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Synthesis of *C*-homoaporphines via microwave-assisted direct arylation

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ABSTRACT

Representatives of the *C*-homoaporphine class of alkaloids have shown interesting biological activities. To date the synthesis of these molecules has never been attempted via a direct-arylation strategy. We report herein the first Pd-mediated intramolecular direct arylation in the synthesis of *C*-homoaporphines via the use of microwaves. Use of tricyclohexylphosphine tetrafluoroborate as ligand gave good percentage conversions and suppressed competing debromination with the substrates evaluated. This arylation strategy should be broadly useful in the synthesis of *C*-homoaporphine alkaloids as demonstrated herein in the synthesis of (±)-homonantenine.

1. Introduction

C-Homoaporphine alkaloids (**1**) are structurally-related to aporphine alkaloids (**2**, Fig. 1); as compared to aporphines these compounds have an additional carbon atom in the C ring. The analogous *B*-homoaporphines are relatively rare in the literature and have not been reported to occur in nature. Members of the *C*-homoaporphine series occur naturally in plants of the Liliaceae family, specifically the *Merendera*, *Colchicum*, *Kreysigia*, *Androcymbium*, *Bulbocodium*, *Iphigenia* and *Gloriosa* genera.[1] With regards to biological activity, some *C*-homoaporphines have been reported to exhibit acetylcholinesterase and butylcholinesterase inhibitory activities and smooth muscle relaxing effects.[2]

A number of approaches to the synthesis of *C*-homoaporphines have been reported. The majority of these methods involve metal-mediated biaryl cyclization of a phenolic or phenol ether tetrahydroisoquinoline precursor as a key step in construction of the homoaporphine core (Fig. 1).[3] This approach is generally undesirable since toxic metal reagents are used and yields are sometimes quite low. A more recent approach uses a photostimulated intramolecular *ortho*-arylation of a phenol with an activated aryl ring to construct the biaryl bond.[4] Acid treatment of *p*-quinol acetates, (prepared from phenethylisoquinolines via lead tetraacetate oxidation) has also been employed to prepare *C*-homoaporphines.[5] A fourth approach to the preparation of these molecules, is via ring-expansion of dehydroaporphines.[6]

Owing to the interesting biological activities exhibited by these compounds and the limited access from natural sources, the development of rapid and efficient methods to prepare libraries of these compounds is desirable.

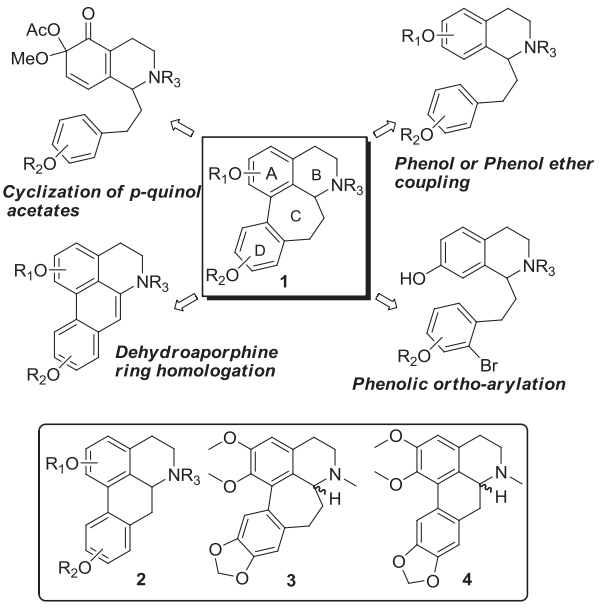

Fig. 1. Approaches to the synthesis of homoaporphines.

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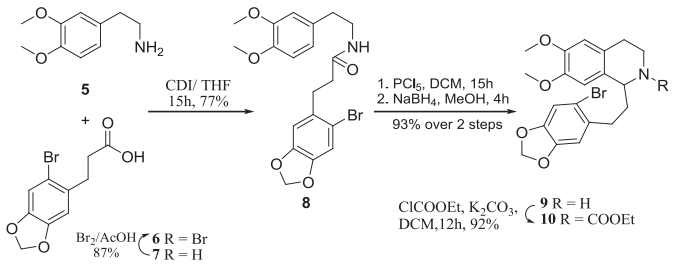
Microwave promoted reactions have become increasingly popular in the literature since the use of microwaves can enhance reaction rates and yields of several reactions.[7a–c] The generation of large compound libraries for medicinal chemistry efforts has benefited from advances made in microwave-assisted chemistry.[7d] The use of microwaves is also a valuable tool for reaction optimization studies.[7a–c]

The synthesis of *C*-homoaporphines by direct arylation has never been reported in the literature. In fact, direct arylation for the synthesis of seven-membered rings via coupling of two arene partners is particularly rare.[8] We recently reported a microwave-assisted direct arylation protocol for the rapid synthesis of aporphines.[9] Perceived challenges notwithstanding and based on our earlier work, we envisaged that microwave-assisted direct arylation might also be applicable to the preparation of *C*-homoaporphines from tetrahydroisoquinoline precursors. Our efforts in this regard are reported herein.

2. Results and discussion

The phenethyl tetrahydroisoquinoline **10** was prepared as a substrate for studying the microwave-assisted direct arylation reaction (Scheme 1). This substrate was also chosen since it would allow for the synthesis of the ring *C*-homolog (**3**) of the aporphine alkaloid nantenine (**4**) as part of our continuing structure–activity relationship studies on aporphine derivatives at human 5-HT_{2A} receptors.[9,10] Thus phenethylamine **5** was coupled to the bromoacid **6** to give amide **8**. Bischler–Napieralski cyclization of **8** furnished an intermediate imine, which was subjected to $NaBH_4$ reduction to afford amine **9**. N-protection of **9** as an ethyl carbamate in the subsequent step gave the arylation substrate **10**.

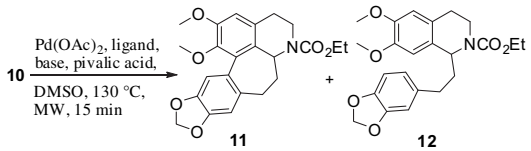


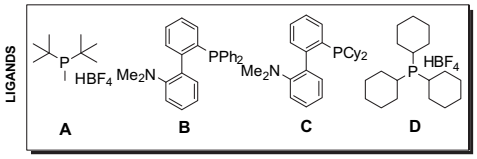
Scheme 1. Synthesis of arylation substrate **10**.

To initiate our study, we then attempted the microwave-assisted direct arylation on **10** using similar conditions as we recently reported for the synthesis of **4** and other aporphines (Table 1).[8]

These conditions (Table 1, entry 1) furnished the expected cyclized product **11** as well as debrominated product **12** in a ratio of 1:5 giving **11** in only 16% isolated yield. Two biphenyl phosphine ligands **B** and **C** were also screened based on the reported utility of these ligands in the synthesis of the structurally similar seven-membered ring containing allocolchicinoids.[8] Unfortunately, only debrominated product **12** (Table 1, entries 2 and 3) was obtained with these ligands. However, we were pleased to find that ligand **D** gave us a slight improvement in the product ratio as compared to ligand **A**, when either K_2CO_3 or Cs_2CO_3 was used as base (Table 1, entries 4 and 5). Spurred by the preceding, we decided to continue our examination of this reaction with other substrates. Our prior success with benzyl ether substrates in the synthesis of nantenine analogs, prompted us to consider similar substrates for this study.[8] Thus, compound **13** (Table 2) was prepared from readily available starting materials using a similar route as delineated above for compound **10**. We decided to screen a number of ligands for the direct arylation of **13**. With ligand **A**, we obtained the desired

Table 1
Initial conditions—microwave-assisted direct arylation on **10**

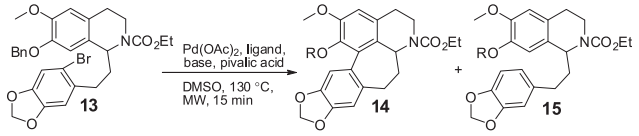


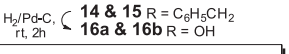


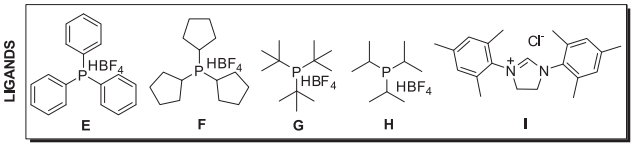
Entry	Ligand	Base	Ratio **11**:**12**[a]	Yield of **11** (%)[b]
1	A	K_2CO_3	1:5	16
2	B	K_2CO_3	0:1	0
3	C[c]	K_2CO_3	0:1	0
4	D	Cs_2CO_3	1:1	13
5	D	K_2CO_3	1:1.5	36

[a] Based on isolated yields of **11** and **12**.
[b] Isolated yield.
[c] Ligand:Pd ratio used was 1:1.

Table 2
Microwave-assisted direct arylation optimization study with substrate **13**







Entry	Ligand	Base	Ligand:Pd[a]	Ratio **14**:**15**:**13**[b]
1	A	K_2CO_3	4:2	1:1:1
2	E	K_2CO_3	4:2	1:4:6
3	F	K_2CO_3	4:2	1:1:8
4	G	K_2CO_3	4:2	2:1:2
5	H	K_2CO_3	4:2	1:3:0
6	I	K_2CO_3	4:2	3:1:16
7	D	K_2CO_3	4:2	4:1:0
8	D	K_2CO_3	4:1	6:1:0
9	D	K_2CO_3	8:4	1:1:1
10	D	Cs_2CO_3	4:2	1:4:7
11	D	Ag_2CO_3	4:2	1:6:0
12	D	K_2CO_3	1:1	2:1:3

[a] Ratio relative to starting material.
[b] Determined by HPLC.

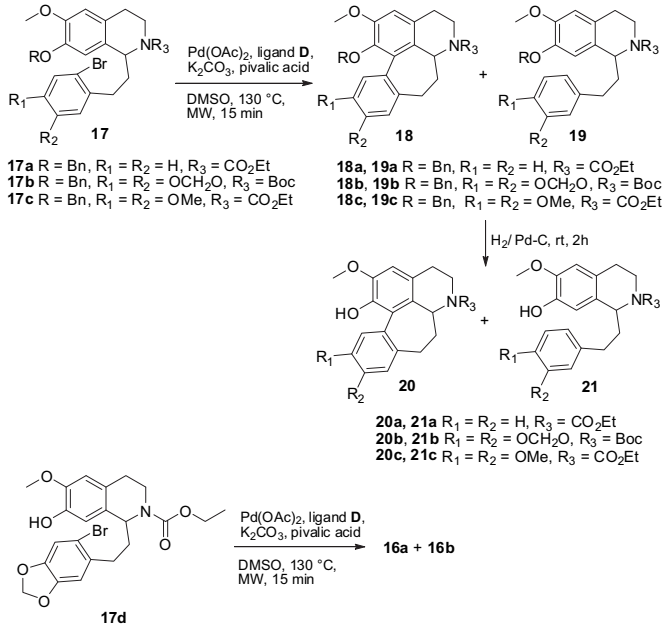
cyclized product **14** and the debrominated by-product **15** in addition to starting material (Table 2, entry 1). Although we could chromatographically separate compound **13** from a mixture of **14**/**15**, the mixture of compounds **14** and **15** could not be separated with a variety of chromatographic procedures attempted.

At this juncture, we decided to investigate other bulky alkyltetrafluoroborate phosphine ligands. In this examination, ligands **E**,**F** and ligand **H** gave poor results—low conversion of starting material and/or sub-optimal ratios of **14**:**15** (Table 2, entries 2, 3 and 5). Ligand **G** gave a slightly better **14**:**15** product ratio of 2:1 (Table 2, entry 4). Marginal improvement in this product ratio (3:1) was observed with the *N*-heterocyclic carbene ligand **I**, but the conversion was too low

to consider for further investigation (Table 2, entry 6). However, we were excited to find that ligand **D** gave a 4:1 ratio of **14**:**15** (Table 2, entry 7) with complete consumption of starting material. This ratio improved to 6:1 when a 4:1 ratio of ligand/Pd was employed (Table 2, entry 8). The **14**/**15** mixture upon hydrogenolysis furnished a mixture of **16a** and **16b**, which was purified by column chromatography to furnish the cyclized phenol **16a** in 71% yield over two steps from **13**. Other bases were ineffective in improving the product ratio or yields of **14** (Table 2, entries 10 and 11). The cyclization of similar substrates in direct arylation reactions is known to be susceptible to changes in the ligand/Pd ratio.[8a] Therefore we decided to investigate the effect of the ligand/Pd ratio. This brief study indicated that a 1:1 ratio or 8:4 ratio of ligand/Pd was not optimal in improving the product ratio (Table 2, entries 9 and 12).

In further examinations of the substrate scope of the microwave-assisted arylation protocol, we prepared arylation substrates **17a**–**c** using similar methods as above, and subjected these substrates to our optimal conditions (Table 3). As in the case of **13**, mixtures of desired cyclized products (**18**) and the corresponding debrominated products (**19**) were obtained; no starting material (**17**) was detected in these reactions.

Table 3
Direct arylation with other substrates

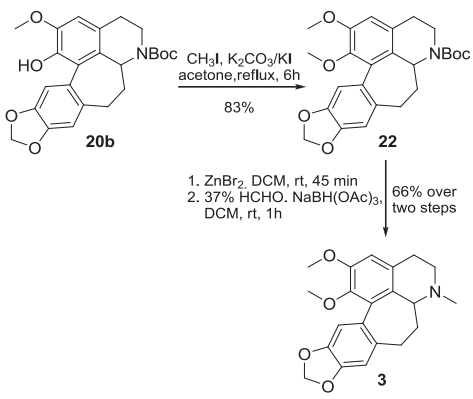


Entry	Substrate	Ratio (**18**:**19**/**16a**:**16b**)[a]	Yield of **20**/**16a** (%)
1	**17a**	6:1	72[b]
2	**17b**	7:1	85[b]
3	**17c**	5:1	70[b]
4	**17d**	5:1	69[c]

[a] No starting material detected.
[b] Isolated yield over two steps from **17a**–**c**.
[c] Isolated yield over single step from **17d**.

Debenzylation of the **18**/**19** product mixtures followed by chromatographic purification of the resultant phenols gave the desired cyclized products in good yields. Cyclization of the phenol **17d** could also be affected in overall yield comparable to that of the phenol ether substrates (Table 3, entry 4).

Following the development of successful microwave-promoted arylation conditions, we then proceeded to prepare (±)-homonantenine (**3**). At the outset, this seemed easiest via LAH reduction of compound **11**; however, we obtained only a 19% yield of **3** in this transformation. An improved route to **3** was executed wherein compound **20b** was sequentially *O*-methylated (**22**), Boc-deprotected, and *N*-methylated (Scheme 2).



Scheme 2. Synthesis of Homonantenine (**3**).

3. Conclusions

This is the first report on the use of a microwave-assisted direct-arylation strategy for the synthesis of *C*-homoaporphine alkaloids. Of several ligands screened, ligand **D**, (tricyclohexylphosphine tetrafluoroborate) proved to be effective for cyclization of a variety of substrates. *N*-ethyl carbamate and *N*-Boc protecting groups are tolerated with the conditions used. Based on the substrates investigated, it is apparent that unsubstituted or oxygenated functionalities in the incipient homoaporphine ring D and phenol ether or phenolic moieties in ring A, are also well tolerated. As compared to our previously reported aporphine-targeted arylation, the present method requires slightly longer reaction times (5 min vs 15 min). This is not surprising given the greater entropic cost in cyclizing a seven-membered versus a six-membered ring. This arylation methodology should find general applicability in the synthesis of naturally occurring and biologically active *C*-homoaporphine alkaloids as well as their analogs. Furthermore, these conditions form a framework for optimizing the challenging seven-membered ring construction in other chemotypes.

4. Experimental

4.1. General experimental procedures

All glass apparatus were oven dried prior to use. A CEM Discover microwave reactor was used to carry out all direct arylation reactions. HRESIMS spectra were obtained using an Agilent 6520 Q-TOF instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker DPX-500 spectrometer (operating at 500 MHz for ^{1}H; 125 MHz, respectively, for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR as solvent unless stated otherwise. Chemical shift (δ 0.00 ppm) values are reported in parts per million and coupling constants in hertz (Hz). Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). Melting points were obtained on a Mel-Temp capillary electrothermal melting point apparatus. Reactions were monitored by TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm) and by staining with vanillin spraying reagent (2 gm vanillin in 1 L of 10% H_2SO_4) followed by heating. Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230–400 mesh, 0.04–0.063 μm particle size). All chemicals and reagents were

obtained from Sigma–Aldrich and Fischer Scientific (USA) and were used without further purification.

4.2. Experimental procedures and characterization data

*4.2.1. Synthesis of 3-(6-bromobenzo[d][1,3] dioxol-5-yl)-N-(3,4-dimethoxyphenethyl) propanamide (**8**).* A solution of 6 (1.375 gm, 5.1 mmol) and 1,1′-carbonyldiimidazole (0.745 gm, 4.6 mmol, CDI) in anhyd THF (40 mL) was stirred at 0 °C for 1.5 h and then, at room temperature for 1 h. The mixture was cooled in an ice-bath and stirred for 1 h; then 3, 4-dimethoxyphenethylamine (5) (0.762 mL, 4.6 mmol) was added and the solution was stirred at 0 °C for 4 h and left stirring overnight at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and extracted with 1 N HCl (25 mL), washed with water (50 mL), satd $NaHCO_3$ solution (25 mL), then with water (50 mL), and finally with brine (50 mL). The organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product was crystallized from EtOAc/Diethylether to furnish amide 8 as a white solid (1.538 gm, 77% yield). Mp: 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.79 (d, 1H, J=8.1 Hz), 6.75 (s, 1H), 6.68 (d, 1H, J=1.8 Hz), 6.65 (dd, 1H, J=8.1, 1.8 Hz), 5.93 (s, 2H), 5.37 (br t, 1H), 3.86 (s, 6H), 3.47 (dd, 1H, J=12.9, 6.8 Hz), 2.97–2.94 (m, 2H), 2.71 (t, 2H, J=6.8 Hz), 2.39–2.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8 (C), 149.2 (C), 147.9 (C), 147.6 (C), 147.1 (C), 133.2 (C), 131.4 (C), 120.8 (CH), 114.3 (C), 112.8 (CH), 111.9 (CH_2), 111.5 (CH), 110.5 (CH), 101.8 (CH_2), 56.1 (CH_3), 56.0 (CH_3), 40.8 (CH_2), 36.9 (CH_2), 35.4 (CH_2), 32.3 (CH_2); HRESIMS calculated for $C_{20}H_{22}BrNO_5$ [M^+]: 435.0681; found 435.0684.

*4.2.2. Synthesis of 1-(2-(6-bromobenzo[d][1,3] dioxol-5-yl) ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9**).* To a magnetically stirred ice-cooled solution of **8** (0.50 g, 1.15 mmol) in dry DCM (25 mL) was added solid phosphorus pentachloride (0.358 g, 1.71 mmol) in several portions over 10 min. The reaction mixture was stirred at 0 °C for 1 h and then left to stir at room temperature for 20 h. The reaction mixture was then poured onto a saturated solution of satd $NaHCO_3$ (20 mL) and the contents of the flask were stirred for 1 h. The aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layer was washed with satd $NaHCO_3$ solution (2×20 mL), washed with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography over deactivated silica gel using 0.7% MeOH/DCM as eluant to furnish a crude imine product as a white solid. To a magnetically stirred ice-cooled solution of this crude imine in a mixture of dry MeOH (20 mL) and dry DCM (20 mL), was added powdered $NaBH_4$ (0.437 g, 11.5 mmol) in three portions over 10 min. The reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with water and extracted with dichloromethane (3×20 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography over deactivated silica gel using 0.7% MeOH/DCM as eluant to furnish pure **9** as a white solid (0.45 g, 93% yield from **8**). Mp: 82–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (s, 1H), 6.81 (s, 1H), 6.61 (s, 1H), 6.57 (s, 1H), 5.93 (dd, 2H, J=2.6, 1.1 Hz), 4.08 (t, 1H, J=5.5 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.36–3.31 (m, 1H), 3.09–3.04 (m, 1H), 2.82 (m, 3H, J=2.6 Hz), 2.73 (td, 1H, J=16.1, 5.1 Hz), 2.0 (dd, 2H, J=14.3, 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7 (C), 147.6 (C), 147.5 (C), 146.8 (C), 134.6 (C), 126.8 (C), 114.3 (C), 112.8 (CH), 111.8 (CH), 110.3 (CH), 109.3 (CH), 101.7 (CH_2), 56.2 (CH_3), 56.0 (CH_3), 55.2 (CH), 41.1 (CH_2), 36.4 (CH_2), 32.8 (CH_2), 28.9 (CH_2); HRESIMS calculated for $C_{20}H_{22}BrNO_4$ [M^+]: 419.0732; found 419.0726.

*4.2.3. Synthesis of ethyl 1-(2-(6-bromobenzo[d][1,3] dioxol-5-yl) ethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**10**).* To a solution of compound **9** (0.46 g, 1.09 mmol) dissolved in dry dichloromethane (25 mL) was added ethyl chloroformate (0.10 mL, 1.09 mmol), and potassium carbonate (0.228 mg, 1.63 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 12 h, quenched with satd NH_4Cl solution (10 mL), and extracted with dichloromethane (3×20 mL). The organic layer was washed with water (10 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resultant crude product, on column chromatography over silica gel using EtOAc/Hexanes (20:80) as eluant furnished a rotameric mixture of **10** (0.497 g, 92% yield) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.78–6.72 (m, 1H), 6.58 (s, 2H), 5.91 (s, 2H), 5.91 (s, 2H), 5.16 (d, 2H, J=5.5 Hz), 4.31–4.10 (m, 3H), 3.84 (s, 3H), 3.36–3.27 (m, 1H), 2.92–2.86 (m, 1H), 2.75 (br s, 2H), 2.65 (d, 1H, J=15.8 Hz), 2.07–2.01 (m, 1H), 1.97 (br s, 1H), 1.30 (t, 3H, J=6.9 Hz); ^{13}C NMR (125, MHz, $CDCl_3$): δ 156.0 and 155.8 (2×C), 147.8 and 147.7 (2×C), 147.4 and 147.4 (2×C), 146.7 (C), 134.4 and 134.1 (2×C), 129.7 and 129.2 (2×C), 126.2 and 125.8 (2×C), 114.2 and 114.1 (2×C), 112.8 and 112.7 (2×CH), 111.6 and 111.4 (2×CH), 110.1 and 110.0 (2×CH), 109.8 (CH), 101.6 (CH_2), 61.5 and 61.4 (2×CH_2), 56.0 and 55.9 (2×CH_3), 54.2 (CH), 38.1 and 37.5 (2×CH_2), 37.2 and 37.0 (2×CH_2), 33.4 (CH_2), 28.1 and 27.8 (2×CH_2), 14.8 and 14.2 (2×CH_3); HRESIMS calculated for $C_{23}H_{26}BrNO_6$ [M^+]: 491.0944; found 491.0943.

*4.2.4. Typical microwave-assisted direct arylation procedure for ethyl 11,12-dimethoxy-1,2,4,5-tetrahydro-[1,3] dioxolo [4″,5″:4′,5′] benzo [1′,2′:6,7] cyclohepta [1,2,3-ij] isoquinoline-3 (3aH)-carboxylate (**11**).* In a microwave reaction vial, compound **10** (50.0 mg, 0.10 mmol), Pd $(OAc)_2$ (4.57 mg, 0.02 mmol), ligand D (14.9 mg, 0.04 mmol), K_2CO_3 (42.2 mg, 0.30 mmol), and pivalic acid (3.1 mg, 0.03 mmol) were added and dissolved in Ar-purged anhyd DMSO (0.5 mL). The mixture was irradiated in the CEM microwave reactor for 15 min at 130 °C with the power level at 200 W. After cooling to room temperature, the reaction mixture was loaded directly onto a deactivated silica gel column and eluted with 10% EtOAc/hexanes to furnish a rotameric mixture of compound **11** (15.2 mg, 36% yield) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 and 6.93 (2×s, 1H), 6.75 and 6.72 (2×s, 1H), 6.68 and 6.65 (2×s, 1H), 6.02–5.94 (m, 2H), 4.74 and 4.60 (2×dd, 1H, J=10.7, 6.9, 10.6, 7.5 Hz), 4.32 and 4.16 (2×dd, 1H, J=13.2, 5.8, 13.5, 5.5 Hz), 4.15–4.01 (m, 2H), 3.88 (s, 3H), 3.49 (s, 3H), 3.26 and 3.17 (2×dt, 1H, J=12.8, 3.4, 12.9, 3.2 Hz), 2.99–2.88 (m, 1H), 2.74–2.69 (m, 1H), 2.46–2.21 (m, 3H), 2.06–2.01 (m, 1H), 1.19 (2×t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4 and 155.0 (2×C), 151.9 and 151.8 (2×C), 147.2 and 147.1 (2×C), 146.0 and 144.5 (2×C), 133.1 and 133.0 (2×C), 132.3 and 132.0 (2×C), 129.3 and 128.8 (2×C), 128.2 and 127.9 (2×C), 127.7 (C), 127.1 and 126.5 (2×C), 111.8 and 111.6 (2×CH), 111.1 (CH), 108.5 and 108.2 (2×CH), 101.1 and 101.0 (2×CH_2), 61.4 (CH_2), 60.6 (CH_3), 56.0 (CH_3), 50.8 and 50.6 (2×CH), 37.4 and 37.1 (2×CH_2), 36.9 and 36.6 (2×CH_2), 30.5 and 29.9 (2×CH_2), 29.3 and 29.1 (2×CH_2), 14.8 and 14.2 (2×CH_3); HRESIMS calculated for $C_{23}H_{25}NO_6$ [M^+]: 411.1682; found 411.1682.

*4.2.5. General procedure for the synthesis of direct arylation substrates **13**, **17a**, **17b** and **17c**: (Compound **13** as representative).* To a solution of the secondary amine precursor (2.876 g, 5.8 mmol) dissolved in dry dichloromethane (25 mL) was added ethyl chloroformate (0.630 mL, 7.8 mmol), and potassium carbonate (1.204 mg, 8.7 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 12 h, quenched with satd NH_4Cl solution (50 mL) and extracted with dichloromethane (3×50 mL). The organic layer was washed with water (50 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The resultant crude product, on column chromatography over silica gel using EtOAc/hexanes (20:80) as eluant, furnished a rotameric mixture of **13** (2.571 g, 78% yield) as a white solid.

*4.2.5.1. Ethyl 7-(benzyloxy)-1-(2-(6-bromobenzo[d][1,3] dioxol-5-yl) ethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**13**).* Mp: 85–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, 2H, J=6.7 Hz),

7.35–7.32 (m, 2H), 7.27–7.25 (m, 1H), 6.96 (d, 1H, *J*=7.7 Hz), 6.72–6.58 (m, 3H), 5.93 (s, 2H), 5.12–5.00 (m, 3H), 4.25–4.06 (m, 3H), 3.85 (s, 3H), 3.29 (m, 1H), 2.90–2.84 (m, 1H), 2.65–2.61 (m, 3H), 1.99–1.91 (m, 1H), 1.82–1.78 (m, 1H), 1.28 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1 and 155.9 (2×C), 148.7 and 148.5 (2×C), 147.5 (C), 146.7 and 146.7 (2×C), 146.6 (C), 137.2 (C), 134.5 and 134.2 (2×C), 129.7 and 129.3 (2×C), 128.7 (CH), 128.0 (CH), 127.5 (CH), 127.1 and 126.7 (2×C), 114.4 (C), 113.3 and 113.2 (2×CH), 112.9 and 112.8 (2×CH), 112.2 and 112.1 (2×CH), 110.2 and 109.9 (2×CH), 101.7 (CH_2), 71.5 (CH_2), 61.6 and 61.5 (2×CH), 56.2 (CH_3), 54.2 (CH), 38.2 and 37.6 (2×CH_2), 37.2 and 37.1 (2×CH_2), 33.4 (CH_2), 28.3 and 28.0 (2×CH_2), 14.9 (CH_3); HRESIMS calculated for $C_{29}H_{30}BrNO_6$ [M^+]: 567.1257; found 567.1260.

*4.2.5.2. Ethyl 7-(benzyloxy)-1-(2-bromophenethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**17a**).* Mp: 71–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.51 (m, 1H), 7.41 (m, 2H), 7.33 (t, 2H, *J*=7.1 Hz), 7.24–7.15 (m, 3H), 7.06–7.04 (m, 1H), 6.61–6.59 (m, 2H), 5.15–5.04 (m, 3H), 4.29–4.07 (m, 3H), 3.85 (s, 3H), 3.36–3.24 (m, 1H), 2.93–2.75 (m, 3H), 2.65–2.62 (m, 1H), 2.04–2.00 (m, 1H), 1.87 (m, 1H), 1.28 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1 and 156.0 (2×C), 148.7 and 148.5 (2×C), 146.6 (C), 141.5 and 141.3 (2×C), 137.2 (C), 133.0 and 132.9 (2×CH), 130.6 and 130.2 (2×CH), 129.7 and 129.3 (2×C), 128.7 (CH), 128.0 (CH), 127.8 and 127.7 (2×CH), 127.6 and 127.5 (2×CH), 127.1 and 126.7 (2×C), 124.6 and 124.5 (2×C), 113.3 and 113.2 (2×CH), 112.2 and 112.1 (2×CH), 71.58 and 71.52 (2×CH_2), 61.6 and 61.5 (2×CH_2), 56.2 (CH_3), 54.3 and 54.2 (2×CH), 38.2 and 37.6 (2×CH_2), 37.2 and 36.9 (2×CH_2), 33.5 (CH_2), 28.3 and 28.1 (2×CH_2), 14.9 (CH_3); HRESIMS calculated for $C_{28}H_{30}BrNO_4$ [M^+]: 523.1358; found 523.1365.

*4.2.5.3. tert-Butyl 7-(benzyloxy)-1-(2-(6-bromobenzo[d][1,3] dioxol-5-yl) ethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**17b**).* Mp: 74–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (br s, 2H), 7.31 (t, 2H, *J*=7.2 Hz), 7.25–7.23 (m, 1H), 6.94 (d, 1H, *J*=8.6 Hz), 6.62–6.61 (m, 3H), 5.87 (s, 2H), 5.11–5.06 (m, 3H), 4.27–4.03 (2×d, 1H, *J*=9.8, 10.4 Hz), 3.82 (s, 3H), 3.28–3.15 (m, 1H), 2.88–2.82 (m, 1H), 2.68–2.59 (m, 3H), 1.97–1.89 (m, 1H), 1.84 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.0 and 154.7 (2×C), 148.4 and 148.2 (2×C), 147.3 (C), 146.5 and 146.4 (2×C), 137.1 (C), 134.4 and 134.1 (2×C), 129.7 and 129.2 (2×C), 128.5 (CH), 127.8 (CH), 127.4 and 127.3 (2×CH), 127.1 and 126.7 (2×C), 114.2 and 114.1 (2×C), 113.1 (CH), 112.6 and 112.6 (2×CH), 112.1 and 111.9 (2×CH), 110.0 and 109.5 (2×CH), 101.5 (CH_2), 79.9 and 79.5 (2×C), 71.3 (CH_2), 55.9 (CH_3), 54.3 and 53.3 (2×CH), 38.3 and 36.9 (2×CH_2), 37.2 and 36.8 (2×CH_2), 33.3 and 31.5 (2×CH_2), 28.5 (CH_3), 28.2 and 28.0 (2×CH_2); HRESIMS calculated for $C_{31}H_{34}BrNO_6$ [M^+]: 595.1570; found 595.1569.

*4.2.5.4. Ethyl-7-(benzyloxy)-1-(2-bromo-4,5-dimethoxyphenethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**17c**).* Mp: 76–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.40 (m, 2H), 7.33 (t, 2H, *J*=7.0 Hz), 7.26–7.25 (m, 1H), 6.98 (s, 1H), 6.79–6.58 (m, 3H), 5.14–5.05 (m, 3H), 4.30–4.06 (m, 3H), 3.84 (s, 6H), 3.83 (s, 3H), 3.37–3.24 (m, 1H), 2.94–2.85 (m, 1H), 2.69–2.62 (m, 3H), 2.04–2.00 (m, 1H), 1.93–1.85 (m, 1H), 1.29 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1 and 155.9 (2×C), 148.7 and 148.5 (2×C), 148.0 and 147.9 (2×C), 146.6 (C), 137.2 (C), 133.4 and 133.2 (2×C), 129.7 and 129.3 (2×C), 128.6 (CH), 128.0 (CH), 127.5 (CH), 127.1 and 126.7 (2×C), 115.7 and 115.6 (2×CH), 114.1 and 113.9 (2×C), 113.4 and 113.2 (2×CH), 112.9 and 112.2 (2×CH), 112.1 and 112.1 (2×CH), 71.5 and 71.5 (2×CH_2), 61.6 and 61.5 (2×CH_2), 56.3 (CH_3), 56.2 (CH_3), 56.1 (CH_3), 54.4 and 54.1 (2×CH), 38.2 and 37.6 (2×CH_2), 37.4 and 36.9 (2×CH_2), 33.3 and 33.2 (2×CH_2), 28.2 and 28.0 (2×CH_2), 14.9 (CH_3); HRESIMS calculated for $C_{30}H_{34}BrNO_6$ [M^+]: 583.1570; found 583.1571.

*4.2.5.5. Ethyl 1-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**17d**).* Mp: 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96–6.56 (m, 4H), 5.92 (s, 2H), 5.55 (s, 1H), 5.17–5.05 (m, 1H), 4.36–4.18 (m, 3H), 3.84 (br s, 3H), 3.33–3.25 (m, 1H), 2.89–2.87 (m, 1H), 2.72–2.60 (m, 3H), 2.53–2.46 and 2.29–2.24 (2×m, 1H), 2.02–1.96 (m, 2H), 1.30–1.287 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9 (C), 147.5 and 147.5 (2×C), 147.4 and 147.3 (2×C), 146.6 (C), 146.6 and 145.6 (2×C), 145.5 and 145.5 (2×C), 145.3 (C), 143.9 (C), 135.9 and 135.6 (2×C), 134.4 and 134.1 (2×C), 130.4 and 130.0 (2×C), 125.5 and 125.2 (2×CH), 121.0 (CH), 114.2 and 114.1 (2×C), 113.0 and 112.9 (2×CH), 112.7 and 112.7 (2×CH), 112.6 (C), 110.8 and 110.7 (2×CH), 110.1 and 110.0 (2×CH), 109.7 (CH), 108.8 and 108.2 (2×CH), 101.6 and 100.6 (2×CH_2), 68.5 (CH_2), 61.4 and 61.4 (2×CH), 55.9 (CH_3), 54.0 and 53.9 (2×CH), 38.8 and 38.1 (2×CH_2), 37.5 and 37.1 (2×CH_2), 33.3 and 32.4 (2×CH_2), 28.2 and 27.9 (2×CH_2), 14.7 (CH_3); HRESIMS calculated for $C_{22}H_{24}BrNO_6$ [M^+]: 477.0787; found 477.0792.

*4.2.6. General procedure for the microwave-assisted direct arylation for the synthesis of **16a**, **20a**, **20b** and **20c** (Table 2, entry 8, compound **16a** as representative).* In a microwave reaction vial, compound **17** (50.0 mg, 0.088 mmol), $Pd(OAc)_2$ (1.98 mg, 8.8 μmol), ligand D (12.98 mg, 0.035 mmol), K_2CO_3 (48.74 mg, 0.35 mmol), and pivalic acid (3.60 mg, 0.035 mmol) were added and dissolved in Ar-purged anhyd DMSO (1.0 mL). The mixture was irradiated in the CEM microwave reactor for 15 min at 130 °C with the power level at 200 W. After cooling to room temperature, the reaction mixture was loaded directly onto a deactivated silica gel column and eluted with 15% EtOAc/hexanes to furnish compounds **14** and **15** in a ratio of 6:1. This mixture on debenzylation with palladium–charcoal furnished the crude cyclized and debrominated mixture of **16a** and **16b**, which on flash column chromatography over silica gel using EtOAc/DCM (5: 95) as eluant, furnished a rotameric mixture of homoaporphine phenol **16a** (25.0 mg, 71% yield from 17) as a white solid.

*4.2.6.1. Ethyl 11-hydroxy-12-methoxy-1,2,4,5-tetrahydro-[1,3] dioxolo [4″,5″:4′,5′] benzo [1′,2′:6,7] cyclohepta [1,2,3-ij] isoquinoline-3 (3aH)-carboxylate (**16a**).* Mp: 140–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 and 6.99 (2×s, 1H), 6.77 and 6.74 (2×s, 1H), 6.63 and 6.60 (2×s, 1H), 6.03–5.95 (m, 2H), 5.69 and 5.66 (2×s, 1H), 4.78 and 4.64 (2×dd, 1H, *J*=10.8, 7.5, 10.4, 7.6 Hz), 4.32 and 4.15 (2×dd, 1H, *J*=13.1, 5.6, 13.0, 5.6 Hz), 4.11–4.00 (m, 2H), 3.91 (s, 3H), 3.28 and 3.19 (dt, 1H, *J*=12.8, 3.4 Hz), 2.97–2.86 (m, 1H), 2.69 (t, 1H, *J*=13.0 Hz), 2.44–2.42 (m, 2H), 2.37–2.21 (m, 1H), 2.04–1.99 (m, 1H), 1.23 and 1.14 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4 and 155.0 (2×C), 147.1 and 147.1 (2×C), 145.9 and 145.9 (2×C), 145.8 (C), 140.5 and 140.5 (2×C), 133.5 and 133.4 (2×C), 127.2 and 127.1 (2×C), 126.7 (C), 124.7 and 124.3 (2×C), 124.1 and 123.8 (2×C), 110.9 and 110.9 (2×CH), 110.0 and 109.9 (2×CH), 108.9 and 108.7 (2×CH), 101.1 and 101.0 (2×CH_2), 61.4 (CH_2), 56.2 (CH_3), 50.8 and 50.7 (2×CH), 37.5 and 37.3 (2×CH_2), 37.0 and 36.8 (2×CH_2), 30.5 and 29.9 (2×CH_2), 29.0 and 28.9 (2×CH_2), 14.7 and 14.7 (2×CH_3); HRESIMS calculated for $C_{22}H_{23}NO_6$ [M^+]: 397.1525; found 397.153.

*4.2.6.2. Ethyl 10-hydroxy-11-methoxy-1,2,4,5-tetrahydrobenzo [6,7] cyclohepta [1,2,3-ij] isoquinoline-3 (3aH)-carboxylate (**20a**).* Mp: 68–70 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, 1H, *J*=7.5 Hz), 7.35–7.29 (m, 2H), 6.64 (s, 1H), 5.66 (s, 1H), 4.78 and 4.63 (2×dd, 1H, *J*=10.5, 7.5, 10.2, 8.0 Hz), 4.32 and 4.16 (2×dd, 1H, *J*=13.0 Hz, 5.8 Hz, *J*=13.1, 5.5 Hz), 4.09–3.97 (m, 2H), 3.92 (s, 3H), 3.29 and 3.20 (dt, 1H, *J*=12.7, 3.2 Hz), 2.98–2.88 (m, 1H), 2.73–2.67 (m, 1H), 2.57–2.48 (m, 2H), 2.35 and 2.26 (m, 1H), 2.14–2.04 (m, 1H), 1.23 and 1.09 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4 (C), 146.0 and 145.9 (2×C), 140.6 (C), 139.5 and 139.4 (2×C), 134.4 and 134.3 (2×C), 130.5 and 130.4 (2×CH), 131.1 and 130.6 (2×C), 128.6 and 128.3 (2×CH), 128.2 and 128.1 (2×CH), 127.1 and 126.7 (2×C), 126.2 and 126.1 (2×C), 124.7 and 124.3 (2×C), 110.3 and 110.1 (2×CH_2), 61.3 (CH_2), 56.2 (CH_3), 50.8 and 50.6 (2×CH),

37.5 and 37.1 (2×CH_2), 37.0 and 36.5 (2×CH_2), 29.9 (CH_2), 29.1 and 28.9 (2×CH_2), 14.8 and 14.8 (2×CH_3); HRESIMS calculated for $C_{21}H_{23}NO_4$ [M^+]: 353.1627; found 353.1628.

*4.2.6.3. tert-Butyl 11-hydroxy-12-methoxy-1,2,4,5-tetrahydro-[1,3] dioxolo [4″,5″:4′,5′] benzo [1′,2′:6,7] cyclohepta [1,2,3-ij] isoquinoline-3 (3aH)-carboxylate (**20b**).* Mp: 58–60 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 and 6.99 (2×s, 1H), 6.76 and 6.73 (2×s, 1H), 6.63 and 6.60 (2×s, 1H), 5.96 (t, 2H, J=16.8 Hz), 5.69 and 5.66 (2×s, 1H), 4.76 and 4.57 (2×dd, 1H, J=10.8, 7.2, 10.4, 7.6 Hz), 4.26 and 4.10 (2×dd, 1H, J=12.8, 5.8, 13.3, 5.5 Hz), 3.91 (s, 3H), 3.24 and 3.13 (2×dt, 1H, J=12.8, 3.7, 12.7, 3.6 Hz), 2.92 and 2.86 (dt, 1H, J=19.5, 6.2, 12.5, 5.9 Hz), 2.72–2.64 (m, 1H), 2.45–2.41 (m, 2H), 2.38–2.21 (m, 1H), 2.02–1.98 (m, 1H), 1.42 (s, 5H), 1.33 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6 and 154.2 (2×C), 147.1 and 147.0 (2×C), 145.9 and 145.9 (2×C), 145.8 and 145.7 (2×C), 140.4 (C), 133.6 and 133.5 (2×C), 127.5 and 127.3 (2×C), 127.2 and 126.9 (2×C), 124.7 and 124.4 (2×C), 124.2 and 123.8 (2×C), 110.9 and 110.8 (2×CH), 110.0 and 109.9 (2×CH), 109.0 and 108.4 (2×CH), 101.0 (CH_2), 79.7 (C), 56.2 (CH_3), 51.1 and 50.1 (2×CH), 37.8 and 37.1 (2×CH_2), 36.8 and 36.4 (2×CH_2), 30.6 (CH_2), 29.9 and 29.8 (2×CH_2), 29.1 and 29.0 (2×CH_2), 28.6 and 28.5 (2×CH_3); HRESIMS calculated for $C_{24}H_{27}NO_6$ [M^+]: 425.1838; found 425.1869.

*4.2.6.4. Ethyl 10-hydroxy-7,8,11-trimethoxy-1,2,4,5-tetrahydrobenzo [6,7] cyclohepta [1,2,3-ij] isoquinoline-3 (3aH)-carboxylate (**20c**).* Mp: 208–210 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 and 7.06 (2×s, 1H), 6.80 and 6.77 (2×s, 1H), 6.64 and 6.61 (2×s, 1H), 5.68 and 5.65 (2×s, 1H), 4.79 and 4.63 (2×dd, 1H, J=10.7, 7.3, 10.4, 7.6 Hz), 4.33 and 4.16 (2×dd, 1H, J=13.1, 5.8, 13.6, 5.8 Hz), 4.14–4.07 and 4.04–4.00 (m, 2H), 3.94 and 3.91 (s, 3H), 3.92 and 3.92 (s, 3H), 3.88 and 3.85 (s, 3H), 3.28 and 3.19 (dt, 1H, J=12.9, 3.4 Hz), 2.98–2.87 (m, 1H), 2.73–2.67 (m, 1H), 2.50–2.46 (m, 1H), 2.41–2.33 and 2.31–2.23 (m, 1H), 2.12–2.09 (m, 1H), 1.23 and 1.11 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9 (C), 159.5 (C), 155.2 (C), 148.4 and 148.2 (2×C), 146.9 and 146.8 (2×C), 145.8 and 145.7 (2×C), 140.2 (C), 132.2 and 132.1 (2×C), 127.1 (C), 126.6 (C), 126.0 and 125.9 (2×C), 124.7 (C), 124.2 (C), 123.8 (C), 113.7 and 113.6 (CH), 111.6 and 111.3 (CH), 109.8 and 109.6 (2×CH), 61.2 (CH_2), 56.1 and 56.0 (2×CH_3), 56.0 (CH_3), 55.9 and 55.8 (2×CH_3), 50.8 and 50.6 (2×CH), 37.3 and 37.2 (2×CH_2), 36.8 and 36.8 (2×CH_2), 30.1 and 29.7 (2×CH_2), 28.9 and 28.7 (2×CH_2), 14.7 (CH_3); HRESIMS calculated for $C_{23}H_{27}NO_6$ [M^+]: 413.1838; found 413.1846.

*4.2.7. Preparation of tert-butyl 11, 12-dimethoxy-1,2,4,5-tetrahydro-[1,3] dioxolo [4″,5″:4′,5′] benzo [1′,2′:6,7] cyclohepta [1,2,3-ij] isoquinoline-3(3aH)-carboxylate (**22**).* To a solution of **20b** (0.025 g, 0.058 mmol) and methyl iodide (0.073 mL, 1.17 mmol) dissolved in dry acetone (20 mL) was added potassium carbonate (0.081 gm, 0.58 mmol) and potassium iodide (0.097 g, 0.58 mmol), and the mixture refluxed for 6 h. The acetone was evaporated; water (10 mL) was added to the residue and extracted with dichloromethane (3×10 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product on flash column chromatography over deactivated silica gel using EtOAc/Hexane (1: 9) as eluant, furnished **22** (0.0215 g, 83% yield) as a white solid (mixture of rotamers). Mp: 74–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 and 6.92 (2×s, 1H), 6.75 and 6.72 (2×s, 1H), 6.68 and 6.65 (2×s, 1H), 5.98–5.91 (s, 2H), 4.73 and 4.53 (2×dd, 1H, J=11.1, 7.1, 10.7, 7.3 Hz), 4.26 and 4.10 (2×dd, 1H, J=13.0 Hz, 5.4 Hz, J=13.1 Hz, 5.8 Hz), 3.88 (s, 3H), 3.49 (s, 3H), 3.23 and 3.12 (2×dt, 1H, J=12.9, 3.6, 12.7, 3.4 Hz), 2.96–2.84 (m, 1H), 2.75–2.67 (m, 1H), 2.47–2.43 (m, 2H), 2.41–2.28 (m, 1H), 2.02–1.98 (m, 1H), 1.42 (s, 6H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3 (C), 151.6 and 151.5 (2×C), 146.9 (C), 145.8 (C), 144.3 (C), 132.8 and 132.1 (2×C), 128.7 and 127.5 (2×C), 127.1 and 126.5 (2×C), 111.4 and 111.0 (2×CH), 108.3 and 107.7 (2×CH), 100.8 (CH_2), 79.5 (C), 60.4 (CH_3), 55.8 (CH_3), 50.8 and 49.9 (2×CH), 37.5 and 36.6 (2×CH_2), 36.3 and 36.1 (2×CH_2), 30.3 and 29.7 (2×CH_2), 29.2 and 29.0 (2×CH_2); HRESIMS calculated for $C_{25}H_{29}NO_6$ [M^+]: 439.1995; found 439.1994.

*4.2.8. Preparation of (±)-Homonantenine 11,12-dimethoxy-3-methyl-1, 2,3,3a,4,5-hexahydro [1,3] dioxolo [4″,5″:4′,5′] benzo [1′,2′:6,7] cyclohepta [1,2,3-ij] isoquinoline (**3**).* To a solution of **22** (9.0 mg, 0.02 mmol) in dry dichloromethane (10 mL), was added dry zinc bromide (18.46 mg, 0.08 mmol). The reaction mixture was allowed to stir at room temperature for 45 min. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layer was washed with water (10 mL), then with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated to give the crude amine. To a solution of this amine in dichloromethane (10 mL) was added 37% formaldehyde solution (0.017 mL, 0.607 mmol) and sodium triacetoxyborohydride (21.8 mg, 0.10 mmol). The reaction mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layer was washed with water (10 mL), then with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated to give crude **3**, which on column chromatography over deactivated silica gel using methanol/dichloromethane (2:98) as eluant, furnished **3** (4.5 mg, 66% yield) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (s, 1H), 6.73 (s, 1H), 6.66 (s, 1H), 5.98 (dd, 2H, J=12.1, 1.1 Hz), 3.88 (s, 3H), 3.48 (s, 3H), 3.27 (dd, 1H, J=11.1, 6.8 Hz), 3.15 (dt, 1H, J=11.4, 3.8 Hz), 3.06–2.99 (m, 1H), 2.81 (dd, 1H, J=12.0, 5.2 Hz), 2.66–2.63 (br s, 1H), 2.46 (dd, 1H, J=12.9, 5.6 Hz), 2.40 (s, 3H), 2.32 (dt, 1H, J=12.9, 6.7 Hz), 2.06–2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.4 (C), 146.7 (C), 145.6 (C), 144.1 (C), 133.1 (C), 132.3 (C), 130.0 (C), 127.9 (C), 111.4 (CH), 110.7 (CH), 108.0 (CH), 100.8 (CH_2), 60.3 (CH_3), 58.10 (CH), 55.8 (CH_3), 45.0 (CH_2), 41.7 (CH_3), 34.7 (CH_2), 30.3 (CH_2), 29.7 (CH_2); HRESIMS calculated for $C_{21}H_{23}NO_4$ [M^+]: 353.1627; found 353.1627.

4.3. HPLC and microwave conditions

HPLC was conducted with an Agilent 1200 system with the following conditions: flow rate: 1 mL/min; detection wavelength: 254 nm; retention times: Compound **14**: 8.33 min, Compound **15**: 9.08 min, Compound **13**: 11.27 min; Column: Agilent Eclipse XDB-C18; Eluant 80:20 (Water: Methanol).

Microwave reactions were conducted in closed vessel in a CEM Discover microwave using the following conditions: temperature: 130 °C; power: 200 W; pressure: 175 Psi; mode: Standard.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra of compounds **8**–**11**, **13**, **16a**, **17a**–**d**, **20a**–**c**, **22** and **3**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.11.059. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Tojo, E. *J. Nat. Prod.* **1989**, *52*, 909–921; (b) Alikulov, R. V.; Levina, E. V.; Yusupov, M. K. *Chem. Nat. Compd.* **2003**, *39*, 212–214; (c) Husek, A.; Sutlupinar, N.; Potesilova, H.; Dvorackova, S.; Hanus, V.; Sedmera, P.; Malon, P.; Simanek, V.

Phytochemistry **1989**, *28*, 3217–3219; (d) Tojo, E.; Abu Zarga, M. H.; Sabri, S. S.; Freyer, A. J.; Shamma, M. *J. Nat. Prod.* **1989**, *52*, 1055–1059.
2. (a) Basova, N. E.; Rozengart, E. V.; Suvorov, A. A. *J. Evol. Biochem. Physiol.* **2006**, *42*, 408–416; (b) Abu-Zarga, M. H.; Abu Ghalyun, Y. Y. *Int. J. Pharm.* **2006**, *2*, 451–454; (c) Basova, N. E.; Rozengart, E. V.; Suvorov, A. A. *Dokl. Biochem. Biophys.* **2006**, *42*, 27–31.
3. (a) Schwartz, M. A.; Rose, B. F.; Holton, R. A.; Scott, S. W.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1977**, *99*, 2571–2578; (b) Herbert, R. B.; Kattah, A. E.; Murtagh, A. J.; Sheldrake, P. W. *Tetrahedron Lett.* **1995**, *36*, 5649–5650; (c) Kupchan, S. M.; Dhingra, O. P.; Kim, C.; Kameswaran, V. *J. Org. Chem.* **1976**, *41*, 4047–4049; (d) Kupchan, S. M.; Dhingra, O. P.; Kim, C. *J. Org. Chem.* **1976**, *41*, 4049–4050; (e) Kupchan, S. M.; Dhingra, O. M.; Kim, C.; Kameswaran, V. *J. Org. Chem.* **1978**, *43*, 2521–2529; (f) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513–6519; (g) Landais, Y.; Rambault, D.; Robin, J. P. *Tetrahedron Lett.* **1987**, *28*, 543–546; (h) Rao, T. V. P. *Curr. Sci.* **1976**, *45*, 453–454; (i) Hara, H.; Hoshino, O.; Umezawa, B.; Iitaka, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, *11*, 2657–2663; (j) Kametani, T.; Fukumoto, K.; Yagi, H.; Satoh, F. *J. Chem. Soc. D* **1967**, 878–879.
4. Barolo, S. M.; Teng, X.; Cuny, G. D.; Rossi, R. A. *J. Org. Chem.* **2006**, *71*, 8493–8499.
5. (a) Hoshino, O.; Toshioka, T.; Ohyama, K.; Umezawa, B. *Chem. Pharm. Bull.* **1974**, *22*, 1307–1312; (b) Hoshino, O.; Hara, H.; Serizawa, N.; Umezawa, B. *Chem. Pharm. Bull.* **1975**, *23*, 2048–2053; (c) Hara, H.; Shinoki, H.; Komatsu, T.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull.* **1986**, *34*, 1924–1928.
6. (a) Castro, J. L.; Castedo, L.; Riguera, R. *J. Org. Chem.* **1987**, *52*, 3579–3584; (b) Castro, J. L.; Castedo, L.; Riguera, R. *Tetrahedron Lett.* **1985**, *26*, 1561–1564.
7. (a) Kapppe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66–77; (c) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2005**, *5*, 51–63; (d) Ersmark, K.; Larhed, M.; Wannberg, J. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 417–427.
8. (a) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849–2852; (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.
9. Chaudhary, S.; Pecic, S.; LeGendre, O.; Harding, W. W. *Tetrahedron Lett.* **2009**, *50*, 2437–2439.
10. Chaudhary, S.; Pecic, S.; LeGendre, O.; Navarro, H. A.; Harding, W. W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2530–2532.