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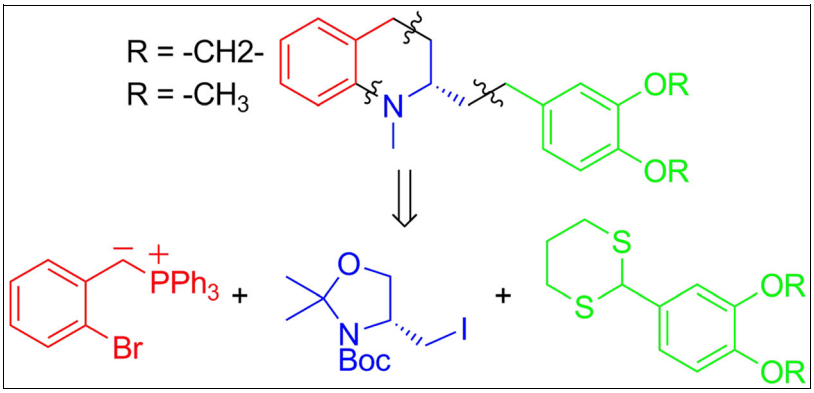

An enantiospecific route to the synthesis of tetrahydroquinoline alkaloids (–)-cuspareine and (–)-galipinine is reported. Coupling of an iodide derivative of D-serine with aromatic dithianes and Pd-catalyzed intramolecular C–N coupling are the key steps in the synthesis.

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INTRODUCTION

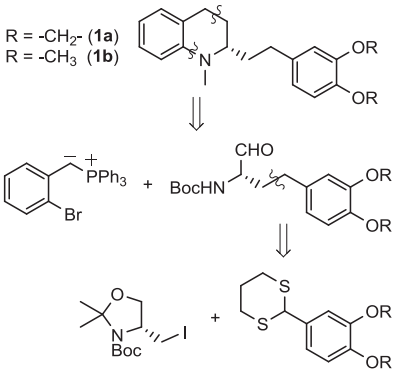
(–)-Cuspareine (**1a**) and (–)-galipinine (**1b**) are among the tetrahydroquinoline alkaloids isolated from the bark of *Galipea officinalis* Hancock, a Venezuelan tree [1]. The potential utility of extracts from these trees as antimalarials and cytotoxic substances [2] has spurred interest in their chemical synthesis. Most of the strategies towards their synthesis are based on asymmetric hydrogenations of 2-alkyl quinolines, which also include transfer-hydrogenations [3]. Other strategies used for the synthesis of tetrahydroquinoline alkaloids in general are asymmetric hydroamination [4], asymmetric aza Diels–Alder reactions [5], enantioselective Petasis-type reaction [6], enantioselective aza-Michael reactions [7], and conjugate addition of chiral lithium amides [8], and there are reports on their racemic synthesis [9].

All of the syntheses available for these compounds are based on asymmetric transformations, which do not always proceed with good selectivity. Enantiospecific strategies based on asymmetric starting materials are available for a related compound (+)-angustureine, but are based on uncommon starting materials, which are not easily available and are difficult to make [10]. We report here an enantiospecific synthesis of **1a** and **1b** starting from an iodide derivative **2**, derived from D-serine (Scheme 1). An umpolung reaction between 2-aryl dithianes as the initial step and a Pd-catalyzed intramolecular C–N coupling later are the key steps (Scheme 1). The strategy is quite general and could potentially be used for the synthesis of related molecules.

RESULTS AND DISCUSSION

We have recently demonstrated the use of an iodide derivative of serine **2**, for the synthesis of unusual amino acid derivatives [11]. Similarly, an umpolung reaction between **2**, prepared from D-serine and aromatic dithianes (**3a** or **3b**) was carried out (*n*-BuLi, THF, −20°C) to get **4** (Scheme 2). The reaction proceeded smoothly and the coupled products were isolated in very good yields. These reactions do not lead to stereo randomization of **3**, and the stereochemistry of the iodide derivative is retained in **4** [11]. The dithiane group was then reduced to get the corresponding oxazolidine derivatives **5** using a recently reported procedure, employing $NiCl_2{\cdot}6H_2O/NaBH_4$ (CH_3OH, THF, r. t.) [12]. **5** was carefully treated with TFA (7% in CH_3OH, r. t.) to selectively cleave the oxazolidine group. Under the conditions used, the Boc group remained intact, and the amino alcohols **6** were obtained in very good yields. The primary hydroxyl group in **6** was oxidized to the corresponding aldehydes using IBX (1.5 equiv, DMSO, r. t.) to obtain the amino aldehyde derivatives **7**. Upon Wittig reaction using the ylide derived from (2-bromobenzyl)triphenylphosphonium bromide (*t*-BuOK, CH_2Cl_2, −10°C), **7** yielded the olefin **8** as a mixture of *cis–trans* isomers. The diastereomers of **8** were purified as a mixture and were subjected to hydrogenation using Rh/Al_2O_3 (C_2H_5OH, H_2, r. t.), which yielded the Boc protected amine **9** in very good yields. The reduction of **8** to **9** could be carried out only using Rh; the use of Pd/C resulted in the debromination of the aromatic ring. Compound **9** was then subjected to an intramolecular C–N

Scheme 1. Retrosynthetic strategy for **1a** and **1b**.



coupling using $Pd(OAc)_2$ as a catalyst (*rac*-BINAP, Cs_2CO_3, toluene, reflux) to get the tetrahydroquinoline derivative **10** in very high yields. Reduction of the *N*-Boc group to an *N*-methyl group using $LiAlH_4$ (7 equiv. in THF, reflux) yielded **1** from **10** in excellent yields. This enantiospecific strategy employed for the synthesis of **1a** and **1b** starting from **2** is very efficient and is completed in eight steps with an overall yield of 32% for **1a** and 33% for **1b**. The methodology can be extended to the synthesis of other 2-alkyltetrahydroquinoline derivatives by choosing suitable dithiane derivatives.

CONCLUSION

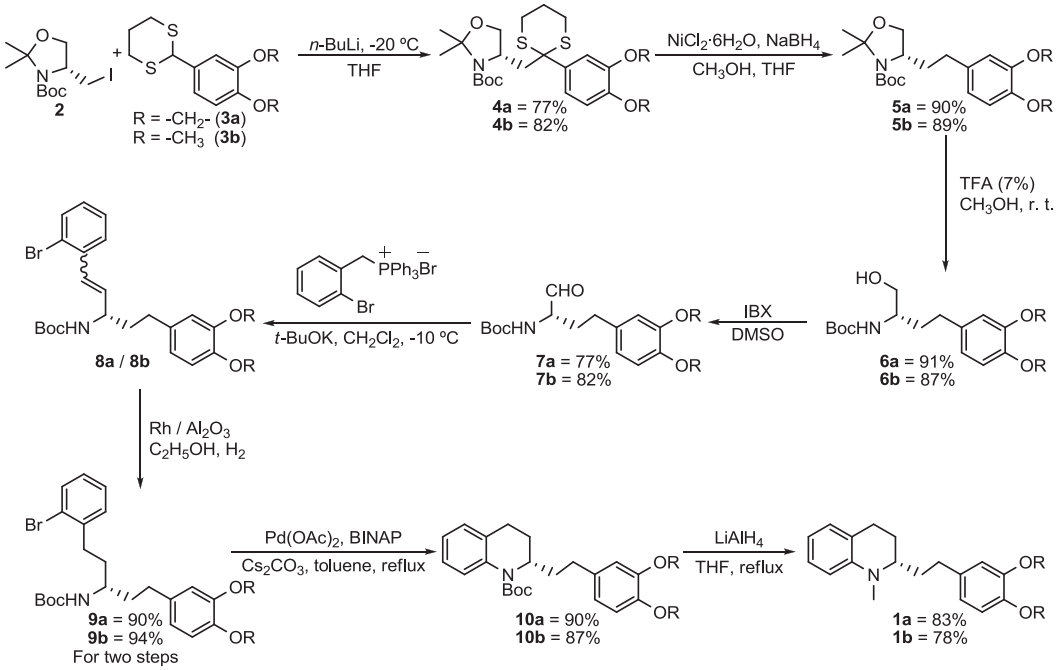
In conclusion, we have achieved a very efficient enantiospecific synthesis of **1a** and **1b** starting from readily available materials. The reactions employed for individual transformations are simple and high yielding. The strategy could be extended for the synthesis of other 2-alkyltetrahydroquinolines.

EXPERIMENTAL

General. All the chemicals were purchased from commercial sources and were used without further purification. ^1H and ^{13}C NMR spectra were recorded either on a 400 MHz (100 MHz for ^{13}C) or on a 500 MHz (125 MHz for ^{13}C) JEOL-Lambda NMR spectrometer at 25°C. The ^1H NMR signals are referenced to TMS (δ = 0.00 ppm) and the ^{13}C NMR peaks are referenced to the residual CHCl3 signal (δ = 77.0 ppm). The chemical shifts are reported in parts per million and coupling constants in Hz. The multiplicities are assigned as s (singlet), d (doublet), t (triplet), bs (broad singlet), dd (double doublet), and m (multiplet). High-resolution mass spectra were obtained using a Waters Q/Tof Premier micromass HAB 213 spectrometer with an ESI source. IR spectra were recorded on a Bruker Vector 22 FTIR instrument, and melting points were recorded on a DBK Automatic Programmable digital instrument. Column chromatography was performed using 100–200 mesh silica gel, and appropriate mixtures of petroleum ether (PE) and EtOAc were used as eluent.

Synthesis of 4a and 4b. Aromatic dithiane **3** (1.200 g of **3a** or 1.280 g of **3b**, 5 mmol) was dissolved in dry THF (10 mL) and was cooled to −20°C; *n*-BuLi (3.4 mL of 1.6 M solution in hexane, 5.5 mmol) was added to the above solution drop wise. The reaction mixture turned orange indicating the formation of the anion, which was stirred for 40 min at −20°C and the iodide **2** (1.023 g, 3 mmol) in THF (3 mL) was added over a period of 15 min and the stirring continued. The reaction was monitored with TLC, until the complete disappearance of the iodide (1 to 1.5 h). The reaction was

Scheme 2. Synthesis of **1a** and **1b**.



quenched with a saturated solution of NH_4Cl (10 mL) and was extracted with EtOAc (3 × 50 mL). The organic layers were pooled, dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The crude product (**3**) was purified by column chromatography.

N-Boc-(S)-4-((2-(benzo[d][1,3]dioxol-5-yl)-1,3-dithian-2-yl) methyl)-2,2-dimethyloxazolidine, 4a. Clear oil (1.046 g, 77%). $[\alpha]_D$ = 21.9 (c = 0.86, $CHCl_3$); IR (thin film): 2977, 2927, 1694, 1490, 1389, 1365, 1245, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz), mixture of rotamers: δ = 7.46–7.43 (m, 2H), 6.78–6.77 (m, 1H), 5.96 (s, 2H), 4.16–3.98 (m, 1H), 3.55–3.46 (m, 1H), 3.07–2.92 (m, 1H), 2.72–2.47 (m, 4H), 2.49–2.26 (m, 1H), 2.16–2.03 (m, 1H), 1.95–1.87 (m, 2H), 1.48,1.33 (2 bs, 15H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz), mixture of rotamers: δ = 151.5, 148.5, 148.4, 146.8, 135.4, 135.0, 122.7, 122.4, 109.4, 109.2, 108.3, 101.4, 101.3, 93.2, 92.6, 80.4, 80.1, 67.4, 57.6, 57.3, 54.2, 53.9, 48.1, 47.4, 28.8, 28.5, 27.6, 27.5, 26.9, 24.9, 24.4 ppm; HRMS (ES): m/z calcd for $C_{22}H_{31}NO_5S_2$ [M+H^+]: 454.1722; found: 454.1726.

N-Boc-(S)-4-((2-(3,4-dimethoxyphenyl)-1,3-dithian-2-yl) methyl)-2,2-dimethyloxazolidine, 4b. Clear oil (1.154 g, 82%). $[\alpha]_D$ = 20.0 (c = 0.20, $CHCl_3$); IR (thin film): 2931, 1695, 1387, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz), mixture of rotamers: δ = 7.50–7.47 (m, 2H), 6.85–6.84 (m, 1H), 4.15–4.01 (m, 1H), 3.87 (s, 6H), 3.50–3.44 (m, 1H), 2.99–2.89 (m, 1H), 2.72–2.52 (m, 4H), 2.17–2.09 (m, 1H), 1.92–1.90 (m, 2H), 1.49, 1.33 (2 bs, 15H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz), mixture of rotamers: δ = 151.5, 149.3, 149.2, 148.2, 133.6, 133.5, 121.6, 121.2, 112.1, 111.8, 111.2, 111.1, 111.0, 93.0, 92.6, 80.4, 80.1, 67.4, 57.0, 57.2, 56.1, 55.9, 54.3, 54.0, 48.1, 47.2, 29.7, 28.8, 28.5, 27.7, 25.0 ppm; HRMS (ES): m/z calcd for $C_{23}H_{35}NO_5S_2$ [M+Na^+]: 492.1854; found: 492.1856.

Reduction of 4 to 5. To a stirred solution of the dithiane (0.453 g of **4a** or 0.469 g of **4b**, 1 mmol) in MeOH:THF (8:2, 10 mL), $NiCl_2{\cdot}6H_2O$ (1.66 g, 7 mmol) was added at 0°C and was vigorously stirred for 5 min; $NaBH_4$ (0.76 g, 20 mmol) was added to this mixture in small portions over a period of 5 min. The temperature was allowed to attain r. t. (30°C) and the progress of the reaction was monitored through TLC. On complete disappearance of the starting material, reaction was quenched by the addition of saturated $NaHCO_3$ (10 mL) and the crude product was extracted with dichloromethane (3 × 15 mL). The crude solution containing the product was dried by passing through a bed of anhydrous Na_2SO_4 and the oxazolidine derivatives (**5**) were further purified by column chromatography.

N-Boc-(S)-4-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2,2-dimethyloxazolidine, 5a. Clear oil (0.314 g, 90%). $[\alpha]_D$ = 49.1 (c = 0.55, $CHCl_3$); IR (thin film): 2977, 2918, 2850, 1694, 1481, 1387, 1237, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.68–6.58 (m, 3H), 5.88 (s, 2H), 3.91–3.71 (m, 3H), 2.58–2.42 (m, 2H), 2.07–1.90 (m, 1H), 1.82–1.70 (m, 1H), 1.58, 1.42 (bs, 15H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 152.2, 151.8, 147.7, 147.6, 145.8, 145.7, 135.5, 135.2, 121.0, 108.9, 108.2, 100.8, 93.7, 93.2, 80.1, 79.5, 66.8, 66.7, 57.5, 56.8, 35.5, 34.9, 32.5, 28.5, 27.6, 26.8, 24.5, 23.3 ppm; HRMS (ES): m/z calcd for $C_{19}H_{27}NO_5$ [M+Na^+]: 372.1787; found: 372.1789.

N-Boc-(S)-4-(3,4-dimethoxyphenethyl)-2,2-dimethyloxazolidine, 5b. Clear oil (0.325 g, 89%). $[\alpha]_D$ = 9.0 (c = 0.08, $CHCl_3$); IR (thin film): 2927, 1693, 1515, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.78–6.66 (m, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.92–3.76 (m, 3H), 2.60–2.46 (m, 2H), 1.93–1.77 (m, 2H), 1.47 (s, 9H), 1.42 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.5, 148.9, 147.3, 134.1, 120.2, 111.7, 111.3, 93.7, 79.7, 65.9, 57.9, 55.9, 55.8, 33.5, 32.4, 31.0, 28.4 ppm; HRMS (ES): m/z calcd for $C_{20}H_{31}NO_5$ [M+Na^+]: 388.2100; found: 388.2101.

Acidolysis of 5 to 6. The oxazolidine (0.349 g of **5a** or 0.365 g of **5b**, 1 mmol) was cooled to 0°C and a solution of trifluoroacetic acid (7%) in methanol (3 mL) was added drop wise. The reaction was monitored through TLC, until the complete disappearance of the starting material and was neutralized with $NaHCO_3$ (0.500 g). The solution was diluted with methanol (5 mL) and filtered; the filtrate was concentrated under vacuum and the crude *N*-protected amino alcohols (**6**) were purified by column chromatography.

(S)-2-(tert-Butyloxycarbonylamino)-amino-4-(benzo[d][1,3] dioxol-5-yl)butan-1-ol, 6a. White solid (0.281 g, 91%). Mp 88–89°C. $[\alpha]_D$ = 42.8 (c = 0.58, $CHCl_3$); IR (KBr): 3395, 2975, 2926, 1686, 1503, 1489, 1245, 1169, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.70 (d, *J* = 7.75 Hz, 1H), 6.66 (s, 1H), 6.61 (d, *J* = 7.75 Hz, 1H), 5.90 (s, 2H), 4.69 (d, *J* = 7.4 Hz, 1H), 3.64–3.54 (m, 3H), 2.65–2.53 (m, 2H), 1.80–1.74 (m, 1H), 1.72–1.64 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.5, 147.7, 145.8, 135.3, 121.1, 108.8, 108.3, 100.8, 79.7, 65.9, 52.4, 33.5, 32.2, 28.4 ppm; HRMS (ES): m/z calcd for $C_{16}H_{23}NO_5$ [M+Na^+]: 332.1474; found: 332.1472.

(S)-2-(tert-Butyloxycarbonylamino)-4-(3,4-dimethoxyphenyl) butan-1-ol, 6b. Clear oil (0.283 g, 87%). $[\alpha]_D$ = 36.8 (c = 0.51, $CHCl_3$); IR (thin film): 3360, 2927, 1687, 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.78–6.70 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.69–3.63 (m, 2H), 3.56–3.53 (m, 1H), 2.68–2.56 (m, 2H), 1.84–1.69 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.3, 148.0, 147.1, 133.9, 120.1, 111.7, 79.7, 66.0, 56.0, 55.9, 52.4, 33.5, 32.0, 28.4 ppm; HRMS (ES): m/z calcd for $C_{17}H_{27}NO_5$ [M+Na^+]: 348.1787; found: 348.1780.

Oxidation of 6 to 7. The *N*-protected amino alcohol (0.309 g of **6a** or 0.325 g of **6b**, 1 mmol) was dissolved in DMSO (5 mL) and IBX (0.420 g, 1.5 mmol) was added at r. t. (30°C). The reaction mixture was stirred for 5 h and was quenched with saturated $NaHCO_3$ solution (10 mL). The aldehyde was extracted from the crude solution with ethyl acetate (3 × 15 mL); the organic layers were pooled together and washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography.

(S)-2-(tert-Butyloxycarbonylamino)-4-(benzo[d][1,3]dioxol-5-yl)butanal, 7a. Clear oil (0.236 g, 77%). $[\alpha]_D$ = 17.7 (c = 0.45, $CHCl_3$); IR (thin film): 3376, 2976, 2919, 1702, 1503, 1490, 1246, 1166, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.52 (s, 1H), 6.71 (d, *J* = 7.75 Hz, 1H), 6.65 (s, 1H), 6.61 (d, *J* = 7.75 Hz, 1H), 5.91 (s, 2H), 5.08 (bs, 1H), 4.21–4.20 (m, 1H), 2.61 (t, *J* = 6.9 Hz, 2H), 2.20–2.13 (m, 1H), 1.85–1.78 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 199.6, 155.6, 147.8, 146.1, 134.3, 121.3, 108.9, 100.9, 80.2, 59.5, 31.2, 28.3 ppm; HRMS (ES): m/z calcd for $C_{16}H_{21}NO_5$ [M+Na^+]: 330.1317; found: 330.1317.

(S)-2-(tert-Butyloxycarbonylamino)-4-(3,4-dimethoxyphenyl) butanal, 7b. Clear oil (0.265 g, 82%). $[\alpha]_D$ = 25.7 (c = 0.16, $CHCl_3$); IR (thin film): 3356, 2934, 2836, 1707, 1516, 1261, 1159, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.53 (s, 1H), 6.78–6.76 (m, 1H), 6.71–6.67 (m, 2H), 5.08 (bs, 1H), 4.24–4.23 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.64 (t, *J* = 7.47 Hz, 2H),

2.21–2.15 (m, 1H), 1.87–1.79 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 199.7, 155.6, 149.0, 147.5, 133.1, 120.3, 111.8, 111.3, 80.2, 59.5, 55.9, 55.9, 31.1, 31.1, 28.3 ppm; HRMS (ES): m/z calcd for $C_{17}H_{25}NO_5$ [M+Na$^+$]: 346.1630; found: 346.1647.

Conversion of 7 to 9 through 8. Amino aldehyde (0.368 g of **7a** or 0.388 g of **7b**, 1.2 mmol) in anhydrous DCM (4 mL) was added drop wise to a precooled (to −10°C) solution of (2-bromobenzyl)triphenylphosphonium bromide (1.229 g, 2.4 mmol) and *t*-BuOK (0.171 g, 1.4 mmol) in dry DCM (20 mL) under nitrogen atmosphere. After completion of reaction as observed in TLC, the mixture was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (2 × 15 mL). The product **8** was isolated as a mixture of diastereomers by passing through a silica bed and was taken to the next step without further purification.

To a stirred solution of **8** (as obtained from the previous step), in ethanol (25 mL) Rh on alumina (5%, 100 mg) was added. The reaction mixture was stirred for 2 h at r. t. (30°C) under H_2 atmosphere (1 atm). On completion of the reaction, the inorganic residues were removed by filtration through a celite pad and the solvent evaporated under vacuum and the crude product was purified by column chromatography.

(S)-1-(Benzo[d][1,3]dioxol-5-yl)-5-(2-bromophenyl)-3-(tert-butyloxycarbonylamino)pentane, 9a. White solid (0.499 g, 90% after two steps). Mp: 84–85°C. $[\alpha]_D$ = 12.5 (c = 0.40, $CHCl_3$); IR (KBr): 3349, 2922, 2852, 1697, 1503, 1489, 1244, 1169, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.50 (d, *J* = 7.7 Hz, 1H), 7.28–7.15 (m, 2H), 7.06–7.02 (m, 1H), 6.71- 6.61 (m, 3H), 5.90 (s, 2H), 4.40–4.33 (m, 1H), 3.72–3.64 (m, 1H), 2.84–2.78 (m, 1H), 2.74–2.53 (m, 3H), 1.81–1.58 (m, 4H), 1.46 (s, 9H), ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.7, 147.6, 145.7, 135.8, 132.9, 130.5, 128.4, 128.4, 127.6, 127.6, 121.1, 108.9, 108.2, 100.8, 79.2, 50.4, 37.8, 35.9, 32.8, 32.2, 28.5 ppm; HRMS (ES): m/z calcd for $C_{23}H_{28}BrNO_4$ [M+Na$^+$]: 484.1099; found: 484.1090.

(S)-1-(2-Bromophenyl)-5-(3,4-dimethoxyphenyl)-3-(tert-butyloxycarbonylamino)pentane, 9b. White solid (0.538 g, 94% after two steps). Mp: 80–81°C. $[\alpha]_D$ = 18.0 (c = 0.16, $CHCl_3$); IR (KBr): 3363, 2931, 1685, 1519, 1240, 1155, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43 (d, *J* = 8.0 Hz, 1H), 7.14–7.08 (m, 2H), 6.99–6.95 (m, 1H), 6.72–6.64 (m, 3H), 4.35 (bs, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.67–3.63 (m, 1H), 2.79–2.48 (m, 4H), 1.78–1.52 (m, 4H), 1.39 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.8, 148.9, 147.2, 141.3, 134.6, 132.8, 130.5, 128.4, 127.7, 127.6, 120.2, 111.8, 111.3, 79.2, 56.0, 55.9, 50.3, 37.8, 36.0, 32.8, 32.0, 28.5 ppm; HRMS (ES): m/z calcd for $C_{24}H_{32}BrNO_4$ [M+Na$^+$]: 502.1392; found: 502.1386.

Cyclization of 9 to 10. A solution of **9** (0.461 g of **9a** or 0.477 g of **9b**, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), *rac*-BINAP (0.075 g, 0.12 mmol), and Cs_2CO_3 (0.456 g, 1.4 mmol) in dry toluene (15 mL) was refluxed for 6 h. After completion of the reaction, solvent was removed under reduced pressure and the residue purified through column chromatography.

Boc-(S)-2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-1,2,3,4-tetrahydroquinoline, 10a. Clear oil (0.342 g, 90%). $[\alpha]_D$ = 24.7 (c = 0.56, $CHCl_3$); IR (thin film): 2919, 2850, 1691, 1490, 1331, 1245, 1167, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.47 (d, *J* = 7.75 Hz, 1H), 7.15–7.12 (m, 1H), 7.07–7.06 (m, 1H), 7.01–6.99 (m, 1H), 6.69–6.67 (m, 1H), 6.60–6.56 (m, 2H), 5.88 (s, 2H), 4.53 (q, *J* = 6.3 Hz, 1H), 2.70 (t, *J* = 6.3 Hz, 2H), 2.60–2.49 (m, 2H), 2.21–2.17 (m, 1H), 1.82–1.75 (m, 1H), 1.68–1.56 (m, 2H), 1.49 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 154.1, 147.5, 145.6, 137.0, 135.8, 130.9, 128.1, 125.9, 125.8, 123.8, 121.0, 108.9, 108.1, 100.7, 80.6, 52.0, 34.9, 32.3, 28.5, 28.4, 24.5 ppm; HRMS (ES): m/z calcd for $C_{23}H_{27}NO_4$ [M+Na$^+$]: 404.1838; found: 404.1830.

Boc-(S)-2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline, 10b. Clear oil (0.345 g, 87%). $[\alpha]_D$ = 29.3 (c = 0.71, $CHCl_3$); IR (thin film): 2928, 2852, 1692, 1515, 1332, 1258, 1159, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.41 (m, 1H), 7.16–6.94 (m, 3H), 6.71–6.59 (m, 3H), 4.56–4.50 (m, 1H), 3.78 (2 bs, 6H), 2.68–2.65 (m, 2H), 2.57–2.51 (m, 2H), 2.21–2.12 (m, 1H), 1.83–1.73 (m, 1H), 1.68–1.58 (m, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 154.1, 148.8, 147.1, 137.0, 134.7, 131.0, 128.1, 126.0, 125.7, 123.9, 120.1, 111.7, 111.2, 80.6, 56.0, 55.8, 52.2, 34.9, 32.1, 28.6, 28.4, 24.6 ppm; HRMS (ES): m/z calcd for $C_{24}H_{31}NO_4$ [M+Na$^+$]: 420.2151; found: 420.2155.

Reduction of 10 to 1. $LiAlH_4$ (0.266 g, 7 mmol) was added portion wise to a solution of 10 (0.381 g of **10a** or 0.397 g of **10b**, 1 mmol) in dry THF (20 mL) at r. t. and refluxed until the complete disappearance of **10** on TLC. After the completion, reaction mixture was cooled to 0°C and was quenched by the drop wise addition of water and the solution was basified with 10% NaOH solution. The mixture was extracted with diethyl ether (3 × 15 mL) and the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude products were purified by column chromatography.

(–)-Cuspareine (1a). Clear oil (0.244 g, 83%). $[\alpha]_D$ = –22.4 (c = 1.33, $CHCl_3$), lit:[1b] –22.8; IR (thin film): 2926, 1602, 1500, 1489, 1244, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.08 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.15 Hz, 1H), 6.73–6.71 (m, 1H), 6.68 (s, 1H), 6.64–6.63 (m, 1H), 6.59 (t, *J* = 7.15 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 5.91 (s, 2H), 3.29–3.24 (m, 1H), 2.9 (s, 3H), 2.87–2.80 (m, 1H), 2.70–2.60 (m, 2H), 2.53–2.47 (m, 1H), 1.97–1.84 (m, 3H), 1.73–1.66 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 147.6, 145.6, 145.3, 135.9, 128.7, 127.2, 121.7, 121.0, 115.0, 110.7, 108.8, 108.2, 100.8, 58.3, 38.1, 33.2, 32.1, 24.4, 23.6 ppm; HRMS (ES): m/z calcd for $C_{19}H_{21}NO_2$ [M+H$^+$]: 296.1651; found: 296.1655.

(–)-Galipinine (1b). Yellow oil (0.242 g, 72%). $[\alpha]_D$ = –33.9 (c = 1.38, $CHCl_3$), lit:[1b] –33.4; IR (thin film): 2924, 2853, 1515, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.01 (t, *J* = 9.3 Hz, 1H), 6.91 (d, *J* = 8.85 Hz, 1H), 6.72–6.70 (m, 1H), 6.66–6.63 (m, 2H), 6.54–6.50 (m, 1H), 6.45 (d, *J* = 9.7 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.23–3.20 (m, 1H), 2.84 (s, 3H), 2.82–2.73 (m, 1H), 2.64–2.56 (m, 2H), 2.49–2.41 (m, 1H), 1.98–1.78 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.9, 147.2, 145.3, 134.7, 128.7, 127.2, 121.7, 121.7, 120.1, 115.4, 111.2, 110.6, 58.2, 55.7, 55.7, 37.9, 32.9, 31.8, 24.3, 23.5 ppm; HRMS (ES): m/z calcd for $C_{20}H_{25}NO_2$ [M+H$^+$]: 312.1964; found: 312.1967.

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