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The enantioselective total synthesis of alkaloid (−)-galipeine

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Abstract—The first total synthesis of (−)-galipeine was accomplished in seven steps with 54% overall yield from isovanillin based on Ir-catalyzed asymmetric hydrogenation of a quinoline derivative as a key step, with its absolute stereochemistry being established.

1. Introduction

Galipea officinalis Hancock (Rutaceae) is a Venezuelan shrubby tree that is acclaimed in folk medicine as a tonic and stimulant and can be used against fevers.[1] *Galipea* species are known to contain 2-substituted tetrahydroquinoline alkaloids (Fig. 1), whose structures have been known for some time.[2] The biological activity of an ethanolic extract of *Galipea officinalis* bark against *Mycobacterium tuberculosis* was initially tested by Houghton's group,[3] with some differences in the bioactivities of 2-substituted tetrahydroquinolines (angustureine, galipinine, cuspareine, and galipeine) being reported.[1]

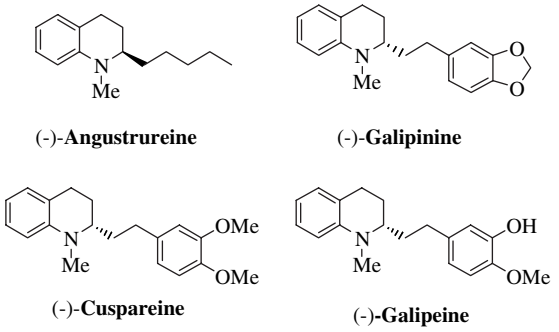

Figure 1. Structures of some quinoline alkaloids isolated from *Galipea officinalis*.

(−)-Galipeine was first isolated from the bark of *Galipea officinalis* Hancock by Jacquemond-Collet et al.[2a] in 1999. The isolated yield was low with only 14 mg of (−)-galipeine being obtained from 1 kg of the dried bark. Its structure was determined by extensive NMR spectroscopy studies, but the absolute configuration of the natural product was not assigned. To study this fascinating novel molecule and its biological activity, finding an appropriately efficient and economic way to synthesize (−)-galipeine is required.

Very recently, Bräse et al.[4] introduced a general methodology for the syntheses of much simpler 2-alkyl tetrahydroquinolines via intramolecular aza-xylylene Diels–Alder reactions, but the long synthetic route was a major problem. Moreover, the methodology could not be used for the enantioselective syntheses of naturally occurring 2-alkyl tetrahydroquinoline alkaloids.

In continuing efforts directed toward the development of catalytic asymmetric hydrogenation of aromatic and heteroaromatic compounds,[5a,b] we reported the first catalytic asymmetric hydrogenation of quinolines using $[Ir(COD)Cl]_2$/MeO-Biphep/I_2 as the catalyst with high enantioselectivities.[5c] As an application of our developed method, the first total synthesis of (−)-galipeine is reported herein, featuring Ir-catalyzed asymmetric hydrogenation of quinoline derivatives as a key step. Furthermore, the synthesis serves to define the absolute configuration of (−)-galipeine.

2. Result and discussions

A retrosynthetic analysis for (−)-galipeine **1** is shown in Scheme 1. Target molecule **1** can be synthesized via asymmetric hydrogenation of the corresponding hydroxy-protected quinoline derivative **6**, followed by

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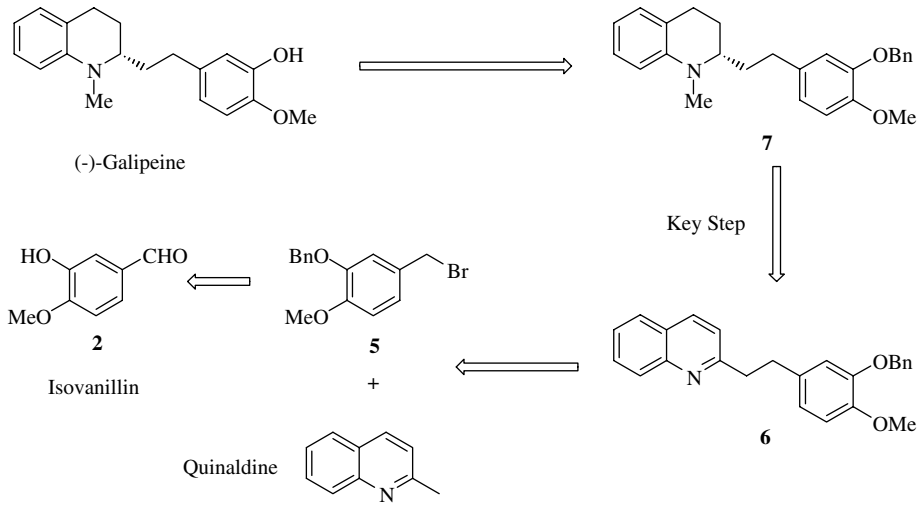
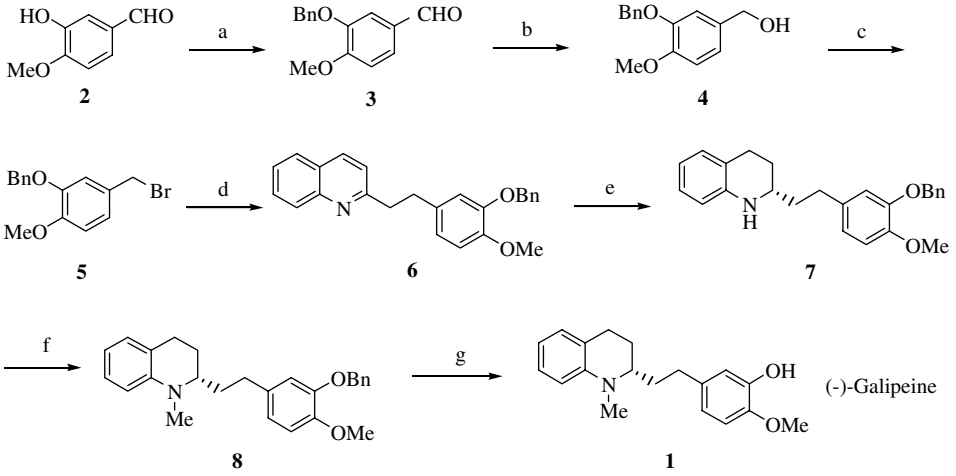


Scheme 1. Retrosynthetic analysis.

N-methylation and deprotection of the *O*-benzyl. Compound **6** can be constructed by alkylation of the quinaldine with the bromide **5**, which can be synthesized in three steps through the protection of the free hydroxy, the reduction of the aldehyde, and bromination from commercially available isovanillin **2**. Among the above synthetic steps, the asymmetric hydrogenation of quinoline derivative **6** and protection of the free hydroxy of isovanillin **2** are the key steps. Asymmetric hydrogenation can be solved via our previous work on asymmetric hydrogenation of heteroaromatic compounds.[5c] Due to potential problems in carrying a free hydroxy group through several steps of the synthesis, we decided to protect the hydroxy functional group by benzylation of the starting material **2**.

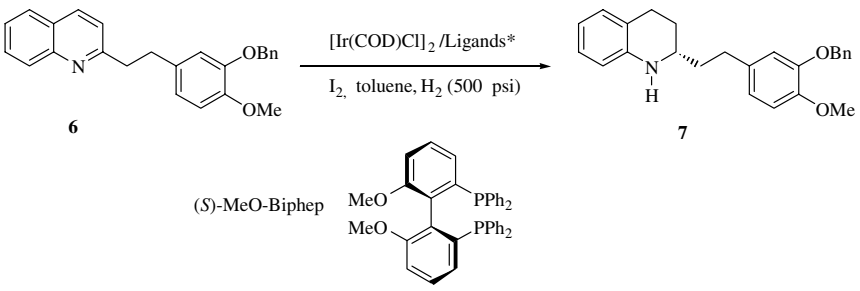
The synthetic route to (−)-galipeine is outlined in Scheme 2. The synthesis of **1** starts from the commercially available aldehyde **2**. Treatment of **2** with benzyl chloride and sodium bicarbonate gave the benzyl group protected compound **3** in 89% yield via an adaptation of Mendelson's method.[6] Compound **3** was reduced with sodium borohydride to afford the corresponding alcohol **4** in 96% yield, followed by bromination with phosphorus tribromide in the presence of pyridine to give compound **5** in 85% yield, which was directly employed in the next alkylation without further purification. A carbanion was generated from the quinaldine in Et_2O by treatment with *n*-butyllithium; it was then alkylated with the bromide **5** to give the key intermediate **6**.

Asymmetric hydrogenation of the quinoline derivative **6** was the key step. Firstly we used the previous standard conditions to screen several commercially available bisphosphine ligands with the results shown in Table 1. Axial chirality ligands BINAP and MeO-Biphep gave



Scheme 2. Enantioselective total synthesis of (−)-galipeine. Reagents and conditions: (a) BnCl, $NaHCO_3$/KI, CH_3CN, 89%; (b) $NaBH_4$, CH_3OH, 96%; (c) PBr_3, Et_2O/pyridine, 85%; (d) Quinaldine, *n*-BuLi/Et_2O, 86%; (e) $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep, I_2, toluene, H_2 (500 psi), 94%; (f) HCHO/HOAc, $NaBH_3CN$, CH_3CN, 96%; (g) 5% Pd/C, EtOAc/HOAc, 95%.

Table 1. Iridium-catalyzed asymmetric hydrogenation of **6**[a]



Entry	Ligands	Yield[b] (%)	Ee[c] (%)	Config.[d]
1	(*S*,*S*)-Me-DuPhos	65	18	*R*
2	(*S*)-BINAP	84	82	*S*
3	(*S*)-MeO-Biphep	94	96	*S*

[a] Reaction conditions: 1.0 mmol 2-(3′-benzyloxy-4′-methoxy-phenethyl)quinoline, $[Ir(COD)Cl]_2$ (0.5%), chiral ligand (1.1%), I_2 (10%), 5 mL toluene.
[b] Isolated yield based on compound **6**.
[c] Determined by HPLC analysis with Chiralpak AS-H column.
[d] The absolute configuration of the product was assigned by analogy with the previous paper[5c] on the asymmetric sense of the product.

higher ee's and conversions (entries 2 and 3). Me-DuPhos, which is generally a good ligand for asymmetric hydrogenation of functionalized olefins,[8] proved not to be effective herein. As a result we choose MeO-Biphep as the ligand, with 96% ee being obtained.

N-Methylation of **7** using $HCHO/NaBH_3CN$ gave **8** in 96% yield by Borch's method.[7] The final step was the removal of the benzyl protective group of **8**. This process was sluggish with Pd on carbon (200 psi H_2) in EtOH, but could be accomplished with EtOH/AcOH (10:1) to give the tetrahydroquinoline alkaloid (−)-galipeine **1** $\{[\alpha]_D^{15} = -26.1, \quad (c = 0.44, \quad CHCl_3), \quad \text{lit.}^{2a}$ $[\alpha]_D^{25} = -13.6\}$ in 95% yield. The spectral data (^1H NMR, ^{13}C NMR) were identical to that reported for the natural product. The specific rotation of (−)-galipeine synthesized by us is higher than the naturally occurring (−)-galipeine isolated from the bark of *Galipea officinalis* Hancock by Jacquemond-Collet et al.,[2a] who stated that the hexane and chloroform extracts from the bark of *Galipea officinalis* Hancock, tetrahydroquinoline alkaloids were obtained as a racemic mixture in the latter paper on testing the bioactivities of 2-substituted tetrahydroquinolines (angustureine, galipinine, cuspareine, and galipeine).[1] The (−)-galipeine was perhaps racemized partially over the course of extraction and so the authors did not determine the ee values. To verify this, we synthesized the racemic galipeine using a similar route. The enantiomeric purity of the (−)-galipeine synthesized by us was 96% by HPLC analysis,[9] which is the same with the hydrogenation product **7**. This suggested that N-methylation and hydrogenolysis of the *O*-benzyl group afforded the corresponding compounds **8** and **1** without deterioration of the enantiomeric purity. In our previous paper on asymmetric hydrogenation of quinoline derivatives,[5c] the asymmetric sense of the product was (*S*) when (*S*)-MeO-Biphep was used. As a result, the absolute configuration of the naturally occurring (−)-galipeine can be assumed to be (*S*).

3. Conclusion

In conclusion, the first total synthesis of (−)-galipeine was achieved in seven steps with 54% overall yield from commercially available isovanillin, using the asymmetric hydrogenation of the quinoline derivative as a key step with the absolute configuration estimated to be (*S*). Further studies on the biology of this and other members of this class of natural products are currently underway in our laboratory and will be reported in due course.

4. Experimental section

4.1. General

Melting points were determined on a Metter FP5 capillary melting point apparatus and are uncorrected. Ee values were determined by chiral HPLC with Chiralpak AS-H and Chiralcel OD-H columns. Optical rotations were measured with a JASCO P-1010 polarimeter. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 Hz. Chemical shifts are given in parts per million relative to TMS as an internal standard. All reactions were performed under a nitrogen atmosphere using oven-dried glassware. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 ev.

4.2. Materials

Commercially available reagents and solvents were used throughout without further purification other than those detailed below. Solvents were treated prior to use according to the standard methods. Flash column chromatography was performed on silica gel (200–300 mesh). Sodium bicarbonate was grounded to a fine powder and dried under vacuum at 120 °C for 24 h. 3-Hydroxy-4-methoxy-benzaldehyde 2 was purchased

from Aldrich and quinaldine from Fluka. *n*-Butyllithium (1.6 M solution in hexane) was purchased from Acros. Sodium borohydride and sodium cyanoborohydride were purchased from Rohm and Hass. (*S*)-BINAP, (*S*,*S*)-Me-DuPhos and (*S*)-MeO-Biphep were purchased from Strem.

4.3. Experimental procedures

4.3.1. 3-Benzyloxy-4-methoxybenzaldehyde 3. A mixture of isovanillin **2** (3.04 g, 20 mmol, 1.00 equiv), anhydrous $NaHCO_3$ (1.92 g, 22.8 mmol, 1.14 equiv) and KI (332 mg, 2.0 mmol, 0.10 equiv) in dry acetonitrile (50 mL) was stirred and heated. When the temperature reached 60 °C, benzyl chloride (3.3 g, 26 mmol, 1.30 equiv) was added in a single portion with a small volume of acetonitrile as rinse. The resulting mixture was refluxed for about 10 h under nitrogen, at which point TLC analysis indicated all the starting materials had been consumed. After removal of acetonitrile under reduced pressure, the reaction mixture was poured into 30 mL of water, hydrochloric acid (3 M, 10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with 3% aqueous K_2CO_3, water, and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to afford compound **3** as a white solid (4.3 g, 89% yield): mp 63.4 °C (lit.[10] mp 63.5 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.83 (s, 1H), 7.49–7.47 (m, 4H), 7.41–7.33 (m, 3H), 7.01 (d, J = 7.92 Hz, 1H), 5.20 (s, 2H), 3.98 (s, 3H).

4.3.2. 3-Benzyloxy-4-methoxybenzyl alcohol 4. Compound **3** (2.42 g, 10 mmol) was dissolved in methanol (20 mL) in a round-bottomed flask and the solution cooled in an ice-bath to produce a fine suspension. $NaBH_4$ (0.5 g, 12 mmol) was carefully added and allowed to stand for 15 min; the solution was allowed to warm up to room temperature and stirred for 2 h. TLC analysis indicated when the reaction was complete. After removal of methanol under reduced pressure, the reaction mixture was poured into 20 mL of water, and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed successively with a saturated NH_4Cl solution, water, and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to afford compound **4** as a white solid (2.35 g, 96% yield): mp 71.5 °C (lit.[10] mp 71–72 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 7.36 Hz, 2H), 7.39–7.35 (m, 2H), 7.32 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 1.44 Hz, 1H), 6.93–6.87 (m, 2H), 5.16 (s, 2H), 4.58 (s, 2H), 3.89 (s, 3H).

4.3.3. 3-Benzyloxy-4-methoxybenzyl bromide 5. To a solution of compound **4** (2.20 g, 9 mmol) and ca. 0.3 mL of pyridine in dry ether (30 mL) was added phosphorous tribromide (975 mg, 3.6 mmol) in dry ether (20 mL) at a rate maintaining reflux. After heating and stirring for an additional 2 h under a nitrogen atmosphere, TLC analysis indicated all the starting materials had been consumed. The mixture was cooled and poured into 20 mL of water and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed successively with a saturated Na_2CO_3 solution, water, and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give compound **5** (2.35 g, 85% yield): mp 94.5 °C (lit.[10] mp 94–95 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.20 (m, 5H), 7.00–6.65 (m, 3H), 5.10 (s, 2H), 4.40 (s, 2H), 3.83 (s, 3H). This material was used in the next step without further purification.

4.3.4. 2-(3′-Benzyloxy-4′-methoxy-phenethyl)quinoline 6. To a stirred solution of quinaldine (1.29 g, 9.08 mmol) in dry ether (50 mL) was added a hexane solution of *n*-butyllithium (1.6 M solution, 9.08 mmol) at 0 °C. After the mixture was stirred for 30 min, compound **5** (2.3 g, 7.5 mmol) in dry ether (20 mL) was added dropwise at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. The reaction was worked up with a saturated Na_2CO_3 solution (10 mL), the mixture extracted with ethyl acetate (3 × 20 mL), and the combined organic layer washed sequentially with a saturated NH_4Cl solution, water, and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to afford compound **6** as a white solid (2.40 g, 86% yield): mp 84.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05–3.09 (m, 2H), 3.21–3.25 (m, 2H), 3.87 (s, 3H), 5.06 (s, 2H), 6.78–6.81 (m, 3H), 7.16 (d, J = 8.44 Hz 1H) 7.27–7.31 (m, 1H), 7.34–7.42 (m, 4H), 7.51 (d, J = 7.52 Hz, 1H), 7.72 (m, 1H), 7.78 (d, J = 8.12 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.44 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 35.4, 41.0, 56.0, 71.0, 111.8, 114.7, 121.0, 121.6, 125.8, 126.7, 127.2, 127.5, 127.7, 128.4, 128.8, 129.4, 134.0, 136.1, 137.2, 148.0, 161.9; HRMS Calcd for $C_{25}H_{23}NO_2$ (M+1) 370.1802, found 370.1791.

4.3.5. (−)-(*S*)-2-(3′-Benzyloxy-4′-methoxy-phenethyl)-1,2,3,4-tetrahydroquinoline 7. In a glovebox, the Ir–phosphine complex was made in situ by mixing $[Ir(COD)Cl]_2$ (3.4 mg, 0.005 mmol) and (*S*)-MeO-Biphep (6.4 mg, 0.011 mmol) in toluene (3 mL). After the mixture was stirred at room temperature for 30 min, the solution was transferred by a syringe to a stainless steel autoclave, in which I_2 (12.7 mg, 0.05 mmol) and 2-(3′-benzyloxy-4′-methoxy-phenethyl)quinoline **6** (370.0 mg, 1.0 mmol) were placed beforehand in a toluene solution (2 mL). The hydrogenation was performed at room temperature under H_2 (500 psi) for 12–15 h. After carefully releasing the hydrogen, the reaction mixture was diluted with dichloromethane (20 mL), saturated Na_2CO_3 solution (5 mL) was added, then stirred for 15 min, the aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organic layers washed sequentially with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under

vacuum, and the residue purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to afford pure 2-(3′-benzyloxy-4′-methoxy-phenethyl)-1,2,3,4-tetrahydroquinoline **7** 354 mg with 94% yield. Ee: 96%, $[\alpha]_D^{20} = -38.6$ (*c* 1.0, $CHCl_3$), HPLC (AS-H, elute: Hexanes/*i*-PrOH = 97:3, detector: 254 nm, flow rate: 0.5 mL/min), (*R*) $t_1 = 31.7$ min, (*S*) $t_2 = 34.3$ min. The absolute configuration was assigned as *S* by analogue. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (m, 1H), 1.77 (m, 2H), 1.96 (m, 1H), 2.65 (m, 2H), 2.77 (m, 2H), 3.23 (m, 1H), 3.70 (br-s, 1H), 3.89 (s, 3H), 5.17 (s, 2H), 6.46 (d, $J = 7.8$ Hz, 1H), 6.62 (m, 1H), 6.78 (m, 2H), 6.85 (d, $J = 8.68$ Hz, 1H), 6.98 (m, 2H), 7.30 (m, 1H), 7.37 (m, 2H), 7.46 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) 26.1, 27.9, 31.5, 38.2, 50.9, 56.1, 71.0, 112.0, 114.1, 114.6, 117.0, 120.8, 121.3, 126.7, 127.3, 127.8, 128.5, 129.2, 134.3, 137.2, 144.4, 148.0; HRMS Calcd for $C_{25}H_{27}NO_2$ (M+1) 374.2115, found 374.2110.

4.3.6. (−)-(*S*)-2-(3′-Benzyloxy-4′-methoxy-phenethyl)- 2,3,4-tetrahydro-1-methylquinoline 8. To a stirred solution of 2-(3′-benzyloxy-4′-methoxy-phenethyl)-1,2,3,4-tetrahydroquinoline **7** (373 mg, 1.0 mmol) and 0.8 mL (10 mmol) of 37% aqueous formaldehyde in 5 mL of acetonitrile was added 200 mg of sodium cyanoborohydride. Glacial acetic acid (200 μL) was added and the reaction stirred at room temperature for 30 min. An additional 200 μL of glacial acid was added and stirring continued for 30 min more. The reaction mixture was poured into 30 mL of ether and then washed with three 10 mL portions of 1 M KOH and one portion of brine. The ether solution was dried over potassium carbonate and evaporated in vacuo to give the crude product as yellow oil. Purification was performed by a silica gel column eluted with petroleum ether/EtOAc to give pure 2-(3′-benzyloxy-4′-methoxy-phenethyl)-2,3,4-tetrahydro-1-methylquinoline **8** 372 mg with 96% yield. $[\alpha]_D^{20} = -16.1$ (*c* 0.8, $CHCl_3$), the absolute configuration was assigned as *S*. ^{1}H NMR ($CDCl_3$, 400 MHz) 1.68 (m, 1H), 1.90 (m, 3H), 2.50 (m, 1H), 2.65 (m, 2H), 2.83 (m, 1H), 2.86 (s, 3H), 3.21 (m, 1H), 3.89 (s, 3H), 5.16 (s, 2H), 6.53 (d, $J = 8.20$ Hz, 1H), 6.61 (m, 1H), 6.75 (m, 2H), 6.83 (d, $J = 8.48$ Hz, 1H), 6.99 (d, $J = 7.24$ Hz, 1H), 7.09 (d, $J = 7.92$ Hz, 1H), 7.30 (m, 1H), 7.37 (m, 2H), 7.45 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) 23.5, 24.2, 31.6, 32.8, 38.0, 56.0, 58.1, 110.5, 111.9, 114.6, 115.3, 120.8, 121.7, 127.1, 127.3, 127.7, 128.5, 128.6.134.5, 137.2, 145.2, 148.0; HRMS Calcd for $C_{26}H_{29}NO_2$ (M+1) 388.2246, found 388.2271.

4.3.7. (−)-Galipeine or (−)-(*S*)-2-(3′-hydroxy-4′-methoxy-phenethyl)-2,3,4-tetrahydro-1-methylquinoline 1. To a solution of 387 mg (1 mmol) of **8** in 8 mL of mixing solvent system of EtOAc/AcOH (10:1) was added 88 mg of 5% Pd/C, and the mixture stirred under 10 atm of hydrogen at room temperature for 10 h. After carefully releasing the hydrogen, the mixture was filtered through a pad of celite topped with a layer of anhydrous Na_2SO_4 to separate the catalyst. The filtrate was concentrated to give crude **1** as colorless oil. Purification was performed by a silica gel column eluted with petroleum ether/EtOAc to give pure 2-(3′-hydroxy-4′-methoxy-phenethyl)-2,3,4-tetrahydro-1-methylquinoline 282 mg with 95% yield. Ee: 96%, $[\alpha]_D^{20} = -26.1$ (*c* 0.44, $CHCl_3$), HPLC (OD-H, elute: Hexanes/*i*-PrOH = 70:30, detector: 254 nm, flow rate: 1.0 mL/min), (*R*) $t_1 = 8.2$ min, (*S*) $t_2 = 9.2$ min. The absolute configuration was estimated to be *S*. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (m, 2H), 1.92 (m, 2H), 1.96 (s, 2H), 2.52 (m, 1H), 2.66 (m, 1H), 2.86 (m, 1H), 2.92 (s, 3H), 3.29 (m, 1H), 3.88(s, 3H), 5.60 (m, 1H), 6.54 (d, $J = 8.12$ Hz, 1H), 6.61 (m, 1H), 6.68 (d, $J = 8.08$ Hz, 1H), 6.78 (m, 2H), 7.0 (d, $J = 7.16$ Hz, 1H), 7.10 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 23.5, 24.3, 31.6, 32.9, 38.0, 56.0, 58.2, 110.6, 114.5, 115.3, 119.5, 121.7, 127.1, 128.6, 135.3, 144.7, 145.3, 145.5.

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9. (−)-Galipeine: HPLC (Chiralcel OD-H, elute: Hexanes/*i*-PrOH = 70:30, detector: 254 nm, flow rate: 1.0 mL/min), (*R*) $t_1 = 8.2$ min, (*S*) $t_2 = 9.2$ min. Ee: 96%. The absolute configuration was assigned as *S*.
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