b** (0.34 g, 1.00 mmol).

Yield: 82% (2 steps); $[\alpha]_D^{20}$ +75.5 (*c* 0.35, EtOH).

^1H NMR: δ = 2.49 (s, 3 H), 2.47–2.63 (m, 1 H), 2.71–2.89 (m, 3 H), 3.04–3.22 (m, 2 H), 3.64 (s, 3 H), 3.69–3.81 (m, 1 H), 5.91 (s, 2 H), 6.28 (d, *J* = 2.8 Hz, 1 H), 6.55–6.97 (m, 4 H), 6.99 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR: δ = 24.6, 41.1, 42.6, 46.9, 55.0, 65.3, 100.7, 107.9, 109.9, 112.4, 112.7, 122.4, 126.1, 129.6, 133.6, 138.3, 145.7, 147.3, 157.0.

MS (EI): *m*/*z* (%) = 311 (M^+, 1), 309 (28), 266 (62), 176 (100), 174 (65).

(+)-(1*S*)-1-(3,4-Dimethoxybenzyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (7c)
Isoquinoline **7c** (0.20 g, 0.65 mmol) was obtained following the typical procedure starting from amine **5c** (0.23 g, 0.72 mmol).

Yield: 86% (2 steps); $[\alpha]_D^{20}$ +85.8 (*c* 0.3, EtOH).

^1H NMR: δ = 2.50 (s, 3 H), 2.48–2.61 (m, 1 H), 2.70–2.86 (m, 3 H), 3.08–3.19 (m, 2 H), 3.58 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 3.70–3.90 (m, 1 H), 6.22 (d, *J* = 2.4 Hz, 1 H), 6.56–6.77 (m, 4 H), 6.97 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR: 24.9, 40.8, 42.6, 47.0, 54.9, 55.5, 55.7, 65.2, 110.7, 112.3, 112.5, 112.6, 121.5, 126.1, 129.4, 132.2, 138.3, 147.0, 148.2, 156.8.

MS (EI): *m*/*z* (%) = 176 (100).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.61; H, 7.64; N, 4.02.

Oxidative Coupling of 1-Benzyltetrahydroisoquinolines (7a–c); Typical Procedure
a) Oxidation with $RuO_2 \cdot xH_2O$
A solution of tetrahydroisoquinoline **7a** (0.10 g, 0.28 mmol) in CH_2Cl_2 (8 mL) was added over a stirred suspension of $RuO_2 \cdot xH_2O$ (0.15 g, 1.12 mmol) in CH_2Cl_2 (17 mL), TFA (1.70 mL), and TFAA (0.88 mL) at –10 ºC under argon and then, $BF_3 \cdot OEt_2$ (0.2 mL, 1,58 mmol) was added in one portion. The mixture was stirred at r.t. for 24 h and then the solvent was removed under reduced pressure. H_2O (15 mL) was added, the mixture was basified to pH 9 with NH_4OH (10 mL), extracted with EtOAc (3 × 15 mL), and washed with brine. The combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (CH_2Cl_2–MeOH, 99:1) to afford aporphine **8a** (70 mg, 0.21 mmol); yield: 75%.

b) Oxidation with $Ce(OH)_4$
TFA (3,5 mL) and TFAA (0.60 mL) were added over a stirred suspension of $Ce(OH)_4$ (0.43 g, 2.06 mmol) in CH_2Cl_2 (15 mL) at 0 ºC under argon. At this temperature $BF_3 \cdot OEt_2$ (0.4 mL, 3.15 mmol) was added followed immediately by a solution of tetrahydroisoquinoline **7a** (0.10 g, 0.28 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at r.t for 48 h and, quenched with a sat. solution of $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent

was removed under reduced pressure. The resulting residue was purified by column chromatography CH_2Cl_2–MeOH, 99:1) to afford aporphine **8a** (60 mg, 0.17 mmol); yield: 60%.

c) Oxidation with PIFA

A solution of PIFA (0.23 g, 0.52 mmol) in CH_2Cl_2 (10 mL) was added at –20 ºC to a solution of tetrahydroisoquinoline **7a** (0.15 g, 0.42 mmol) and $BF_3{\cdot}OEt_2$ (0.14 mL, 1.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 30 min and then quenched with MeOH (5 mL). The solvent was removed under reduced pressure and the crude reaction product was purified by column chromatography (CH_2Cl_2–MeOH, 99:1) to afford aporphine **8a** (0.11 g, 0.31mmol); yield: 75%.

(+)-(*S*)-Glaucine (8a)

$[\alpha]_D^{20}$ +106.0 (*c* 0.2, CH_2Cl_2) [Lit.[21] +100 (*c* 3.2, $CHCl_3$].

^{1}H NMR: δ = 2.48–2.70 (m, 3 H), 2.53 (s, 3 H), 2.97–3.07 (m, 4 H), 3.64 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 6.58 (s, 1 H), 6.77 (s, 1 H), 8.08 (s, 1 H).

^{13}C NMR: 29.2, 34.4, 44.0, 53.3, 55.7, 55.9, 60.1, 62.5, 110.3, 110.7, 111.4, 124.4, 126.8, 127.0, 128.8, 129.2, 144.2, 147.4, 147.9, 151.9.

MS (EI): *m*/*z* (%) = 355 (M^+, 100), 354 (M^+ – 1, 61), 340 (32).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.94; H, 7.11; N, 3.97.

(+)-(6*S*)-1-Methoxy-6-methyl-9,10-methylenedioxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (8b)

Aporphine **8b** (0.19 g, 0.60 mmol) was obtained following the typical procedure starting from isoquinoline **7b** (0.25 g, 0.80 mmol).

Yield: 75%; $[\alpha]_D^{20}$ +95 (*c* 0.2, CH_2Cl_2).

^{1}H NMR: δ = 2.56 (s, 3 H), 2.60–2.66 (m, 3 H), 3.00–3.07 (m, 4 H), 3.86 (s, 3 H), 5.92 (s, 2 H), 6.78 (s, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.99 (d, *J* = 8.2, 1 H), 7.92 (s, 1 H).

^{13}C NMR: δ = 28.7, 34.2, 44.0, 53.2, 55.9, 63.2, 100.7, 110.7, 111.1, 112,5, 122.1, 124.7, 125.5, 127.9, 129.0, 135.7, 146.9, 147.4, 154.2;

MS (EI): *m*/*z* (%) = 309 (M^+, 100), 308 (50), 294 (15).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.35; H, 5.90; N, 4.81.

(+)-(6*S*)-1,9,10-Trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (8c)

Aporphine **8c** (0.15 g, 0.47 mmol) was obtained following the typical procedure starting from isoquinoline **7c** (0.20 g, 0.60 mmol).

Yield: 78%; $[\alpha]_D^{20}$ +23.4 (*c* 0.2, CH_2Cl_2).

^{1}H NMR: δ = 2.55 (s, 3 H), 2.59–2.65 (m, 3 H), 2.99–3.07 (m, 4 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 6.78 (s, 1 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.92 (s, 1 H).

^{13}C NMR: δ = 28.6, 34.2, 44.1, 53.3, 55.8, 55.9, 56.0, 63.2, 110.7, 111.0, 112,5, 127.8, 122.1, 124.6, 125.6, 129.1, 135.7, 146.9, 147.6, 154.3.

MS (EI): *m*/*z* (%) = 325 (M^+, 100), 324 (76), 282 (47), 251 (53).

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.64; H, 7.04; N, 4.27.

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