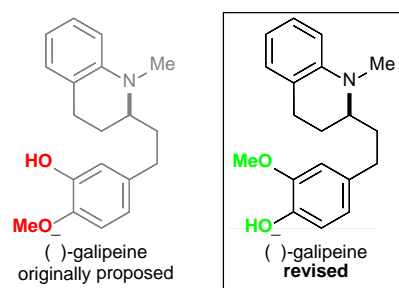


# Structural Revision of the Hancock Alkaloid (–)-Galipeine

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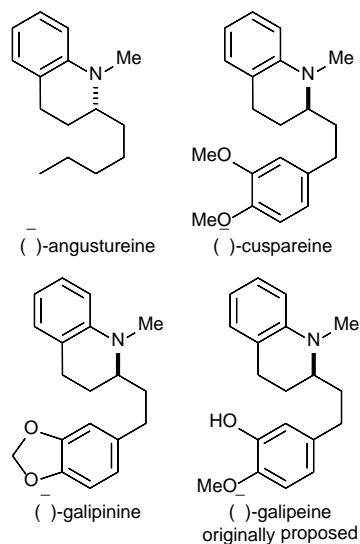
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**ABSTRACT:** The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of synthetic samples of (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline, the originally proposed structure of the Hancock alkaloid (–)-galipeine, do not match those of the natural product. Herein, the preparation of the regioisomer (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline is reported, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of which are in excellent agreement with those of (–)-galipeine. Comparison of specific rotation data enables assignment of the absolute (*S*)-configuration of the alkaloid and together, these data engender the structural revision of (–)-galipeine to (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline.

The isolation of the alkaloid (–)-galipeine from the angostura (trunk bark) of *Galipea officinalis* Hancock was first reported by Jacquemond-Collet *et al.* in 1999.<sup>1,2</sup> Following interrogation by NMR spectroscopy and mass spectrometry, it was assigned the gross structure of *N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline (its absolute configuration was not determined).<sup>1</sup> (–)-Galipeine together with (–)-angostureine, (–)-cuspareine and (–)-galipinine (Figure 1) comprise a small family of congeneric angostura alkaloids based on a 2-substituted 1,2,3,4-tetrahydroquinoline core, which are popular targets for laboratory syntheses.<sup>3–10</sup> However, galipeine has received scant attention from the synthetic community compared to the remainder of the tetrad: more than ten syntheses of each of the other alkaloids have been reported, whilst only two studies concerning galipeine have appeared to date. Zhou *et al.* were first to report their synthesis of enantiopure (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline [possessing the gross structure assigned to (–)-galipeine] in 2004,<sup>11</sup> and concluded that the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of this material were identical to those of the natural product. Comparison of their specific rotation value of  $[\alpha]_{\text{D}}^{20} -26.1$  ( $c$  0.44 in  $\text{CHCl}_3$ )<sup>12</sup> with that reported for the natural product of  $[\alpha]_{\text{D}} -13.6$  (temperature, concentration nor solvent were specified)<sup>1</sup> led Zhou *et al.* to propose the absolute (*S*)-configuration for the natural product.<sup>11</sup> Subsequently, Hii *et al.* reported an alternative approach to (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline in 2012<sup>13</sup> and asserted the congruency of their synthetic sample with the natural product by comparison of NMR data and sign of the specific rotation value. In fact,

inspection of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data reported for (–)-galipeine with those of both Zhou *et al.*<sup>11</sup> and Hii *et al.*<sup>13</sup> for their synthetic samples of (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline shows some discrepancies. In this manuscript, we report the preparation of an independent sample of (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline by a new route involving conjugate addition of lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methyl-*p*-methoxybenzyl)amide to 4-(*o*-bromophenyl)-*N*-methoxy-*N*-methylpent-2-enamide to set the stereochemistry, and use of a Buchwald-Hartwig coupling reaction to construct the 1,2,3,4-tetrahydroquinoline core. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (as well as the specific rotation value) of our sample of this material are in accord with those of Zhou *et al.*<sup>11</sup> and Hii *et al.*<sup>13</sup> but these data do *not* match those for the natural product (–)-galipeine, as expected.<sup>1</sup> A more detailed analysis of the available data led us to propose that (–)-galipeine is in fact the regioisomeric compound *N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline. We prepared an authentic, enantiopure sample of this material and its  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were found to be effectively identical to those of the natural product. Comparison of specific rotation data allowed us to assign the absolute (*S*)-configuration to (–)-galipeine. Together, these data thus call for the structural revision of (–)-galipeine to (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline and the studies contained herein comprise the unambiguous structural determination of (–)-galipeine, its first asymmetric synthesis, and assignment of its absolute configuration.

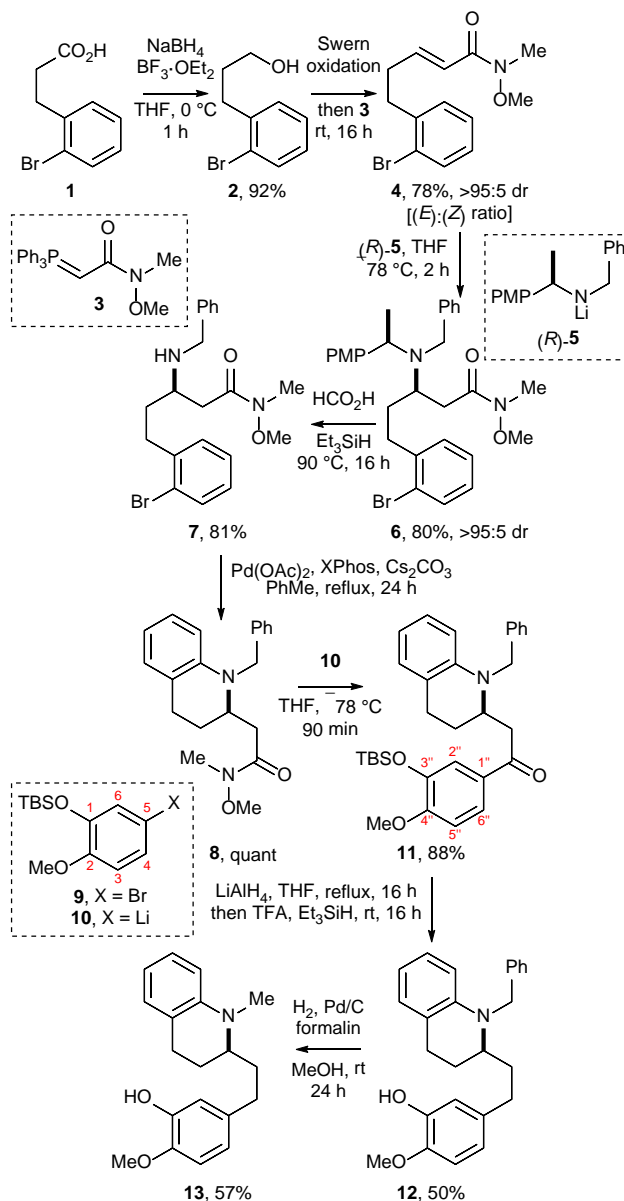


**Figure 1.** Structures of tetrahydroquinoline Hancock alkaloids.

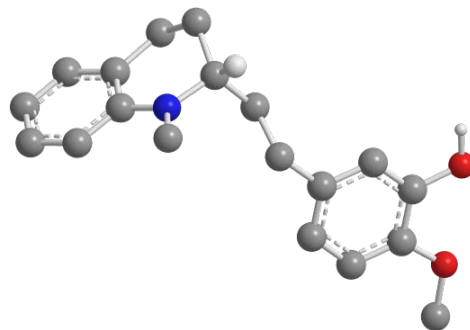
Alerted to discrepancies in the reported data, our initial goal was the preparation of an independent sample of (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline [the structure originally assigned to (-)-galipeine].<sup>1</sup> Our synthesis commenced from commercially available 3-(*o*-bromophenyl)propanoic acid **1**. Reduction of **1** using NaBH<sub>4</sub> in the presence of BF<sub>3</sub>·OEt<sub>2</sub><sup>14</sup> gave the corresponding alcohol **2** in 92% yield. One-pot Swern oxidation/Wittig reaction of **2** using Ph<sub>3</sub>P=CHCON(Me)(OMe) **3** as the ylide then gave **4** as a single diastereoisomer [ $>95:5$  dr, (*E*):(*Z*) ratio], which was isolated in 78% yield. The geometry of the olefin within **4** was assigned on the basis of the diagnostic <sup>1</sup>H NMR <sup>3</sup>*J*<sub>H-2,H-3</sub> = 15.4 Hz. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methyl-*p*-methoxybenzyl)amide **5** then delivered  $\beta$ -amino amide **6** as a single diastereoisomer ( $>95:5$  dr), which was isolated in 80% yield. The absolute configuration of the newly formed C(3)-stereogenic center of **6** was assigned by reference to the transition state mnemonic devised by us to predict the stereochemical outcome of this type of conjugate addition reaction.<sup>15</sup> Subsequent treatment of **6** with HCO<sub>2</sub>H in the presence of Et<sub>3</sub>SiH<sup>16–18</sup> effected chemoselective removal of the *N*- $\alpha$ -methyl-*p*-methoxybenzyl group to furnish **7** in 81% yield. Treatment of **7** with 5 mol% Pd(OAc)<sub>2</sub> in the presence of XPhos and Cs<sub>2</sub>CO<sub>3</sub> in PhMe at reflux for 24 h gave tetrahydroquinoline **8** quantitatively. *O*-*tert*-Butyldimethylsilyl-5-bromoguaiacol **9** was converted to the corresponding aryllithium reagent **10** upon reaction with *n*-BuLi; addition of **8** to the reaction flask then produced ketone **11** after work-up, which was isolated in 88% yield. Treatment of **11** with LiAlH<sub>4</sub> and then TFA in the presence of Et<sub>3</sub>SiH gave **12** in 50% yield (i.e., in addition to reduction of the ketone functionality, deprotection of the *O*-silyl group had also occurred during this two-step sequence). Subjection of **12** to an atmosphere of hydrogen in the presence of Pd/C and aqueous formaldehyde (formalin) resulted in hydrogenolytic *N*-debenzylation and reductive *N*-methylation, giving **13** in 57% yield (Scheme 1). The identity of **13** was unambiguously secured by single crystal X-ray diffraction analysis,<sup>19</sup> and the determination of a Flack *x* parameter<sup>20,21</sup> for the crystal structure of  $-0.1(2)$ , which satisfies the criterion for reliable configurational assignment of a material known to be enantiopure, confirmed its absolute (*S*)-

configuration. Thus, the absolute configurations that had been assigned to the precursors **6–8**, **11** and **12** were also confirmed (Figure 2).

**Scheme 1.** (*S*)-*N*(1)-Methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline **13**



PMP = *p*-methoxyphenyl. TBS = *tert*-butyldimethylsilyl.



**Figure 2.** Chem3D representation of the X-ray crystal structure of (*S*)-**13** (selected H atoms are omitted for clarity).

The specific rotation of our sample of **13** was  $[\alpha]_{\text{D}}^{25} -26.2$  ( $c$  1.0 in  $\text{CHCl}_3$ ) whilst Zhou *et al.* measured  $[\alpha]_{\text{D}}^{20} -26.1$  ( $c$  0.44 in  $\text{CHCl}_3$ )<sup>11,12</sup> and Hii *et al.* obtained  $[\alpha]_{\text{D}}^{25} -27.0$  ( $c$  0.7 in  $\text{CHCl}_3$ ),<sup>13</sup> demonstrating truly remarkable parity. The  $^{13}\text{C}$  NMR data of all three samples also display excellent agreement ( $\Delta\delta_{\text{C}} \leq 0.2$  ppm),<sup>22</sup> as do the  $^1\text{H}$  NMR data of our sample of **13** and those of Hii *et al.* ( $\Delta\delta_{\text{H}} \leq 0.05$  ppm).<sup>22</sup> Our  $^1\text{H}$  NMR chemical shift values of **13** are in very good accord with those reported by Zhou *et al.* ( $\Delta\delta_{\text{H}} \leq 0.04$  ppm)<sup>22</sup> although the relative integrations of some of the multiplets below  $\sim 2.7$  ppm are not the same. There are, however, clearly issues associated with the relative integrations of the  $^1\text{H}$  NMR data presented by Zhou *et al.* as twenty-four protons are listed in total<sup>11</sup> (the formula of **13** being  $\text{C}_{19}\text{H}_{23}\text{NO}_2$ ). Notwithstanding these differences, it is unequivocal that the three samples of (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline **13** are the same.<sup>23</sup>

Concerning comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of **13** with those of (–)-galipeine, we must first express our gratitude to Professor Nicolas Fabre who supplied us with copies of the NMR spectra of (–)-galipeine for this purpose. Unfortunately, some transcription errors (mainly concerning determination of the relative integrations of the multiplets below  $\sim 2.7$  ppm) were noted when the raw  $^1\text{H}$  NMR spectrum of (–)-galipeine was compared to the reported data.<sup>1</sup> We therefore first corrected the  $^1\text{H}$  NMR data of (–)-galipeine from the original spectrum (Figure 3). Whilst casual inspection of the  $^1\text{H}$  NMR data of **13** and (–)-galipeine indicates broad agreement, more careful analysis reveals that **13** shows a 1H multiplet at 6.66 ppm and a 2H multiplet at 6.77 ppm; in (–)-galipeine the relative integrations associated with the analogous signals are transposed. Perhaps less subtle, the  $^{13}\text{C}$  NMR data displays  $\Delta\delta_{\text{C}} \geq 1.0$  ppm<sup>22</sup> for four of the carbon atoms. Such large differences clearly suggest that the structures of **13** and (–)-galipeine are *not* the same, and it followed that the structure of the alkaloid had been erroneously assigned (Figure 3).

**13**

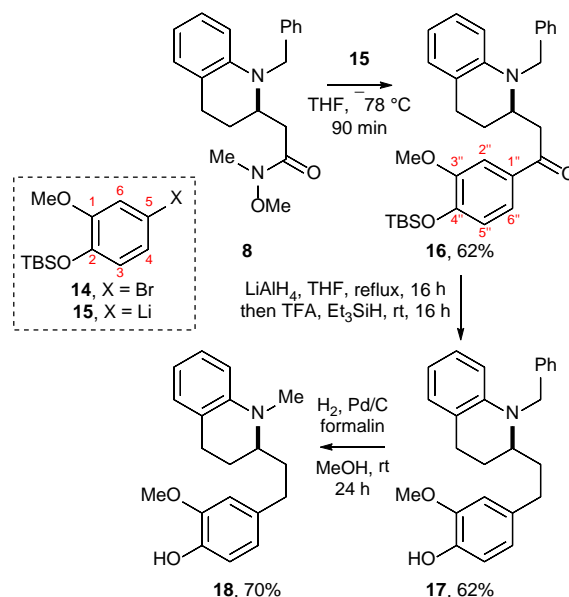
$^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )		$^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )	
<b>13</b>	(–)-galipeine	<b>13</b>	(–)-galipeine
1.71 (1H, m)	1.70 (1H, m) <sup>a</sup>	23.5	23.6 (0.1)
1.92 (3H, m)	1.90 (3H, m) <sup>a</sup>	24.3	24.4 (0.1)
2.49 (1H, ddd)	2.50 (1H, m) <sup>a</sup>	31.6	32.1 (0.5)
2.66 (2H, m)	2.68 (2H, m) <sup>a</sup>	32.9	33.2 (0.3)
2.84 (1H, ddd)	2.82 (1H, m)	38.0	38.2 (0.2)
2.90 (3H, s)	2.89 (3H, s)	56.0	56.0 (0.0)
3.27 (1H, m)	3.26 (1H, m)	58.2	58.5 (0.3)
3.87 (3H, s)	3.85 (3H, s)	110.5	110.7 (0.2)
5.56 (1H, s)	5.45 (1H, s) <sup>a</sup>	110.6	110.8 (0.2)
6.52 (1H, d)	6.51 (1H, d)	114.5	114.3 (0.2)
6.59 (1H, td)	6.57 (1H, td)	115.3	115.4 (0.1)
6.66 (1H, dd)	6.65 (2H, m)	119.5	120.9 (1.4)
6.77 (2H, m)	6.80 (1H, d)	121.7	121.8 (0.1)
6.98 (1H, d)	6.96 (1H, d)	127.1	127.2 (0.1)
7.08 (1H, td)	7.06 (1H, t)	128.6	128.8 (0.2)
		135.3	134.0 (1.3)
		144.7	143.7 (1.0)
		145.3	145.4 (0.1)
		145.5	146.5 (1.0)

**Figure 3.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of **13** and (–)-galipeine. Mid-points of all multiplets are quoted. Values of  $\Delta\delta_{\text{C}}$  are given in parentheses. <sup>a</sup>These  $^1\text{H}$  NMR data of (–)-galipeine are corrected

here (compared to those reported in Ref 1) by analysis of the  $^1\text{H}$  NMR spectrum of the natural product.

Further analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of **13** and the data reported for (–)-galipeine<sup>1</sup> revealed a likely origin of the structural misassignment. Much of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of the two compounds is effectively identical and is entirely consistent with them both sharing a 2-substituted *N*(1)-methyl-1,2,3,4-tetrahydroquinoline moiety, whilst the variances suggest that differentially substituted aryl rings cap the C(2)-side chain. As the locations of the hydroxy and methoxy substituents within (–)-galipeine were assigned on the basis of the interpretation of its  $^1\text{H}$ – $^{13}\text{C}$  HMBC NMR spectrum,<sup>1</sup> we proposed that (–)-galipeine is in fact the regioisomer (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline **18**. In order to investigate this hypothesis, an authentic sample of **18** was prepared. *O*-*tert*-Butyldimethylsilyl-4-bromoguaiacol **14** was converted to the aryllithium reagent **15**, which reacted with **8** to give ketone **16** in 62% yield. Sequential treatment of **16** with  $\text{LiAlH}_4$  and then TFA and  $\text{Et}_3\text{SiH}$  gave **17** in 62% yield. Finally, hydrogenolysis of **17** in the presence of formalin gave **18** in 70% yield (Scheme 2).

**Scheme 2.** (*S*)-*N*(1)-Methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline **18**



TBS = *tert*-butyldimethylsilyl.

Comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of **18** and (–)-galipeine showed excellent agreement, with the spectra being effectively superimposable ( $\Delta\delta_{\text{H}} \leq 0.04$  ppm,  $\Delta\delta_{\text{C}} \leq 0.2$  ppm).<sup>22</sup> These data therefore validate our proposal that **18** and (–)-galipeine are the same (Figure 4). We surmise that the structural misassignment of Jacquemond-Collet *et al.* arose due to misinterpretation of a  $^3J_{\text{C-4'-H-2'}}$  HMBC correlation (observed for **18**) as  $^2J_{\text{C-4'-H-5'}}$  in the data of the natural product,<sup>1</sup> as well as a  $^3J_{\text{C-3'-H-5'}}$  HMBC correlation (observed for **18**) as  $^2J_{\text{C-3'-H-2'}}$  in the data of natural product,<sup>1</sup> as this has the result of transposing the positions of the hydroxy and methoxy substituents. (–)-Galipeine was reported to have  $[\alpha]_{\text{D}} -13.6$ <sup>1</sup> although the conditions under which this value was measured, i.e., temperature, concentration and solvent, were not specified.<sup>24</sup> We investigated the effect of concentration and solvent

on the observed value of the specific rotation of **18** and obtained the following data:  $[\alpha]_D^{25} -22.0$  ( $c$  0.2 in  $\text{CHCl}_3$ );  $[\alpha]_D^{25} -22.4$  ( $c$  1.0 in  $\text{CHCl}_3$ );  $[\alpha]_D^{25} -14.0$  ( $c$  1.0 in  $\text{MeOH}$ );  $[\alpha]_D^{25} -11.9$  ( $c$  1.0 in  $\text{EtOH}$ ). Given the uniform negative value observed in these common solvents, it seems certain that (–)-galipeine possesses the absolute (*S*)-configuration. On the basis of all of our data, therefore, the structure of (–)-galipeine should henceforth be revised to (*S*)-*N*(1)-methyl-2-[2'-(3'-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline **18**.

**18**

<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> )		<sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> )	
<b>18</b>	(–)-galipeine	<b>18</b>	(–)-galipeine
1.73 (1H, m)	1.70 (1H, m) <sup>a</sup>	23.5	23.6 (0.1)
1.93 (3H, m)	1.90 (3H, m) <sup>a</sup>	24.3	24.4 (0.1)
2.52 (1H, ddd)	2.50 (1H, m) <sup>a</sup>	32.0	32.1 (0.1)
2.68 (2H, m)	2.68 (2H, m) <sup>a</sup>	33.1	33.2 (0.1)
2.86 (1H, ddd)	2.82 (1H, m)	38.1	38.2 (0.1)
2.92 (3H, s)	2.89 (3H, s)	55.9	56.0 (0.1)
3.30 (1H, m)	3.26 (1H, m)	58.3	58.5 (0.2)
3.88 (3H, s)	3.85 (3H, s)	110.5	110.7 (0.2)
5.47 (1H, s)	5.45 (1H, s) <sup>a</sup>	110.7	110.8 (0.1)
6.54 (1H, d)	6.51 (1H, d)	114.2	114.3 (0.1)
6.60 (1H, td)	6.57 (1H, td)	115.3	115.4 (0.1)
6.69 (2H, m)	6.65 (2H, m)	120.7	120.9 (0.2)
6.84 (1H, d)	6.80 (1H, d)	121.6	121.8 (0.2)
6.99 (1H, d)	6.96 (1H, d)	127.1	127.2 (0.1)
7.10 (1H, m)	7.06 (1H, t)	128.6	128.8 (0.2)
		133.9	134.0 (0.1)
		143.6	143.7 (0.1)
		145.2	145.4 (0.2)
		146.3	146.5 (0.2)

**Figure 4.** <sup>1</sup>H and <sup>13</sup>C NMR data of **18** and (–)-galipeine. Mid-points of all multiplets are quoted. Values of  $\Delta\delta_c$  are given in parentheses. <sup>a</sup>These <sup>1</sup>H NMR data of (–)-galipeine are corrected here (compared to those reported in Ref 1) by analysis of the <sup>1</sup>H NMR spectrum of the natural product.

In conclusion, we have prepared authentic samples of the regioisomers (*S*)-*N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline and (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline. Comparison of their <sup>1</sup>H and <sup>13</sup>C NMR data with those reported for (–)-galipeine clearly shows that the data of (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline match those of the natural product, i.e., the structure of (–)-galipeine was misassigned as *N*(1)-methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline in the original isolation study, and this error has been perpetuated in two subsequent synthetic investigations. Comparison of specific rotation data allowed us to assign the absolute (*S*)-configuration for the natural product. The structure of (–)-galipeine is thus herein revised to that of (*S*)-*N*(1)-methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline. This study constitutes the unambiguous structural determination of (–)-galipeine, its first total asymmetric synthesis, and assignment of its absolute (*S*)-configuration.

## EXPERIMENTAL SECTION

**General Experimental Details.** Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using

standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.<sup>25</sup> Water was purified by an Elix® UV-10 system. *n*-BuLi was purchased as a 2.5 M solution in hexanes and titrated against diphenylacetic acid before use. Organic layers were dried over  $\text{MgSO}_4$  unless otherwise stated. Thin layer chromatography was performed on aluminium plates coated with 60 F<sub>254</sub> silica. Flash column chromatography was performed on Kieselgel 60 silica on a glass column.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$  and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module. Selected characteristic peaks are reported in  $\text{cm}^{-1}$ . NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuterium resonance. <sup>1</sup>H–<sup>1</sup>H COSY and <sup>1</sup>H–<sup>13</sup>C HMQC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

**3-(2'-Bromophenyl)propan-1-ol 2.** NaBH<sub>4</sub> (225 mg, 6.74 mmol) was added portionwise to a stirred solution of **1** (771 mg, 3.37 mmol) in THF (7 mL) at 0 °C, then BF<sub>3</sub>·Et<sub>2</sub>O (0.84 mL, 6.7 mmol) was added dropwise. The resultant mixture was stirred at 0 °C for 1 h, then MeOH (4 mL) and 1 M aq HCl (4 mL) were added sequentially. The resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 50:50:1) gave **2** as a colourless oil (664 mg, 92%);<sup>26</sup>  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 1.37 (1H, t, *J* 5.8, OH), 1.87–1.96 (2H, m, C(2)*H*), 2.85 (2H, t, *J* 7.8, C(3)*H*), 3.72 (2H, app q, *J* 5.8, C(1)*H*), 7.04–7.11 (1H, m, C(4')*H*), 7.23–7.29 (2H, m, C(5')*H*, C(6')*H*), 7.55 (1H, d, *J* 8.1, C(3')*H*).

**(E)-5-(2'-Bromophenyl)-*N*-methoxy-*N*-methylpent-2-enamide 4.** DMSO (0.53 mL, 7.4 mmol) was added dropwise to a stirred solution of (COCl)<sub>2</sub> (0.32 mL, 3.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at –78 °C and the resultant solution was stirred at –78 °C for 20 min. A solution of **2** (400 mg, 1.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was then added and the resultant solution was stirred at –78 °C for 40 min. Et<sub>3</sub>N (1.7 mL, 11 mmol) was then added, the resultant solution was allowed to warm to rt and **3** (1.01 g, 2.79 mmol) was added portionwise. The resultant solution was stirred at rt for 16 h. Satd aq K<sub>2</sub>CO<sub>3</sub> (20 mL) was added and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organics were washed with brine (60 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 50:50:1) gave **4** as a pale yellow oil (435 mg, 78%, >95:5 dr [(*E*):(*Z*) ratio]);  $\nu_{\text{max}}$  2935, 1663, 1632;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 2.61 (2H, app q, *J* 7.5, C(4)*H*), 2.95 (2H, t, *J* 7.5, C(5)*H*), 3.28 (3H, s, *NMe*), 3.70 (3H, s, *OMe*), 6.54 (1H, d, *J* 15.4, C(2)*H*), 7.02–7.14 (2H, m, C(3)*H*, C(4')*H*), 7.23–7.32 (2H, m, C(5')*H*, C(6')*H*), 7.58 (1H, d, *J* 7.9, C(3')*H*);  $\delta_c$  (100 MHz, CDCl<sub>3</sub>) 32.3 (C(4)), 32.5 (*NMe*), 34.9 (C(5)), 61.6 (*OMe*), 119.5 (C(2)), 124.3 (C(2')), 127.5 (C(5')), 127.8 (C(4')), 130.4 (C(6')), 132.8 (C(3')), 140.2 (C(1')), 146.0 (C(3)), 166.7 (C(1)); *m/z* (ESI<sup>+</sup>) 300 ([M(<sup>81</sup>Br)+H]<sup>+</sup>, 100%), 298 ([M(<sup>79</sup>Br)+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>13</sub>H<sub>17</sub><sup>81</sup>BrNO<sub>2</sub><sup>+</sup> ([M(<sup>81</sup>Br)+H]<sup>+</sup>) requires 300.0417; found 300.0414; C<sub>13</sub>H<sub>17</sub><sup>79</sup>BrNO<sub>2</sub><sup>+</sup> ([M(<sup>79</sup>Br)+H]<sup>+</sup>) requires 298.0437; found 298.0435.

**(R,R)-3-[*N*-Benzyl-*N*-( $\alpha$ -methyl-*p*-methoxybenzyl)amino]-5-(2'-bromophenyl)-*N*-methoxy-*N*-methylpentanamide 6.** *n*-BuLi (2.3 M in hexanes, 0.45 mL, 1.0 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-( $\alpha$ -methyl-*p*-methoxybenzyl)amide (259 mg, 1.07 mmol, >98% ee) in THF (2 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of **4** (200 mg, 0.671 mmol, >95:5 dr [(*E*):(*Z*) ratio]) in THF (1 mL) at –78 °C was then added and the resultant solution was stirred at –78 °C for 2 h. Satd aq NH<sub>4</sub>Cl (1 mL) was then added and the resultant mixture was allowed

to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and 10% aq citric acid (10 mL), and the organic layer was washed sequentially with satd aq NaHCO<sub>3</sub> (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **6** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 50:50:1) gave **6** as a pale yellow oil (273 mg, 80%, >95:5 dr); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +21.8 (c 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  2998, 2981, 2969, 2932, 2905, 2886, 2868, 1659;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.39 (3H, d, *J* 7.0, C( $\alpha$ )Me), 1.55–1.66 (1H, m, C(4)H<sub>A</sub>), 1.73–1.84 (1H, m, C(4)H<sub>B</sub>), 2.00 (1H, d, *J* 14.0, C(2)H<sub>A</sub>), 2.21–2.31 (1H, m, C(2)H<sub>B</sub>), 2.70 (1H, ddd, *J* 13.8, 11.8, 5.0, C(5)H<sub>A</sub>), 3.07 (3H, s, NMe), 3.19 (1H, ddd, *J* 13.8, 11.6, 4.9, C(5)H<sub>B</sub>), 3.43 (3H, s, NMe), 3.59–3.66 (1H, m, C(3)H), 3.60 (1H, d, *J* 14.8, NCH<sub>A</sub>H<sub>B</sub>Ph), 3.79 (3H, s, ArOMe), 3.87 (1H, q, *J* 7.0, C( $\alpha$ )H), 3.93 (1H, d, *J* 14.8, NCH<sub>A</sub>H<sub>B</sub>Ph), 6.85 (2H, d, *J* 8.6, C(3')H, C(5')H), 6.99–7.05 (1H, m, C(4')H), 7.16–7.28 (5H, m, C(5')H, C(6')H, C(2'')H, C(6'')H, Ph), 7.36 (2H, t, *J* 7.5, Ph), 7.50 (1H, d, *J* 7.8, C(3')H), 7.54 (2H, d, *J* 7.5, Ph);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 20.0 (C( $\alpha$ )Me), 32.1 (NMe), 33.8 (C(2)), 33.9 (C(4)), 34.2 (C(5)), 50.2 (NCH<sub>2</sub>Ph), 52.9 (C(3)), 55.2 (NMe), 56.6 (C( $\alpha$ )), 60.8 (ArOMe), 113.4 (C(3'')), 124.4 (C(2'')), 126.6 (*p*-Ph), 127.2 (C(4')), 127.4 (C(5')), 128.3, 128.3 (*o,m*-Ph), 129.0 (C(2'')), C(6'')), 130.2 (C(6')), 132.6 (C(3')), 135.1 (C(1'')), 141.5 (*i*-Ph), 142.1 (C(1')), 158.5 (C(4'')), 173.4 (C(1));  $m/z$  (ESI<sup>+</sup>) 541 ([M(<sup>81</sup>Br)+H]<sup>+</sup>, 100%), 539 ([M(<sup>79</sup>Br)+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>29</sub>H<sub>36</sub><sup>81</sup>BrN<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M(<sup>81</sup>Br)+H]<sup>+</sup>) requires 541.1883; found 541.1882; C<sub>29</sub>H<sub>36</sub><sup>79</sup>BrN<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M(<sup>79</sup>Br)+H]<sup>+</sup>) requires 539.1904; found 539.1902.

**(R)-3-(N-Benzylamino)-5-(2'-bromophenyl)-N-methoxy-N-methylpentanamide 7.** Et<sub>3</sub>SiH (25  $\mu$ L, 0.16 mmol) was added to a stirred solution of **6** (87 mg, 1.10 mmol, >95:5 dr) in HCO<sub>2</sub>H (0.6 mL) at rt and the resultant solution was heated at 90 °C for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and satd aq NaHCO<sub>3</sub> (5 mL) and the organic layer was washed with brine (5 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 50:50:1) gave **7** as a colourless oil (35 mg, 81%); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –7.1 (c 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  3324, 3085, 3027, 2965, 2935, 2861, 1658;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.79–1.89 (2H, m, C(4)H<sub>2</sub>), 2.67 (2H, app d, *J* 5.8, C(2)H<sub>2</sub>), 2.80–2.86 (2H, m, C(5)H<sub>2</sub>), 3.16–3.23 (1H, m, C(3)H), 3.18 (3H, s, NMe), 3.67 (3H, s, OMe), 3.81 (1H, d, *J* 12.9, NCH<sub>A</sub>H<sub>B</sub>Ph), 3.85 (1H, d, *J* 12.9, NCH<sub>A</sub>H<sub>B</sub>Ph), 7.01–7.08 (1H, m, C(4')H), 7.20–7.39 (7H, m, C(5')H, C(6')H, Ph), 7.52 (1H, d, *J* 7.8, C(3')H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 32.0 (C(3)), 32.4 (C(5)), 34.3 (C(4)), 36.4 (C(2)), 51.0 (NCH<sub>2</sub>Ph), 53.8 (NMe), 61.2 (OMe), 124.4 (C(2'')), 126.8, 127.5, 127.5 (C(4'), C(5'), *p*-Ph), 128.2, 128.3 (*o,m*-Ph), 130.3 (C(6')), 132.7 (C(3')), 140.6 (*i*-Ph), 141.6 (C(1')), 173.3 (C(1));  $m/z$  (ESI<sup>+</sup>) 407 ([M(<sup>81</sup>Br)+H]<sup>+</sup>, 100%), 405 ([M(<sup>79</sup>Br)+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>20</sub>H<sub>26</sub><sup>81</sup>BrN<sub>2</sub>O<sub>2</sub><sup>+</sup> ([M(<sup>81</sup>Br)+H]<sup>+</sup>) requires 407.1152; found 407.1148; C<sub>20</sub>H<sub>26</sub><sup>79</sup>BrN<sub>2</sub>O<sub>2</sub><sup>+</sup> ([M(<sup>79</sup>Br)+H]<sup>+</sup>) requires 405.1172; found 405.1169.

**(R)-2-[N(1'-Benzyl-1',2',3',4'-tetrahydroquinolin-2'-yl)-N-methoxy-N-methylacetamide 8.** Pd(OAc)<sub>2</sub> (26 mg, 0.12 mmol) was added to a stirred suspension of **7** (943 mg, 2.33 mmol), XPhos (163 mg, 0.349 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.51 g, 4.65 mmol) in PhMe (30 mL) and the resultant solution was heated at reflux for 24 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and H<sub>2</sub>O (100 mL) and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 50:50:1) gave **8** as a pale yellow solid (751 mg, quant); mp 58–60 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> –11.0 (c 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  3027, 2968, 2935, 2865, 1658;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.97–2.13 (2H, m, C(3')H<sub>2</sub>), 2.71 (2H, app d, *J* 6.5, C(2)H<sub>2</sub>), 2.78 (1H, dt, *J* 16.5, 3.7, C(4')H<sub>A</sub>), 2.97 (1H, ddd, *J* 16.5, 12.8, 5.7, C(4')H<sub>B</sub>), 3.16 (3H, s, NMe), 3.58 (3H, s, OMe), 4.04–4.10 (1H, m, C(2')H), 4.53 (1H, d, *J* 17.2, NCH<sub>A</sub>H<sub>B</sub>Ph), 4.59 (1H, d, *J* 17.2, NCH<sub>A</sub>H<sub>B</sub>Ph), 6.45 (1H, d, *J* 7.7, C(8')H), 6.60 (1H, t, *J* 7.7, C(6')H), 6.97 (1H, t, *J* 7.7, C(7')H), 7.04 (1H, d, *J* 7.7, C(5')H), 7.19–7.33 (5H, m, Ph);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.6 (C(4')), 25.3 (C(3')), 32.0 (NMe), 34.9 (C(2)), 53.9 (NCH<sub>2</sub>Ph), 54.8 (C(2')), 61.3 (OMe), 111.7 (C(8')), 115.9 (C(6')), 121.2 (C(4'a)), 126.4 (*o*-Ph), 126.7 (*p*-Ph), 127.1 (C(7')), 128.5 (*m*-Ph), 129.1 (C(5')), 139.0 (*i*-Ph), 144.0 (C(8'a)),

172.5 (C(1));  $m/z$  (ESI<sup>+</sup>) 325 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 325.1911; found 325.1909.

**(R)-N(1-Benzyl-2-[2'-Oxo-2'-(3'-tert-butylidimethylsilyloxy-4'-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 11.** *Step 1.* Preparation of *O*-tert-butylidimethylsilyl-5-bromoguaiaicol **9**. *tert*-Butyldimethylsilyl chloride (1.50 g, 10.0 mmol) was added to a stirred solution of 5-bromoguaiaicol (2.00 g, 9.85 mmol) and imidazole (1.36 g, 20.0 mmol) in DMF (5 mL) at rt and the resultant solution was stirred at rt for 16 h. H<sub>2</sub>O (15 mL) was then added and the resultant mixture was extracted with hexane (5  $\times$  15 mL). The combined organics were dried and concentrated *in vacuo* to give **9** as a colourless oil (2.92 g, 93%);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 0.15 (6H, s, SiMe<sub>2</sub>), 0.99 (9H, s, SiCMe<sub>3</sub>), 3.78 (3H, s, OMe), 6.71 (1H, d, *J* 8.6, C(3)H), 6.98 (1H, d, *J* 2.4, C(6)H), 7.02 (1H, dd, *J* 8.6, 2.4, C(4)H).

*Step 2.* *n*-BuLi (2.3 M in hexanes, 1.9 mL, 4.3 mmol) was added dropwise to a stirred solution of **9** (1.37 g, 4.32 mmol) in THF (15 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of **8** (200 mg, 0.616 mmol) in THF (2 mL) at –78 °C was then added and the resultant solution was stirred at –78 °C for 90 min. Satd aq NH<sub>4</sub>Cl (3 mL) was then added and the resultant mixture was allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and H<sub>2</sub>O (20 mL), and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 85:17:1) gave **11** as a yellow oil (273 mg, 88%); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –7.7 (c 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  2953, 2930, 2857, 1671;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 0.15 (6H, s, SiMe<sub>2</sub>), 0.99 (9H, s, SiCMe<sub>3</sub>), 1.97 (1H, ddt, *J* 13.1, 5.7, 2.9, C(3)H<sub>A</sub>), 2.09 (1H, tt, *J* 13.1, 4.8, C(3)H<sub>B</sub>), 2.74–2.81 (1H, m, C(4)H<sub>A</sub>), 2.96 (1H, ddd, *J* 16.7, 13.1, 5.7, C(4)H<sub>B</sub>), 3.15 (2H, d, *J* 6.7, C(1')H<sub>2</sub>), 3.86 (3H, s, OMe), 4.15–4.21 (1H, m, C(2')H), 4.49 (1H, d, *J* 17.2, NCH<sub>A</sub>H<sub>B</sub>Ph), 4.56 (1H, d, *J* 17.2, NCH<sub>A</sub>H<sub>B</sub>Ph), 6.45 (1H, app d, *J* 8.2, C(8)H), 6.62 (1H, td, *J* 7.3, 0.9, C(6)H), 6.83 (1H, d, *J* 8.5, C(5')H), 6.95–7.00 (1H, m, C(7)H), 7.04 (1H, d, *J* 7.3, C(5)H), 7.18–7.31 (5H, m, Ph), 7.43 (1H, d, *J* 2.2, C(2'')H), 7.49 (1H, dd, *J* 8.5, 2.2, C(6'')H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) –4.6 (SiMe<sub>2</sub>), 18.4 (SiCMe<sub>3</sub>), 23.6 (C(4)), 25.4 (C(3)), 25.7 (SiCMe<sub>3</sub>), 40.8 (C(1')), 54.0 (NCH<sub>2</sub>Ph), 54.9 (C(2)), 55.5 (OMe), 110.8 (C(5'')), 111.8 (C(8)), 116.0 (C(6)), 120.3 (C(2'')), 121.2 (C(4a)), 123.3 (C(6'')), 126.4 (*o,m*-Ph), 126.8 (*p*-Ph), 127.2 (C(7)), 128.6 (*o,m*-Ph), 129.1 (C(5)), 130.5 (C(1'')), 138.9 (*i*-Ph), 144.1 (C(8a)), 145.0 (C(3'')), 155.5 (C(4'')), 197.6 (C(2''));  $m/z$  (ESI<sup>+</sup>) 502 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>31</sub>H<sub>40</sub>NO<sub>3</sub>Si<sup>+</sup> ([M+H]<sup>+</sup>) requires 502.2772; found 502.2768.

**(S)-N(1-Benzyl-2-[2'-(3'-hydroxy-4'-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 12.** *Step 1.* LiAlH<sub>4</sub> (2.0 M in THF, 0.46 mL, 0.91 mmol) was added dropwise to a stirred solution of **11** (229 mg, 0.456 mmol) in THF (3.2 mL) at 0 °C. The resultant solution was heated at reflux for 16 h and then allowed to cool to rt. 2 M aq NaOH (0.5 mL) was then added and the resultant mixture was heated at reflux for 3 h. The resultant mixture was allowed to cool to rt and then concentrated *in vacuo*. The residue was dissolved in Et<sub>2</sub>O and filtered through a short plug of silica (eluent Et<sub>2</sub>O), and the filtrate was concentrated *in vacuo*.

*Step 2.* Et<sub>3</sub>SiH (0.73 mL, 4.6 mmol) was added to a stirred solution of the residue from the previous step in TFA (2.2 mL) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and satd aq NaHCO<sub>3</sub> (10 mL), and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 75:25:1) gave **12** as a pale yellow oil (85 mg, 50%); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +0.5 (c 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  3513, 3027, 2980, 2971, 2933, 2860, 1600, 1510, 1498;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.77–2.09 (4H, m, C(3)H<sub>2</sub>, C(1')H<sub>2</sub>), 2.45 (1H, ddd, *J* 14.0, 9.6, 6.8, C(2')H<sub>A</sub>), 2.61 (1H, ddd, *J* 14.0, 9.6, 5.4, C(2')H<sub>B</sub>), 2.75 (1H, dt, *J* 16.5, 3.9, C(4)H<sub>A</sub>), 2.93 (1H, ddd, *J* 16.5, 12.3, 5.9, C(4)H<sub>B</sub>), 3.35–3.42 (1H, m, C(2)H), 3.85 (3H, s, OMe), 4.40 (1H, d, *J* 17.0, NCH<sub>A</sub>H<sub>B</sub>Ph), 4.56 (1H, d, *J* 17.0, NCH<sub>A</sub>H<sub>B</sub>Ph), 5.54 (1H, s, OH), 6.41 (1H, d, *J* 8.0, C(8)H), 6.55–6.62 (2H, m, C(6)H, C(6'')H), 6.72–6.75 (2H, m, C(2'')H, C(5'')H), 6.94 (1H, t, *J* 8.0, C(7)H), 7.01 (1H, d, *J* 7.3, C(5)H), 7.19–7.31 (5H, m, Ph);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.6 (C(4)), 24.2 (C(3)), 31.6 (C(2')), 33.5 (C(1')), 54.0 (NCH<sub>2</sub>Ph), 56.0 (OMe), 57.2 (C(2)), 110.6 (C(5'')), 111.7 (C(8)), 114.4 (C(2'')), 115.5 (C(6)), 119.5 (C(6'')),



121.6 (C(4a)), 126.5 (*o,m*-Ph), 126.6 (*p*-Ph), 127.0 (C(7)), 128.5 (*o,m*-Ph), 128.9 (C(5)), 135.1 (C(1')), 139.2 (*i*-Ph), 144.5 (C(4')), 144.7 (C(8a)), 145.5 (C(3')); *m/z* (ESI<sup>+</sup>) 374 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>28</sub>NO<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 374.2115; found 374.2115.

**(S)-N(1)-Methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 13.** Pd/C (27 mg, 40% w/w of substrate **12**) was added to a stirred solution of **12** (68 mg, 0.18 mmol) and formalin (37% aq HCHO, 0.13 mL, 1.8 mmol) in degassed MeOH (3 mL) at rt. The resultant suspension was stirred under H<sub>2</sub> (1 atm) at rt for 24 h. The resultant suspension was filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 66:33:1) gave **13** as a pale orange solid (31 mg, 57%);<sup>11,13</sup> mp 134–138 °C; [α]<sub>D</sub><sup>25</sup> –26.2 (c 1.0 in CHCl<sub>3</sub>); ν<sub>max</sub> 3501, 2980, 2934, 1601, 1510, 1501; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.66–1.76 (1H, m, C(1')H<sub>A</sub>), 1.84–1.99 (3H, m, C(3)H<sub>2</sub>, C(1')H<sub>B</sub>), 2.49 (1H, ddd, *J* 13.9, 9.9, 6.6, C(2')H<sub>A</sub>), 2.59–2.72 (2H, m, C(4)H<sub>A</sub>, C(2')H<sub>B</sub>), 2.84 (1H, ddd, *J* 17.6, 11.7, 5.2, C(4)H<sub>B</sub>), 2.90 (3H, s, NMe), 3.24–3.30 (1H, m, C(2)H), 3.87 (3H, s, OMe), 5.56 (1H, s, OH), 6.52 (1H, app d, *J* 8.1, C(8)H), 6.59 (1H, td, *J* 7.3, 1.0, C(6)H), 6.66 (1H, dd, *J* 8.2, 2.1, C(6')H), 6.75–6.79 (2H, m, C(2')H, C(5')H), 6.98 (1H, app d, *J* 7.3, C(5)H), 7.08 (1H, td, *J* 7.3, 1.2, C(7)H); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 23.5 (C(4)), 24.3 (C(3)), 31.6 (C(2')), 32.9 (C(1')), 38.0 (NMe), 56.0 (OMe), 58.2 (C(2)), 110.5 (C(8)), 110.6 (C(5')), 114.5 (C(2')), 115.3 (C(6)), 119.5 (C(6')), 121.7 (C(4a)), 127.1 (C(7)), 128.6 (C(5)), 135.3 (C(1')), 144.7 (C(4')), 145.3 (C(8a)), 145.5 (C(3')); *m/z* (ESI<sup>+</sup>) 298 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>19</sub>H<sub>24</sub>NO<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 298.1802; found 298.1800.

**(R)-N(1)-Benzyl-2-[2'-oxo-2'-(3''-methoxy-4''-tert-butylidimethylsilyloxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 16.** Step 1. Preparation of *O*-tert-butylidimethylsilyl-4-bromoguaiacol **14**. *tert*-Butyldimethylsilyl chloride (1.50 g, 10.0 mmol) was added to a stirred solution of 4-bromoguaiacol (2.00 g, 9.85 mmol) and imidazole (1.36 g, 20.0 mmol) in DMF (5 mL) at rt and the resultant solution was stirred at rt for 16 h. H<sub>2</sub>O (15 mL) was then added and the resultant mixture was extracted with hexane (5 × 15 mL). The combined organics were dried and concentrated *in vacuo* to give **14** as a colourless oil (2.98 g, 95%);<sup>28</sup> δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 0.14 (6H, s, SiMe<sub>2</sub>), 0.98 (9H, s, SiCMe<sub>3</sub>), 3.79 (3H, s, OMe), 6.71 (1H, d, *J* 8.3, C(6)H), 6.93 (1H, dd, *J* 8.3, 2.4, C(5)H), 6.95 (1H, d, *J* 2.4, C(3)H).

Step 2. *n*-BuLi (2.3 M in hexanes, 2.4 mL, 5.4 mmol) was added dropwise to a stirred solution of **14** (1.71 g, 5.39 mmol) in THF (19 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of **8** (250 mg, 0.771 mmol) in THF (2 mL) at –78 °C was then added and the resultant solution was stirred at –78 °C for 90 min. Satd aq NH<sub>4</sub>Cl (4 mL) was then added and the resultant mixture was allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and H<sub>2</sub>O (20 mL), and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 90:9:1) gave **16** as a yellow oil (239 mg, 62%); [α]<sub>D</sub><sup>25</sup> –11.6 (c 1.0 in CHCl<sub>3</sub>); ν<sub>max</sub> 2953, 2930, 2857, 1672; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 0.17 (6H, s, SiMe<sub>2</sub>), 0.99 (9H, s, SiCMe<sub>3</sub>), 1.98 (1H, ddt, *J* 13.3, 5.7, 2.8, C(3)H<sub>A</sub>), 2.10 (1H, tt, *J* 13.3, 4.9, C(3)H<sub>B</sub>), 2.74–2.82 (1H, m, C(4)H<sub>A</sub>), 2.97 (1H, ddd, *J* 17.1, 13.3, 5.7, C(4)H<sub>B</sub>), 3.13 (1H, dd, *J* 16.1, 8.3, C(1')H<sub>A</sub>), 3.21 (1H, dd, *J* 16.1, 5.1, C(1')H<sub>B</sub>), 3.81 (3H, s, OMe), 4.16–4.22 (1H, m, C(2)H), 4.48 (1H, d, *J* 17.1, NCH<sub>A</sub>H<sub>B</sub>Ph), 4.55 (1H, d, *J* 17.1, NCH<sub>A</sub>H<sub>B</sub>Ph), 6.45 (1H, d, *J* 8.3, C(8)H), 6.62 (1H, td, *J* 7.3, 0.9, C(6)H), 6.83 (1H, d, *J* 8.3, C(5')H), 6.95–7.00 (1H, m, C(7)H), 7.04 (1H, d, *J* 7.3, C(5)H), 7.18–7.31 (5H, m, Ph), 7.38 (1H, dd, *J* 8.3, 2.0, C(6')H), 7.44 (1H, d, *J* 2.0, C(2')H); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) –4.6 (SiMe<sub>2</sub>), 18.5 (SiCMe<sub>3</sub>), 23.5 (C(4)), 25.5 (C(3)), 25.6 (SiCMe<sub>3</sub>), 40.8 (C(1')), 54.1 (NCH<sub>2</sub>Ph), 54.9 (C(2)), 55.4 (OMe), 111.0 (C(2')), 111.9 (C(8)), 116.0 (C(6)), 120.3 (C(5')), 121.1 (C(4a)), 122.6 (C(6')), 126.4 (*o,m*-Ph), 126.8 (*p*-Ph), 127.2 (C(7)), 128.6 (*o,m*-Ph), 129.2 (C(5)), 131.3 (C(1')), 138.9 (*i*-Ph), 144.1 (C(8a)), 150.2, 151.1 (C(3'), C(4')), 197.9 (C(2')); *m/z* (ESI<sup>+</sup>) 502 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>31</sub>H<sub>40</sub>NO<sub>3</sub>Si<sup>+</sup> ([M+H]<sup>+</sup>) requires 502.2772; found 502.2768.

**(S)-N(1)-Benzyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 17.** Step 1. LiAlH<sub>4</sub> (2.4 M in THF, 0.47

mL, 0.95 mmol) was added dropwise to a stirred solution of **16** (238 mg, 0.474 mmol) in THF (3.3 mL) at 0 °C. The resultant solution was heated at reflux for 16 h and then allowed to cool to rt. 2 M aq NaOH (0.5 mL) was then added and the resultant mixture was heated at reflux for 3 h. The resultant mixture was allowed to cool to rt, filtered through Celite® (eluent EtOAc), and the filtrate was concentrated *in vacuo*.

Step 2. Et<sub>3</sub>SiH (0.76 mL, 4.7 mmol) was added to a stirred solution of the residue from the previous step in TFA (2.3 mL) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and satd aq NaHCO<sub>3</sub> (10 mL), and the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 50:50:1) gave **17** as a pale yellow oil (109 mg, 62%); [α]<sub>D</sub><sup>25</sup> +0.4 (c 1.0 in CHCl<sub>3</sub>); ν<sub>max</sub> 3502, 2934, 1605, 1530; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.78–2.08 (4H, m, C(3)H<sub>2</sub>, C(1')H<sub>2</sub>), 2.47 (1H, ddd, *J* 13.9, 9.9, 6.6, C(2')H<sub>A</sub>), 2.64 (1H, ddd, *J* 13.9, 10.6, 5.1, C(2')H<sub>B</sub>), 2.76 (1H, dt, *J* 16.5, 3.9, C(4)H<sub>A</sub>), 2.94 (1H, ddd, *J* 16.5, 11.9, 6.2, C(4)H<sub>B</sub>), 3.38–3.44 (1H, m, C(2)H), 3.84 (3H, s, OMe), 4.42 (1H, d, *J* 17.1, NCH<sub>A</sub>H<sub>B</sub>Ph), 4.57 (1H, d, *J* 17.1, NCH<sub>A</sub>H<sub>B</sub>Ph), 5.45 (1H, s, OH), 6.43 (1H, app d, *J* 8.2, C(8)H), 6.58 (1H, td, *J* 7.3, 1.1, C(6)H), 6.61 (1H, d, *J* 1.9, C(2')H), 6.63 (1H, dd, *J* 8.0, 1.9, C(6')H), 6.81 (1H, d, *J* 8.0, C(5')H), 6.93–6.98 (1H, m, C(7)H), 7.02 (1H, d, *J* 7.3, C(5)H), 7.19–7.32 (5H, m, Ph); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 23.6 (C(4)), 24.2 (C(3)), 31.9 (C(2')), 33.9 (C(1')), 54.1 (NCH<sub>2</sub>Ph), 55.9 (OMe), 57.3 (C(2)), 110.7 (C(2')), 111.7 (C(8)), 114.2 (C(5')), 115.6 (C(6)), 120.7 (C(6')), 121.6 (C(4a)), 126.4 (*o,m*-Ph), 126.7 (*p*-Ph), 127.1 (C(7)), 128.5 (*o,m*-Ph), 128.9 (C(5)), 133.7 (C(1')), 139.2 (*i*-Ph), 143.6 (C(4')), 144.5 (C(8a)), 146.3 (C(3')); *m/z* (ESI<sup>+</sup>) 374 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>28</sub>NO<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 374.2115; found 374.2118.

**(S)-N(1)-Methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline [(–)-Galipeine] 18.** Pd/C (42 mg, 40% w/w of substrate **17**) was added to a stirred solution of **17** (106 mg, 0.284 mmol) and formalin (37% aq HCHO, 0.21 mL, 2.84 mmol) in degassed MeOH (5 mL) at rt. The resultant suspension was stirred under H<sub>2</sub> (1 atm) at rt for 24 h. The resultant suspension was filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et<sub>2</sub>O/NH<sub>4</sub>OH, 66:33:1) gave **18** as a colourless oil (59 mg, 70%);<sup>1</sup> [α]<sub>D</sub><sup>25</sup> –22.0 (c 0.2 in CHCl<sub>3</sub>); [α]<sub>D</sub><sup>25</sup> –22.3 (c 1.0 in CHCl<sub>3</sub>); [α]<sub>D</sub><sup>25</sup> –14.0 (c 1.0 in MeOH); [α]<sub>D</sub><sup>25</sup> –11.9 (c 1.0 in EtOH); ν<sub>max</sub> (ATR) 3510, 2935, 2860, 2844, 1602, 1514, 1500; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.68–1.78 (1H, m, C(1')H<sub>A</sub>), 1.86–2.00 (3H, m, C(3)H<sub>2</sub>, C(1')H<sub>B</sub>), 2.52 (1H, ddd, *J* 13.9, 10.2, 6.4, C(2')H<sub>A</sub>), 2.62–2.73 (2H, m, C(4)H<sub>A</sub>, C(2')H<sub>B</sub>), 2.86 (1H, ddd, *J* 17.5, 11.6, 6.1, C(4)H<sub>B</sub>), 2.92 (3H, s, NMe), 3.26–3.33 (1H, m, C(2)H), 3.88 (3H, s, OMe), 5.47 (1H, s, OH), 6.54 (1H, app d, *J* 8.1, C(8)H), 6.60 (1H, td, *J* 7.3, 0.9, C(6)H), 6.67–6.71 (2H, m, C(2')H, C(6')H), 6.84 (1H, d, *J* 8.5, C(5')H), 6.99 (1H, d, *J* 7.3, C(5)H), 7.07–7.12 (1H, m, C(7)H); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 23.5 (C(4)), 24.3 (C(3)), 32.0 (C(2')), 33.1 (C(1')), 38.1 (NMe), 55.9 (OMe), 58.3 (C(2)), 110.5 (C(8)), 110.7 (C(2')), 114.2 (C(5')), 115.3 (C(6)), 120.7 (C(6')), 121.6 (C(4a)), 127.1 (C(7)), 128.6 (C(5)), 133.9 (C(1')), 143.6 (C(4')), 145.2 (C(8a)), 146.3 (C(3')); *m/z* (ESI<sup>+</sup>) 298 ([M+H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>19</sub>H<sub>24</sub>NO<sub>2</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 298.1802; found 298.1801.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxx.

Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF)  
X-ray data for structure CCDC 1557564 (CIF)

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## Notes

The authors declare no competing financial interest.

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