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ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDROQUINOLINE ALKALOIDS (-)-ANGUSTUREINE AND (-)-CUSPAREINE FROM CHIRAL *tert*-BUTANESULFINYL IMINES

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Abstract – The addition of a Grignard reagent to both enantiomeric *N*-*tert*-butanesulfinyl imines derived from 3-(2-bromophenyl)propanal **8** proceeded with high diastereoselectivity. The resulting sulfinamides **9** and **12** were easily transformed into tetrahydroquinoline alkaloids (-)-angustureine (**4**) and (-)-cuspareine (**5**) after three steps: *N*-desulfinylation, intramolecular *N*-arylation and *N*-methylation.

INTRODUCTION

The enantioselective synthesis of 2-substituted tetrahydroquinolines has attracted much attention among organic chemists because they are widespread subunits in natural alkaloids and pharmaceuticals as well. For instance, simple synthetic 1,2,3,4-tetrahydroquinolines with interesting biological properties includes oxamniquine (**1**), which has been used to combat parasitic disease schistosomiasis,[1] the novel antibiotic virantmycin (**2**),[2] and the tetrahydroquinoline L-689,560 (**3**),[3] one of the most potent NMDAR (*N*-methyl *d*-aspartate receptor) antagonists yet described (Figure 1). On the other hand, among natural alkaloids, (-)-angustureine (**4**), (-)-cuspareine (**5**), (-)-galipeine (**6**) and (-)-galipinine (**7**) were isolated from *Galipea officinalis* Hancock (Figure 1),[4] a Venezuelan shrubby tree used in folk medicine as tonic in dyspepsia, dysentery, chronic diarrhea and also as antipyretic.[5] The majority of the enantioselective synthesis of these tetrahydroquinolines reported until today are based on asymmetric catalytic hydrogenation of the corresponding quinolines.[6] Other recent synthesis of (-)-angustureine (**4**) and (-)-cuspareine (**5**) included as key steps a highly regio- and enantioselective intermolecular iridium-catalyzed allylic amination,[7] the conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated

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This paper is dedicated to Professor Victor Snieckus on occasion of his 77th birthday.

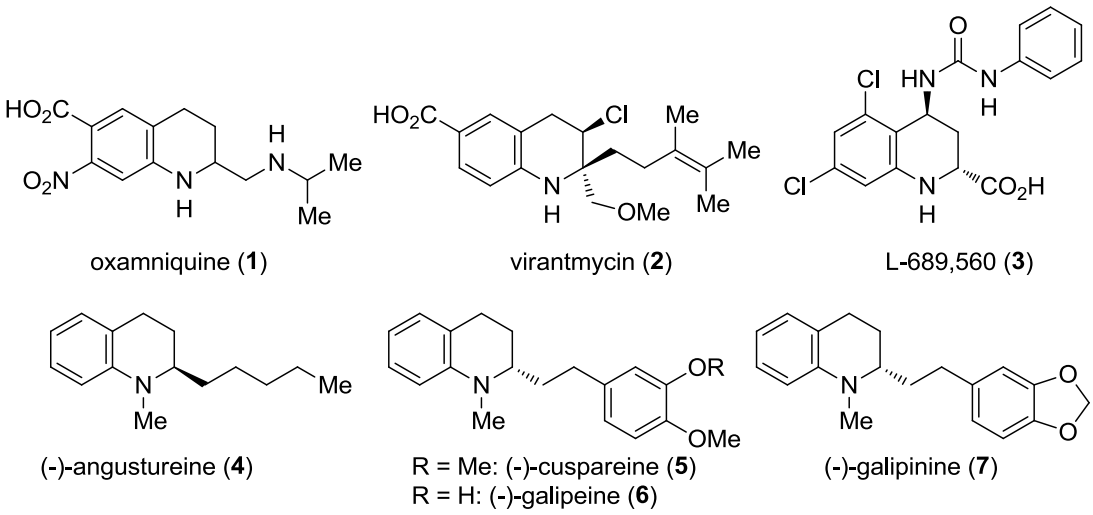
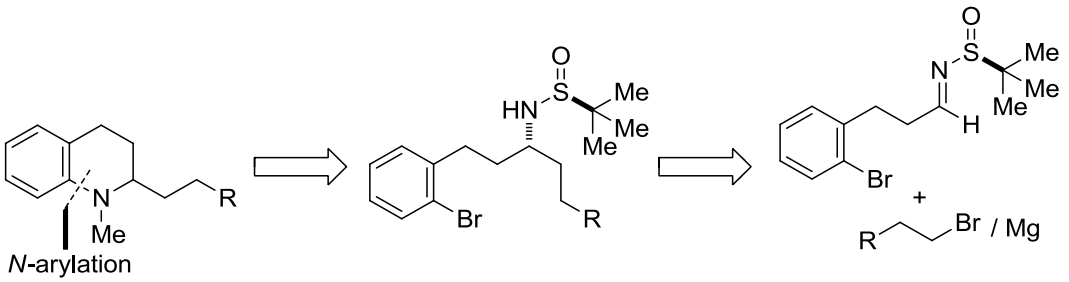


Figure 1

4-methoxyphenyl ester[8] and the alkynylation of a chiral cyclic β-amino ester.[9] Interestingly, Wang and co-workers provided also a synthesis of (+)-angustureine and (-)-cuspareine (**5**) involving a highly diastereoselective addition of an alkynylmagnesium chloride to a (R_S)-*tert*-butanesulfinyl imine as a key step.[10] Continuing our interest in the use of *N*-*tert*-butanesulfinyl imines[11] as electrophiles, we envisioned a straightforward synthesis of (-)-angustureine (**4**) and (-)-cuspareine (**5**), based on the diastereoselective addition of Grignard reagents to these chiral imines,[12] which have found high applicability in synthesis because both enantiomers are accessible in large-scale processes[13] and because the chiral auxiliary is easily removed under acidic conditions. In addition, practical processes for recycling the *tert*-butanesulfinyl group upon deprotection of *N*-*tert*-butanesulfinyl amines have also been reported.[14] In our synthetic strategy, similar to that provided by Wang,[10] a palladium-catalyzed intramolecular *N*-arylation will be also involved (Scheme 1).

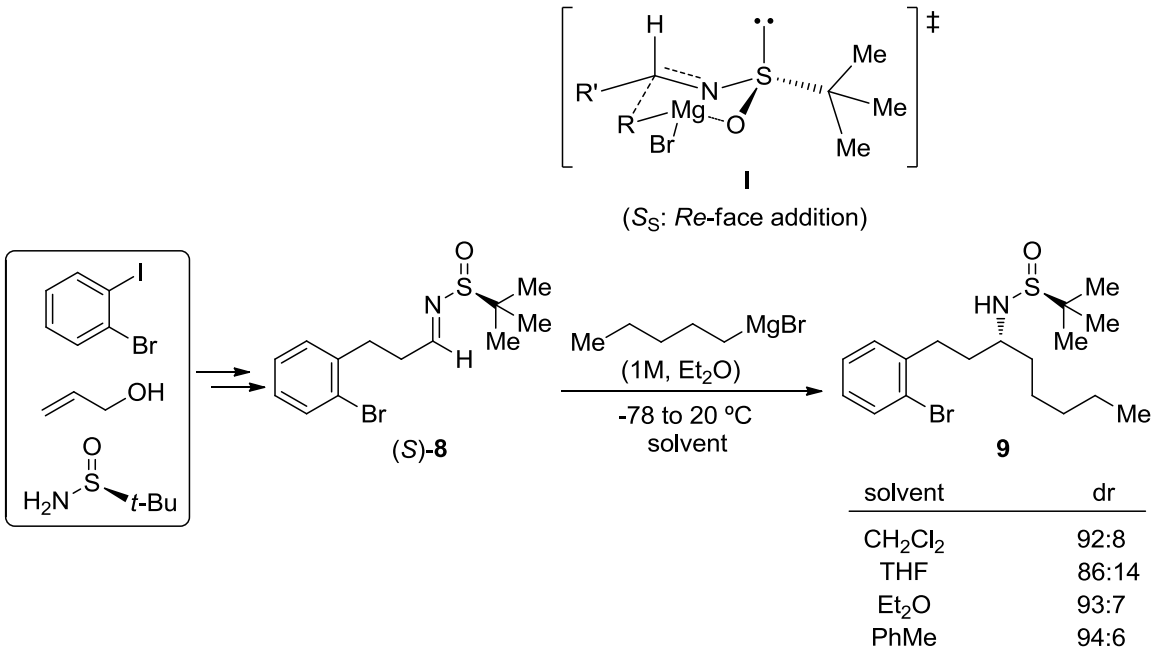


Scheme 1

RESULTS AND DISCUSSION

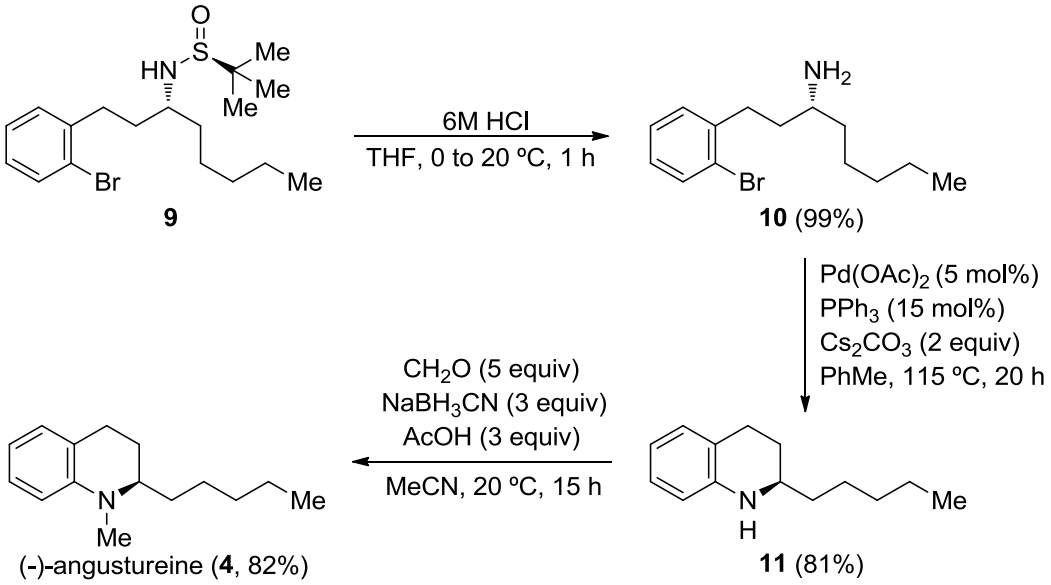
As depicted in Scheme 1, our synthesis commenced with the diastereoselective addition of the corresponding Grignard reagent to (*E*)-*N*-[3-(2-bromophenyl)propylydene]-*tert*-butanesulfinamide (**8**). Chiral imines **8** were easily accessible from the corresponding *tert*-butanesulfinamide and

3-(2-bromophenyl)propanal (obtained from commercially available 1,2-bromoiodobenzene and allylic alcohol through a type-Heck coupling reaction).[15] Ellman and co-workers reported for the first time the addition of Grignard reagents to *N*-*tert*-butanesulfinyl aldimines.[16] Interestingly, they found a marked solvent effect on the stereoselectivity of the addition, no coordinating solvents, such as dichloromethane, leading to the best results.[17] In addition, and considering the configuration of the resulting diastereomers, a chelated transition state **I** was proposed, which was also consistent with the observed solvent effect (competitive coordination of ethereal solvents such as THF would interfere with the formation of the six-membered-ring transition state). According to this model, the attack of the Grignard reagent occurred on the *Re* face of the imine with the *S* configuration at the sulfur atom (Scheme 2). For that reason, we studied first the addition of 1M solution of pentylmagnesium bromide in ether to the imine (*S*)-**8** in different solvents (Scheme 2). The addition was carried out at -78 ºC, and after that the reaction mixture was allowed to reach room temperature. The highest diastereoselectivity was obtained performing the reaction in toluene (94:6 dr), although similar levels of diastereocontrol were achieved using dichloromethane and diethyl ether (92:8 and 93:7 dr, respectively). As it could be anticipated, the lowest diastereoselectivity was reached in THF as solvent. The diastereomeric ratios were easily determined by ^{1}H-NMR analysis of the crude reaction mixtures through the comparison of the integrals of the *t*-Bu group and the N–H for each of the diastereoisomer (the largest chemical shift difference was always observed for the diastereomeric signals of the N–H). In all cases complete conversion was observed using two equivalents of the Grignard reagent, giving rise to the expected product **9** with *R* configuration at the newly created stereogenic center (Scheme 2).



Scheme 2

Free amine **10** was generated in quantitative yield from sulfinamide **9** upon reaction with 6M HCl in THF at room temperature. Intramolecular *N*-arylation to produce the tetrahydroquinoline derivative **11** was achieved in 81% yield under palladium catalysis, using Cs_2CO_3 as a base in toluene in a high pressure tube at 115 ºC for 20 hours.[15,18] Finally, *N*-methylation of **11** was achieved with paraformaldehyde and sodium cyanoborohydride leading to (-)-angustureine (**4**) in 82% yield (Scheme 3).

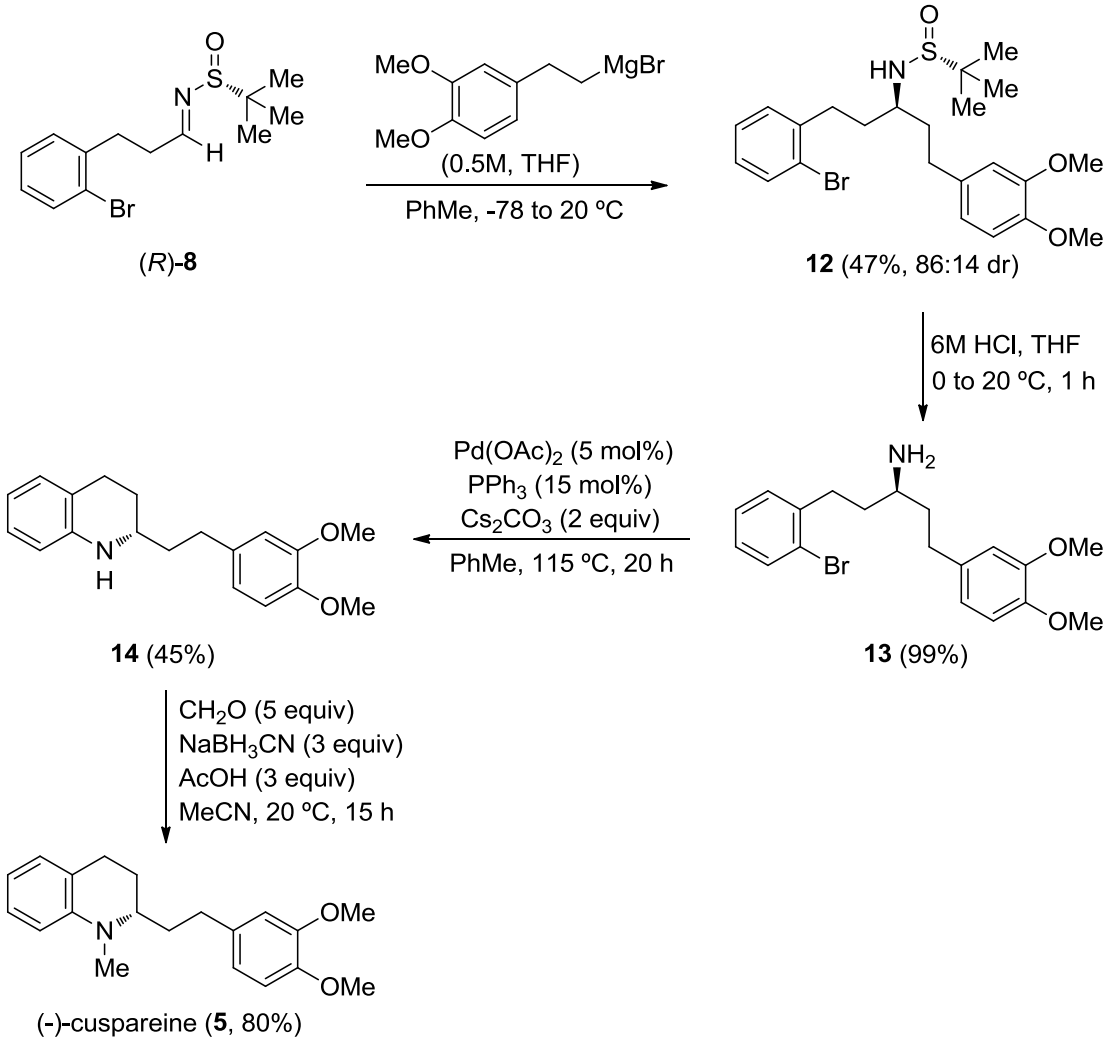


Scheme 3

The same strategy was applied to the synthesis of (-)-cuspareine (**5**), starting in this case from the enantiomeric aldimine (*R*)-**8**, since the configuration at the C2 position of the tetrahydroquinoline unit is the opposite to that of the (-)-angustureine (**4**). The reaction of 1.5 equivalents of 2-(3,4-dimethoxyphenyl)ethylmagnesium bromide (prepared from the corresponding alkyl bromide and magnesium in THF at 67 ºC) with aldimine (*R*)-**8** in toluene proceeded in this case in moderate yield (47%) and stereoselectivity (86:14 dr). Acidic hydrolysis of sulfonamide **12** led to free amine **13** in high yield. Further palladium-catalyzed intramolecular *N*-arylation gave tetrahydroquinoline derivative **14** in lower yield when comparing with the angustureine precursor shown above. Finally, methylation of **14** produced (-)-cuspareine (**5**) in 80% yield (Scheme 4).

In summary, 2-substituted tetrahydroquinoline alkaloids (-)-angustureine (**4**) and (-)-cuspareine (**5**) were easily accessible from the imines derived from 3-(2-bromophenyl)propanal and (*S*)- or (*R*)-*tert*-butanesulfinamide, respectively. The methodology presented here comprised as key steps a diastereoselective addition of a Grignard reagent to a chiral sulfinyl imine, and a palladium-catalyzed intramolecular *N*-arylation, following a strategy similar to that provided by Wang,[10] without the need of

sophisticated ligands for asymmetric metal catalyzed processes, which are required in other stereoselective synthesis.[6,7]



Scheme 4

EXPERIMENTAL

All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and hexane/EtOAc as eluent. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and high resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatograph (UPLC) model Waters ACQUITY H CLASS. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. NMR spectra

were recorded with a Bruker AC-300 using $CDCl_3$ as the solvent and TMS as internal standard. Optical rotations were measured on a Perkin Elmer 341 polarimeter.

(3*R*,S_S)-*N*-(*tert*-Butanesulfinyl)-1-(2-bromophenyl)octan-3-amine (9). To solution of aldimine (*S*)-**8** (322 mg, 1.0 mmol) in dry toluene (4 mL) was added dropwise a 1M solution of pentylmagnesium bromide in Et_2O (2.0 mmol, 2.0 mL) at -78 ºC. The reaction was allowed to reach room temperature and after 4 h, it was cooled down to 0 ºC, hydrolyzed with water (5 mL) and extracted with EtOAc (4 × 15 mL). The organic layers were successively washed with water (15 mL), brine (10 mL) and then dried over magnesium sulfate and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 4/1) to yield 291 mg of pure product **9** (75% yield, 94:6 dr). Physical and spectroscopic data follow: Yellow oil; $[\alpha]^{20}_D$ +28 (*c* 1.15, CH_2Cl_2); R_f 0.48 (hexane/EtOAc: 1/1); IR ν (film) 1622, 1471, 1084, 1025, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.8 Hz, CH_3), 1.25 [9H, s, $(CH_3)_3$], 1.27-1.47 (6H, m, CH_2), 1.53-1.93 (4H, m, CH_2), 2.70 (1H, ddd, *J* = 13.5, 11.1, 5.6 Hz, CH_2), 2.90 (1H, ddd, *J* = 13.5, 11.1, 5.1 Hz, CH_2), 3.08 (1H, br d, *J* = 6.9 Hz, NH), 3.24-3.37 (1H, m, CH), 7.02-7.09 (1H, m, ArH), 7.19-7.24 (2H, m, ArH), 7.52 (1H, d, *J* = 7.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.7 (CH_2), 22.9 (CH_3), 25.5 (CH_2), 31.8 (CH_2), 32.6 (CH_2), 36.0 (CH_2), 36.6 (CH_2), 56.0 (C), 56.8 (CH), 124.4 (C), 127.7 (CH), 127.8 (CH), 130.4 (CH), 133.0 (CH), 141.5 (C); LRMS (EI) *m/z* 331 [M^+ - 58 (^{81}Br), 5%], 329 (5), 260 (7), 258 (7), 250 (24), 185 (33), 183 (33), 171 (46), 169 (48), 147 (100), 130 (19), 104 (29), 103 (17), 91 (31), 90 (17), 89 (10), 83 (14), 77 (28), 70 (11), 55 (10); HRMS (ESI) calcd for $C_{18}H_{31}BrNOS$ (M+H) 388.1310, found 388.1302.

(3*R*)-1-(2-Bromophenyl)octan-3-amine (10). To solution of sulfinamide **9** (245 mg, 0.63 mmol) in THF (1.5 mL) was added dropwise a 6M solution of HCl (0.6 mmol, 0.10 mL) at 0 ºC. The reaction mixture was stirred at 20 ºC for 1 h. Then it was cooled down to 0 ºC and basified with 2M NaOH (1.0 mmol, 0.5 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL), dried over magnesium sulfate, filtered through a short pad of Celite and concentrated under vacuum (15 Torr) to give 177 mg of pure product **10** (99%). Physical and spectroscopic data follow: Yellow oil; $[\alpha]^{20}_D$ -6 (*c* 1.07, CH_2Cl_2); R_f 0.30 (CH_2Cl_2/methanol: 9/1); IR ν (film) 2925, 1469, 1022, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.7 Hz, CH_3), 1.20-1.40 (7H, m, CH_2), 1.40-1.63 (2H, m, CH_2), 1.67-1.90 (3H, m, CH_2), 2.69-2.92 (3H, m, CH_2, NH_2), 6.99-7.09 (1H, m, ArH), 7.18-7.25 (2H, m, ArH), 7.52 (1H, d, *J* = 7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8 (CH_2), 25.9 (CH_2), 32.1 (CH_2), 33.0 (CH_2), 38.0 (CH_2), 38.3 (CH_2), 51.2 (CH), 124.5 (C), 127.6 (2 x CH), 130.4 (CH), 132.9 (CH), 141.8 (C); LRMS (EI) *m/z* 284 [M^+ (^{81}Br), 1%], 282 (1), 214 (60), 212 (62), 204 (43), 171 (34), 169 (35), 100 (100); HRMS (ESI) calcd

for $C_{14}H_{23}BrN$ (M+H) 284.1014, found 284.1004.

(*R*)-2-Pentyltetrahydroquinoline (11).[6a] To a solution of amine **10** (152 mg, 0.53 mmol) in dry toluene (5 mL) in a high pressure flask was successively added triphenylphosphine (21 mg, 0.081 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol) and Cs_2CO_3 (345 mg, 1.06 mmol). The reaction mixture was stirred at 115 ºC for 20 h. The mixture was allowed to reach room temperature and hydrolyzed, first with 3M HCl (3.0 mmol, 1 mL) and then with 2M NaOH (8.0 mmol, 4 mL), and extracted with EtOAc (4 × 15 mL). The organic layers were washed with brine (15 mL) and then dried over magnesium sulfate and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 20/1) to yield 87 mg of pure product **11** (81% yield). Physical and spectroscopic data follow: Colorless oil; $[\alpha]^{20}_D$ +75 (*c* 1.10, CH_2Cl_2); R_f 0.44 (hexane/EtOAc: 16/1); IR ν (film) 3400, 2925, 2853, 1606, 1483, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 6.8 Hz, CH_3), 1.25-1.52 (8H, m, CH_2), 1.53-1.65 (1H, m, CH_2), 1.95 (1H, dddd, *J* = 12.7, 5.5, 4.1, 3.0 Hz, CH_2), 2.61-2.87 (2H, m, CH_2), 3.22 (1H, dtd, *J* = 9.4, 6.2, 3.0 Hz, CH), 6.46 (1H, dd, *J* = 8.4, 1.2 Hz, ArH), 6.58 (1H, td, *J* = 7.4, 1.2 Hz, ArH), 6.90-6.98 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8 (CH_2), 25.5 (CH_2), 26.6 (CH_2), 28.3 (CH_2), 32.1 (CH_2), 36.8 (CH_2), 51.7 (CH), 114.2 (CH), 117.0 (CH), 121.5 (C), 126.8 (CH), 129.4 (CH), 144.9 (C); LRMS (EI) *m/z* 203 [M^+ , 22%], 133 (13), 132 (100), 130 (11), 117 (11).

(-)-Angustureine [**(*R*)-1-Methyl-2-pentyltetrahydroquinoline (4)].** To a solution of tetrahydroquinoline **11** (36 mg, 0.18 mmol) in acetonitrile (2 mL) in a 10 mL round-botton flask was successively added paraformaldehyde (27 mg, 0.9 mmol), $NaBH_3CN$ (38 mg, 0.6 mmol) and acetic acid (0.034 mL, 0.6 mmol). The reaction mixture was stirred at 20 ºC for 15 h, then hydrolyzed with 2M NaOH (10.0 mmol, 5 mL), and extracted with EtOAc (4 × 15 mL). The organic layers were washed with brine (15 mL), then dried over magnesium sulfate, and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 20/1) to yield 32 mg of pure product **4** (82% yield). Physical and spectroscopic data follow: Colorless oil; $[\alpha]^{25}_D$ -6.8 (*c* 1.00, $CHCl_3$) {lit.[4a] $[\alpha]^{25}_D$ -7.16 (*c* 1.00, $CHCl_3$)}; R_f 0.18 (hexane); IR ν (film) 2926, 1602, 1498, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 9.9 Hz, CH_3), 1.20-1.45 (7H, m, CH_2), 1.53-1.64 (1H, m, CH_2), 1.83-1.92 (2H, m, CH_2), 2.64 (1H, dt, *J* = 16.2, 4.2 Hz, CH_2), 2.73-2.84 (1H, m, CH_2), 2.91 (3H, s, CH_3), 3.21 (1H, dq, *J* = 8.5, 4.2 Hz, CH), 6.51 (1H, d, *J* = 8.2 Hz, ArH), 6.57 (1H, td, *J* = 7.3, 1.0 Hz, ArH), 6.95 (1H, d, *J* = 7.3 Hz, ArH), 7.06 (1H, t, *J* = 7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8 (CH_2), 23.7 (CH_2), 24.6 (CH_2), 25.9 (CH_2), 31.4 (CH_2), 32.2 (CH_2), 38.1 (CH_3), 59.1 (CH), 110.5 (CH), 115.3 (CH), 122.0 (C), 127.2 (CH), 128.7 (CH), 145.5 (C); LRMS (EI) *m/z* 217 [M^+ (^{81}Br), 14%], 147 (11), 146 (100), 144 (8).

(3*S*,R_S)-*N*-(*tert*-Butanesulfinyl)-1-(2-bromophenyl)-5-(3,4-dimethoxyphenyl)pentan-3-amine (12). To solution of aldimine (*R*)-**8** (632 mg, 2.0 mmol) in dry toluene (8 mL) was added dropwise a 0.5M solution of 2-(3,4-dimethoxyphenyl)ethylmagnesium bromide in THF (3.0 mmol, 6.0 mL) at -78 ºC. The reaction was allowed to reach room temperature and after 4 h, it was cooled down to 0 ºC and hydrolyzed with water (5 mL), and extracted with EtOAc (4 × 15 mL). The organic layers were successively washed with water (15 mL), brine (10 mL) and then dried over magnesium sulfate and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 1/1) to yield 452 mg of pure product **12** (47% yield, 86:14 dr). Physical and spectroscopic data follow: Yellow oil; $[\alpha]^{20}_D$ -30 (*c* 0.99, CH_2Cl_2); R_f 0.27 (hexane/EtOAc: 1/2); IR ν (film) 3262, 1515, 1261, 1235, 1024, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 [9H, s, $(CH_3)_3$], 1.71-1.85 (2H, m, CH_2), 1.85-2.07 (3H, m, CH_2), 2.65-2.76 (2H, m, CH_2), 2.83-2.95 (1H, m, CH_2), 3.14 (1H, br d, *J* = 7.1 Hz, NH), 3.29-3.38 (1H, m, CH), 3.85 (3H, s, CH_3), 3.88 (3H, s, CH_3), 6.69-6.80 (3H, m, ArH), 7.03-7.09 (1H, m, ArH), 7.17-7.26 (2H, m, ArH), 7.52 (1H, dd, *J* = 8.0, 1.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (CH_3), 31.6 (CH_2), 32.6 (CH_2), 36.2 (CH_2), 38.2 (CH_2), 56.00 (CH_3), 56.04 (CH_3), 56.08 (C), 56.4 (CH), 111.4 (CH), 112.0 (CH), 120.4 (CH), 124.4 (C), 127.7 (CH), 127.9 (CH), 130.4 (CH), 133.0 (CH), 134.1 (C), 141.3 (C), 147.4 (C), 149.0 (C); LRMS (EI) *m/z* 425 [M^+ - 58 (^{81}Br), 33%], 423 (32), 376 (16), 374 (16), 261 (13), 259 (13), 197 (15), 195 (15), 192 (16), 171 (22), 169 (22), 165 (11), 164 (32), 152 (11), 151 (100), 132 (11), 117 (13), 107 (10), 91 (11), 77 (12); HRMS (ESI) calcd for $C_{23}H_{33}BrNO_3S$ (M+H) 482.1365, found 482.1351.

(3*S*)-1-(2-Bromophenyl)-5-(3,4-dimethoxyphenyl)pentan-3-amine (13). To solution of sulfinamide **12** (177 mg, 0.367 mmol) in THF (1.5 mL) was added dropwise a 6M solution of HCl (0.6 mmol, 0.10 mL) at 0 ºC. The reaction mixture was stirred at 20 ºC for 1 h. Then it was cooled down to 0 ºC and basified with 2M NaOH (1.0 mmol, 0.5 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL), dried over magnesium sulfate, filtered through a short pad of Celite, and concentrated under vacuum (15 Torr) to give 137 mg of pure product **13** (99%). Physical and spectroscopic data follow: Yellow oil; $[\alpha]^{20}_D$ +3.1 (*c* 1.09, CH_2Cl_2); R_f 0.38 (CH_2Cl_2/methanol: 9/1); IR ν (film) 2930, 1514, 1259, 1234, 1023, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54-1.70 (2H, m, CH_2), 1.70-1.92 (4H, m, CH_2), 2.60 (1H, ddd, *J* = 13.8, 10.0, 6.1 Hz, CH_2), 2.66-2.91 (4H, m, CH_2, NH_2), 3.85 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.71-6.75 (2H, m, ArH), 6.76-6.81 (1H, m, ArH), 7.00-7.08 (1H, m, ArH), 7.19-7.24 (2H, m, ArH), 7.52 (1H, d, *J* = 7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2 (CH_2), 32.9 (CH_2), 38.3 (CH_2), 40.0 (CH_2), 50.8 (CH), 55.9 (CH_3), 56.0 (CH_3), 111.4 (CH), 111.8 (CH), 120.2 (CH), 124.4 (C), 127.6 (CH), 127.7 (CH), 130.4 (CH), 132.9 (CH), 134.9 (C), 141.6 (C), 147.3 (C), 148.9 (C); LRMS (EI) *m/z* 379 [M^+ (^{81}Br), 2%], 377 (2), 362 (20), 360 (19), 298 (41), 214 (25), 212 (26), 177 (22), 171 (19), 169 (20), 152 (33), 151 (100);

HRMS (ESI) calcd for $C_{19}H_{25}BrNO_2$ (M+H) 378.1069, found 378.1066.

(*S*)-2-(3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (14).[6h] To a solution of amine **13** (124 mg, 0.328 mmol) in dry toluene (5 mL) in a high pressure flask was successively added triphenylphosphine (19 mg, 0.073 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol) and Cs_2CO_3 (214 mg, 0.656 mmol). The reaction mixture was stirred at 115 ºC for 20 h. The mixture was left cooling to room temperature and hydrolyzed, first with 3M HCl (3.0 mmol, 1 mL) and then with 2M NaOH (8.0 mmol, 4 mL), and extracted with EtOAc (4 × 15 mL). The organic layers were successively washed with brine (15 mL) and then dried over magnesium sulfate and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 20/1) to yield 44 mg of pure product **14** (45% yield). Physical and spectroscopic data follow: Yellow oil; $[\alpha]^{20}_D$ -37 (*c* 1.00, CH_2Cl_2); R_f 0.41 (hexane/EtOAc: 3/1); IR ν (film) 3392, 2932, 1605, 1514, 1140, 1027, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.74 (1H, m, CH_2), 1.76-1.86 (2H, m, CH_2), 1.99 (1H, dddd, *J* = 8.5, 5.5, 4.7, 2.4 Hz, CH_2), 2.62-2.89 (4H, m, CH_2), 3.30 (1H, dtd, *J* = 9.3, 6.3, 3.0 Hz, CH), 3.85 (3H, s, CH_3), 3.87 (3H, s, CH_3), 6.44 (1H, dd, *J* = 8.4, 1.1 Hz, ArH), 6.60 (1H, td, *J* = 7.4, 1.1 Hz, ArH), 6.71-6.83 (3H, m, ArH), 6.92-6.99 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3 (CH_2), 28.1 (CH_2), 31.9 (CH_2), 38.5 (CH_2), 51.3 (CH), 56.0 (CH_3), 56.1 (CH_3), 111.4 (CH), 111.7 (CH), 114.2 (CH), 117.1 (CH), 120.2 (CH), 121.4 (C), 126.8 (CH), 129.3 (CH), 134.6 (C), 144.6 (C), 147.4 (C), 149.0 (C); LRMS (EI) *m/z* 297 (M^+, 38%), 298 (8), 152 (7), 133 (11), 132 (100), 117 (8).

(-)-Cuspareine [(*S*)-2-(3,4-Dimethoxyphenethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (5)]. To a solution of tetrahydroquinoline **14** (30 mg, 0.10 mmol) in MeCN (1.2 mL) in a 10 mL round-botton flask was successively added paraformaldehyde (27 mg, 0.9 mmol), $NaBH_3CN$ (38 mg, 0.6 mmol) and acetic acid (0.034 mL, 0.6 mmol). The reaction mixture was stirred at 20 ºC for 15 h, then hydrolyzed with 2M NaOH (10.0 mmol, 5 mL) and extracted with EtOAc (4 × 15 mL). The organic layers were washed with brine (15 mL) and then dried over magnesium sulfate and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc: 20/1) to yield 25 mg of pure product **5** (80% yield). Physical and spectroscopic data follow: Colorless oil; $[\alpha]^{25}_D$ -18.8 (*c* 1.00, $CHCl_3$) {lit.[19] $[\alpha]^{25}_D$ -22.8 (*c* 1.00, $CHCl_3$)}; R_f 0.50 (hexane/EtOAc: 3/1); IR ν (film) 2932, 1498, 1260, 1233, 1028, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67-1.79 (1H, m, CH_2), 1.86-2.01 (3H, m, CH_2), 2.53 (ddd, *J* = 13.9, 10.1, 6.5 Hz, CH_2), 2.62-2.75 (2H, m, CH_2), 2.79-2.90 (1H, m, CH_2), 2.91 (3H, s, CH_3), 3.28 (1H, td, *J* = 8.4, 4.2 Hz, CH), 3.85 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.53 (1H, d, *J* = 8.2 Hz, ArH), 6.56-6.62 (1H, m, ArH), 6.69-6.75 (2H, m, ArH), 6.79 (1H, d, *J* = 8.0 Hz, ArH), 6.98 (1H, d, *J* = 7.3 Hz,

ArH), 7.08 (1H, t, J = 7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (CH_2), 24.5 (CH_2), 32.1 (CH_2), 33.2 (CH_2), 38.2 (CH_3), 55.99 (CH_3), 56.05 (CH_3), 58.5 (CH), 110.7 (CH), 111.4 (CH), 111.7 (CH), 115.5 (CH), 120.2 (CH), 121.8 (C), 127.2 (CH), 128.8 (CH), 134.8 (C), 145.4 (C), 147.3 (C), 149.0 (C); LRMS (EI) *m/z* 311 (M^+, 25%), 147 (11), 146 (100).

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REFERENCES

1. G. O. Kokwaro and G. Taylor, *Drug Chem. Toxicol.*, 1990, **13**, 347.
2. S. Omura and A. Nakagawa, *Tetrahedron Lett.*, 1981, **22**, 2199.
3. P. D. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall, and K. Hoogsteen, *J. Med. Chem.*, 1992, **35**, 1954.
4. (a) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fourasté, and C. Moulis, *Phytochemistry*, 1999, **51**, 1167; (b) I. Jacquemond-Collet, F. Benoit-Vical, M. A. Valentin, E. Stanislas, M. Mallié, and I. Fourasté, *Planta Med.*, 2002, **68**, 68.
5. P. J. Houghton, T. Z. Woldemariam, T. Watanabe, and M. Yates, *Planta Med.*, 1999, **65**, 250.
6. (a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 10536; (b) S.-M. Lu, Y.-Q. Wang, X.-W. Han, and Y.-G. Zhou, *Angew. Chem. Int. Ed.*, 2006, **45**, 2260; (c) W.-J. Tang, S.-F. Zhu, L.-J. Xu, Q.-L. Zhou, Q.-H. Fan, H.-F. Zhou, K. Lam, and A. S. C. Chan, *Chem. Commun.*, 2007, 613; (d) Z.-J. Wang, G.-J. Deng, Y. Li, Y.-M. He, W.-J. Tang, and Q.-H. Fan, *Org. Lett.*, 2007, **9**, 1243; (e) C. Deport, M. Buchotte, K. Abecassis, H. Tadaoka, T. Ayad, T. Ohshima, J.-P. Genet, K. Mashima, and V. Ratovelomanana-Vidal, *Synlett*, 2007, 2743; (f) D.-W. Wang, W. Zeng, and Y.-G. Zhou, *Tetrahedron: Asymmetry*, 2007, **18**, 1103; (g) M. Jahjah, M. Alame, S. Pellet-Rostaing, and M. Lemaire, *Tetrahedron: Asymmetry*, 2007, **18**, 2305; (h) X.-B. Wang and Y.-G. Zhou, *J. Org. Chem.*, 2008, **73**, 5640; (i) F.-R. Gou, W. Li, X. Zhang, and Y.-M. Liang, *Adv. Synth. Catal.*, 2010, **352**, 2441; (j) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 9878.
7. (a) G. Satyanarayana, D. Pflästerer, and G. Helmchen, *Eur. J. Org. Chem.*, 2011, 6877; (b) K.-Y. Ye,

H. He, W.-B. Liu, L.-X. Dai, G. Helmchen, and S.-L. You, *J. Am. Chem. Soc.*, 2011, **133**, 19006.

8. S. A. Bentley, S. G. Davies, J. A. Lee, P. M. Roberts, and J. E. Thomson, *Org. Lett.*, 2011, **13**, 2544.
9. J. Tummatorn, G. Diaz Muñoz, and G. B. Dudley, *Tetrahedron Lett.*, 2013, **54**, 1312.
10. B.-L. Chen, B. Wang, and G.-Q. Lin, *J. Org. Chem.*, 2010, **75**, 941.
11. (a) F. Foubelo and M. Yus, *Tetrahedron: Asymmetry*, 2004, **15**, 3823; (b) J. C. González-Gómez, F. Foubelo, and M. Yus, *Synlett*, 2008, 2777; (c) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Heterocycles*, 2008, **76**, 569; (d) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2009, **74**, 7859; (e) H. K. Dema, F. Foubelo, and M. Yus, *Heterocycles*, 2010, **80**, 125; (f) J. C. González-Gómez, M. Medjahdi, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2010, **75**, 6308; (g) H. K. Dema, F. Foubelo, and M. Yus, *Heterocycles*, 2011, **82**, 1411; (h) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Eur. J. Org. Chem.*, 2011, 2230; (i) H. K. Dema, F. Foubelo, and M. Yus, *Jordan J. Chem.*, 2011, **6**, 247; (j) J. C. González-Gómez, F. Foubelo, and M. Yus, *Org. Synth.*, 2012, **89**, 88; (k) I. Bosque, J. C. González-Gómez, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2012, **77**, 780 (correction: I. Bosque, J. C. González-Gómez, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2012, **77**, 4190); (l) I. Bosque, J. C. González-Gómez, A. Guijarro, F. Foubelo, and M. Yus, *J. Org. Chem.*, 2012, **77**, 10340; (m) J. A. Sirvent, F. Foubelo, and M. Yus, *Chem. Commun.*, 2012, **48**, 2543; (n) H. K. Dema, F. Foubelo, and M. Yus, *Helv. Chim. Acta*, 2012, **95**, 1790; (o) M. Medjahdi, J. C. González-Gómez, F. Foubelo, and M. Yus, *Heterocycles*, 2012, **86**, 727; (q) M. J. García-Muñoz, F. Foubelo, and M. Yus, *Eur. J. Org. Chem.*, 2013, 1287; (r) J. A. Sirvent, F. Foubelo, and M. Yus, *Eur. J. Org. Chem.*, 2013, 2461.
12. For reviews, see: (a) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong, and X.-W. Sun, *Acc. Chem. Res.*, 2008, **41**, 831; (b) F. Ferreira, C. Botuha, F. Chemla, and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162; (c) M. A. T. Robak, M. A. Herbage, and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600.
13. (a) D. J. Weix and J. A. Ellman, *Org. Lett.*, 2003, **5**, 1317; (b) D. J. Weix and J. A. Ellman, *Org. Synth.*, 2005, **82**, 157.
14. (a) M. Wakayama and J. A. Ellman, *J. Org. Chem.*, 2009, **74**, 2646; (b) V. K. Aggarwal, N. Barbero, E. M. McGarrigle, G. Mickle, R. Navas, J. R. Suárez, M. G. Unthank, and M. Yar, *Tetrahedron Lett.*, 2009, **50**, 3482.
15. G. S. Lemen and J. P. Wolfe, *Org. Lett.*, 2011, **13**, 3218.
16. G. Liu, D. A. Cogan, and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913.
17. D. A. Cogan, G. Liu, and J. Ellman, *Tetrahedron*, 1999, **55**, 8883.
18. For similar *N*-arylation examples, see: (a) M. Liu, J. Li, X. Xiao, Y. Xie, and Y. Shi, *Chem. Commun.*, 2013, **49**, 1404; (b) T. Guo, R. Song, B.-H. Yuan, X.-Y. Chen, X.-W. Sun, and G.-Q. Lin, *Chem. Commun.*, 2013, **49**, 5402.

19. J. H. Rokotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, I. Fourasté, and C. Moulis, *Planta Med.*, 1998, **64**, 762.