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TOTAL SYNTHESIS OF (*S*)-(−)-STEPHOLIDINE USING (*S*)-*TERT*-BUTANESULFINYLIMINE

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Abstract – A new synthetic strategy of (*S*)-(−)-stepholidine, a promising antipsychotic drug candidate, is described. Nucleophilic addition of a laterally lithiated nitrile to a (*S*)-*tert*-butanesulfinylimine was used as the key step, which was complished in 94 % *de* and the main isomer was isolated in 52% yield. (*S*)-(−)-Stepholidine was prepared after another 5 steps, with an overall yield of 18.3% and > 98% *ee*.

INTRODUCTION

Tetrahydroprotoberberines (THPBs) represent a large class of naturally occurring alkaloids which possess a wide range of biological activities.[1] Asymmetric syntheses of THPBs which mostly emphasize the construction of chiral amines have attracted much attention these years.[2] Among the diverse methods to prepare chiral amines, addition of nucleophile to enantiopure sulfinimine has become a method of choice since this methodology showed advantages in both enantioselectivity and substrate diversity (Figure 1).[3,4] Addition of laterally lithiated amides or nitriles **1** to enantiopure sulfinimines **2** has been developed and used in the syntheses of 6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**4**),[5] (−)-normalindine (**5**),[6] (*S*)-(−)-xylopinine (**6**),[7] and (*S*)-(−)-*O*-methylbharatamine (**7**).[8] Among them, **6** and **7** represent typical structures of THPBs.

(*S*)-(−)-Stepholidine (*l*-SPD, **10**), a prototypical member of THPBs, which is extracted from *Stephanie intermedi*, a traditional Chinese herb, has attracted a great deal of attention since it was reported to display a unique pharmacological profile toward the central nervous system.[9] Clinical trials and animal studies have demonstrated that *l*-SPD is a potential candidate for the treatment of schizophrenia and/or drug abuse.[10]

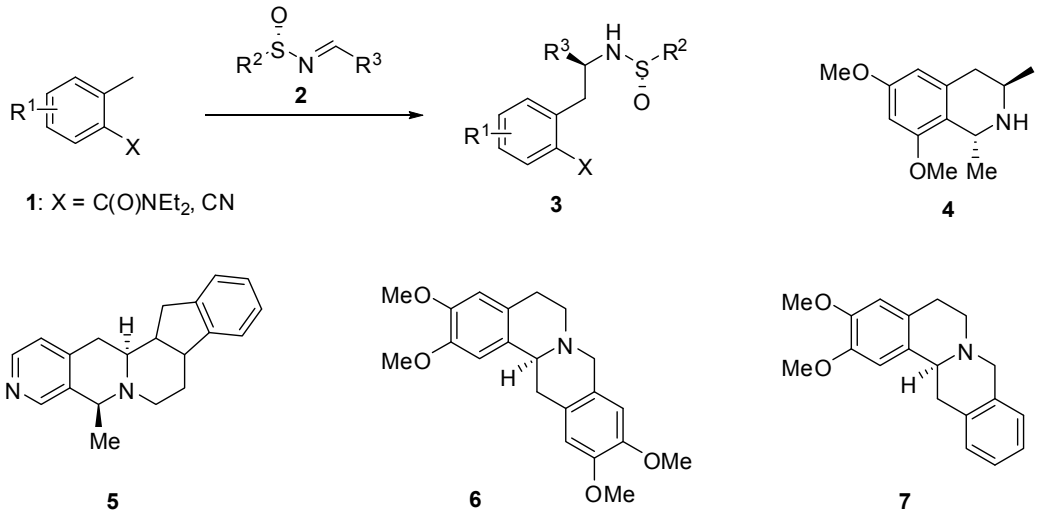
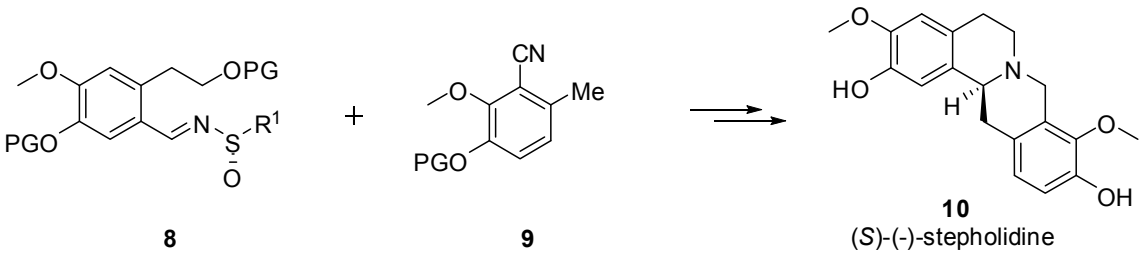


Figure 1. Addition of nucleophiles to enantiopure sulfinimines as a synthetic approach

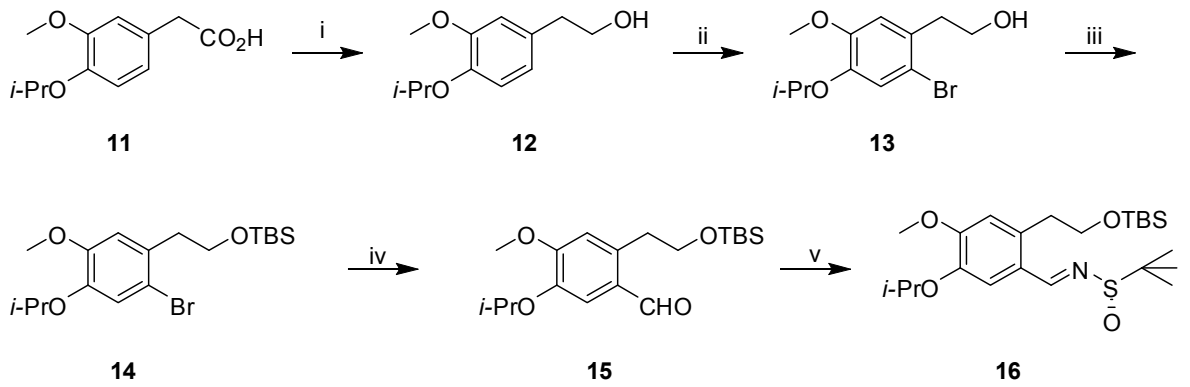
Recently, we have reported the first enantioselective synthesis of *l*-SPD using Noyori's enantioselective reduction of cyclic imine as the key step.[11] However, due to the high price of the Ru (II) catalyst and the harsh conditions needed for the catalytic reduction, new and smooth method for producing this alkaloid is still necessary. Herein, we report the synthesis of (*S*)-(−)-stepholidine **10** by applying chiral (*S*)-*N*-*tert*-butanesulfinimine **8** and benzonitrile **9** as building blocks (Scheme 1), *via* a similar approach for the synthesis of (*S*)-(−)-xylopinine. [7]



Scheme 1. New synthetic approach of (*S*)-(−)-stepholidine

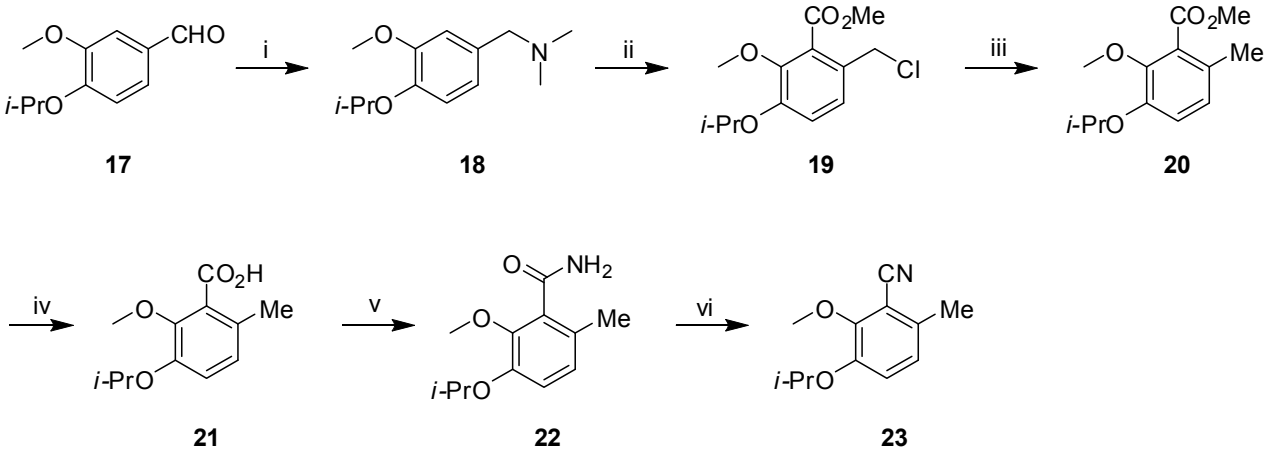
RESULTS AND DISCUSSION

Phenylacetic acid **11** was prepared according to the reported method [12] and used as starting material for the synthesis of (*S*)-*N*-*tert*-butanesulfinimine (Scheme 2). Reduction of **11** with $LiAlH_4$ afforded phenethyl alcohol **12** in high yield, and bromination of **12** with NBS in DMF at room temperature gave **13** in almost quantitative yield. The alcohol group of **13** was protected as a silyl ether **14** and lithium halogen exchange was accomplished using *n*-BuLi at -78 ^{o}C, which was quenched with anhydrous DMF to give aldehyde **15**. Sulfinimine **16** was prepared similarly according to Ellmans' procedure with **15** and (*S*)-*tert*-butanesulfinylamide in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ in 92% yield.[13]



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, reflux 2 h, 98%; (ii) NBS, DMF, rt, 12 h, 98%; (iii) TBSCl, imidazole, CH_2Cl_2, rt, 91%; (iv) *n*-BuLi, THF, DMF, -78 ~ 0 °C, 93%; (v) (*S*)-*tert*-butane-sulfinylamide, Ti(O*i*-Pr)$_4$, THF, reflux 4 h, 92%.

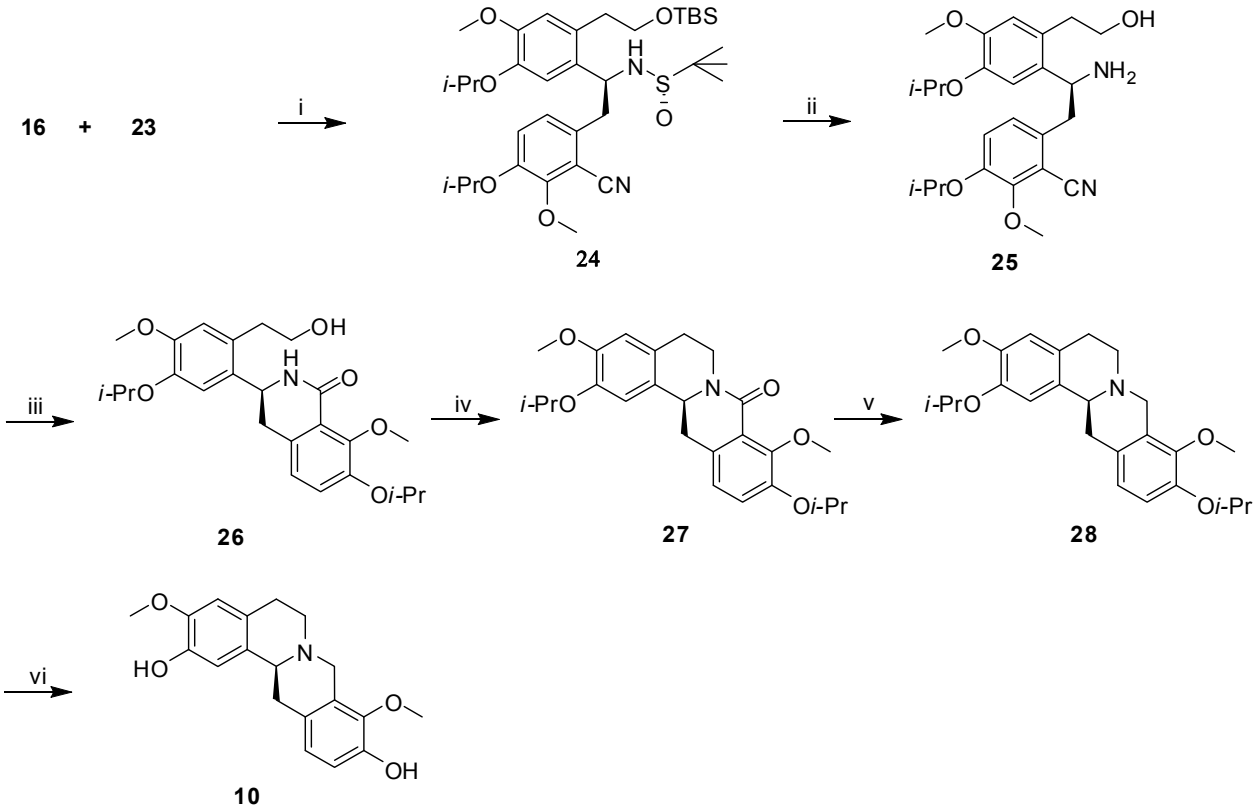
Synthesis of the requisite benzonitrile started from isopropyl ether of vanillin **17**, as shown in Scheme 3. Reductive amination of **17** afforded benzylic amine **18**, treatment of which with *n*-BuLi and $ClCO_2Me$ using reported method afforded **19** in high yield.[14] Hydrogenation of the benzylic chloride followed by hydrolyzation of the ester group gave benzoic acid **21**, which was converted to amide **22** with oxalyl chloride and ammonia. Dehydration of this amide was accomplished using cyanuric chloride, giving the desired benzonitrile **23** in 95% yield.[15]



Scheme 3. Reagents and conditions: (i) a. $Me_2NH{\cdot}HCl$, Et_3N, Ti(O*i*-Pr)$_4$, EtOH, rt, 12 h; b. $NaBH_4$, 8 h, 82%; (ii) *n*-BuLi, THF, $ClCO_2Me$, -78 ~ 0 °C, 93%; (iii) H_2, Pd/C, MeOH, 4 h, 97%; (iv) NaOH, H_2O-EtOH, reflux 2 h, 96%; (v) a. $(COCl)_2$, reflux 2 h; b. NH_4OH, 88%; (vi) cyanuric chloride, DMF, rt, 16 h, 95%.

With both **16** and **23** in hand, the key step was carried out, as shown in Scheme 4. Thus, benzonitrile **23** was treated with LDA at -78 °C to give a dark red solution of the laterally lithiated *o*-tolylnitrile. To this solution was added 1.0 equiv of sulfinimine **16** and the reaction was quenched with aqueous NH_4Cl after 0.5 h. It was reported that in the asymmetric synthesis of (*S*)-(−)-xylopinine (**6**), the addition of laterally

lithiated derivative of *o*-tolunitrile to enantiopure sulfinimine derived from *tert*-butanesulfinamide lead to complex mixture of products and the corresponding sulfinamide was not detected.[7] Fortunately for us, the addition of lithiated **23** to sulfinimine **16** gave the the corresponding sulfinamide in moderate yield and 97:3 *dr*, determined by LC-MS. The major isomer **24** was isolated by chromatography in 52% yield, using CH_2Cl_2/CH_3OH as the eluent. The reason for the low yield of this reaction is probably the self-condensation of **23**, and attempts to improve the yield of **24**, such as changing the solvent, base or reaction temperature failed (data not shown).



Scheme 4. Reagents and conditions: (i) LDA, THF, -78 °C, 52%; (ii) MeOH, conc. HCl, rt, 81%; (iii) KOH, H_2O-EtOH, reflux 20 h, 87%; (iv) TsCl, pyridine, rt, 8 h; NaH, THF, 0 °C, 2 h. 67% for 2 steps; (v) $LiAlH_4$, THF, reflux 2 h, 91%; (vi) BCl_3, CH_2Cl_2, -78 °C, 82%.

Removal of the *N*-sulfinyl auxiliary along with the silyl protecting group of **24** was accomplished in one step with hydrochloric acid to give the priamry amine **25** in 81% yield. Refluxing of **25** in aqueous KOH for 20 h afforded the lactam **26**, which was converted to its tosylate and treated with NaH to give **27**. Reduction of the lactam **27** was accomplished with $LiAlH_4$ and the following deprotection of the isopropyl groups using BCl_3 in CH_2Cl_2 afforded the title compound **10** successfully, in an overall yield of 18.3% based on **16** and **23**.

In conclusion, total synthesis of (*S*)-(−)-stepholidine **10**, a protoberberine alkaloid, using addition of laterally lithiated nitriles to enantiopure sulfinimine was reported. Enantiopure sulfinimine **16** was

prepared in 5 steps and 76% overall yield from the known phenylacetic acid, and the requisite benzonitrile **23** was prepared in 6 steps and 55% overall yield from isopropyl ether of vanillin. Addition of lithiated **23** to sulfinimine **16** yielded the desired sulfinamide in 97:3 *dr*, and the desired isomer was isolated in 52% yield. (*S*)-(−)-stepholidine was prepared after another 5 steps, with an overall yield of 18.3% and > 98% *ee*. Spectral properties, specific rotation of the title compound were in agreement with the reported ones.[11]

EXPERIMENTAL

All solvents used were of analytical grade, purified and dried by standard methods prior to use. Melting points (uncorrected) were determined on an X-4 melting point apparatus. EI-MS spectra were obtained on a Finnigan MAT 95 mass spectrometer and ESI-MS spectra were obtained on a Kratos MS 80 mass spectrometer. Column chromatography was performed on silica gel H (200-300 mesh), and the solvent proportions were expressed on a volume/volume basis.

2-(4-Isopropoxy-3-methoxyphenyl)ethanol (12)

To a suspension of $LiAlH_4$ (11.4 g, 0.30 mol) in anhydrous THF (500 mL) cooled at 0 ^oC was added dropwise a solution of 2-(4-isopropoxy-3-methoxyphenyl)acetic acid **6** (44.8 g, 0.20 mol) in the same solvent (200 mL). The mixture was refluxed for 1 h and then cooled to 0 ^oC again. Water (30 mL) was added slowly followed by 10% aq. NaOH (30 mL), and water (100 mL). Then the mixture was filtered and the filtrate was extracted with Et_2O. The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo to yield a colorless oil **12** (41.2 g, 98%). ^1H NMR (300 MHz, $CDCl_3$): 6.84 (d, 1H, J = 10.4 Hz), 6.76-6.70 (m, 2H), 4.51-4.43 (m, 1H), 3.86-3.76 (m, 5H), 2.80 (t, 2H, J = 6.6 Hz), 1.35 (d, 6H, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 150.4, 145.9, 131.4, 120.9, 116.2, 112.9, 71.5, 63.7, 55.9, 38.7, 22.1 (×2). EI-MS: m/z (%) 137 (100), 168 (20), 210 (14); HRMS calcd for $C_{12}H_{18}O_3$: 210.1256, found: 210.1263.

2-(2-Bromo-4-isopropoxy-5-methoxyphenyl)ethanol (13)

A solution of **12** (44.2 g, 0.21 mol) in anhydrous DMF (200 mL) was cooled to 0 ^oC, and NBS (41.1 g, 0.23 mol) was added portionwise. The mixture was stirred at room temperature overnight before saturated aq. $Na_2S_2O_3$ was added and the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O, brine, dried over Na_2SO_4, then concentrated to give a brown oil, which was purified by fast chromatography (EtOAc/petroleum ether = 1/3) to yield a yellow oil (59.3 g, 98%). ^1H NMR (400 MHz, $CDCl_3$): 7.03 (s, 1H), 6.77 (s, 1H), 4.50–4.46 (m, 1H), 3.86 (t, 2H, J = 6.6 Hz), 3.83 (s, 3H), 2.94 (t, 2H, J = 6.6 Hz), 1.36 (d, 6H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 149.6, 146.6, 130.0, 119.7, 114.4, 114.2, 71.9, 62.2, 56.1, 39.0, 21.9 (×2); EI-MS: m/z (%) 215 (100), 217 (97), 246 (33), 248

(31), 288 (18), 290 (17); HRMS: calcd for $C_{12}H_{17}BrO_3$: 288.0361, found: 288.0356.

(2-Bromo-4-isopropoxy-5-methoxyphenethyloxy)(*tert*-butyl)dimethylsilane (14)

To a stirred solution of the alcohol **13** (10.4 g, 36 mmol) in anhydrous CH_2Cl_2 (200 mL) was added imidazole (4.9 g, 72 mmol), followed by TBSCl (8.1 g, 54 mmol). The mixture was stirred at room temperature for 1 h. CH_2Cl_2 (200 mL) was added and the organic phase was washed with H_2O, brine, dried over Na_2SO_4, concentrated and purified by chromatography (EtOAc/petroleum ether = 1/6) to yield a yellow oil (13.9 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.03 (s, 1H), 6.78 (s, 1H), 4.51–4.42 (m, 1H), 3.86-3.74 (m, 5H), 2.87 (t, 2H, J = 6.7 Hz), 1.34 (d, 6H, J = 6.1 Hz), 0.86 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 149.4, 146.2, 130.8, 119.6, 114.8, 114.0, 71.8, 62.6, 55.9, 39.2, 25.8 (×3), 21.9 (×2), 18.2, -5.5 (×2); EI-MS: m/z (%) 73 (41), 223 (47), 345 (100), 347 (96), 402 (6), 404 (6); HRMS: calcd for $C_{18}H_{31}SiBrO_3$: 402.1226, found: 402.1218.

2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-5-isopropoxy-4-methoxybenzaldehyde (15)

A solution of **14** (8.07 g, 20 mmol) in anhydrous THF (200 mL) was cooled to -78 °C, and *n*-BuLi (1.6 M in hexane, 16 mL) was added dropwise under N_2 and the solution was stirred at the same temperature for 30 min before DMF (2.3 mL, 30 mmol) was added. Saturated aq. NH_4Cl was added after another 30 min and the mixture was warmed to room temperature. Water was added and the mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (ethyl acetate/petroleum ether = 1/4) to give a yellow oil (6.4 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): 10.15 (s, 1H), 7.39 (s, 1H), 6.74 (s, 1H), 4.47-4.58 (m, 1H), 3.91 (s, 3H), 3.83 (t, 2H, J = 6.3 Hz), 3.17 (t, 2H, J = 6.3 Hz), 1.37 (d, 6H, J = 6.0 Hz), 0.82 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 190.4, 154.8, 145.9, 137.4, 127.4, 115.4, 114.2, 71.4, 64.4, 56.0, 34.9, 25.8 (×3), 21.9 (×2), 18.2, -5.6 (×2). EI-MS: m/z (%) 75 (31), 214 (31), 216 (31), 221 (32), 295 (100), 352 (1); HRMS: calcd for $C_{19}H_{32}SiO_4$: 352.2070, found: 352.2081.

Condensation of aldehyde 15 with *(S)-tert*-butanesulfinylamide

To a solution of the benylaldehyde **15** (3.6 g, 10 mmol) in anhydrous THF (100 mL) was added (*S*)-*tert*-butanesulfinylamide (1.27 g, 10.5 mmol), Ti(O*i*-Pr)$_4$ (7.4 mL, 25 mmol) under argon, and the mixture was refluxed for 4 h before it was cooled to room temperature and water (10 mL) was added. The mixture was filtered, and the filtrate cake was washed with THF. The filtrate was extracted with CH_2Cl_2, and the combined extracts was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (EtOAc/petroleum ether = 1/4) to yield a red thick oil (3.8 g, 95%). $[\alpha]^{20}_D$ +41.5 (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 8.72 (s, 1H), 7.50 (s, 1H), 6.76 (s, 1H), 4.62-4.51 (m, 1H), 3.91 (s, 3H), 3.86-3.71 (m, 2H), 3.16-3.05 (m, 2H), 1.36 (d, 6H, J = 6.3

Hz), 1.24 (s, 9H), 0.81 (s, 9H), -0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.2, 153.3, 145.7, 135.6, 124.7, 115.4, 114.2, 71.4, 64.2, 57.4, 55.8, 35.6, 25.8 (×3), 22.5 (×3), 21.9, 21.7, 18.2, -5.6 (×2); EI-MS: m/z (%) 73 (65), 177 (100), 219 (63), 267 (72), 399 (84), 455 (3); HRMS: calcd for $C_{23}H_{41}NO_4SSi$: 455.2526, found: 455.2558.

(4-Isopropoxy-3-methoxyphenyl)-*N,N*-dimethylmethanamine (18)

To an ice-cooled solution of isopropylvanillin **17** (77.7 g, 0.40 mol) in EtOH (400 mL) was added Et_3N (112 mL, 0.80 mol), Me_2NH·HCl (65.2 g, 0.80 mol), Ti(O*i*-Pr)$_4$ (238 mL, 0.80 mol) and the mixture was stirred at 30 °C for 16 h. $NaBH_4$ (24 g, 0.60 mol) was added and the stirring was continued for another 14 h. The mixture was poured into 3 N aqueous ammonia with ice (2 L) and filtered after 1 h standing at room temperature. The filtrate cake was washed with CH_2Cl_2, and the filtrate was extracted with the same solvent. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to yield a colorless oil (73.2 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.86 (d, 1H, *J* = 2.0 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 6.76 (dd, 1H, *J* = 8.0, 2.0 Hz), 4.52-4.44 (m, 1H), 3.84 (s, 3H), 3.33 (s, 2H), 2.22 (s, 6H), 1.34(d, 6H, *J* = 6.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): 150.2, 146.2, 131.8, 121.1, 115.4, 112.7, 71.3, 64.2, 55.9, 45.2 (×2), 22.0 (×2); EI-MS: m/z (%) 137 (100), 138 (18), 163 (16), 180 (15), 223 (26); HRMS: calcd for $C_{13}H_{21}NO_2$: 223.1572, found: 223.1573.

Methyl 6-(chloromethyl)-3-isopropoxy-2-methoxybenzoate (19)

To a cooled (-10 °C) solution of **18** (32.0 g, 0.14 mol) in anhydrous THF (300 mL) was added *n*-BuLi (1.6 M in hexane, 100 mL) under argon and the stirring was continued for 1 h at the same temperature. The solution was then cooled to -78 °C, and $ClCO_2Me$ (27.5 mL, 0.35 mol) was added. The mixture was stirred for 15 min before it was warmed to room temperature and stirred overnight. With ice cooling, water was added and the mixture was extracted with *t*-BuOMe. The combined extracts was washed with brine, dried over Na_2SO_4, and concentrated to afford a red oil which was purified by chromatography (EtOAc/petroleum ether = 1/6) to give the benzylic chlorine **19** as colorless oil (35.0 g, 92%).^{1}H NMR (300 MHz, $CDCl_3$): 7.06 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 4.59-4.51 (m, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 1.35 (d, 6H, *J* = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.3, 151.2, 147.7, 128.9, 127.2, 125.5, 116.4, 71.1, 61.3, 52.4, 43.6, 21.9 (×2); EI- MS: m/z (%) 163 (81), 198 (100), 200 (34), 230 (42), 232 (13), 272 (41), 274 (14); HRMS: calcd for $C_{13}H_{17}ClO_4$: 272.0815, found: 272.0818.

Methyl 3-isopropoxy-2-methoxy-6-methylbenzoate (20)

The benzylic chlorine **19** (17.5 g, 64 mmol) was dissolved in MeOH (200 mL), and 10% Pd/C (1.8 g) was added. The mixture was hydrogenated at 1 atm for 8 h at room temperature. Pd/C was filtered off and the filtrate was concentrated under reduced pressure to give **20** as colorless oil (14.1 g, 92%). ^{1}H NMR (300

MHz, $CDCl_3$): 6.85 (d, 1H, *J* = 8.6 Hz), 6.83 (d, 1H, *J* = 8.6 Hz), 4.53-4.42 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.21 (s, 3H), 1.32 (d, 6H, *J* = 6.1Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.4, 148.4, 147.4, 129.3, 127.8, 125.3, 117.8, 71.5, 61.2, 52.0, 22.0 (×2), 18.4; EI-MS: m/z (%) 164 (100), 196 (48), 207 (14), 238 (30); HRMS: calcd for $C_{13}H_{18}O_4$: 238.1205, found: 238.1200.

3-Isopropoxy-2-methoxy-6-methylbenzoic acid (21)

To a solution of the methyl ester **20** (7.9 g, 33 mmol) in EtOH (100 mL) was added 20% aqueous NaOH (100 mL) and the mixture was refluxed for 4 h. The solution was cooled to room temperature and EtOH was removed under vacuo. The resultant basic solution was washed with Et_2O, acidified with conc. HCl, and extracted with EtOAc. The combined EtOAc was washed with brine, dried over Na_2SO_4 and concentrated to yield a yellow solid (6.9 g, 94%). mp 61-62 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 6.94 (d, 1H, *J* = 8.4 Hz), 6.90 (d, 1H, *J* = 8.4 Hz), 4.53 (m, 1H), 3.95 (s, 3H), 2.40 (s, 3H), 1.36 (d, 6H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 148.5, 148.2, 130.4, 126.5, 126.3, 118.6, 71.6, 61.7, 22.1 (×2), 19.9; EI-MS: m/z (%) 121 (26), 135 (28), 136 (32), 164 (100), 165 (21), 182 (53), 207 (27), 224 (36); HRMS: calcd for $C_{12}H_{16}O_4$: 224.1049, found: 224.1049.

3-Isopropoxy-2-methoxy-6-methylbenzamide (22)

Benzoic acid **21** (10.0 g, 44.6 mmol) was dissolved in oxalyl chloride (50 mL) and refluxed for 2 h. Oxalyl chloride was removed under reduced pressure and the residual benzoyl chloride was dissolved in anhydrous Et_2O (50 mL). Saturated aq. ammonia (100 mL) was stirred and cooled at 0 ^{o}C, and the solution of the benzoyl chloride was added dropwise. The resultant slurry was stirred at room temperature for 1 h before *n*-hexane (100 mL) was added and the stirring was continued for 15 min. The mixture was filtered and the solid was washed with water, petroleum ether, and dried to give the amide **22** (8.8 g, 88 %). mp 80-81 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6): 7.69 (br, 1H), 7.40 (br, 1H), 6.91 (d, 1H, *J* = 8.5 Hz), 6.85 (d, 1H, *J* = 8.5 Hz), 4.59-4.51 (m, 1H), 3.74 (s, 3H), 2.16 (s, 3H), 1.27 (d, 6H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 168.8, 148.1, 145.8, 134.1, 126.1, 125.0, 115.4, 70.1, 60.6, 21.9 (×2), 18.0; EI-MS: m/z (%) 135 (48), 164 (100), 181 (78), 223 (62); HRMS: calcd for $C_{12}H_{17}NO_3$: 223.1208, found: 223.1204.

3-Isopropoxy-2-methoxy-6-methylbenzonitrile (23)

To an ice-cooled solution of benzamide **22** (8.8 g, 39.4 mmol) in DMF (100 mL) was added cyanuric chloride (18.4 g, 0.1 mol), and the slurry was stirred at room temperature for 16 h. Water was added dropwise and the solvent was removed in vacuo. The residue was dissolved in EtOAc, washed with water, brine, dried over Na_2SO_4, concentrated and the residue was purified by chromatography (EtOAc /petroleum ether = 1/6) to give a colorless oil (7.7 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.01 (d, 1H, *J* =

8.5 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 4.54-4.42 (m, 1H), 3.98 (s, 3H), 2.42 (s, 3H), 1.34 (d, 6H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 152.9, 148.3, 134.6, 125.0, 120.9, 115.5, 108.3, 72.0, 61.4, 22.0 (×2), 19.7; EI-MS: m/z (%) 120 (26), 148 (26), 163 (100), 205 (15); HRMS: calcd for $C_{12}H_{15}NO_2$: 205.1103, found: 205.1096.

Addition of lithiated nitrile 23 to sulfinimine 16

LDA (purchased from Acros Organics, 2 M in THF, 5.0 mL) was diluted with anhydrous THF (20 mL) at -78 °C under argon, and a solution of compound **23** (1.03 g, 5 mmol) in the same solvent (5 mL) was added dropwise in 10 min. After the addition, the solution was stirred at -78 °C for 30 min, and a solution of compound **16** (2.28 g, 5 mmol) in anhydrous THF (5 mL) was added in 10 min and the mixture was stirred at -60 °C for 30 min. Sat. aq. NH_4Cl (10 mL) was added dropwise and the mixture was warmed up to room temperature and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography (CH_2Cl_2/MeOH = 100/1) to give the major isomer as a brown thick oil (1.72 g, 52%). $[\alpha]^{20}_D$ +34.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 6.99 (d, 1H, *J* = 8.5 Hz), 6.94 (s, 1H), 6.89 (d, 1H, *J* = 8.5 Hz), 6.68 (s, 1H), 4.78-4.70 (m, 1H), 4.56-4.42 (m, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 3.79-3.68 (m, 2H), 3.46 (d, 1H, *J* = 4.4 Hz), 3.34 (dd, 1H, *J* = 14.1, 6.6 Hz), 3.11 (dd, 1H, *J* = 14.1, 6.6 Hz), 2.84-2.66 (m, 2H), 1.38-1.28 (m, 12H), 1.11 (s, 9H), 0.84 (s, 9H), -0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.7, 149.7, 149.1, 145.8, 134.2, 131.1, 129.8, 125.7, 120.2, 115.5, 114.8, 114.2, 109.0, 71.7 (×2), 64.0, 61.4, 56.1, 55.8, 55.7, 41.2, 35.4, 25.9 (×3), 22.4 (×3), 22.1 (×2), 21.9 (×2), 18.3, -5.3 (×2); ESI-MS: 683 (M + Na); HRMS: 683.3524 ($C_{35}H_{56}N_2O_6NaSSi$, M + Na).

The *de* determination of the crude product was carried out using LC-MS (LC column: C18, 5 μm, 0.46 cm × 25 cm, gradient eluent with MeCN/H_2O from 10/90 to 90/10 in 20 min, and 90/10 after that), minor isomer: RT_1 = 26.6 min (3%); major isomer: RT_2 = 27.0 min (97%).

(*S*)-6-(2-Amino-2-(2-(2-hydroxyethyl)-5-isopropoxy-4-methoxyphenyl)ethyl)-3-isopropoxy-2-methoxybenzonitrile (25)

To a solution of compound **24** (0.50 g, 0.82 mmol) in MeOH (20 mL) was added conc. HCl (1.0 mL) and the mixture was stirred at room temperature for 2 h. MeOH was removed under reduced pressure and the residue was basified with 10% aq. NaOH. The mixture was then extracted with CH_2Cl_2 and the combined extracts was washed with brine, dried over Na_2SO_4 and concentrated to give a white solid (0.27 g, 81%). mp 70-71 °C; $[\alpha]^{20}_D$ -4.7 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.05 (s, 1H), 7.02 (d, 1H, *J* = 8.5 Hz), 6.92 (d, 1H, *J* = 8.5 Hz), 6.68 (s, 1H), 4.58-4.42 (m, 3H), 4.00 (s, 3H), 3.86-3.75 (m, 4H), 3.73-3.64 (m, 1H), 3.22-3.12 (m, 1H), 3.04-2.73 (m, 3H), 1.38-1.29 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 153.0, 149.6, 149.2, 145.8, 135.1, 134.1, 130.2, 125.8, 120.1, 115.7, 113.8 (×2), 107.9, 71.7 (×2), 63.9, 61.5,

55.9, 51.1, 43.1, 35.6, 22.1 (×4); ESI-MS: 443 (M + H); HRMS: 465.2363 ($C_{25}H_{34}N_2O_5Na$, M + Na).
ee determination: Chiralpak IA column (0.46 cm × 25 cm, 5 μm), mobile phase: hexane/*i*-PrOH/*i*-Pr_2NH = 80/20/0.1 (v/v/v), flow rate: 0.7 mL/min, UV 230 nm. RT_1 = 12.6 min (*R* isomer, 0.6%); RT_2 = 14.2 min (*S* isomer, 99.4%).

(*S*)-3-(2-(2-Hydroxyethyl)-5-isopropoxy-4-methoxyphenyl)-7-isopropoxy-8-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (26)

To a solution of compound **25** (0.35 g, 0.79 mmol) in EtOH (15 mL) was added 20 % aqueous KOH (15 mL) and the mixture was refluxed for 12 h before it was cooled to room temperature, and EtOH was removed under reduced pressure. The resultant mixture was extracted with CH_2Cl_2, and the combined extracts was washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography (CH_2Cl_2/MeOH = 40/1) to give a light yellow foam (0.30 g, 87%). $[\alpha]^{20}_D$ -97.1 (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.00 (d, 1H, *J* = 8.1 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 6.72 (s, 1H), 6.57 (s, 1H), 4.93 (dd, 1H, *J* = 11.6, 3.3 Hz), 4.53-4.45 (m, 2H), 3.90 (s, 3H), 3.86-3.75 (m, 5H), 3.17-3.06 (m, 1H), 2.92-2.76 (m, 3H), 1.36-1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.9, 152.1, 151.1, 150.0, 146.0, 132.0, 130.6, 129.4, 122.8, 122.5, 121.1, 114.1, 113.9, 72.2, 71.6, 63.5, 61.3, 56.0, 51.2, 37.1, 35.2, 22.2 (×4); ESI-MS: 466 (M + Na); HRMS: 466.2210 ($C_{25}H_{33}NO_6Na$, M + Na).

Intramolecular cyclization of 26

Compound **26** (130 mg, 0.29 mmol) was dissolved in anhydrous pyridine (10 mL), to which TsCl (95 mg, 0.5 mmol) was added and the mixture was stirred at room temperature overnight. Pyridine was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2, which was washed with water, brine, dried over Na_2SO_4 and concentrated to yield an oil. The oil was dissolved in anhydrous THF (10 mL), NaH (60% in mineral oil, 100 mg) was added, and the mixture was stirred for 2 h at room temperature before it was cooled to 0 ^{o}C and water (10 mL) was added dropwise. The mixture was then extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography (EtOAc/petroleum ether = 1/2) to give a light yellow thick oil (90 mg, 72%). $[\alpha]^{20}_D$ -247.9 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.03 (d, 1H, *J* = 8.2 Hz), 6.92 (d, 1H, *J* = 8.2 Hz), 6.73 (s, 1H), 6.70 (s, 1H), 4.72 (dd, 1H, *J* = 13.0, 3.2 Hz), 4.60-4.43 (m, 2H), 4.02 (s, 3H), 3.87 (s, 3H), 3.04-2.72 (m, 6H), 1.42-1.31 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): 162.7, 151.8, 151.2, 149.4, 146.0, 131.7, 128.2, 127.6, 123.8, 121.9, 120.2, 114.3, 111.9, 72.0, 71.9, 61.3, 55.9, 54.8, 39.2, 38.1, 29.4, 22.1 (×4); ESI-MS: 448 (M + Na); HRMS: 448.2092 ($C_{25}H_{31}NO_5Na$, M + Na).

14-(*S*)-3,9-Dimethoxyl-2,10-diisopropoxy-tetrahydroprotoberberine (28)

To a solution of compound **27** (108 mg, 0.25 mmol) in anhydrous THF (20 mL) was added $LiAlH_4$ (20

mg, 0.5 mmol), and the mixture was refluxed under an argon atmosphere for 2 h before it was cooled to 0 ^{o}C and water was added. The mixture was filtered, and the filtrate was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography (CH_2Cl_2/MeOH = 100/1) to yield a light yellow foam (94 mg, 91%). $[\alpha]^{20}_D$ -190.5 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 6.87-6.78 (m, 3H), 6.63 (s, 1H), 4.57-4.46 (m, 2H), 4.24 (d, 1H, *J* = 15.9 Hz), 3.88 (s, 3H), 3.85 (s, 3H), 3.62-3.50 (m, 2H), 3.31-3.08 (m, 3H), 2.88-2.61 (m, 3H), 1.45-1.34 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): 148.9, 148.1, 146.4, 145.4, 129.6, 128.8, 128.0, 127.5, 123.7, 115.0, 113.9, 111.8, 71.8, 71.1, 60.0, 59.1, 55.8, 54.0, 51.4, 36.3, 29.1, 22.1 (×4); ESI-MS: 412 (M + H); HRMS: 412.2490 ($C_{25}H_{34}NO_4$, M + H).

(*S*)-(−)-Stepholidine (10)

To a solution of compound **28** (140 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (15 mL) cooled at -78 ^{o}C, BCl_3 (1 M in CH_2Cl_2, 1.4 mL) was added dropwise under argon and the solution was stirred for 0.5 h at the same temperature before it was warmed to room temperature and stirred overnight. The solution was cooled to -78 ^{o}C again, MeOH (10 mL) was added and the stirring was continued for 2 h at room temperature. The mixture was then concentrated and the residue was dissolved in CH_2Cl_2 (20 mL) and THF (10 mL), which was washed with saturated aq. $NaHCO_3$, brine, dried over Na_2SO_4, concentrated and recrystallized in MeOH to give the title compound (96 mg, > 98% *ee*, 86%). mp 127-128 ^{o}C; $[\alpha]^{20}_D$ -279.4 (*c* 1.0, CH_3OH); NMR, MS data were in accordance with previous report.[11]

ee determination: Chiralpak OJ-H column (0.46 cm × 25 cm, 5 μm), mobile phase: hexane/*i*-PrOH = 50/50 (v/v), flow rate: 0.7 mL/min, UV 230 nm. RT_1 = 9.8 min (*R* isomer, 0.9%); RT_2 = 17.2 min (*S* isomer, 99.1%).

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