Graphical Abstract

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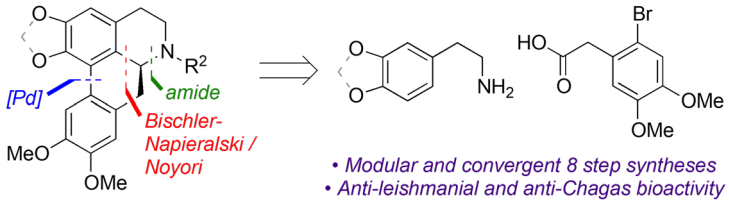

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Enantioselective synthesis and anti-parasitic properties of aporphine natural products

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Natural products
Aporphine
Leishmania infantum
Trypanosoma cruzi
Alkaloid
Palladium catalyzed arylation

ABSTRACT

Chagas disease and visceral leishmaniasis are neglected protozoan diseases with significant impact in developing countries. Due to the limited number and toxicity of current therapies, new drug leads are urgently needed. In this work, four aporphine natural products were synthesized using an enantioselective, modular and convergent strategy, comprising eight steps in the longest linear sequence; key steps included Bischler-Napieralski cyclization / Noyori asymmetric reduction to construct the tetrahydroisoquinolines, and palladium-catalyzed arylation to close the C ring. Norglaucine, nordicentrine and dicentrine showed promising bioactivity against T. cruzi and L. infantum, suggesting potential for further development of these scaffolds as antiparasitic agents.

Dedicated to Prof. Steve Davies in recognition of his contributions to organic chemistry

Introduction

The aporphines comprise a large group of plant-derived tetracyclic alkaloids featuring a 1,2,3,4-tetrahydroisoquinoline motif. Many members of the aporphine family display interesting biological activities, such as anti-inflammatory [1], antimicrobial [2], anticancer [3,4] and antiparasitic [5,6] properties. In the latter context, a handful of aporphines have been evaluated for bioactivity against protozoan parasites; for example dicentrine, isolated from *Cassytha filiformis L.*, demonstrated antiparasitic activity against *Trypanosoma T. brucei,* potentially by acting as an intercalating agent with the parasite DNA (the kinetoplast) [7].

Leishmaniases, neglected tropical diseases caused by protozoan parasites of the *Leishmania* genus, affect more than 12 million people worldwide [8]. Human visceral leishmaniasis (VL) is the most severe clinical form of the disease, affecting internal organs such as the spleen, liver, bone marrow and lymph nodes [9]; it is the second largest cause of parasitic death after malaria. The VL chemotherapeutic arsenal consists of just three frontline drugs: pentavalent antimonials, amphotericin B (administered as a liposomal formulation), and miltefosine. These exhibit several limitations, including long administration periods (often with hospitalization), high cost, and adverse side effects [10]. The related protozoan disease Chagas disease, which affects some 8 million people worldwide, presents a similar challenge from the perspective of limited treatments (benznidazole and nifurtimox) and economic / health consequences. Particularly prevalent in South America, Chagas disease leads to eventual cardiac failure and enlargement of the colon / oesophagus, and is fatal in >90% cases when untreated.

The search for new drug leads for both diseases therefore remains a pressing goal, especially for developing countries where they predominate. In the past few years, our laboratory has been interested in exploiting natural products as prototypes for the discovery of new antiparasitic agents for the treatment of the causal parasites of VL (*Leishmania infantum* and *L. donovani*) and Chagas disease (*Trypanosoma cruzi*) [11, 12]. Our initial focus was on semi-synthetic derivatives of the neolignan dehydrodieugenol B, a number of which were found to exhibit promising activity against intracellular forms of *L. infantum*, with a phenotypic mechanism of action suggestive of impairment of mitochondria and cell division machinery [11]. In light of the potential anti-parasitic activity of the aporphine natural products, four aporphines that have been shown to possess anti-trypanosomal properties against other parasites were identified as synthetic targets (norglaucine **1**[13], nordicentrine **2** [14], and their *N*-methylated analogues glaucine **3** [15, 16] and dicentrine **4** [7], Figure 1). Here we report enantioselective syntheses of these four natural products, along with the evaluation of their anti-parasitic properties against *L. infantum* and *T. cruzi*.

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Results and Discussion

A number of synthetic approaches have been developed to access the aporphine scaffold. These can broadly be classified into two categories, according to which is the final ring built during the synthesis, specifically: i) B-ring formation by heterocyclization [17], or ii) C-ring formation by connection of the A and D rings through C–C bond formation including a AIBN-Bu_3SnH induced aryl radical cyclization [18, 19]. Among the latter methodologies, the most widely used are direct Pd-catalyzed C–H arylations of halo-benzyltetrahydroisoquinolines [20, 21], and intramolecular oxidative coupling using hypervalent iodine reagents [22, 23]. In light of the modular and potentially enantioselective nature of the latter approach, we also elected to study the A–D connection tactic for the preparation of aporphines **1**–**4**.

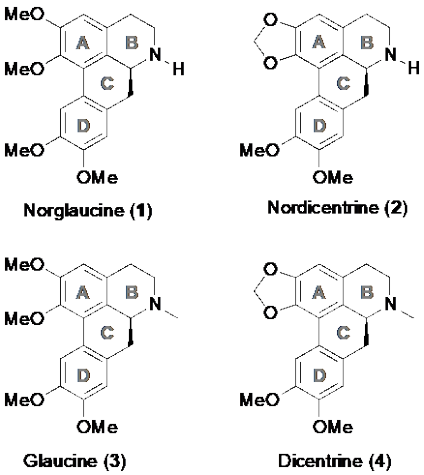
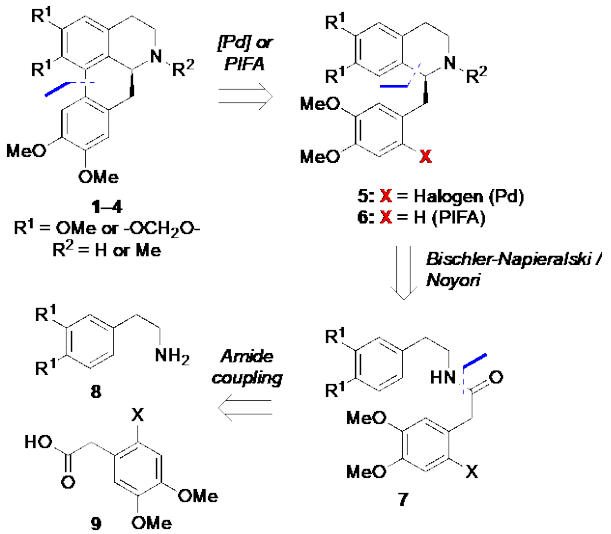
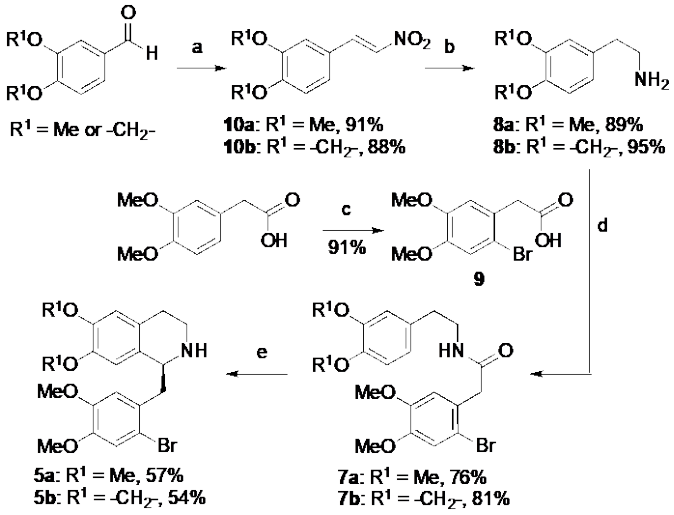


Figure 1. Aporphine natural products targeted in this work.

Our strategy for construction of aporphines **1**–**4** is outlined in more detail in Scheme 1. As discussed above, we anticipated using either palladium-catalyzed arylation of a halogenated benzyltetrahydroisoquinoline (BI) **5**, or oxidative C–C coupling re action of a non-halogenated BI **6** in the late phase of the synthesis. The required BIs would be obtained via Bischler-Napieralski cyclization upon mild electrophilic activation of an amide **7** [24], followed by an asymmetric Noyori hydrogenation reduction [25]. Disconnection of the amide **7** reveals the constituent amine (**8**) and carboxylic acid (**9**) building blocks. Of the two cyclization strategies, the Pd-catalyzed cyclization has significantly greater precedent, and we therefore prioritized this approach to the aporphine scaffold.



Scheme 1. Retrosynthetic Analysis of the Aporphines.

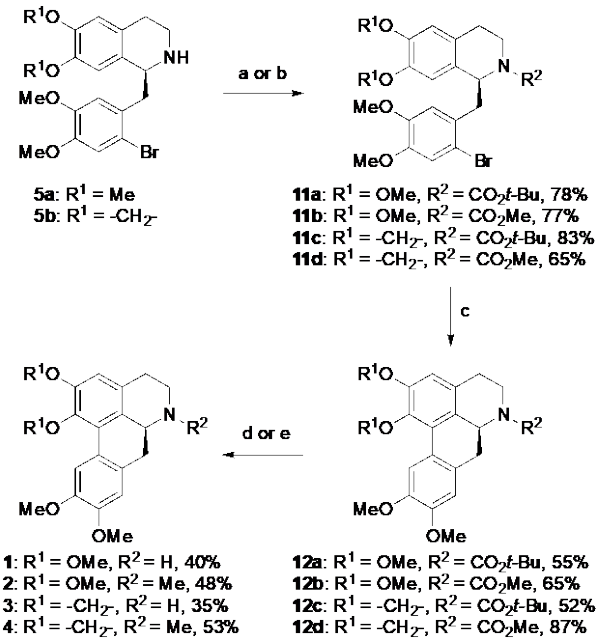


Scheme 2. Reagents and conditions: a) CH_3NO_2, AcOH, ethylenediamine, 70 °C, 12 h (**10a**: 91%, **10b**: 88%); b) $LiAlH_4$, THF, 70 °C, 12 h (**8a**: 89%, **8b**: 95%); c) Br_2, AcOH, 0 °C to 60 °C, 1 h, 91%; d) EDC.HCl, HOBt, NMM, DMF, 0 °C to rt, 4h (**7a**: 76%, **7b**: 81%); e) 1. Tf_2O, 2-chloropyridine, DCM, -78 °C to 0 °C, 15 min. 2. RuCl[(*R*,*R*)-TsDPEN](*p*-cymene), Et_3N / HCO_2H (2:5), 0 °C to rt, 10 h (**5a**: 57% over 2 steps, 93% *ee*, **5b**: 54% over 2 steps, 94% *ee*).

The syntheses commenced (Scheme 2) with the preparation of amides **7a** and **7b**. These were constructed by an EDC/HOBt-mediated coupling of phenylethylamines **8a** and **8b** with carboxylic acid **9** [26]. Amines **8a** and **8b** were in turn readily prepared from veratraldehyde and piperonal respectively by a sequence of Henry reaction with nitromethane and $LiAlH_4$ reduction of the resulting β-nitrostyrenes **10a**/**b** (81-84% over two steps); acid **9** was synthesized in a single step by bromination of 2-(3,4-dimethoxyphenyl)acetic acid [27]. On treatment of **7a** and **7b** with trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine at low temperature (conditions optimized by Movassaghi *et al.*) [24], Bischler-Napieralski cyclodehydration occurred to form air-sensitive benzyldihydroisoquinolines, which were directly reduced by Noyori asymmetric transfer hydrogenation to form tetrahydroisoquinolines **5a** and **5b** (**5a**: 57% yield over two steps, 93% *ee*; **5b**: 54%, 94% ee).

Before C ring formation, amines **5a** and **5b** were first *N*-protected as either the *tert*-butyl carbamates (**11a**/**c**, Scheme 3) or methyl carbamates (**11b**/**d**). The direct palladium-catalyzed *ortho*-arylation was next achieved using $Pd(OAc)_2$ with di-*tert*-butyl(methyl)phosphine as ligand (added as the air-stable HBF_4 salt) [21], which gave the aporphine carbamates **12a-d** in good yields (52-87%). The nature of the catalyst proved crucial, as low yields were obtained with PhDavePhos (**11a**: 12%, **11c**: 30%) [21]. Even under the former conditions, a significant amount of starting material remained after a reaction time of 24 h; under prolonged heating for 48 h, or with addition of fresh catalyst, the reaction did not proceed to completion.

The syntheses of (+)-norglaucine (**1**) and (+)-nordicentrine (**2**) were completed by deprotection of the Boc groups in **12a**/**c** respectively using anhydrous $ZnBr_2$ (Scheme 3); the use of Brønsted acids (e.g. trifluoroacetic acid) led to low yields due to degradation of the sensitive aporphine products. Reduction of the methyl carbamate-protected aporphines **12b**/**d** using $LiAlH_4$ gave (+)-glaucine **3** and (+)-dicentrine **4**. The spectroscopic data for the four natural products matched that reported in the literature [28, 29, 14, 30]. We also briefly examined the alternative approach to obtain (+)-glaucine and (+)-dicentrine using hypervalent iodine-mediated oxidative biaryl coupling (PIFA) of



Scheme 3. Reagents and conditions: a) Boc_2O, *i*-Pr_2EtN, DMAP, CH_2Cl_2, rt, 2 h (**11a**: 78%, **11c**: 83%); b) MeOCOCl, *i*-Pr_2EtN, DMAP, CH_2Cl_2, rt, 10 h (**11b**: 77%, **11d**: 65%); c) $Pd(OAc)_2$, (*t*-Bu)$_2$PMeHBF$_4$, K_2CO_3, DMA, 130 °C, 52%-87%; d) $ZnBr_2$, CH_2Cl_2, rt, 8 h (**1**: 40%, **3**: 35%); e) $LiAlH_4$, THF, 0 °C to rt, 20 h (**2**: 48%, **4**: 53%).

the corresponding non-halogenated benzyltetrahydroisoquinolines (**6** (X = H), Scheme 1) [23]; however, this led only to decomposition of starting material, even at low temperatures (-40 °C).

As noted above, a number of aporphine alkaloids have been shown to display bioactivity against protozoan parasites, and continuing with our interests in antiparasitic natural products [11, 12], we studied the effects of **1**–**4** against *Trypanosoma cruzi* and *Leishmania infantum* (Table 1). Norglaucine (**1**) has previously been shown to possess antimalarial activity, with an EC_{50} value of 66 μM against a chloroquine-sensitive strain (D10) and 94 μM against a chloroquine-resistant strain (Dd2) of *Plasmodium falciparum* [13]. In this work, **1** reduced the number of intracellular amastigotes of *Leishmania*-infected macrophages, with an EC_{50} value of 21.7 μM. Although norglaucine showed no mammalian cytotoxicity in previous work in a CHO cell line (>300 μM) [13], our studies demonstrated a potential toxicity to NCTC cells, with a CC_{50} value of 71 μM. **1** also showed activity against the intracellular amastigote form of *T. cruzi* (EC_{50} = 38 μM), and against the extracellular trypomastigote form (EC_{50} = 62 μM).

Nordicentrine (**2**) has also been reported to exhibit activity against *P. falciparum* with an EC_{50} of 0.3 μg/mL [31], and against *P. falciparum* (strain D6) with an EC_{50} value of 0.47 μg/mL [14]. We observed activity against both the intracellular amastigote (EC_{50} of 7 μM) and extracellular trypomastigote (EC_{50} of 19 μM) forms of *T. cruzi*, but no activity against *L. infantum* amastigotes. This compound exhibited the highest mammalian cytotoxicity among the four aporphines, with a CC_{50} value of 21 μM.

In contrast to the secondary amine-containing aporphines, the *N*-methylated glaucine (**3**) demonstrated neither antileishmanial nor antitrypanosomal activity against the clinically relevant intracellular amastigotes. In previous work, glaucine showed poor activity against the insect-borne form of *T. cruzi* (epimastigotes), with an EC_{50} value of 90 μM [16]. Despite the lack of antiparasitic activity of glaucine in our assays, the compound showed a similar mammalian cytotoxicity to norglaucine, with a CC_{50} value of 70 μM.

Finally, dicentrine (**4**) has been shown to exhibit activity against *Trypanosoma brucei brucei* [7] with an EC_{50} value of 14 μM; however considerable mammalian cytotoxicity was observed for dicentrine on HeLa cells, with a CC_{50} value of 8.2 μM. In our studies, **4** was found to be bioactive against *L. (L.) infantum*, with an EC_{50} value of 10.5 μM against the intracellular amastigote form. In contrast, **4** lacked activity against the intracellular amastigotes of *T. cruzi*, with a weak activity against the trypomastigote form (EC_{50} 71 μM). However, it also showed similar levels of mammalian cytotoxicity as nordicentrine.

To our knowledge, this is the first report on the bioactivities against *L. infantum* and *T. cruzi* of the aporphines norglaucine, nordicentrine and dicentrine. In spite of the relatively high levels of cytotoxicity, that three of the four aporphines tested showed respectable activity against at least one of the parasites suggests potential for further development of these scaffolds as antiparasitic agents.

Conclusion

In conclusion, four aporphine natural products were synthesized using an enantioselective, modular and convergent eight step strategy. Key processes in these syntheses were the Bischler-Napieralski cyclization / Noyori asymmetric transfer hydrogenation to form the tetrahydroisoquinoline ring, and Pd-catalyzed C–H arylation to construct the C ring. The natural products were evaluated for bioactivity against *T. cruzi* and *L. infantum*, the causal parasites of visceral leishmaniasis and Chagas disease. Three of the four compounds showed promising bioactivity in these assays.

Experimental Section

*(E)-1,2-Dimethoxy-4-(2-nitrovinyl)benzene (**10a**)* [32]. To a flask containing acetic acid and activated 4Å molecular sieves was added 3,4-dimethoxybenzaldehyde (3.00 g, 18.0 mmol). Nitromethane (4.86 mL, 90.0 mmol) and ethylenediamine (0.12 mL, 1.80 mmol) were added sequentially, and the reaction was stirred at 70 °C overnight. Upon completion, the reaction mixture was cooled to room temperature, poured into cold water, filtered, and washed with more cold water to give the *title compound* **10a** (3.43 g, 16.4 mmol, 91%) as yellow solid. R_f 0.37 (1:1 pentane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 13.5 Hz, 1 H), 7.53 (d, *J* = 13.6 Hz, 1 H), 7.17 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 149.5, 139.4, 135.2, 124.7, 122.8, 111.3, 110.2, 56.1, 56.0; IR (ν_{max} / cm^{-1}) 3128, 2958, 2923, 1500, 1334; HRMS (ES^+) calc. for $C_{10}H_{12}O_4N$ $[M+H]^+$ 210.0766, found 210.0763; mp 138–140 °C.

*(E)-5-(2-Nitrovinyl)benzo[d][1,3]dioxole (**10b**)* [33]. **10b** was prepared from benzo[d][1,3]dioxole-5-carbaldehyde (3.50 g, 23.3 mmol) following the same procedure as for **10a** to give *the title compound* **10b** (3.96 g, 20.5 mmol, 88%) as a yellow solid. R_f 0.77 (1:1 pentane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 13.5 Hz, 1H), 7.47 (d, *J* = 13.5 Hz, 1H), 7.08 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 148.8, 139.1, 135.4, 126.6, 124.2, 109.1, 107.0, 102.1; IR (ν_{max} / cm^{-1}) 3105, 2918,

Table 1. Bioactivity against *Trypanosoma cruzi* and *Leishmania (L.) infantum,* and mammalian cytotoxicity of aporphine alkaloids **1**–**4**.[a]

Compound	EC_{50} Trypomastigote *T.cruzi* (μM) ± SD	EC_{50} Amastigote *T.cruzi* (μM) ± SD	EC_{50} Amastigote *L.infantum* (μM) ± SD	CC_{50} NCTC cells (μM) ± SD
Norglaucine (**1**)	62.6 ± 0.4	38.4 ± 15.3	21.7 ± 7.5	71.3 ± 8.5
Nordicentrine (**2**)	19.8 ± 0.6	7.0 ± 2.0	NA	21.2 ± 12.7
Glaucine (**3**)	>150	NA	NA	70.6 ± 5.7
Dicentrine (**4**)	71.8 ± 0.2	NA	10.5 ± 5.4	27.6 ± 5.9
miltefosine	ND	ND	6.5 ± 3.0	119.7 ± 4.2
benznidazole	17.7 ± 1.9	5.0 ± 1.5	ND	190.6 ± 13.4

[a] EC_{50}: 50% Effective Concentration; CC_{50}: 50% Cytotoxic Concentration; SD: Standard Deviation; ND: Not Determined; NA: Not Active.

2852, 1654, 1602, 1578, 1501, 1448, 1420, 1336, 1262, 1099, 1036, 814, 655; HRMS (ES^+) calc. for $C_9H_7O_4NNa$ $[M+Na]^+$ 216.0273, found 216.0273; mp 163 °C.

*2-(3,4-*Dimethoxyphenyl*)ethanamine (**8a**)* [34]. To a flask containing anhydrous THF (60 mL) was added $LiAlH_4$ (4 M solution in Et_2O, 8.96 mL, 35.8 mmol), and the solution was cooled to 0 °C. A solution of nitroalkene **10a** (2.50 g, 11.9 mmol) in anhydrous THF (20 mL) and added dropwise. The mixture was allowed to reach rt and was then refluxed under N_2 overnight. Upon completion, the reaction mixture was cooled to 0 °C. Et_2O (5 mL) and water (1.15 mL) were added slowly. After 15 mins, 15 % (w/w) aq. sodium hydroxide (1.15 mL) was added. After another 15 mins, water (3.41 mL) was added. The resultant mixture was stirred for 30 mins at rt. Following this, $MgSO_4$ was added, and the mixture was filtered through a Celite pad (CH_2Cl_2 wash). The filtrate was concentrated to give the *title compound* **8a** (1.92 g, 10.9 mmol, 89%) as an amber oil, which was of sufficient purity to use without further purification. R_f 0.05 (9:1 EtOAc/MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.82–6.79 (m, 1H), 6.76–6.71 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.94 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.5, 132.4, 120.8, 112.1, 111.3, 56.0, 55.9, 43.7, 39.5; IR (ν_{max} / cm^{-1}) 3370, 2934, 1606, 1591, 1516, 1464, 1417, 1331, 1261, 1237, 1190, 1157, 1142, 1028, 935, 855, 808, 764, 633; HRMS (ES^+) calc. for $C_{10}H_{16}O_2N$ $[M+H]^+$ 182.1176, found 182.1176; mp 154–155 °C.

*2-(Benzo[d][1,3]dioxol-5-yl)ethanamine (**8b**)* [34]. Amine **8b** was prepared following from **10b** (3.10 g, 48.1 mmol) using the same procedure as for **8a**, to give the *title compound* (2.52 g, 15.2 mmol, 95%) as an amber oil. R_f 0.16 (9:1 EtOAc/MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 6.64 (dd, J = 7.8, 1.6 Hz, 1H), 5.92 (s, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.9, 133.6, 121.7, 109.1, 108.2, 100.8, 43.7, 39.8; IR (ν_{max} / cm^{-1}) 3636, 3368, 2923, 1846, 1607, 1503, 1489, 1443, 1362, 1246, 1190, 1123, 1098, 1040, 933, 928, 864, 818, 637, 601; HRMS (ES^+) calc. for $C_9H_{12}O_2N$ $[M+H]^+$ 166.0863, found 166.0864.

*2-(2-Bromo-4,5-dimethoxyphenyl)acetic acid (**9**)* [27]. 2-(3,4-dimethoxyphenyl)acetic acid (5.00 g, 25.5 mmol) was dissolved in glacial acetic acid (10 mL) and cooled to 0 °C. Br_2 (1.31 mL, 25.5 mmol) dissolved in glacial acetic acid (10 mL) was added dropwise. The ice bath was removed, and the reaction was heated at 60 °C for 1 h. Upon completion, the reaction mixture was cooled, poured into ice water, and the precipitate was filtered off. This solid was washed with $Na_2S_2O_3$ (sat., aq.) and H_2O to afford the *title compound* **9** (6.41 g, 23.3 mmol, 91%) as white solid. R_f 0.48 (EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.79 (s, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.77 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 149.1, 148.5, 125.4, 115.5, 115.2, 114.0, 56.3, 56.2, 41.0; IR (ν_{max} / cm^{-1}) 3550, 1688, 1417, 1281, 1189, 1144, 1045 ; HRMS (ES^+) calc. for $C_{10}H_{10}O_4{}^{79}Br$ $[M-H]^-$ 272.9768, found 272.9767; mp 113–114 °C.

*2-(2-Bromo-4,5-dimethoxyphenyl)-N-(3,4-dimethoxyphenethyl)acetamide (**7a**)* [35]. To a solution of amine **8a** (981 mg, 5.41 mmol) and carboxylic acid **9** (1.48 g, 5.41 mmol) in dry DMF (20 mL) was added 1-hydroxybenzotriazole (1.07 g, 7.95 mmol). The reaction mixture was cooled to 0 °C, then 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.30 g, 6.62 mmol) and *N*-methylmorpholine (2.03 mL, 18.0 mmol) were added. The reaction mixture was warmed slowly to room temperature, and then stirred for 4 h before being quenched by addition of $NaHCO_3$ (10 mL, sat., aq.) and extracted with ethyl acetate (3 × 10mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography over silica gel (2:1 petroleum ether/EtOAc) to give the *title compound* **7a** (1.80 g, 4.11 mmol, 76%) as a white solid. R_f 0.8 (2:1 petrol ether/EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.76 (s, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 8.2, 2.0 Hz, 1H), 5.44 (br s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.59 (s, 2H), 3.46 (app q, J = 6.7 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 149.0, 148.9, 148.7, 147.6, 131.0, 126.5, 120.5, 115.5, 114.7, 113.7, 111.7, 111.2, 56.1, 56.0, 55.8, 55.8, 43.6, 40.7, 34.9; IR (ν_{max} / cm^{-1}) 3414, 2935, 1633, 1549, 1463, 1384, 1244, 1028; HRMS (ES+) calc. for $C_{20}H_{24}O_5N^{79}BrNa$ $[M+Na]^+$ 460.0730, found 460.0729; mp 150–151 °C.

*N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**7b**).* Amide **7b** was prepared from **8b** **(**675 mg, 4.08 mmol) and **9** (1.12 g, 4.08 mmol) following the same procedure as for **9a** to give the *title compound **7b*** (1.40 g, 3.32 mmol, 81%) as a white solid. R_f 0.33 (1:1 pentane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.76 (s, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 1.7 Hz, 1H), 6.50 (dd, J = 7.8, 1.7 Hz, 1H), 5.92 (s, 2H), 5.42 (br s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.59 (s, 2H), 3.43-3.40 (m, 2H), 2.66 (t, J = 6.7 Hz, 2 H); ^{13}C NMR 101 MHz, $CDCl_3$): δ 169.9, 149.1, 148.8, 147.9, 146.2, 132.4, 126.7, 121.7, 115.7, 114.9, 113.8, 109.1, 108.4, 101.0, 56.3, 56.2, 43.8, 40.9, 35.3; IR (ν_{max} / cm^{-1}) 3271, 2981, 2889, 1634, 1606; HRMS (ES+) calc. for $C_{19}H_{21}O_5N^{79}Br$ $[M+H]^+$ 422.0598, found 422.0595; mp 138–141 °C.

*(S)-1-(2-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5a**)* [24]. Trifluoromethanesulfonic anhydride (419 μL, 2.49 mmol) was added via syringe over 5 min to a stirred mixture of amide **7a** (1.00 g, 2.49 mmol) and 2-chloropyridine (259 μL, 2.74 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After 10 min, the reaction mixture was warmed to 0 °C by placing

in an ice-water bath. After 5 min, the solution was allowed to warm to 23 °C, and then quenched by addition of NaOH (15 mL, 1N aq.). CH_2Cl_2 (10 mL) was added and the layers were separated. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure to afford the crude imine, which was immediately used in the next step without further purification. The imine was dissolved in anhydrous DMF (10 mL) at room temperature, then RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (52 mg, 0.092 mmol) was added, and the mixture was placed under a nitrogen atmosphere. The mixture was then cooled to 0 °C, then Et_3N (910 μL) and formic acid (2.0 mL) were added. The reaction was allowed to warm to room temperature and stirred for 24 h before being quenched by addition of $NaHCO_3$ (10 mL, sat., aq.), and extracted with CH_2Cl_2 (3 × 10mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (1:0→0:1 petrol/EtOAc, silica gel deactivated with 0.1% Et_3N) to afford the *title compound* **5a** (598 mg, 1.42 mmol, 57% over 2 steps) as a green oil. R_f 0.06 (99 : 1 EtOAc / MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.89 (s, 1H), 6.60 (s, 1H), 6.38 (s, 1H), 4.59–4.49 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.69 (s, 3H), 3.50–3.16 (m, 4H), 3.03–2.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 148.7, 148.6, 147.4, 127.3, 123.9, 123.2, 115.6, 115.4, 115.2, 111.3, 109.9, 56.5, 56.2, 55.9, 55.6, 54.4, 40.8, 39.1, 25.5; IR (ν_{max} / cm^{-1}) 3662, 3283, 2980, 2890, 1641; HRMS (ES+) calc. for $C_{20}H_{25}O_4N^{79}Br$ $[M+H]^+$ 422.0962, found 422.0966; mp 205–207 °C; $[\alpha]_D^{20}$ +33 (c 0.94, $CHCl_3$).

*(S)-5-(2-Bromo-4,5-dimethoxybenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (**5b**).* Tetrahydroisoquinoline **5b** was prepared from **7b** (1.50 g, 3.56 mmol) following the same procedure as for **5a** to afford the *title compound* **5b** (786 mg, 1.94 mmol, 54% over 2 steps) as a green oil. R_f 0.17 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.81 (s, 1H), 6.79 (s, 1H), 6.58 (s, 1H), 5.91 (s, 2H), 4.25–4.18 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.29 (dd, *J* = 13.8, 3.5 Hz, 1H), 3.23 (ddd, *J* = 12.0, 6.8, 3.5 Hz, 1H), 2.94 (ddd, *J* = 11.7, 6.2, 5.2 Hz, 1H), 2.87 (dd, *J* = 13.8, 10.2 Hz, 1H), 2.81-2.67 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 148.3, 145.9, 145.7, 131.5, 130.4, 128.3, 115.8, 114.7, 114.3, 108.8, 106.4, 100.6, 56.2, 56.1, 55.6, 42.7, 40.4, 30.0; IR (ν_{max} / cm^{-1}) 3322, 2959, 2928, 1602; HRMS (ES+) calc. for $C_{19}H_{21}O_4N^{79}Br$ $[M+H]^+$ 406.0649, found 406.0654; mp 124–125 °C; $[\alpha]_D^{20}$ +28 (c 0.98, $CHCl_3$).

General procedure A for the synthesis of benzyltetrahydroisoquinoline carbamates 11a and 11c. To a stirred solution of the tetrahydroisoquinoline (**5a** and **5b**) (1.0 equiv.), diisopropylethylamine (2.0 equiv.), and 4-dimethylaminopyridine (1–3 mg) in CH_2Cl_2 (0.2 M) was slowly added di-*tert*-butyl dicarbonate (1.2 equiv.), and the resulting mixture was stirred for 2 h at room temperature. Upon completion, the reaction was quenched by addition of NH_4Cl (sat. aq.), and extracted with CH_2Cl_2 (x 3). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (1:1 pentane/EtOAc).

*(S)-Tert-butyl 1-(2-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**11a**)* [35]. Prepared following **General procedure A** from **5a** (362 mg, 0.86 mmol) to give the *title compound* **11a** (350 mg, 0.67 mmol, 78%) as a white solid. R_f 0.14 (2:1 pentane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$. Analysis revealed the presence of two rotamers in a 3:1 ratio denoted Major (M) and minor (m)) δ 7.04 (s, 1H, (M)), 6.97 (s, 0.33H, (m)), 6.74 (s, 1H, (M)), 6.66 (s, 0.33H (m)), 6.62 (s, 1H, (M)), 6.58 (s, 0.33, (m)), 6.52 (s, 1H, (M)), 6.48 (s, 0.33H, (m)), 5.40–5.36 (m, 0.33H, (m)), 5.25 (dd, *J* = 10.0, 3.9 Hz, 1H, (M)), 4.34 (ddd, *J* = 13.2, 6.0, 2.4 Hz, 1H, (M)), 3.86 (s, 6H, (M)), 3.85 (s, 4H, both rotamers), 3.83 (s, 1H, (m)), 3.80 (s, 4H, both rotamers), 3.74 (s, 1H, (m)), 3.40–3.34 (m, 1H, (m)), 3.30–3.19 (m, 2.33H, both rotamers), 3.06–3.01 (m, 0.33H, (m)), 2.95–2.86 (m, 2H, (M)), 2.82–2.76 (m, 0.33H, (m)), 2.65–2.63 (m, 1H, (M)), 2.59–2.55 (m, 0.33H, (m)), 1.39 (s, 3H, (m)), 1.18 (s, 9H, (M)); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer): δ 154.2, 148.5, 148.4, 147.9, 147.4, 130.3, 128.8, 126.6, 115.5, 114.9, 114.4, 111.5, 110.0, 79.4, 56.3, 56.2, 56.0, 55.9, 54.3, 42.1, 36.5, 28.4, 28.0; IR (ν_{max} / cm^{-1}) 3661, 3021, 2981, 1678, 1639, 1609; HRMS (ES+) calc. for $C_{25}H_{33}O_6N^{79}Br$ $[M+H]^+$ 522.1486, found 522.1487; 93% *ee.* The ee value was determined by comparison of HPLC analyses of the optically enriched product (+)-**11a**, and (±)-**11a** obtained by reduction of **9a** with $NaBH_4$. Daicel Chiralpak IB-3 (ϕ 0.46 cm × 25 cm), 5.0 μL/min, room temperature, 5% isopropyl alcohol / 95% *n*-hexane, 210 nm, t = 16.02 min; $[\alpha]_D^{20}$ +51 (c 0.95, $CHCl_3$).

*(S)-Tert-butyl 5-(2-bromo-4,5-dimethoxybenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate (**11c**).* Prepared following **General procedure A** from **5b** (347 mg, 0.86 mmol) to give compound the *title compound* **11c** (360 mg, 0.71 mmol, 83%) as a white solid. R_f 0.35 (7:3 pentane / EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, analysis revealed the presence of two amide rotamers in a 1:0.39 ratio, denoted Major (M) and minor (m)) δ: 7.04 (s, 1H, M), 6.98 (s, 0.39H, m), 6.79 (s, 1H, (M)), 6.62-6.56 (m, 2.17H, both rotamers), 6.52 (s, 1H, (M)), 5.92 (dd, *J* = 5.2, 1.3 Hz, 2H, (M)), 5.90-5.88 (m, 0.78H, (m)), 5.36-5.34 (m, 0.39, (m)), 5.23 (dd, *J* = 10.4, 3.4 Hz, 1H, (M)), 4.33-4.28 (m, 1H, (M)), 3.86 (s, 3H, (M)), 3.83 (s, 1.17H, (m)), 3.80 (s, 4.27H, both), 3.38-3.37 (m, 0.39H, (m)), 3.29-3.15 (m, 3H, (M)), 3.01-2.95 (m, 0.39H, (m)), 2.92-2.83 (m, 2H, (M)), 2.77-2.71 (m, 0.39H, (m)), 2.65-2.61 (m, 0.78H, (m)), 2.58-2.54 (m, 0.39, (m)), 1.36 (s, 3.51H, (m)), 1.14 (s, 9H, (M)); ^{13}C NMR (400 MHz, $CDCl_3$, major rotamer) δ 148.7, 148.5, 148.3, 146.6, 146.2, 130.2, 130.2, 127.9, 115.7, 115.1, 114.5, 108.9, 107.2, 101.0, 79.5, 56.5, 56.3, 54.8, 42.3, 28.8, 28.5, 22.1. HRMS (ES+) calc. for $C_{24}H_{29}NO_6$ $[M+H]^+$ 506.1172, found: 506.1152. 94% *ee.* The ee value was determined by comparison of HPLC analyses of the optically enriched product (+)-**11b**, and (±)-**11b** obtained by reduction of **9b** with $NaBH_4$. Daicel Chiralpak IB-3 (ϕ 0.46 cm× 25 cm), 5.0 μL/min, room temperature, 5% isopropyl alcohol / 95% *n*-hexane, 210 nm, t = 10.02 min; $[\alpha]_D^{20}$ +56 (c 0.98, $CHCl_3$).

General procedure B for the synthesis of benzyltetrahydroisoquinoline carbamates 11b and 11d. Methyl chloroformate (2 eq.) was added slowly to a solution of tetrahydroisoquinoline (**5a** and **5b**) (1 eq.), diisopropylethylamine (2 eq.) and 4-(dimethylamino)pyridine (1-5 mg) in CH_2Cl_2 (0.2 M) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then quenched by adding saturated ammonium chloride solution and extracted with CH_2Cl_2. The combined organic phases were purified by column chromatography on silica gel (pentane/EtOAc, 1:1).

*(S)-Methyl 1-(2-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**11b**).* Prepared following **General procedure B** from **5a** (459 mg, 1.09 mmol) to give compound the *title compound* **11b** (414 mg, 0.86 mmol, 77%). R_f 0.43 (2:1 pentane / EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, analysis revealed the presence of two rotamers in a 1:0.75 ratio, denoted Major (M) and minor (m)) δ 7.03 (s, 1H, (M)), 6.97 (s, 0.75H (m)), 6.63-6.58 (m, 3.5H, both rotamers), 6.49 (s, 1H, (M)), 6.36 (s, 0.75H, (m)), 5.37 (t, *J* = 6.9 Hz, 0.75H, (m)), 5.28 (m, 1H, (M)), 4.25 (ddd, *J* = 13.0, 5.7, 3.0 Hz, 1H, (M)), 3.95-3.89 (m, 0.75H, (m)), 3.87 (s, 6H, (M)), 3.85-3.84 (m, 4.5H, (m)), 3.79 (s, 2.25H, (m)), 3.77 (s, 6H, (M)), 3.70 (s, 2.25H, (m)), 3.67 (s,

2.25H, (m)), 3.46-3.42 (m, 0.75H, (m)), 3.39 (s, 3H, (M)), 3.55-3.31 (m, 0.75H (m)), 3.26-3.19 (m, 1.75H, both rotamers), 3.12-3.07 (m, 0.75H, (m)), 3.03-2.97 (m, 0.75H, (m)), 2.92-2.80 (m, 2H, (M)), 2.68-2.60 (m, 2H, (M)); ^{13}C NMR (101 MHz, $CDCl_3$ major rotamer) δ 156.0, 148.4, 148.2, 148.0, 147.4, 129.9, 128.2, 126.6, 115.4, 114.3, 113.9, 111.5, 110.2, 56.4, 56.3, 56.0, 56.1, 54.5, 52.5, 42.3, 37.7, 28.2; IR (ν_{max} / cm^{-1}) 2953, 2363, 1689, 1508, 1216, 905; HRMS (ES+) calc. for $C_{22}H_{26}O_6N^{79}Br$ $[M+H]^+$ 480.10163, found 480.1093. $[\alpha]_D^{20}$ +77 (c 1.0, $CHCl_3$).

(S)-Methyl-5-(2-bromo-4,5-dimethoxybenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate ***(11d)***. Prepared following **General procedure B** from **5b** (646 mg, 1.59 mmol) to give the *title compound* **11d** (481 mg, 1.03 mmol, 65%). R_f 0.45 (2:1 pentane / EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, analysis revealed the presence of two amide rotamers in a 1:0.75 ratio, denoted Major (M) and minor (m)) δ 7.03 (s, 1H, (M)), 6.97 (s, 0.67H (m)), 6.59 (br s, 1.67H, both rotamers), 6.56 (s, 0.67H, (m)), 6.48 (s, 1H, (M)), 6.47 (s, 0.67H, (m)), 5.92 (s, 2H, (M)), 5.89 (d, *J* = 2.2 Hz, 1.34H, (m)), 5.36 (t, *J* = 6.9 Hz, 0.67H, (m)), 5.26 (dd, *J* = 9.5, 4.2 Hz, 1H, (M)), 4.21 (ddd, *J* = 13.0, 5.7, 3.4 Hz, 1H, (M)), 3.86 (s, 3H, (M)), 3.85 (s, 2H, (m)), 3.79 (s, 3H, (M)), 3.78 (s, 2H, (m)), 3.45-3.36 (m, 1.34, (m)), 3.34 (s, 3H, (M)), 3.25-3.17 (m, 2H, (M)), 3.08-3.02 (m, 0.67H, (m)), 2.99-2.93 (m, 1H, (M)), 2.89-2.81 (m, 1.34H, (m)), 2.79-2.73 (m, 0.65H, (m)), 2.67-2.57 (m, 2H, (M)); ^{13}C NMR (101 MHz, $CDCl_3$ major rotamer) δ 156.0, 148.4, 148.2, 146.6, 146.2, 129.8, 129.6, 127.7, 115.4, 115.3, 114.2, 108.7, 107.2, 101.0, 56.4, 56.3, 54.8, 52.4, 42.4, 37.8, 28.6. IR (ν_{max} / cm^{-1}) 2952, 2361, 1696, 1603, 1505, 1284, 1449, 1259, 1273, 1036, 930; HRMS (ES+) calc. for $C_{21}H_{23}O_6N^{79}Br$ $[M+H]^+$ 464.07033, found 464.07043; $[\alpha]_D^{20}$ +75 (c 0.92, $CHCl_3$).

General procedure C for the synthesis of Aporphine carbamates (12a-d). K_2CO_3 (3.0 eq.), di-*tert*-butyl(methyl)phosphonium tetrafluoroborate (0.1 eq.), $Pd(OAc)_2$ (0.2 eq.) and the tetrahydroisoquinoline carbamate **11a-d** (1.0 eq.) were weighed out into a vial, which was purged with N_2 three times. Degassed the anhydrous DMA (0.2M) is then added and the resulting mixture heated to 130 °C for 8 h. The reaction mixture was then washed with water and extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (28 : 1 pentane / EtOAc).

(S)-Tert-butyl 1,2,9,10-tetramethoxy-6a,7-dihydro-4H-dibenzo[de,g]quinoline-6(5H)-carboxylate ***(12a)*** [35]. Prepared from **11a** (348 mg, 0.66 mmol) following **General procedure C** to give the *title compound* **12a** (163 mg, 0.37 mmol, 55%) as a white solid. R_f 0.60 (1:1 pentane / EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 6.77 (s, 1H), 6.63 (s, 1H), 4.67 (d, *J* = 10.9 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 3.92 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.66 (s, 3H), 3.05–2.73 (m, 4H), 2.68–2.60 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 151.9, 148.2, 147.4, 144.7, 130.1, 130.0, 127.7, 125.8, 124.1, 111.7, 110.9, 110.5, 79.8, 60.0, 55.9, 55.8, 51.9, 31.9, 30.5, 29.4, 28.6; IR (ν_{max} / cm^{-1}) 2922, 2852, 1688, 1596, 1513; HRMS (ES+) calc. for $C_{25}H_{31}O_6NNa$ $[M+Na]^+$ 464.2044, found 464.2045. $[\alpha]_D^{20}$ +95 (c 1.0, $CHCl_3$).

(S)-Methyl 1,2,9,10-tetramethoxy-6a,7-dihydro-4H-dibenzo[de,g]quinoline-6(5H)-carboxylate ***(12b)***. Prepared from **11b** (404 mg, 0.84 mmol) following **General procedure C** to give the *title compound* **12b** (219 mg, 0.55 mmol, 65%) as a white solid. R_f 0.42 (4:1 pentane / EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.79 (s, 1H), 6.63 (s, 1H), 4.75 (d, *J* = 12.8 Hz, 1H), 4.45 (br s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 3.00 (m, 1H), 2.91–2.77 (m, 3H), 2.65 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 152.2, 148.4, 147.6, 144.9, 130.1, 129.86, 127.8, 125.5, 124.2, 111.9, 111.3, 110.7, 60.1, 56.1, 56.0, 55.9, 55.8, 52.8, 52.0, 39.2, 30.5. IR (ν_{max} / cm^{-1}) 2981, 2358, 1698, 1509, 1457, 1394, 1253, 1110, 904; HRMS (ES+) calc. for $C_{22}H_{26}O_6N$ $[M+H]^+$ 400.1755, found 400.1756; $[\alpha]_D^{20}$ +99 (c 1.0, $CHCl_3$).

(S)-Tert-butyl 10,11-dimethoxy-7a,8-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinoline-7(6H)-carboxylate ***(12c)***. Prepared from **11c** (360mg, 0.71mmol) following **General procedure C** to give the *title compound* **12c** (157 mg, 0.36 mmol, 52%) as a white solid. R_f 0.38 (4:1 pentane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.77 (s, 1H), 6.56 (s, 1H), 6.09 (d, *J* = 1.5 Hz, 1H), 5.97 (d, *J* = 1.5 Hz, 1H), 4.85–4.72 (m, 1H), 4.45–4.30 (m, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.04–2.76 (m, 4H), 2.60 (td, *J* = 15.4, 2.3 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 148.4, 147.6, 146.6, 142.1, 131.33, 129.0, 128.0, 127.3, 125.3, 123.2, 111.4, 110.6, 106.8, 100.8, 86.18, 79.9, 56.1, 55.9, 51.9, 31.9, 30.9, 30.5, 28.6; IR (ν_{max} / cm^{-1}) 2971, 2925, 2852, 2252, 1688; HRMS (ES+) calc. for $C_{24}H_{27}O_6NNa$ $[M+Na]^+$ 448.1731, found 448.1729; $[\alpha]_D^{20}$ +78 (c 1.0, $CHCl_3$).

(S)-Methyl 10,11-dimethoxy-7a,8-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinoline-7(6H)-carboxylate ***(12d)***. Prepared from **11d** (470 mg, 1.03 mmol) following **General procedure C** to give the *title compound* **12d** (348 mg, 0.90 mmol, 87%) as a white solid. R_f 0.49 (4:1 pentane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.78 (s, 1H), 6.56 (s, 1H), 6.09 (d, *J* = 1.4 Hz, 1H), 5.97 (d, *J* = 1.4 Hz, 1H), 4.84 (d, *J* = 13.6 Hz, 1H), 4.43 (br s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.77 (s, 3H), 3.02–2.96 (m, 2H), 2.87–2.78 (m, 2H), 2.62-2.59 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 148.6, 147.8, 146.8, 142.9, 128.8, 128.0, 125.0, 123.3, 117.6, 111.6, 110.8, 106.9, 100.9, 56.2, 56.0, 52.8, 52.1, 39.3, 30.9, 30.5; IR (ν_{max} / cm^{-1}) 2984, 1691, 1515, 1453, 1390, 1214, 1119, 906; HRMS (ES+) calc. for $C_{21}H_{22}O_6N$ $[M+H]^+$ 384.1442, found 384.1442; $[\alpha]_D^{20}$ +85 (c 1.0, $CHCl_3$).

General procedure D for the deprotection of carbamates 11a and 11c to synthesise (+)-norglaucine (1) and (+)-nordicentrine (3). Anhydrous $ZnBr_2$ (4 equiv.) was added to a solution of compound **12a** or **12c** (1 equiv.) in dry CH_2Cl_2 (0.1M) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 8 h. The reaction was quenched by addition of with a $NaHCO_3$ (10 mL, sat., aq.), and then extracted with CH_2Cl_2 (x 3). The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was dissolved in a 1 M solution of HCl in diethyl ether (5 mL), stirred for 5 min at 0 °C, and then filtered to give the natural product hydrochloride salt as a yellow solid.

(S)-1,2,9,10-Tetramethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline ((+)-norglaucine, ***1)*** [36]. Prepared from **12a** (101 mg, 0.29mmol) following **General Procedure D** to give the *title compound* **1** (40 mg, 0.12 mmol, 40%) as yellow solid. R_f 0.38 (4:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, MeOD) δ 8.08 (s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 4.33 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.83–3.81 (m, 1H), 3.73 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.68 (s, 3H), 3.39 (td, *J* = 12.7, 4.7 Hz, 1H), 3.28–3.25 (m, 1H), 3.09–3.03 (m, 2H), 2.97–2.87 (m, 1H); ^{13}C NMR (126 MHz, MeOD) δ 155.2, 150.4, 149.6, 146.7, 127.9, 127.5, 127.5, 125.3, 121.9, 121. 1, 113.6, 112.7, 112.2, 60.6, 56.7, 56.5, 54.4, 42.6, 34.5, 26.3; IR (ν_{max} / cm^{-1}) 3019, 1578, 1514, 1466, 1110; HRMS (ES+) calc. for $C_{20}H_{24}O_4N$ $[M+H]^+$ 342.1700, found 342.1699. $[\alpha]_D^{20}$ +83 (c 1.0, MeOH) [Lit. +80 (c 1.0, MeOH)] [28].

(*S)-10,11-Dimethoxy-6,7,7a,8-tetrahydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinoline ((+)-*

*nordicentrine, **3)*** [14]. Prepared from **12c** (135 mg, 0.31 mmol) following **General procedure D** to give the *title compound* **3** (38 mg, 0.11 mmol, 35%) as yellow solid. R_f 0.43 (4:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, MeOD) δ 7.76 (s, 1H), 6.98 (s, 1H), 6.72 (s, 1H), 6.18 (s, 1H), 6.05 (s, 1H), 4.46 (dd, *J* = 14.2, 4.5 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.73 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.40 (td, *J* = 12.8, 4.9 Hz, 1H), 3.25 (td, *J* = 12.2, 5.0 Hz, 1H), 3.12 (dd, *J* = 13.9, 5.0 Hz, 1H), 3.02 (dd, *J* = 18.6, 4.6 Hz, 1H), 2.94 (t, *J* = 14.4 Hz, 1H); ^{13}C NMR (126 MHz, MeOD) δ 150.5, 150.0, 149.8, 144.1, 126.3, 125.4, 124.2, 121.3, 117.4, 112.8, 112.3, 107.9, 102.8, 56.5, 56.4, 54.4, 42.8, 33.8, 26.3; IR (ν_{max} / cm^{-1}) 2981, 2361, 2341, 1558, 1540, 1457, 1248, 1114; HRMS (ES+) calc. for $C_{19}H_{20}O_4N$ $[M+H]^+$ 326.1387, found 326.1385. $[\alpha]_D^{20}$ +70 (c 1.0, MeOH).

General procedure E for the reduction of carbamates 11b and 11d to synthesise (+)-glaucine (2) and (+)-dicentrine (4). $LiAlH_4$ (2.0 M solution in THF, 1.2 equiv.) was added to a stirred solution of aporphine carbamate **12b** or **12d** (1 equiv.) in dry THF (0.2M) at 0 °C under a nitrogen atmosphere, and the resulting mixture was allowed to warm to room temperature, and then stirred for 24 h. The reaction was quenched by slow addition of H_2O (3 mL) and 1 M NaOH (5 mL) and then extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (1:0.2 CH_2Cl_2 / MeOH, silica gel deactivated with 0.1% Et_3N).

*(S)-1,2,9,10-Tetramethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline ((+)-glaucine, **2)*** [30]. Prepared from **12b** (210 mg, 0.51 mmol) following **General procedure E** to give the *title compound* **2** (91 mg, 0.25 mmol, 48%) as white solid. R_f 0.23 (4:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 6.78 (s, 1H), 6.59 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.65 (s, 3H), 3.19–3.11 (m, 1H), 3.05–2.99 (m, 3H), 2.70–2.58 (m, 2H), 2.55 (s, 3H), 2.53–2.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 148.2, 147.6, 144.5, 129.5, 129.1, 127.4, 127.0, 124.7, 111.8, 111.0, 110.6, 62.7, 60.3, 56.1, 56.0, 55.9, 53.5, 44.2, 34.7, 29.5; IR (ν_{max} / cm^{-1}) 3052, 1579, 1321, 1170; HRMS (ES+) calc. for $C_{21}H_{26}O_4N$ $[M+H]^+$ 356.1856, found 356.1865; mp 110–115 °C [Lit. 117–118 °C][28]; $[\alpha]_D^{20}$ +93 (c 1.0, $CHCl_3$).

*(S)-10,11-Dimethoxy-7-methyl-6,7,7a,8-tetrahydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinoline ((+)-dicentrine, **4)*** [29]. Prepared from **12d** (340 mg, 0.88 mmol) following **General procedure E** to give the *title compound* **4** (161 mg, 0.47 mmol, 53%) as a white solid. R_f 0.45 (4:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 6.78 (s, 1H), 6.52 (s, 1H), 6.08 (d, *J* = 1.4 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.16–2.61 (m, 4H), 2.68–2.61 (m, 2H), 2.55 (s, 3H), 2.52–2.48 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 147.8, 146.7, 141.9, 128.5, 126.8, 126.6, 123.7, 116.7, 111.4, 110.6, 106.9, 100.7, 62.6, 56.2, 56.0, 53.7, 44.1, 34.4, 29.4; IR (ν_{max} / cm^{-1}) 2957, 1607, 1515, 1462, 1266, 1215, 1095; HRMS (ES+) calc. for $C_{20}H_{22}O_4N$ $[M+H]^+$ 340.1543, found 340.1543; mp 166–169 °C. [Lit. mp 176–177 °C][38]. $[\alpha]_D^{20}$ +72 (c 1.0, $CHCl_3$) [Lit. +62 (c 1.0, $CHCl_3$)] [38].

Biological Assays: Animals. Male golden hamsters (*Mesocricetus auratus*) and female BALB/c mice were obtained from the animal breeding facility at the Instituto Adolfo Lutz, Brazil. The animals were maintained in sterilized cages under a controlled environment, receiving water and food *ad libitum*. All procedures performed were previously approved by the Animal Care and Use Committee from Instituto Adolfo Lutz – Secretary of Health of São Paulo State (Project number CTC 21H/2015, CEUA 04/2016) in agreement with the Guide for the Care and Use of Laboratory Animals from the National Academy of Sciences.

Parasites and mammalian cell maintenance. *Leishmania (L.) infantum* amastigotes were obtained from the spleen of golden hamsters previously infected and purified by differential centrifugation [39]. Peritoneal macrophages were collected by washing the peritoneal cavity of BALB/c mice with RPMI-1640 medium (Sigma-Aldrich) supplemented with 10% FBS, and were maintained at 37 ºC in a 5% CO_2 humidified incubator [40]. Murine fibroblasts NCTC (clone L929, ATCC) were maintained in RPMI-1640 supplemented with 10% FBS at 37 ºC in a 5% CO_2 humidified incubator. *Trypanosoma cruzi* (Y strain) trypomastigotes were maintained in Rhesus monkey kidney cells (LLC-MK2 – ATCC CCL 7), cultivated in RPMI-1640 medium supplemented with 2% fetal calf serum at 37ºC in 5% CO_2 humidified incubator.

Evaluation of 50% Effective Concentration (EC_{50}). *Leishmania (L.) infantum*. Peritoneal macrophages (1x10^5 cells/well) were seeded in 16-well slide chambers (NUNC) and mantained for 18 h at 37 ºC in 5% CO_2 humidified incubator. Cells were infected with amastigotes at a ratio of 10:1 (amastigotes/macrophage) and treated with compounds (20 to 1 μM) for 96 h. Stained slides (Giemsa) were observed in a light microscope EVOS M5000 (Thermo, USA) using the EVOS M5000 software for quantification of the infectivity index. The infectivity index was used for the determination of the EC_{50} values and it was defined by the number of infected macrophages X number of intracellular amastigotes/number of total macrophages [11]. Miltefosine was used as standard and untreated cells as a negative control with 0.5% DMSO (v/v).

Trypanosoma cruzi. Trypomastigotes were counted in a hemocytometer chamber and seeded at 1 x 10^6 cells/well in 96 well microplates. The compounds were dissolved in DMSO, diluted (150 to 0.29 μM) in RPMI-1640 medium and incubated for 24h at 37ºC in a 5% CO_2 humidified incubator. The parasite viability was determined using the resazurin (0.011% in PBS). The optical density was read at 570 nm using control wells without drugs (100% viability) and without cells (blank). The control group consisted of trypomastigotes incubated with 0.5% (v/v) DMSO [41]. Benznidazole was used as a positive control. For the intracellular amastigote assay, peritoneal macrophages were dispensed (1 x 10^5/well) in 16 well chamber slides (NUNC, Thermo, USA) and maintained for 24 h in the same medium at 37ºC in a 5% CO_2 humidified incubator for attachment. Non-adherent cells were removed by two step washings with medium. After 24 h, these cells were infected with 5 x 10^5 culture trypomastigotes for 4 h. Cells were treated with compounds for 48 h. After fixation with methanol and staining with Giemsa, the slides were observed in a light microscope EVOS M5000 (Thermo, USA) using the EVOS M5000 software for quantification of the infectivity index. The infectivity index was used for the determination of the EC_{50} values and it was defined by the number of infected macrophages X number of intracellular amastigotes/number of total macrophages Benznidazole was used as the standard drug (50 to 0.78 μM) and untreated cells as a negative control with 0.5% DMSO (v/v).

Determination of the 50% Cytotoxic Concentration (CC_{50}) **in mammalian cells.** The murine conjunctive cells (NCTC clone 929, ATCC®) were counted in a hemocytometer chamber, seeded at 6 x 10^4/well and incubated (200 to 0.19 μM) for 48 h at 37 ºC in a 5% CO2 humidified incubator. The cell viability was determined using the MTT assay Benznidazole was used as a positive control.

The selectivity index (SI) was determined using the relationship between CC_{50} / EC_{50} in intracellular amastigotes (*T. cruzi* or *Leishmania*) [11].

Statistical analysis. The determination of the CC_{50} and EC_{50} values was obtained from sigmoid dose-response curves. The statistical significance (p value) between the samples was evaluated through the One-way ANOVA method using the Tukey's Multiple Comparison test. All analyzes were performed using Graph Pad Prism 5.0 software. The samples were tested in duplicate or triplicate and the assays were repeated at least twice independently.

Acknowledgments

PP thanks the Swiss National Science Foundation for an SNSF Fellowship, and the Marie Skłodowska-Curie actions for an Individual Fellowship (GA No 832700). EAA thanks the Oxford Internal GCRF Research England Fund (Grant no. 0006019), and the EPSRC for additional support (EP/M019195/1). MA and AGT thank the São Paulo State Research Foundation (FAPESP 2018/10279-6, 2018/25128-3). AGT thanks Conselho Nacional de Pesquisa e Desenvolvimento for a Scientific Research Award.

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra and HPLC traces. This information is available via the publisher website.

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