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The Hancock Alkaloids (−)-Cuspareine, (−)-Galipinine, (−)-Galipeine, and (−)-Angustureine: Asymmetric Syntheses and Corrected ^{1}H and ^{13}C NMR Data

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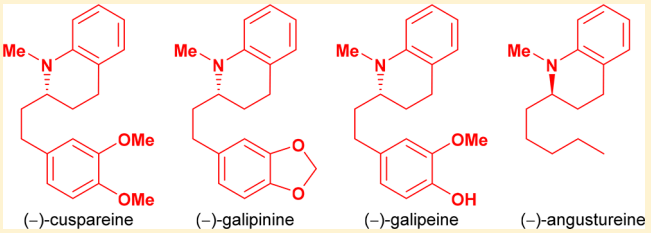
Supporting Information

ABSTRACT: The asymmetric syntheses of all members of the Hancock alkaloid family based upon a 2-substituted *N*-methyl-1,2,3,4-tetrahydroquinoline core are delineated. The conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to 5-(*o*-bromophenyl)-*N*-methoxy-*N*-methylpent-2-enamide is used to generate the requisite C-2 stereogenic center of the targets, while an intramolecular Buchwald−Hartwig coupling is used to form the 1,2,3,4-tetrahydroquinoline ring. Late-stage diversification completes construction of the C-2 side chains. Thus, (−)-cuspareine, (−)-galipinine, (−)-galipeine, and (−)-angustureine were prepared in overall yields of 30%, 28%, 15%, and 39%, respectively, in nine steps from commercially available 3-(*o*-bromophenyl)propanoic acid in all cases. Unambiguously corrected ^{1}H and ^{13}C NMR data for the originally isolated samples of (−)-cuspareine, (−)-galipinine, and (−)-angustureine are also reported, representing a valuable reference resource for these popular synthetic targets.



Galipea officinalis Hancock[1] is a shrubby tree that can be found growing on the mountainsides of Venezuela and on the banks of the Orinoco River and which is revered in the indigenous folk medicine for its healing properties. Reports concerned with the determination of the alkaloid content of the trunk bark (called angostura) of this plant appeared from the 1880s,[2,3] and one of the alkaloids identified in early reports was given the name cuspareine (without a structure).[4,5] It was not until 1950 that Schläger and Leeb proposed the gross structure of *N*-methyl-2-[2′-(3″,4″-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline for cuspareine (Figure 1), on the basis of degradation studies.[6] They confirmed their postulate by preparing a synthetic sample of this material as the racemate,[6] although the natural product itself was evidently nonracemic {$[\alpha]_D^{20}$ −20.4 (*c* 6.8 in EtOH)}.[6] Cuspareine was then largely ignored for over 50 years, with the only other syntheses (of the racemate) being reported by Staněk in 1957[7] and by Terashima et al. in 1985,[8] with limited accompanying characterization data. However, Jacquemond-Collet et al. described their re-evaluation of the alkaloid content of angostura, which culminated in the isolation, identification, and biological profiling of a range of known and new alkaloids, in a series of reports that appeared at the end of the 1990s and in the early 2000s.[9−12] Cuspareine was one of the alkaloids isolated in these studies {$[\alpha]_D$ −22.8 (*c* 0.0135 in $CHCl_3$)},[13] and it was fully characterized by NMR spectroscopy (^{1}H, ^{13}C) for the first time.[9,14] Three other alkaloids with an *N*-methyl-1,2,3,4-tetrahydroquinoline scaffold bearing a C-2 substituent

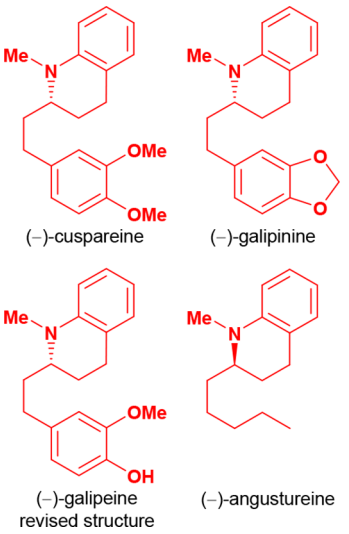


Figure 1. Structures of the Hancock alkaloids (naturally occurring isomers shown).

were also isolated and identified, and these were named galipinine {$[\alpha]_D$ −33.4 (*c* 0.0055 in $CHCl_3$)},[9,13,14] galipeine {$[\alpha]_D$ −13.6},[10,15] and angustureine {$[\alpha]_D$ −7.16}[10,15] (Figure 1). This tetrad has since captivated the interest of the synthetic

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community:[16−26] relatively simple structures coupled with biological activity have no doubt contributed to their subsequent and common occurrence as targets to validate the synthetic utility of newly developed methods to enable the preparation of tetrahydroquinolines or else to showcase the use of the same. These synthetic studies have also enabled the absolute configurations of the alkaloids to be determined, with the assignments being based upon comparison of specific rotation values in all cases. Considering the interest that has been lavished on them since 2000 (16 syntheses of cuspareine, 14 of galipinine, and 27 of angustureine reported to date),[16−26] it is incredible that discrepancies between the ^{1}H and ^{13}C NMR spectroscopic data reported by Jacquemond-Collet et al.[9,10] for the natural products and synthetic samples thereof did not attract comment for over 15 years. In 2017, however, Diaz-Muñoz et al.[25] reported their approach to the alkaloids in racemic form and noted differences between the ^{13}C NMR data of their synthetic samples of cuspareine and galipinine and those reported by Jaquemond-Collet et al.[9] for the natural samples isolated from angostura. These observations led Diaz-Muñoz et al. to propose that Jaquemond-Collet et al. had inadvertently transposed some of the ^{13}C NMR data for cuspareine and galipinine.[25] Although Diaz-Muñoz et al. made no comment regarding the agreement of NMR spectroscopic data for galipeine and angustureine, we[26] simultaneously reported the results of our own, independent investigations into discrepancies that we had noted between the ^{1}H and ^{13}C NMR data reported by Jaquemond-Collet et al.[10] for (−)-galipeine and the analogous data for purported synthetic samples thereof.[27,28] In fact, our study revealed that the originally proposed structure of this alkaloid was, unfortunately, erroneous and culminated in its structural revision; our study therefore also constitutes the first time (and to date the only time)[29] that a synthetic sample of this alkaloid has been prepared.[26] In this article, we delineate the full development of our approach to enable access to all of the members of this alkaloid family, which thus enabled preparation of (−)-cuspareine, (−)-galipinine, and (−)-angustureine, as well as (−)-galipeine. Furthermore, we report unambiguously corrected ^{1}H and ^{13}C NMR data for (−)-cuspareine, (−)-galipinine, and (−)-angustureine from analysis of the original ^{1}H and ^{13}C NMR spectra for these alkaloids, which were kindly supplied to us by Professor Nicolas Fabre (a member of the team involved in the seminal studies describing the isolation of these alkaloids).[30]

RESULTS AND DISCUSSION

Syntheses of (−)-cuspareine, (−)-galipinine, (−)-galipeine, and (−)-angustureine that involved late-stage construction of the C-2 side chains from a common intermediate alongside the ability to access either enantiomeric form were envisaged, given the differences in both structure and absolute configuration of the four alkaloids. In the forward sense, conjugate addition of an enantiopure, secondary lithium amide **2** (derived from the corresponding enantiomer of *α*-methyl-*p*-methoxybenzylamine) to an *α*,*β*-unsaturated amide **1** [derived from 3-(*o*-bromophenyl)propanoic acid] would give the corresponding enantiopure *β*-amino amide **3**. Mono-*N*-deprotection of the *N*-*α*-methyl-*p*-methoxybenzyl substituent under acidic conditions would leave the aryl bromide functionality untouched, thus enabling subsequent intramolecular Buchwald−Hartwig coupling to give the common 1,2,3,4-tetrahydroquinoline scaffold **4**. Addition of the requisite aryl- or alkyllithium reagent to the amide functionality within **4** would then allow the construction of the C-2 side chains, with functional group manipulation then giving the target alkaloids **5** (Figure 2).

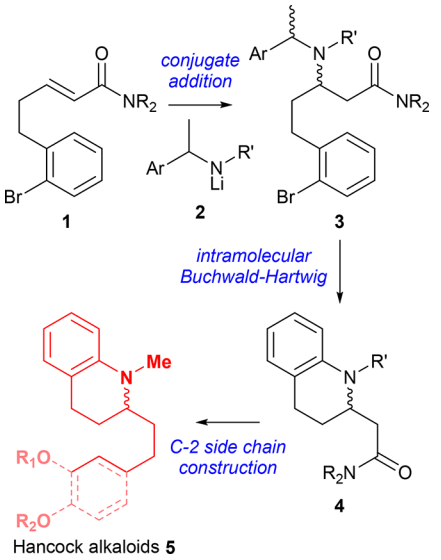

Figure 2. Proposed synthesis of the Hancock alkaloids (−)-cuspareine, (−)-galipinine, (−)-galipeine, and (−)-angustureine.

(−)-Cuspareine, (−)-Galipinine, and (−)-Galipeine. The preparation of the three members of the Hancock alkaloid family based upon an *N*-methyl-2-(2′-arylethyl)-1,2,3,4-tetrahydroquinoline core, viz. (−)-cuspareine, (−)-galipinine, and (−)-galipeine, was first pursued. *α*,*β*-Unsaturated Weinreb amide **9** was prepared from commercially available 3-(*o*-bromophenyl)propanoic acid **6**. Attempted reduction of **6** with $LiAlH_4$ was accompanied by significant debromination (∼50%), as has been previously observed,[31] and therefore reduction of **6** was carried out using $NaBH_4$ in the presence of $BF_3{\cdot}OEt_2$[32] to give the corresponding alcohol **7** in 97% yield. One-pot Swern oxidation and Wittig olefination of **7** using $Ph_3P{=}CHCON(Me)(OMe)$ **8** (prepared from bromoacetyl bromide) as the ylide gave **9** as a single diastereoisomer [>95:5 dr, (*E*):(*Z*) ratio], which was isolated in 87% yield; the diagnostic value $^{3}J_{2,3}$ = 15.4 Hz enabled confident assignment of the geometry of the newly formed olefin functionality (Scheme 1).

As the naturally occurring isomers of the three *N*-methyl-2-(2′-arylethyl)-1,2,3,4-tetrahydroquinoline alkaloid targets share an (*S*)-configuration, and given the presence of the *N*-methyl group in the targets, the conjugate addition of lithium (*R*)-*N*-methyl-*N*-(*α*-methyl-*p*-methoxybenzyl)amide (*R*)-**10** to *α*,*β*-unsaturated Weinreb amide **9** was first assessed. However, this produced a 75:25 mixture of the two diastereoisomeric *β*-amino amides **12** and **13** in 93% combined yield. The reaction diastereoselectivity was determined by integration of both of the singlet resonances associated with both of the *N*-methyl groups of the major diastereoisomer **12** at δ_H 2.24 and δ_H 3.14 and those of the minor diastereoisomer **13** at δ_H 2.09 and δ_H 3.17 in the ^{1}H NMR spectrum of the crude reaction mixture; the relative configurations of **12** and **13** were not, however, unambiguously assigned. In contrast, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(*α*-methyl-*p*-methoxybenzyl)amide (*R*)-**11** to **9** delivered *β*-amino amide (3*R*,*αR*)-**14** as a single

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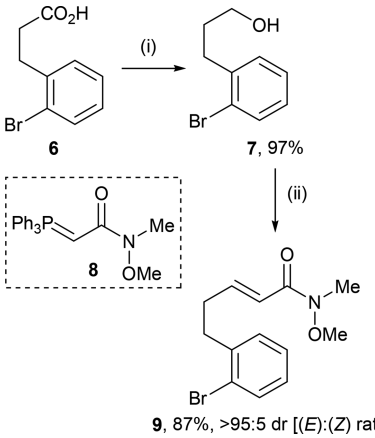
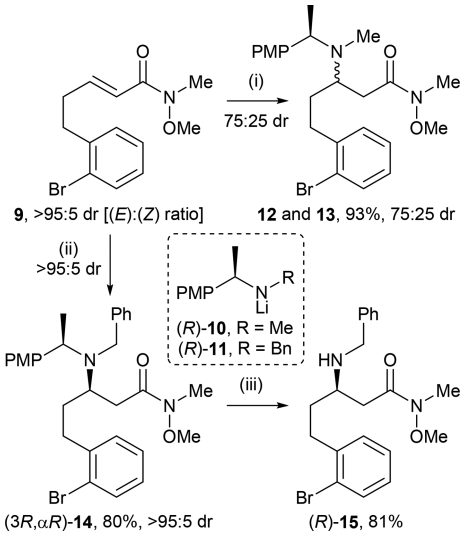
Scheme 1. Preparation of α,β-Unsaturated Weinreb Amide 9[a]



[a]Reagents and conditions: (i) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, 0 °C, 1 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 30 min, then **8**, rt, 16 h.

diastereoisomer (>95:5 dr), which was isolated in 80% yield. The absolute configuration at the newly formed C-3 stereogenic center of (3*R*,α*R*)-**14** was assigned by reference to the transition state mnemonic that we have developed to predict the stereochemical outcome of this class of conjugate addition reactions.[33] Subsequent treatment of (3*R*,α*R*)-**14** with HCO_2H in the presence of Et_3SiH[34−36] effected chemoselective removal of the *N*-α-methyl-*p*-methoxybenzyl group to furnish (*R*)-**15** in 81% yield (Scheme 2).

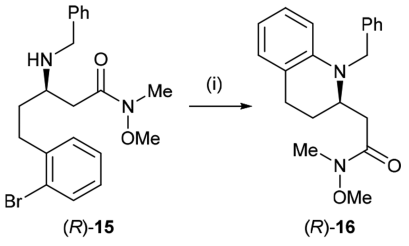
Scheme 2. Preparation of Enantiopure β-Amino Amides 14 and 15[a]



[a]Reagents and conditions: (i) (*R*)-**10**, THF, −78 °C, 2 h; (ii) (*R*)-**11**, THF, −78 °C, 2 h; (iii) HCO_2H, Et_3SiH, 90 °C, 16 h. PMP = *p*-methoxyphenyl.

Treatment of (*R*)-**15** with 5 mol % $Pd(OAc)_2$ in the presence of PPh_3 and Cs_2CO_3 in PhMe at reflux for 24 h[37] gave 43% conversion to tetrahydroquinoline (*R*)-**16**, which was isolated in 37% yield. Increasing the catalyst loading to 15 mol % resulted in quantitative conversion, and (*R*)-**16** was isolated in 79% yield. Alternatively, the use of XPhos in place of PPh_3 also gave quantitative conversion, and (*R*)-**16** was isolated in quantitative yield in this case (Scheme 3).

Scheme 3. Preparation of 1,2,3,4-Tetrahydroquinoline Scaffold (*R*)-16[a]

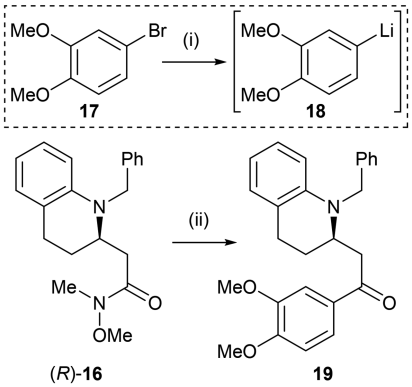


Entry	$Pd(OAc)_2$ mol %	ligand	conversion	yield
1	5	PPh_3	43%	37%
2	15	PPh_3	quant	79%
3	5	XPhos	quant	quant

[a]Reagents and conditions: (i) $Pd(OAc)_2$, ligand, Cs_2CO_3, PhMe, reflux, 24 h.

It was envisaged that the aryllithium reagents required for diversification of the common intermediate (*R*)-**16** to the alkaloid targets could be prepared in situ upon treatment of the corresponding aryl bromides with *n*-BuLi.[38,39] Reaction of (*R*)-**16** with the aryllithium reagent **18** (derived from 4-bromoveratrole **17**) was first investigated for purposes of optimization (Scheme 4). Initially, 1.0 equiv of *n*-BuLi was

Scheme 4. Preparation of Ketone 19[a]



Entry	BuLi	17	time	temp	conversion	yield
1	1 equiv	1 equiv	1.5 h	−78 °C	40%	37%
2	1 equiv	1 equiv	16 h	−78 °C	43%	-
3	1 equiv	1 equiv	1.5 h	0 °C	33%	-
4	2 equiv	2 equiv	1.5 h	−78 °C	59%	55%
5	7 equiv	7 equiv	1.5 h	−78 °C	quant	79%

[a]Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 30 min; (ii) **18**, THF, see table.

added to 1.0 equiv of **17** in tetrahydrofuran (THF) at −78 °C, followed by the addition of Weinreb amide (*R*)-**16**. Under these conditions, however, only 40% conversion to ketone **19** was observed after 90 min, and thus **19** was isolated in only 37% yield. Neither increasing the reaction duration (to 16 h) nor increasing the reaction temperature (to 0 °C) had a significant impact upon the conversion to **19** (43% and 33% conversion, respectively). To ascertain whether reaction of *n*-BuLi with *n*-BuBr (formed in situ as the side product of the lithium−halogen exchange) was depleting the amount of base,

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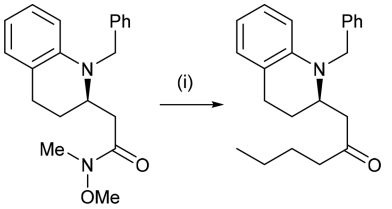
and so was responsible for the low levels of conversion observed, an experiment was performed using 2.0 equiv of *n*-BuLi and 1.0 equiv of **17**. In this case, 84% conversion of (*R*)-**16** into a 30:70 mixture of ketone **19** and *n*-butyl ketone **20** was observed, indicating that the excess *n*-BuLi had not been consumed and was able to undergo reaction with Weinreb amide (*R*)-**16**. The identity of **20** was confirmed upon treatment of (*R*)-**16** with 2.0 equiv of *n*-BuLi alone, which (interestingly) gave quantitative conversion to **20** as the exclusive product, which was isolated in 71% yield (Scheme 5).

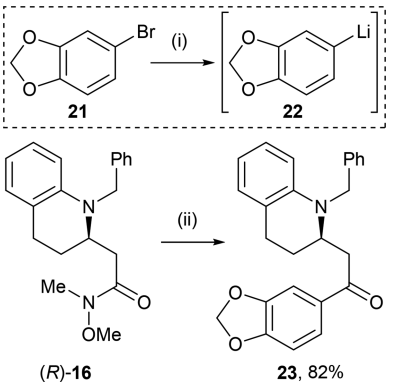
Scheme 5. Preparation of Ketone 20[a]



[a]Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 1.5 h.

The effect of reaction stoichiometry was next investigated in order to promote formation of the target aryl ketone **19**. It was found that the use of 7.0 equiv of *n*-BuLi and 7.0 equiv of **17** delivered quantitative conversion to **19**, allowing its isolation in 79% yield (Scheme 4). Using this protocol, ketone **23** was produced in a similar manner from (*R*)-**16** and the requisite aryl bromide, viz., 5-bromo-1,3-benzodioxole **21**, in 82% isolated yield (Scheme 6).

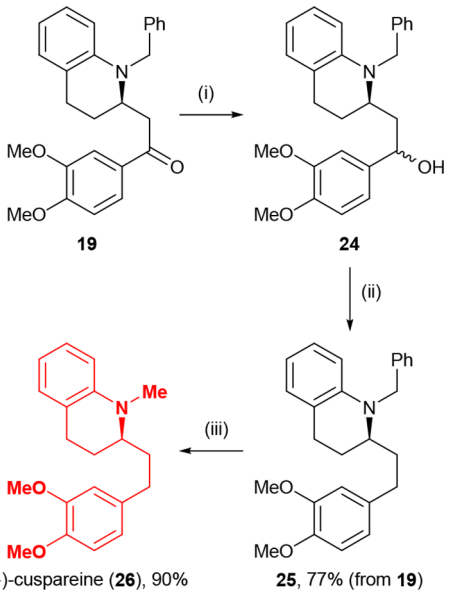
Scheme 6. Preparation of Ketone 23[a]



[a]Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 30 min; (ii) **22**, THF, −78 °C, 1.5 h.

Initial attempts at the reduction of ketone **19** to give **25**, or to provide (−)-cuspareine (**26**) directly, were unsuccessful under a range of conditions, and therefore a stepwise approach to the alkaloid target was investigated. Reduction of **19** with $LiAlH_4$ gave the corresponding alcohol **24** (of undetermined and unimportant stereoisomeric constitution at the carbinol stereocenter) and was followed by treatment of **24** with tetrafluoroacetic acid (TFA) in the presence of Et_3SiH for 6 h, which gave an 80:20 mixture of **25** and the corresponding styrene derivative. Hydrogenolysis of this mixture in the presence of formalin resulted in convergence to (−)-cuspareine (**26**), which was thus isolated in 35% yield from **19**. Alternatively, when the TFA/Et_3SiH reaction was left to run for 16 h, **25** was formed as the only product and isolated in 77% yield from **19**. Subjection of **25** to an atmosphere of hydrogen in the presence of Pd/C and formalin (37% aqueous HCHO) resulted in tandem hydrogenolytic *N*-debenzylation and reductive *N*-methylation, giving (−)-cuspareine (**26**) in 90% yield, corresponding to 27% yield over nine steps from commercially available 3-(*o*-bromophenyl)propanoic acid **6** (Scheme 7).

Scheme 7. Preparation of (−)-Cuspareine (26)[a]



[a]Reagents and conditions: (i) $LiAlH_4$, THF, reflux, 16 h; (ii) TFA, Et_3SiH, 70 °C, 16 h; (iii) H_2, formalin, Pd/C, MeOH, rt, 24 h.

With an end-game established, sequential treatment of ketone **23** with $LiAlH_4$ and then TFA and Et_3SiH gave **28** in 77% yield. Subsequent one-pot hydrogenolytic *N*-debenzylation and reductive *N*-methylation of **28** gave (−)-galipinine (**29**) in 81% yield, corresponding to 25% yield over nine steps from commercially available 3-(*o*-bromophenyl)propanoic acid **6** (Scheme 8).

We again wish to extend our gratitude to Professor Nicolas Fabre for supplying us with copies of the NMR spectra recorded for the samples of the alkaloids isolated from angostura.[30] Unfortunately, when we analyzed these spectra for (−)-cuspareine and (−)-galipinine, we noted that several transcriptional errors had occurred between the raw ^1H and ^{13}C NMR data and those reported.[9] We therefore first validated the ^1H and ^{13}C NMR data for the natural samples of both (−)-cuspareine (Figure 3) and (−)-galipinine (Figure 4); this included correction of the reference frequencies in the ^1H and ^{13}C NMR spectra for cuspareine and the ^1H NMR spectrum for galipinine (for ^1H NMR, $CHCl_3$, δ_H = 7.26; for ^{13}C NMR, $CDCl_3$, δ_C = 77.16).[40,41] It was not possible to determine (and hence correct if necessary) the reference frequency in the ^{13}C NMR spectrum for galipinine due to the poor resolution of the copy of the original spectrum. As a result of this analysis, we are able to confirm unambiguously that a large amount of the ^{13}C NMR data reported for cuspareine and galipinine was indeed transposed,[9] as Diaz-Muñoz et al. had speculated.[25] With these data in hand, it was apparent that the

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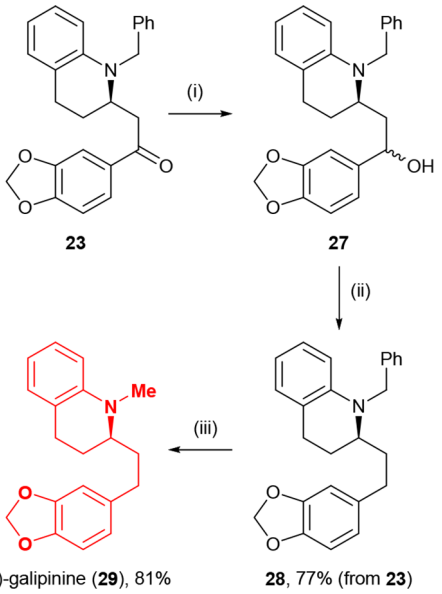
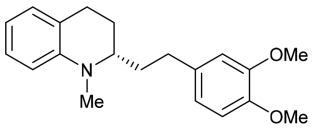
Scheme 8. Preparation of (−)-Galipinine (29)[a]



[a]Reagents and conditions: (i) $LiAlH_4$, THF, reflux, 16 h; (ii) TFA, Et_3SiH, 70 °C, 16 h; (iii) H_2, formalin, Pd/C, MeOH, rt, 24 h.



^{1}H NMR (400 MHz, $CDCl_3$)

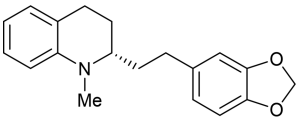
(−)-cuspareine	26
1.76 (1H, m)	1.74 (1H, dddd)
1.94 (3H, m)	1.95 (3H, m)
2.50 (1H, m)	2.54 (1H, ddd)
2.63 (2H, m)	2.69 (2H, m)
2.83 (1H, m)	2.86 (1H, m)
2.92 (3H, s)	2.92 (3H, s)
3.29 (1H, m)	3.30 (1H, m)
3.85 (3H, s)	3.86 (3H, s)
3.88 (3H, s)	3.88 (3H, s)
6.54 (1H, d)	6.54 (1H, d)
6.60 (1H, t)	6.60 (1H, td)
6.75 (3H, m)*	6.73 (2H, m)
6.75 (3H, m)*	6.80 (1H, d)
6.99 (1H, d)	6.99 (1H, d)
7.10 (1H, t)	7.09 (1H, m)

^{13}C NMR (100 MHz, $CDCl_3$)

(−)-cuspareine	26
23.7	23.7 (0.0)
24.5	24.5 (0.0)
32.1	32.1 (0.0)
33.2	33.2 (0.0)
38.3	38.3 (0.0)
56.0	56.0 (0.0)
56.1	56.1 (0.0)
58.6	58.6 (0.0)
110.7	110.7 (0.0)
111.4	111.4 (0.0)
111.7	111.7 (0.0)
115.5	115.5 (0.0)
120.2	120.2 (0.0)
121.9	121.9 (0.0)
127.3	127.3 (0.0)
128.8	128.8 (0.0)
134.8	134.8 (0.0)
145.4	145.4 (0.0)
147.3	147.3 (0.0)
149.0	149.0 (0.0)

Figure 3. ^{1}H and ^{13}C NMR data of **26** and natural (−)-cuspareine. Midpoints of all multiplets are quoted. Values of $\Delta\delta_C$ are given in parentheses. NMR data of natural (−)-cuspareine are corrected here (compared to those reported in ref 9) by analysis of the NMR spectra of the natural product. Reference frequencies employed are $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (refs 40, 41). *These (overlapping) resonances were not resolvable in the spectrum of the natural product but could be resolved in the spectrum of **26**.

spectra of our synthetic samples of **26** and **29** were effectively superimposable with those for the natural materials: for **26** and natural (−)-cuspareine, $\Delta\delta_H \leq 0.06$[42,43] and $\Delta\delta_C = 0.0$[42] (Figure 3), while for **29** and natural (−)-galipinine, $\Delta\delta_H \leq 0.04$[41,42] and $\Delta\delta_C \leq 0.2$[41] (Figure 4). In addition, the specific rotation values of our synthetic samples were in good agreement with those reported for the natural products:



^{1}H NMR (400 MHz, $CDCl_3$)

(−)-galipinine	29
1.70 (1H, m)	1.70 (1H, m)
1.92 (3H, m)	1.92 (3H, m)
2.68 (4H, m)*	2.50 (1H, ddd)
2.68 (4H, m)*	2.66 (2H, m)
2.68 (4H, m)*	2.84 (1H, m)
2.93 (3H, s)	2.91 (3H, s)
3.31 (1H, m)	3.27 (1H, m)
5.92 (2H, s)	5.92 (2H, s)
6.68 (5H, m)*	6.52 (1H, d)
6.68 (5H, m)*	6.59 (1H, td)
6.68 (5H, m)*	6.63 (1H, dd)
6.68 (5H, m)*	6.69 (1H, d)
6.68 (5H, m)*	6.73 (1H, d)
6.99 (1H, d)	6.98 (1H, d)
7.11 (1H, t)	7.08 (1H, m)

^{13}C NMR (100 MHz, $CDCl_3$)

(−)-galipinine	29
23.6	23.7 (0.1)
24.4	24.5 (0.1)
32.1	32.2 (0.1)
33.2	33.3 (0.1)
38.1	38.2 (0.1)
58.3	58.4 (0.1)
100.8	100.9 (0.1)
108.2	108.3 (0.1)
108.8	108.9 (0.1)
110.7	110.8 (0.1)
115.5	115.6 (0.1)
121.0	121.1 (0.1)
121.8	121.9 (0.1)
127.2	127.3 (0.1)
128.7	128.8 (0.1)
135.9	136.0 (0.1)
145.4	145.5 (0.1)
145.7	145.8 (0.1)
147.6	147.8 (0.2)

Figure 4. ^{1}H and ^{13}C NMR data of **29** and natural (−)-galipinine. Midpoints of all multiplets are quoted. Values of $\Delta\delta_C$ are given in parentheses. NMR data of natural (−)-galipinine are corrected here (compared to those reported in ref 9) by analysis of the NMR spectra of the natural product. Reference frequencies employed are $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (refs 40, 41), although it was not possible to determine the reference frequency of the ^{13}C NMR spectrum for natural (−)-galipinine. *These (overlapping) resonances were not resolvable in the spectrum of the natural product but could be resolved in the spectrum of **29**.

natural (−)-cuspareine was reported to have $[\alpha]_D^{20}$ −20.4 (*c* 6.8 in EtOH)[6] and $[\alpha]_D$ −22.8 (*c* 0.0135 in $CHCl_3$),[9] while for **26** we obtained $[\alpha]_D^{25}$ −17.6 (*c* 0.2 in EtOH) and $[\alpha]_D^{25}$ −25.0 (*c* 0.3 in $CHCl_3$), and natural (−)-galipinine was reported to have $[\alpha]_D$ −33.4 (*c* 0.0055 in $CHCl_3$),[9] while for **29** we obtained $[\alpha]_D^{25}$ −23.7 (*c* 1.0 in $CHCl_3$).

We have previously reported the application of this methodology to the synthesis of (−)-galipeine and the analysis of its NMR and specific rotation data; in this case the alkaloid could be prepared in 15% yield over nine steps from commercially available 3-(*o*-bromophenyl)propanoic acid **6**.[26]

(−)-Angustureine. The preparation of the final member of this natural product family, i.e., (−)-angustureine, was next pursued. As it has been determined that the naturally occurring isomer has the (*R*)-configuration, the enantiomeric tetrahydroquinoline (*S*)-**16** was first prepared. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide (*S*)-**11** to α,β-unsaturated Weinreb amide **9** gave β-amino amide (3*S*,α*S*)-**14** as a single diastereoisomer (>95:5 dr), in 99% yield. Chemoselective removal of the *N*-α-methyl-*p*-methoxybenzyl group from (3*S*,α*S*)-**14** using HCO_2H in the presence of Et_3SiH[34−36] gave (*S*)-**15** in 80% yield. Finally, intramolecular Buchwald−Hartwig coupling provided (*S*)-**16** quantitatively (Scheme 9).

In order to facilitate construction of the *n*-pentyl side chain required for the natural product, the addition of *n*-propyllithium to the Weinreb amide functionality of (*S*)-**16** was evaluated. It was envisaged that *n*-propyllithium could be prepared in situ upon lithium−halogen exchange of *t*-BuLi and *n*-propyl bromide. The key to the success of this reaction was the mode of addition of the two reagents. When 2.0 equiv of *n*-

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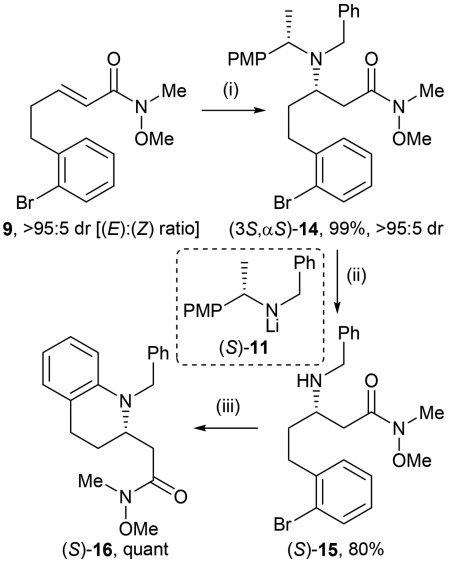
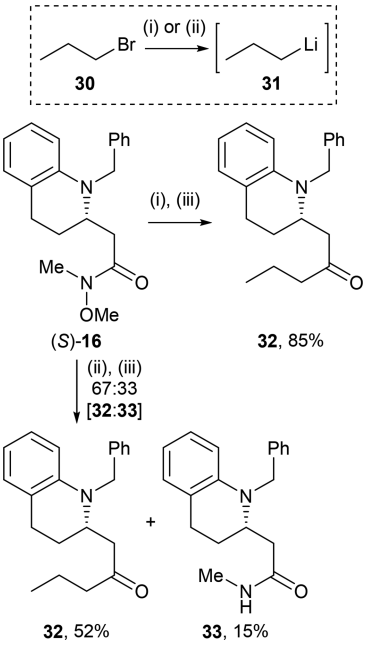
Scheme 9. Preparation of 1,2,3,4-Tetrahydroquinoline Scaffold (*S*)-16[a]



[a]Reagents and conditions: (i) (*S*)-**11**, THF, −78 °C, 2 h; (ii) HCO_2H, Et_3SiH, 90 °C, 16 h; (iii) $Pd(OAc)_2$, XPhos, Cs_2CO_3, PhMe, reflux, 24 h. PMP = *p*-methoxyphenyl.

Scheme 10. Preparation of Ketone 32[a]



[a]Reagents and conditions: (i) add *n*-PrBr to *t*-BuLi, THF, −78 °C, 30 min; (ii) add *t*-BuLi to *n*-PrBr, THF, −78 °C, 30 min; (iii) add **16**, THF, −78 °C, 1.5 h.

propyl bromide were added to a solution of 4.0 equiv of *t*-BuLi in THF at −78 °C followed by addition of (*S*)-**16**, the result was formation of **32** exclusively, and thus **32** was isolated in 85% yield. In contrast, when 4.0 equiv of *t*-BuLi was added to a solution of 2.0 equiv of *n*-propyl bromide in THF at −78 °C (i.e., the inverse addition to the previous experiment), followed by addition of (*S*)-**16**, a 67:33 mixture of ketone **32** and *N*-methyl amide **33** was formed, and **32** and **33** were isolated in 52% and 15% yields, respectively. Such demethoxylation of Weinreb amides upon exposure to strongly basic conditions has been previously documented.[44] Plausibly, addition of 4.0 equiv of *t*-BuLi to 2.0 equiv of *n*-propyl bromide allows deleterious reaction of in situ formed *n*-propyllithium with *t*-BuBr (the other product of the lithium−halogen exchange), depleting the amount of the former reagent. Complete consumption of the *t*-BuLi cannot therefore occur under these conditions, and at the end of the addition, unreacted *t*-BuLi is present in solution; upon introduction of (*S*)-**16**, deprotonation of either the α-proton (forming the enolate) or the methoxy group by *t*-BuLi is followed by liberation of formaldehyde and the anion of *N*-methyl amide **33** (Scheme 10).

Reduction of the carbonyl group of **32** to a methanediyl group could not be achieved in the same manner as that employed in the syntheses of other members of the alkaloid family, as that process was reliant upon formation of a highly stabilized, benzylic cation.[45] Attempted deoxygenation via a Wolff−Kischner reduction under standard (NH_2NH_2, KOH)[46] or modified (NH_2NHTs, $ZnCl_2$, then $NaBH_3CN$)[47,48] conditions or under modified Clemmensen-type conditions (Zn, TMSCl, H_2O, THF)[49] resulted in low mass return and/or a complex mixture of products. A Mozingo reaction (reduction of the corresponding dithiolane by Raney-Ni) was therefore explored. Initial attempts at formation of dithiolane **34** using ethane-1,2-dithiol in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2[50] were accompanied by formation of inseparable (and thus unidentifiable) byproducts, and only an impure sample of **34** could be isolated in ∼35% yield. When the solvent was swapped to AcOH,[51] a marked improvement in reaction efficiency was noted; optimization of the reaction then gave **34** in 99% isolated yield. Reduction of **34** using Raney-Ni in a mixture of EtOH and THF for 1 h effected complete desulfurization to give predominantly **35**, although partial *N*-debenzylation was also evident; when the reaction was left to run for extended time periods, hydrogenation of the aromatic ring also occurred (in addition to *N*-debenzylation). Thus, the crude reaction mixture was subjected to the conditions successfully employed for one-pot hydrogenolytic *N*-debenzylation and reductive *N*-methylation in the synthesis of the other alkaloids, which in this case gave (−)-angustureine (**36**) in 69% yield from **34**, corresponding to 39% yield over nine steps from commercially available 3-(*o*-bromophenyl)-propanoic acid **6** (Scheme 11).

We next validated the ^1H and ^{13}C NMR data for the natural sample of (−)-angustureine,[30] which were generally in accord with those reported, with the exception of the resonance for $C(5')H_3$;[10] in addition to correction of this value, we corrected the reference frequency for the ^{13}C NMR spectrum ($CDCl_3$, δ_C = 77.16)[40,41] in our analysis (Figure 5). The ^{13}C NMR spectroscopic data for **36** were thus found to be in excellent agreement with data for the natural product ($\Delta\delta_C \leq 0.2$). It was not possible to determine (and hence correct if necessary) the reference frequency in the ^1H NMR spectrum, as no residual solvent signal was evident; a systematic error of 0.13 ppm (±0.02 ppm) was noted when the data for **36** were compared with those for the natural product, which may arise from differences in the referencing of the spectra. The ^1H and ^{13}C NMR data acquired for a synthetic sample of (*R*)-angustureine previously prepared in our laboratory,[52] however, matched well with the data for the present sample **36** ($\Delta\delta_H \leq 0.03$ and $\Delta\delta_C \leq 0.2$). Comparison of specific rotation data for angustureine is hampered by the fact that the natural product

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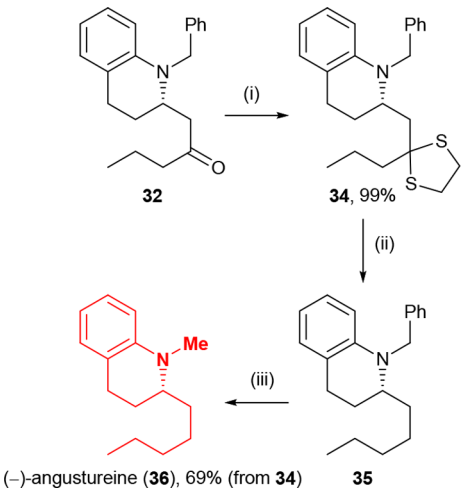
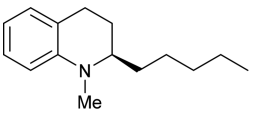
Scheme 11. Preparation of (−)-Angustureine (36)[a]



[a]Reagents and conditions: (i) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, AcOH, rt, 16 h; (ii) Raney-Ni, EtOH, THF, 80 °C, 1 h; (iii) H_2, formalin, Pd/C, MeOH, rt, 24 h.



^{1}H NMR (400 MHz, $CDCl_3$)	
(−)-angustureine	**36**
1.04 (3H, m)	0.89 (3H, t)
1.49 (3H, m)	1.34 (7H, m)
1.73 (1H, m)	1.59 (1H, m)
2.01 (2H, m)	1.88 (2H, m)
2.78 (1H, m)	2.65 (1H, dt)
2.94 (1H, m)	2.80 (1H, m)
3.04 (3H, s)	2.92 (3H, s)
3.35 (1H, d)	3.23 (1H, dq)
6.65 (1H, t)	6.52 (1H, d)
6.71 (3H, m)	6.58 (1H, td)
7.09 (1H, d)	6.97 (1H, d)
7.21 (1H, t)	7.07 (1H, t)

^{13}C NMR (100 MHz, $CDCl_3$)	
(−)-angustureine	**36**
14.1	14.2 (0.1)
22.8	22.8 (0.0)
23.6	23.7 (0.1)
24.5	24.6 (0.1)
25.8	25.9 (0.1)
31.2	31.3 (0.1)
32.1	32.2 (0.1)
38.0	38.1 (0.1)
59.0	59.1 (0.1)
110.4	110.5 (0.1)
115.3	115.3 (0.0)
121.8	122.0 (0.2)
127.1	127.2 (0.1)
128.7	128.8 (0.1)
145.4	145.5 (0.1)

Figure 5. ^{1}H and ^{13}C NMR data of **36** and natural (−)-angustureine. Midpoints of all multiplets are quoted. Values of $\Delta\delta_C$ are given in parentheses. NMR data of natural (−)-angustureine are corrected here (compared to those reported in ref 10) by analysis of the NMR spectra of the natural product. Reference frequencies employed were as follows: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (refs 40, 41) although it was not possible to determine the reference frequency of the ^{1}H NMR spectrum for natural (−)-angustureine.

was reported to have $[\alpha]_D$ −7.16[10] (i.e., the solvent, temperature, and concentration were not reported).[53] However, a synthetic sample of (*S*)-angustureine was determined to have uniform positive sign of specific rotation values determined in a range of common solvents ($[\alpha]_D^{23}$ +7.9 (*c* 1.00, $CHCl_3$); $[\alpha]_D^{26}$ +4.4 (*c* 1.00, CH_2Cl_2); $[\alpha_D^{26}]$ +5.2 (*c* 1.00, MeOH); $[\alpha]_D^{26}$ +5.1 (*c* 1.00, EtOH)),[54] and on this basis the (*R*)-configuration was assigned to the naturally occurring enantiomer of angustureine. More than 20 other synthetic investigations have independently confirmed the positive sign of specific rotation of (*S*)-angustureine (for example, Pandey et al. reported $[\alpha]_D^{25}$ +7.6 (*c* 0.4, $CHCl_3$)[21] and Ma et al. reported $[\alpha]_D^{20}$ +8.0 (*c* 1.00, $CHCl_3$))[55] and the negative sign of specific rotation of (*R*)-angustureine (for example, Aponick et al. reported $[\alpha]_D^{24}$ −7.7 (*c* 1.00, $CHCl_3$)[19] and Fan et al. reported $[\alpha]_D^{20}$ −7.33 (*c* 1.00, $CHCl_3$)).[56] In this study, we obtained $[\alpha]_D^{25}$ −10.6 (*c* 0.2, $CHCl_3$) for **36** {our sample of (*R*)-angustureine previously prepared via an independent synthetic route had $[\alpha]_D^{25}$ −7.0 (*c* 1.0, $CHCl_3$)}.[52] The sign and magnitude of the specific rotation value for **36** are, therefore, entirely as expected (in accord with the wealth of literature data), although it is intriguing that natural angustureine is not homochiral with respect to the remainder of the tetrad isolated from the same plant. Unfortunately we have, to date, been unable to either obtain or isolate an authentic sample of natural angustureine to verify the sign of the specific rotation of the natural product.

In conclusion, asymmetric syntheses of the Hancock alkaloids (−)-cuspareine, (−)-galipinine, (−)-galipeine, and (−)-angustureine have been accomplished in nine steps from commercially available 3-(*o*-bromophenyl)propanoic acid in all cases. Late-stage diversification contributes to the efficiency of this protocol, which delivers the target alkaloids in overall yields of 30%, 28%, 15%, and 39%, respectively. Key steps in the synthesis are the use of the conjugate addition of the requisite enantiomer of lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to 5-(*o*-bromophenyl)-*N*-methoxy-*N*-methylpent-2-enamide to set the configuration at the C-2 stereogenic center of the targets, and the use of a Buchwald–Hartwig coupling reaction to construct the tetrahydroquinoline core. The inherent flexibility of this approach should ensure that this method is applicable to the synthesis of a range of analogues. The ^{1}H and ^{13}C NMR spectroscopic data for the naturally occurring samples of (−)-cuspareine, (−)-galipinine, and (−)-angustureine have been unambiguously corrected, and thus the data contained herein also constitute a reference resource for these popular synthetic targets.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in $CDCl_3$. Reference frequencies employed were as follows: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16.[40,41] ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine. Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and allowed to cool under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[57] Organic layers were dried over Na_2SO_4 or $MgSO_4$. Flash column chromatography was performed on Kieselgel 60 silica.

3-(2′-Bromophenyl)propan-1-ol, 7. $BF_3{\cdot}Et_2O$ (16.0 mL, 130 mmol) was added dropwise to a stirred solution of **6** (14.9 g, 65.0 mmol) and $NaBH_4$ (4.91 g, 130 mmol) in THF (130 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h; then MeOH (65 mL) and 1.0 M aqueous HCl (65 mL) were added sequentially. The resultant mixture was extracted with EtOAc (3 × 150 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave **7** as a colorless oil (13.6 g, 97%):[26,58] ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.37 (1H, t, *J* 5.8, O*H*), 1.88–1.95 (2H, m, C(2)H_2), 2.86 (2H, t, *J* 7.8, C(3)H_2), 3.72 (1H, app q, *J* 5.8, C(1)H_2), 7.04–7.11 (1H, m, C(4′)*H*), 7.23–7.28 (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, 9. DMSO (17.2 mL, 60.4 mmol) was added to a stirred solution

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of $(COCl)_2$ (10.2 mL, 121 mmol) in CH_2Cl_2 (330 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 20 min. A solution of **7** (13.0 g, 60.4 mmol) in CH_2Cl_2 (30 mL) was added, and the resultant solution was stirred at −78 °C for 40 min. Et_3N (50.5 mL, 363 mmol) was added, the resultant solution was allowed to warm to rt over 30 min, then **8** (33.0 g, 90.7 mmol) was added, and the resultant solution was stirred at rt for 16 h. Saturated aqueous K_2CO_3 (300 mL) was added, and the resultant mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with brine (600 mL), then dried and concentrated in vacuo to give (*E*)-**9** in 92:8 dr [(*E*):(*Z*) ratio]. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (*E*)-**9** as a pale yellow oil (15.7 g, 87%, >95:5 dr [(*E*):(*Z*) ratio]):[26] ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.53−2.59 (2H, m, C(4)H_2), 2.91 (2H, t, *J* 7.5, C(5)H_2), 3.23 (3H, s, N*Me*), 3.65 (3H, s, O*Me*), 6.41 (1H, d, *J* 15.4, C(2)*H*), 6.98−7.08 (2H, m, C(3)*H*, C(4′)*H*), 7.19−7.25 (2H, m, C(5′)*H*, C(6′)*H*), 7.52−7.54 (1H, m, C(3′)*H*).

(3*R*,α*R*)- and (3*S*,α*R*)-3-[*N*-Methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-5-(2′-bromophenyl)-*N*-methoxy-*N*-methylpentanamide, 12 and 13. BuLi (2.3 M in hexanes, 3.9 mL, 9.1 mmol) was added dropwise to a stirred solution of (*R*)-*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (1.55 g, 9.39 mmol, >98% ee) in THF (20 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **9** (1.75 g, 5.87 mmol, >95:5 dr [(*E*):(*Z*) ratio]) in THF (5 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 2 h. Saturated aqueous NH_4Cl (5 mL) was added, and the reaction mixture was allowed to warm to rt, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aqueous citric acid (20 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo to give **12** and **13** in 75:25 dr. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 66:33:1) gave **12** and **13** as a colorless oil (2.53 g, 93%, 75:25 dr): IR ν_{max} 2968, 2934, 2864, 2835, 1658; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.7, C(α)*Me*), 1.46−1.57 (1H, m, C(4)H_A), 1.59−1.83 (1H, m, C(4)H_B), 2.09 (0.75H, s, C(3)N*Me*, **13**), 2.24 (2.25H, s, C(3)N*Me*, **12**), 2.30−2.70 (3H, m, C(2)H_2, C(5)H_A), 2.88−3.00 (1H, m, C(5)H_B), 3.15 (2.25H, s, C(1)N*Me*, **12**), 3.18 (0.75H, s, C(1)N*Me*, **13**), 3.31−3.41 (1H, m, C(3)*H*), 3.55−3.66 (4H, m, C(α)*H*, NO*Me*), 3.78 (2.25H, s, ArO*Me*, **12**), 3.79 (0.75H, s, ArO*Me*, **13**), 6.81−6.85 (2H, m, C(3″)*H*, C(5″)*H*), 6.98−7.04 (1H, m, C(4′)*H*), 7.14−7.26 (4H, m, C(5′)*H*, C(6′)*H*, C(2″)*H*, C(6″)*H*), 7.48−7.51 (1H, m, C(3′)*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 21.8, 22.1 (C(α)*Me*), 32.0, 32.2, 32.2, 32.4, 32.6 (*C*(2), *C*(4), C(1)N*Me*, C(3)N*Me*),[59] 33.9, 33.9 (*C*(5)), 55.0, 55.3, 55.4, 55.7, 61.3, 61.6 (*C*(3), *C*(α), NO*Me*, ArO*Me*), 113.6, 113.7 (*C*(3″), *C*(5″)), 124.5 (*C*(2′)), 127.4, 127.5, 127.5 (*C*(3′), *C*(4′)), 128.4, 128.5 (*C*(2″), *C*(6″)), 130.4, 130.6 (*C*(6′)), 132.7, 132.8 (*C*(5′)), 138.3, 138.7 (*C*(1″)), 142.3, 142.3 (*C*(1′)), 158.4, 158.5 (*C*(4″)), 173.8, 173.9 (*C*(1)); *m/z* (ESI$^+$) 465 ([M(^{81}Br) + H]$^+$, 100%), 463 ([M(^{79}Br) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}{}^{81}BrN_2O_3^+$ ([M(^{81}Br) + H]$^+$) requires 465.1570; found 465.1568; $C_{23}H_{32}{}^{79}BrN_2O_3^+$ ([M(^{79}Br) + H]$^+$) requires 463.1591; found 463.1588.

(3*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-5-(2′-bromophenyl)-*N*-methoxy-*N*-methylpentanamide, (3*R*,α*R*)-14. BuLi (2.3 M in hexanes, 0.45 mL, 1.0 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (259 mg, 1.07 mmol, >98% ee) in THF (2 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **9** (200 mg, 0.671 mmol, >95:5 dr [(*E*):(*Z*) ratio]) in THF (1 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 2 h. Saturated aqueous NH_4Cl (1 mL) was added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aqueous citric acid (10 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in vacuo to give (3*R*,α*R*)-**14** in >95:5 dr. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (3*R*,α*R*)-**14** as a pale yellow oil (273 mg, 80%, >95:5 dr):[26] $[\alpha]_D^{25}$ +21.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.0, C(α)*Me*), 1.57−1.65 (1H, m, C(4)H_A), 1.73−1.83 (1H, m, C(4)H_B), 2.00 (1H, app d, *J* 14.0, C(2)H_A), 2.23−2.29 (1H, m, C(2)H_B), 2.71 (1H, ddd, *J* 13.8, 11.8, 5.0, C(5)H_A), 3.07 (3H, s, N*Me*), 3.19 (1H, ddd, *J* 13.8, 11.6, 4.9, C(5)H_B), 3.43 (3H, s, NO*Me*), 3.58−3.64 (1H, m, C(3)*H*) overlapping 3.60 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.79 (3H, s, ArO*Me*), 3.87 (1H, q, *J* 7.0, C(α)*H*), 3.93 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 6.85 (2H, d, *J* 8.6, C(3″)*H*, C(5″)*H*), 7.00−7.04 (1H, m, C(4′)*H*), 7.17−7.28 (5H, m, C(5′)*H*, C(6′)*H*, C(2″)*H*, C(6″)*H*, *p-Ph*), 7.36 (2H, t, *J* 7.5, *m-Ph*), 7.50 (1H, d, *J* 7.8, C(3′)*H*), 7.54 (2H, d, *J* 7.5, *o-Ph*).

(3*S*,α*S*)-3-[*N*-Benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-5-(2′-bromophenyl)-*N*-methoxy-*N*-methylpentanamide, (3*S*,α*S*)-14. BuLi (2.3 M in hexanes, 31.6 mL, 72.8 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (18.1 g, 75.1 mmol, >98% ee) in THF (150 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **9** (14.0 g, 46.9 mmol, >95:5 dr [(*E*):(*Z*) ratio]) in THF (80 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 2 h. Saturated aqueous NH_4Cl (200 mL) was added, and the reaction mixture was allowed to warm to rt, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (200 mL) and 10% aqueous citric acid (200 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated in vacuo to give (3*S*,α*S*)-**14** in >95:5 dr. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (3*S*,α*S*)-**14** as a pale yellow oil (24.7 g, 99%, >95:5 dr); $[\alpha]_D^{25}$ −23.5 (*c* 1.0 in $CHCl_3$).

(*R*)-3-(*N*-Benzylamino)-5-(2′-bromophenyl)-*N*-methoxy-*N*-methylpentanamide, (*R*)-15. Et_3SiH (25 μL, 0.16 mmol) was added to a stirred solution of (3*R*,α*R*)-**14** (87 mg, 1.10 mmol, >95:5 dr) in HCO_2H (0.6 mL), and the resultant solution was heated at 90 °C for 16 h. The resultant mixture was allowed to cool to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the organic extract was washed with brine (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (*R*)-**15** as a colorless oil (35 mg, 81%):[26] $[\alpha]_D^{25}$ −7.1 (*c* 1.0 in $CHCl_3$); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.76−1.90 (2H, m, C(4)H_2), 2.67 (2H, d, *J* 5.8, C(2)H_2), 2.77−2.88 (2H, m, C(5)H_2), 3.16−3.22 (1H, m, C(3)*H*) overlapping 3.18 (3H, s, N*Me*), 3.67 (3H, s, O*Me*), 3.81 (1H, d, *J* 12.9, NC$H_A$$H_B$Ph), 3.86 (1H, d, *J* 12.9, NC$H_A$$H_B$Ph), 7.01−7.08 (1H, m, C(4′)*H*), 7.21−7.37 (7H, m, C(5′)*H*, C(6′)*H*, *Ph*), 7.52 (1H, d, *J* 7.8, C(3′)*H*).

(*S*)-3-(*N*-Benzylamino)-5-(2′-bromophenyl)-*N*-methoxy-*N*-methylpentanamide, (*S*)-15. Et_3SiH (10.2 mL, 63.9 mmol) was added to a stirred solution of (3*S*,α*S*)-**14** (23.0 g, 42.6 mmol, >95:5 dr) in HCO_2H (120 mL), and the resultant solution was heated at 90 °C for 16 h. The resultant mixture was allowed to cool to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (500 mL) and saturated aqueous $NaHCO_3$ (500 mL), and the organic extract was washed with brine (500 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (*S*)-**15** as a colorless oil (13.6 g, 80%): $[\alpha]_D^{25}$ +7.5 (*c* 1.0 in $CHCl_3$).

(*R*)-2-[*N*(1′)-Benzyl-1′,2′,3′,4′-tetrahydroquinolin-2′-yl]-*N*-methoxy-*N*-methylacetamide, (*R*)-16. $Pd(OAc)_2$ (26 mg, 0.12 mmol) was added to a stirred solution of (*R*)-**15** (943 mg, 2.33 mmol), XPhos (163 mg, 0.349 mmol), and Cs_2CO_3 (1.51 g, 4.65 mmol) in PhMe (30 mL), and the resultant mixture was heated at reflux for 24 h. The resultant mixture was allowed to cool to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL), and the organic extract was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (*R*)-**16** as a pale yellow solid (751 mg, quant):[26] $[\alpha]_D^{25}$

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−11.0 (*c* 1.0 in $CHCl_3$); ^1H NMR δ_H (400 MHz, $CDCl_3$) 1.96−2.12 (2H, m, C(3′)H_2), 2.71 (2H, d, *J* 6.5, C(2)H_2), 2.78 (1H, dt, *J* 16.5, 3.7, C(4′)H_A), 2.96 (1H, ddd, *J* 16.5, 12.8, 5.7, C(4′)H_B), 3.16 (3H, s, N*Me*), 3.57 (3H, s, O*Me*), 4.03−4.08 (1H, m, C(2′)*H*), 4.52 (1H, d, *J* 17.2, NC$H_A$$H_B$Ph), 4.58 (1H, d, *J* 17.2, NCH$_A$$H_B$Ph), 6.44 (1H, d, *J* 7.7, C(8′)*H*), 6.60 (1H, t, *J* 7.7, C(6′)*H*), 6.96 (1H, t, *J* 7.7, C(7′)*H*), 7.03 (1H, d, *J* 7.7, C(5′)*H*), 7.19−7.31 (5H, m, *Ph*).

(*S*)-2-[*N*(1′)-Benzyl-1′,2′,3′,4′-tetrahydroquinolin-2′-yl]-*N*-methoxy-*N*-methylacetamide, (*S*)-16. $Pd(OAc)_2$ (319 mg, 1.42 mmol) was added to a stirred solution of (*S*)-**15** (11.5 g, 28.4 mmol), XPhos (2.03 g, 4.26 mmol), and Cs_2CO_3 (18.5 g, 56.8 mmol) in PhMe (350 mL), and the resultant mixture was heated at reflux for 24 h. The resultant mixture was allowed to cool to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL), and the organic extract was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 50:50:1) gave (*S*)-**16** as a pale yellow solid (9.87 g, quant): mp 62−64 °C; $[\alpha]_D^{25}$ +10.2 (*c* 1.0 in $CHCl_3$).

(*R*)-*N*-Benzyl-2-[2′-oxo-2′-(3″,4″-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline, 19. *n*-BuLi (2.3 M in hexanes, 0.47 mL, 1.1 mmol) was added dropwise to a stirred solution of **17** (234 mg, 1.08 mmol) in THF (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of (*R*)-**16** (50 mg, 0.15 mmol) in THF (0.5 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 1.5 h. Saturated aqueous NH_4Cl (0.5 mL) was added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL), and the organic extract was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 80:24:1) gave **19** as an orange oil (49 mg, 79%): $[\alpha]_D^{25}$ −12.7 (*c* 1.0 in $CHCl_3$); IR ν_{max} 3028, 2962, 2933, 2900, 2838, 1669; ^1H NMR δ_H (400 MHz, $CDCl_3$) 1.95−1.99 (1H, m, C(3)H_A), 2.09 (1H, app tt, *J* 13.0, 4.8, C(3)H_B), 2.76−2.80 (1H, m, C(4)H_A), 2.96 (1H, ddd, *J* 16.6, 13.0, 5.7, C(4)H_B), 3.13 (1H, dd, *J* 15.9, 8.2, C(1′)H_A), 3.20 (1H, dd, *J* 15.9, 5.1, C(1′)H_B), 3.88 (3H, s, O*Me*), 3.93 (3H, s, O*Me*), 4.16−4.22 (1H, m, C(2)*H*), 4.47 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.54 (1H, d, *J* 17.0, NCH$_A$$H_B$Ph), 6.45 (1H, d, *J* 7.8, C(8)*H*), 6.62 (1H, app td, *J* 7.8, 0.9, C(6)*H*), 6.83 (1H, d, *J* 8.3, C(5″)*H*), 6.97 (1H, t, *J* 7.8, C(7)*H*), 7.04 (1H, d, *J* 7.8, C(5)*H*), 7.19−7.32 (5H, m, *Ph*), 7.45−7.49 (2H, m, C(2″)*H*, C(6″)*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(4)), 25.6 (*C*(3)), 40.8 (*C*(1′)), 54.3 (NCH$_2$Ph), 55.1 (*C*(2)), 56.1 (O*Me*), 56.2 (O*Me*), 110.1, 110.1 (*C*(2″), *C*(5″)), 112.1 (*C*(8)), 116.2 (*C*(6)), 121.3 (*C*(4a)), 123.0 (*C*(6″)), 126.5 (*o*-*Ph*), 126.9 (*p*-*Ph*), 127.4 (*C*(7)), 128.7 (*m*-*Ph*), 129.3 (*C*(5)), 130.5 (*C*(1″)), 139.0 (*i*-*Ph*), 144.2 (*C*(8a)), 149.2 (*C*(3″)), 153.5 (*C*(4″)), 197.8 (*C*(2′)); *m*/*z* (ESI$^+$) 402 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{28}NO_3^+$ ([M + H]$^+$) requires 402.2064; found 402.2061.

(*R*)-*N*-Benzyl-2-(2′-oxohexanyl)-1,2,3,4-tetrahydroquinoline, 20. A solution of (*R*)-**16** (133 mg, 1.5 mmol) in THF (1.5 mL) at −78 °C was added to a stirred solution of *n*-BuLi (2.3 M in hexanes, 0.36 mL, 0.82 mmol) in THF (2.5 mL), and the resultant solution was stirred at −78 °C for 16 h. Saturated aqueous NH_4Cl (2 mL) was added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between Et_2O (5 mL) and H_2O (5 mL), and the organic extract was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 5:1) gave **20** as a yellow oil (93 mg, 71%): $[\alpha]_D^{25}$ −0.8 (*c* 1.0, $CHCl_3$); IR ν_{max} 3063, 3028, 2956, 2931, 2870, 1709, 1602, 1496, 744; ^1H NMR δ_H (400 MHz, $CDCl_3$) 0.90−0.94 (3H, m, C(6′)H_3), 1.26−1.36 (2H, m, C(5′)H_2), 1.48−1.59 (2H, m, C(4′)H_2), 1.88−1.93 (1H, m, C(3)H_A), 2.04−2.11 (1H, m, C(3)H_B), 2.36 (2H, app t, *J*, 7.9, C(3′)H_2), 2.66 (1H, dd, *J* 16.5, 8.0, C(1′)H_A), 2.75 (1H, dd, *J* 16.5, 4.9, C(1′)H_B), 2.78−2.94 (2H, m, C(4)H_2), 4.04−4.08 (1H, m, C(2)*H*), 4.48 (1H, d, *J* 16.9, NC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 16.9, NCH$_A$$H_B$Ph), 6.48 (1H, d, *J* 8.3, C(8)*H*), 6.64 (1H, app td, *J* 7.3, 1.2, C(6)*H*), 6.99 (1H, app t, *J* 7.7, C(7)*H*), 7.05 (1H, d, *J* 7.3, C(5)*H*), 7.23−7.34 (5H, m, *Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(6′)), 22.4 (*C*(5′)), 23.7 (*C*(4)), 25.8 (*C*(3)), 25.9 (C(4′)), 43.8 (*C*(3′)), 45.7 (*C*(1′)), 53.9 (*C*(2)), 54.3 (NCH$_2$Ph), 112.2 (*C*(8)), 116.2 (*C*(6)), 121.3 (*C*(4a)), 126.6 (*o*,*m*-*Ph*), 126.9 (*p*-*Ph*), 127.3 (*C*(7)), 128.7 (*o*,*m*-*Ph*), 129.2 (*C*(5)), 139.1 (*i*-*Ph*), 144.3 (*C*(8a)), 210.0 (*C*(2′)); *m*/*z* (ESI$^+$) 322 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO^+$ ([M + H]$^+$) requires 322.2165; found 322.2157.

(*R*)-*N*-Benzyl-2-[2′-oxo-2′-(3″,4″-methylenedioxyphenyl)-ethyl]-1,2,3,4-tetrahydroquinoline, 23. *n*-BuLi (2.3 M in hexanes, 2.4 mL, 5.4 mmol) was added dropwise to a stirred solution of **21** (1.08 g, 5.39 mmol) in THF (15 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of (*R*)-**16** (250 mg, 0.771 mmol) in THF (2 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 1.5 h. Saturated aqueous NH_4Cl (3 mL) was added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the organic extract was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 75:25:1) gave **23** as a yellow oil (244 mg, 82%): $[\alpha]_D^{25}$ −6.4 (*c* 1.0 in $CHCl_3$); IR ν_{max} 3036, 3027, 2927, 1671; ^1H NMR δ_H (400 MHz, $CDCl_3$) 1.99 (1H, app ddt, *J* 13.1, 5.7, 2.8, C(3)H_A), 2.10 (1H, app tt, *J* 13.1, 5.0, C(3)H_B), 2.82 (1H, ddd, *J* 16.8, 5.0, 2.8, C(4)H_A), 2.96 (1H, ddd, *J* 16.8, 13.1, 5.7, C(4)H_B), 3.11 (1H, dd, *J* 16.0, 8.0, C(1′)H_A), 3.16 (1H, dd, *J* 16.0, 5.3, C(1′)H_B), 4.17−4.22 (1H, m, C(2)*H*), 4.50 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.58 (1H, d, *J* 17.0, NCH$_A$$H_B$Ph), 6.04 (2H, s, OC$H_2$O), 6.49 (1H, d, *J* 8.1, C(8)*H*), 6.64 (1H, app td, *J* 7.3, 0.9, C(6)*H*), 6.82 (1H, d, *J* 8.2, C(5″)*H*), 6.97−7.02 (1H, m, C(7)*H*), 7.06 (1H, d, *J* 7.3, C(5)*H*), 7.21−7.33 (5H, m, *Ph*), 7.40 (1H, d, *J* 1.7, C(2″)*H*), 7.47 (1H, dd, *J* 8.2, 1.7, C(6″)*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(4)), 25.5 (*C*(3)), 41.0 (*C*(1′)), 54.2 (NCH$_2$Ph), 54.9 (*C*(2)), 102.0 (OCH$_2$O), 107.9, 108.0 (*C*(2″), *C*(5″)), 112.1 (*C*(8)), 116.2 (*C*(6)), 121.3 (*C*(4a)), 124.7 (*C*(6″)), 126.6 (*o*-*Ph*), 126.9 (*p*-*Ph*), 127.4 (*C*(7)), 128.7 (*m*-*Ph*), 129.3 (*C*(5)), 132.2 (*C*(1″)), 139.0 (*i*-*Ph*), 144.2 (*C*(8a)), 148.4 (*C*(3″)), 152.0 (*C*(4″)), 197.2 (*C*(2′)); *m*/*z* (ESI$^+$) 386 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{24}NO_3^+$ ([M + H]$^+$) requires 386.1751; found 386.1752.

(*S*)-*N*-Benzyl-2-[2′-(3″,4″-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline, 25. *Step 1*: $LiAlH_4$ (2.4 M in THF, 0.42 mL, 1.0 mmol) was added dropwise to a stirred solution of **19** (200 mg, 0.498 mmol) in THF (3.5 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h, then allowed to cool to rt. A 2 M aqueous NaOH (0.5 mL) solution was then added, and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt, filtered through Celite (eluent EtOAc), and then concentrated in vacuo to give **24**.

Step 2: Et_3SiH (0.80 mL, 4.89 mmol) was added to a stirred solution of the residue of **24** from the previous step in TFA (2.5 mL), and the resultant solution was stirred at 70 °C for 16 h. The resultant mixture was concentrated in vacuo, and the residue was then partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic extract was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 75:25:1) gave **25** as a yellow oil (148 mg, 77%): $[\alpha]_D^{25}$ +1.8 (*c* 1.0 in $CHCl_3$); IR ν_{max} 3024, 3000, 2934, 2835, 1601, 1515, 1498; ^1H NMR δ_H (400 MHz, $CDCl_3$) 1.80−1.97 (2H, m, C(1′)H_2), 1.97−2.09 (2H, m, C(3)H_2), 2.50 (1H, ddd, *J* 14.0, 9.8, 6.6, C(2′)H_A), 2.66 (1H, ddd, *J* 14.0, 10.0, 5.6, C(2′)H_B), 2.76 (1H, app dt, *J* 16.2, 3.9, C(4)H_A), 2.94 (1H, ddd, *J* 16.2, 12.0, 5.9, C(4)H_B), 3.39−3.44 (1H, m, C(2)*H*), 3.84 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 4.43 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 17.0, NCH$_A$$H_B$Ph), 6.43 (1H, d, *J* 7.6, C(8)*H*), 6.59 (1H, app t, *J* 7.6, C(6)*H*), 6.65 (1H, d, *J* 2.0, C(2″)*H*), 6.68 (1H, dd, *J* 8.1, 2.0, C(6″)*H*), 6.77 (1H, d, *J* 8.1, C(5″)*H*), 6.96 (1H, app t, *J* 7.6, C(7)*H*), 7.03 (1H, d, *J* 7.6, C(5)*H*), 7.20−7.32 (5H, m, *Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.8 (*C*(4)), 24.4 (*C*(3)), 32.0 (*C*(2′)), 33.9 (*C*(1′)), 54.3 (NCH$_2$Ph), 56.0 (O*Me*), 56.1 (O*Me*), 57.5 (*C*(2)), 111.3 (*C*(5″)), 111.6 (*C*(2″)), 111.9 (*C*(8)), 115.7 (*C*(6)), 120.2 (*C*(6″)), 121.7 (*C*(4a)), 126.6 (*o*,*m*-*Ph*), 126.8 (*p*-*Ph*), 127.2 (*C*(7)), 128.7 (*o*,*m*-*Ph*), 129.1 (*C*(5)), 134.6 (*C*(1″)), 139.4 (*i*-*Ph*), 144.6 (*C*(8a)),

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147.3, 149.0 (*C*(3″), *C*(4″)); *m/z* (ESI$^+$) 388 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}NO_2^+$ ([M + H]$^+$) requires 388.2271; found 388.2276.

(*S*)-*N*-Methyl-2-[2′-(3″,4″-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline [(−)-cuspareine], 26. Pd/C (26 mg, 40% w/w of **25**) was added to a stirred solution of **25** (64 mg, 0.17 mmol) and formalin (37% aqueous HCHO, 1.2 mL, 1.7 mmol) in degassed MeOH (3 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite (eluent MeOH), then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 75:25:1) gave **26** as a colorless oil (46 mg, 90%): $[\alpha]_D^{25}$ −25.0 (*c* 0.3 in $CHCl_3$); IR ν_{max} 2981, 2971, 2934, 1602, 1514, 1500; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.74 (1H, dddd, *J* 13.9, 10.1, 8.9, 5.4, C(1′)H_A), 1.88−2.01 (3H, m, C(3)H_2, C(1′)H_B), 2.54 (1H, ddd, *J* 13.9, 10.2, 6.4, C(2′)H_A), 2.65−2.73 (2H, m, C(4)H_A, C(2′)H_B), 2.82−2.90 (1H, m, C(4)H_B), 2.92 (3H, s, N*Me*), 3.27−3.32 (1H, m, C(2)*H*), 3.86 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 6.54 (1H, d, *J* 8.2, C(8)*H*), 6.60 (1H, app td, *J* 7.3, 1.0, C(6)*H*), 6.71−6.75 (2H, m, C(2″)*H*, C(6″)*H*), 6.80 (1H, d, *J* 8.0, C(5″)*H*), 6.99 (1H, d, *J* 7.3, C(5)*H*), 7.07−7.11 (1H, m, C(7)*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 32.1 (*C*(2′)), 33.2 (*C*(1′)), 38.3 (N*Me*), 56.0 (O*Me*), 56.1 (O*Me*), 58.6 (*C*(2)), 110.7 (*C*(8)), 111.4 (*C*(5″)), 111.7 (*C*(2″)), 115.5 (*C*(6)), 120.2 (*C*(6″)), 121.9 (*C*(4a)), 127.3 (*C*(7)), 128.8 (*C*(5)), 134.8 (*C*(1″)), 145.4 (*C*(8a)), 147.3, 149.0 (*C*(3″), *C*(4″)); *m/z* (ESI$^+$) 312 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_2^+$ ([M + H]$^+$) requires 312.1958; found 312.1958.

(*S*)-*N*-Benzyl-2-[2′-(3″,4″-methylenedioxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline, 28. *Step 1:* $LiAlH_4$ (2.4 M in THF, 0.27 mL, 0.53 mmol) was added dropwise to a stirred solution of **23** (103 mg, 0.267 mmol) in THF (2.0 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h, then allowed to cool to rt. A 2.0 M aqueous NaOH (0.3 mL) solution was then added, and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt, filtered through Celite (eluent EtOAc), and then concentrated in vacuo to give **27**.

Step 2: Et_3SiH (0.43 mL, 2.7 mmol) was added to a stirred solution of the residue of **27** from the previous step in TFA (1.3 mL), and the resultant solution was stirred at 70 °C for 16 h. The resultant mixture was concentrated in vacuo, and the residue was then partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic extract was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 100:5:1) gave **28** as a colorless oil (76 mg, 77%): $[\alpha]_D^{25}$ +4.0 (c 1.0 in $CHCl_3$); IR ν_{max} 3027, 2936, 1601, 1500, 1490; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.77−1.97 (2H, m, C(1′)H_2), 1.97−2.07 (2H, m, C(3)H_2), 2.47 (1H, ddd, *J* 14.0, 9.7, 6.8, C(2′)H_A), 2.62 (1H, ddd, *J* 14.0, 9.7, 5.4, C(2′)H_B), 2.76 (1H, dt, *J* 16.4, 4.0, C(4)H_A), 2.93 (1H, ddd, *J* 16.4, 11.5, 6.5, C(4)H_B), 3.36−3.41 (1H, m, C(2)*H*), 4.41 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 5.91 (2H, s, O$CH_2$O), 6.43 (1H, d, *J* 8.0, C(8)*H*), 6.57−6.60 (2H, m, C(6)*H*, C(6″)*H*), 6.62 (1H, d, *J* 1.6, C(2″)*H*), 6.70 (1H, d, *J* 7.8, C(5″)*H*), 6.95 (1H, app t, *J* 8.0, C(7)*H*), 7.02 (1H, d, *J* 7.3, C(5)*H*), 7.20−7.32 (5H, m, *Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.4 (*C*(3)), 32.1 (*C*(2′)), 33.9 (*C*(1′)), 54.3 (NCH_2Ph), 57.3 (*C*(2)), 100.9 (OCH_2O), 108.3 (*C*(5″)), 108.8 (*C*(2″)), 112.0 (*C*(8)), 115.8 (*C*(6)), 121.1 (*C*(6″)), 121.8 (*C*(4a)), 126.7 (*o*,*m*-*Ph*), 126.9 (*p*-*Ph*), 127.2 (*C*(7)), 128.7 (*o*,*m*-*Ph*), 129.1 (*C*(5)), 135.8 (*i*-*Ph*), 139.4 (*C*(1″)), 144.7 (*C*(8a)), 145.8, 147.7 (*C*(3″), *C*(4″)); *m/z* (ESI$^+$) 372 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{26}NO_2^+$ ([M + H]$^+$) requires 372.1958; found 372.1961.

(*S*)-*N*-Methyl-2-[2′-(3″,4″-methylenedioxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline [(−)-galipinine], 29. Pd/C (30 mg, 40% w/w of **28**) was added to a stirred solution of **28** (73 mg, 0.19 mmol) and formalin (37% aqueous HCHO, 0.15 mL, 2.0 mmol) in degassed MeOH (4 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite (eluent MeOH), then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O/NH_4OH, 90:9:1) gave **29** as a colorless oil (47 mg, 81%): $[\alpha]_D^{25}$ −23.7 (*c* 1.0 in $CHCl_3$); IR ν_{max} 2934, 2891, 1602, 1500, 1489; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.65−1.75 (1H, m, C(1′)H_A), 1.84−1.99 (3H, m, C(3)H_2, C(1′)H_B), 2.50 (1H, ddd, *J* 13.9, 9.9, 6.6, C(2′)H_A), 2.60−2.72 (2H, m, C(4)H_A, C(2′)H_B), 2.79−2.88 (1H, m, C(4)H_B), 2.91 (3H, s, N*Me*), 3.24−3.30 (1H, m, C(2)*H*), 5.92 (2H, s, OCH_2O), 6.52 (1H, d, *J* 8.2, C(8)*H*), 6.59 (1H, app td, *J* 7.4, 1.0, C(6)*H*), 6.63 (1H, dd, *J* 7.9, 1.6, C(6″)*H*), 6.69 (1H, d, *J* 1.6, C(2″)*H*), 6.73 (1H, d, *J* 7.9, C(5″)*H*), 6.98 (1H, d, *J* 7.4, C(5)*H*), 7.08 (1H, app t, *J* 8.1, C(7)*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 32.2 (*C*(2′)), 33.3 (*C*(1′)), 38.2 (N*Me*), 58.4 (*C*(2)), 100.9 (OCH_2O), 108.3 (*C*(5″)), 108.9 (*C*(2″)), 110.8 (*C*(8)), 115.6 (*C*(6)), 121.1 (*C*(6″)), 121.9 (*C*(4a)), 127.3 (*C*(7)), 128.8 (*C*(5)), 136.0 (*C*(1″)), 145.5 (*C*(8a)), 145.8, 147.8 (*C*(3″), *C*(4″)); *m/z* (ESI$^+$) 296 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO_2^+$ ([M + H]$^+$) requires 296.1645; found 296.1644.

(*S*)-*N*-Benzyl-2-(2′-oxopentyl)-1,2,3,4-tetrahydroquinoline, 32. *Method A. Addition of t-BuLi to n-Propyl Bromide* ***30****. t*-BuLi (1.7 M in pentane, 4.1 mL, 7.0 mmol) was added dropwise to a stirred solution of *n*-propyl bromide **30** (0.32 mL, 3.48 mmol) in THF (12 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of (*S*)-**16** (565 mg, 1.74 mmol) in THF (6 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 1.5 h. Saturated aqueous NH_4Cl (10 mL) was added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between Et_2O (20 mL) and H_2O (20 mL), and the organic extract was dried and concentrated in vacuo to give a 67:33 mixture of **32** and **33**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 5:1) gave **32** as a colorless oil (276 mg, 52%): $[\alpha]_D^{25}$ +0.8 (*c* 1.0, $CHCl_3$); IR ν_{max} 3063, 3028, 2960, 2932, 2873, 1708, 1602, 1574, 1496, 1452, 1343, 744l; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5, C(5′)H_3), 1.54−1.67 (2H, m, C(4′)H_2), 1.88−1.93 (1H, m, C(3)H_A), 2.04−2.13 (1H, m, C(3)H_B), 2.35 (2H, t, *J*, 7.2, C(3′)H_2), 2.63−2.76 (2H, m, C(1′)H_2), 2.77−2.95 (2H, m, C(4)H_2), 4.06−4.08 (1H, m, C(2)*H*), 4.49 (1H, d, *J* 17.1, NC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 17.1, NC$H_A$$H_B$Ph), 6.47 (1H, d, *J* 8.1, C(8)*H*), 6.64 (1H, app t, *J* 7.3, C(6)*H*), 6.69 (1H, app t, *J* 7.7, C(7)*H*), 7.05 (1H, d, *J* 7.3, C(5)*H*), 7.23−7.35 (5H, m, *Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 13.8 (*C*(5′)), 17.2 (*C*(4′)), 23.7 (*C*(4)), 25.7 (*C*(3)), 45.7 (*C*(1′)), 46.0 (*C*(3′)), 53.9 (*C*(2)), 54.2 (NCH_2Ph), 112.1 (*C*(8)), 116.2 (*C*(6)), 121.2 (*C*(4a)), 126.5, 126.9 (*o*,*m*,*p*-*Ph*), 127.3 (*C*(7)), 128.7 (*C*(5)), 129.2 (*o*,*m*-*Ph*), 139.0 (*i*-*Ph*), 144.2 (*C*(8a)), 210.0 (*C*(2′)); *m/z* (ESI$^+$) 308 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO^+$ ([M + H]$^+$) requires 308.2009; found 308.2009. Further elution (eluent Et_2O/CH_2Cl_2, 10:1) gave **33** as a colorless oil (77 mg, 15%): $[\alpha]_D^{25}$ +12.2 (*c* 1.0, $CHCl_3$); IR ν_{max} 3402, 3293, 3064, 3028, 2934, 2863, 1640, 1602, 1572, 1496, 1451, 745; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.90−1.97 (1H, m, C(3′)H_A), 2.01−2.10 (2H, m, C(3′)H_B), 2.26 (1H, dd, *J* 14.0, 7.3, C(2)H_A), 2.47 (1H, dd, *J* 14.0, 6.4, C(2)H_B), 2.74 (3H, d, *J* 4.5, N*Me*), 2.75−2.92 (2H, m, C(4′)H_2), 3.99−4.04 (1H, m, C(2′)*H*), 4.50 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.55 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 5.81 (1H, br d, *J* 4.5, N*H*), 6.47 (1H, d, *J* 8.1, C(8′)*H*), 6.62 (1H, app td, *J* 7.3, 1.0, C(6′)*H*), 6.96−6.99 (1H, m, C(7′)*H*), 7.02 (1H, d, *J* 7.3, C(5′)*H*), 7.21−7.32 (5H, m, *Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4′)), 25.5 (*C*(3′)), 26.4 (N*Me*), 40.0 (*C*(2)), 54.4 (NCH_2Ph), 55.4 (*C*(2′)), 112.5 (*C*(8′)), 116.3 (*C*(6′)), 121.5 (*C*(4′a)), 126.5 (*o*-*Ph*), 126.8 (*p*-*Ph*), 127.3 (*C*(7′)), 128.6 (*m*-*Ph*), 129.2 (*C*(5′)), 138.9 (*i*-*Ph*), 144.0 (*C*(8′a)), 171.8 (*C*(1)); *m/z* (ESI$^+$) 295 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{23}N_2O^+$ ([M + H]$^+$) requires 295.1805; found 295.1799.

Method B. Addition of n-Propyl Bromide ***30*** *to t-BuLi.* *n*-Propyl bromide **30** (0.56 mL, 6.17 mmol) was added dropwise to a stirred solution of *t*-BuLi (1.7 M in pentane, 7.3 mL, 12.4 mmol) in THF (20 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of (*S*)-**16** (1.00 g, 3.08 mmol) in THF (30 mL) at −78 °C was then added, and the resultant mixture was stirred at −78 °C for 1.5 h. Saturated aqueous NH_4Cl (30 mL) was added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL), and the organic extract was dried and concentrated in

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vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 5:1) gave **32** as a colorless oil (809 mg, 85%).

(*S*)-*N*-Benzyl-2-(2′-oxopentyl)-1,2,3,4-tetrahydroquinoline, 1,2-Ethylenedithioacetal 34. A solution of **32** (200 mg, 0.651 mmol) in AcOH (1.4 mL) was stirred at rt for 30 min. $BF_3{\cdot}OEt_2$ (0.40 mL, 3.25 mmol) and ethane-1,2-dithiol (0.16 mL, 2.0 mmol) were then added sequentially, and the resultant solution was stirred at rt for 16 h. The reaction mixture was diluted with 2 M aqueous KOH (10 mL), then extracted with $CHCl_3$ (3 × 10 mL), and the combined organic extracts were concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 30:1) gave **34** as a colorless oil (248 mg, 99%): $[\alpha]_D^{25}$ +32.4 (*c* 1.0, $CHCl_3$); IR ν_{max} 3061, 3026, 2956, 2926, 2870, 1602, 1500, 1451, 743; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.3, C(5′)H_3), 1.53 (2H, app dq, *J* 15.2, 7.5, C(4′)H_2), 1.84−1.96 (2H, m, C(3)H_2), 2.02−2.14 (2H, m, C(1′)H_A, C(3′)H_A), 2.23−2.34 (2H, m, C(1′)H_B, C(3′)H_B), 2.76−2.78 (1H, m, C(4′)H_A), 2.97−3.06 (1H, m, C(4′)H_B), 3.17−3.33 (4H, m, SCH_2CH_2S), 3.68−3.69 (1H, m, C(2′)*H*), 4.61 (1H, d, *J* 17.4, NC$H_A$$H_B$Ph), 4.65 (1H, d, *J* 17.4, NC$H_A$$H_B$Ph), 6.46 (1H, d, *J* 8.1, C(8)*H*), 6.59 (1H, app t, *J* 7.2, C(6)*H*), 6.96 (1H, app t, *J* 7.7, C(7)*H*), 7.03 (1H, d, *J* 7.3, C(5)*H*), 7.22−7.34 (5H, m, *Ph*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(5′)), 20.2 (*C*(4′)), 23.6 (*C*(4)), 26.5 (*C*(3)), 39.6, 40.0 (SCH_2CH_2S), 44.7 (*C*(1′)), 47.9 (*C*(3′)), 53.2 (NCH_2Ph), 55.7 (*C*(2)), 70.4 (*C*(2′)), 111.7 (*C*(8)), 115.7 (*C*(6)), 121.5 (*C*(4a)), 126.7, 126.8 (*o,m,p-Ph*), 127.2 (*C*(7)), 128.6 (*C*(5)), 129.1 (*o,m-Ph*), 139.4 (*i-Ph*), 144.5 (*C*(8a)); *m/z* (ESI$^+$) 384 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NS_2^+$ ([M + H]$^+$) requires 384.1814; found 384.1811.

(*R*)-*N*-Methyl-2-pentyl-1,2,3,4-tetrahydroquinoline [(−)-angustureine], 36. *Step 1:* A solution of **34** (28 mg, 0.073 mmol) in EtOH/THF (v:v, 1:1, 2 mL) was added to a stirred suspension of Raney-Ni (~0.5 g)[60] in EtOH/THF (v/v, 1:1, 2 mL), and the resultant suspension was heated at 80 °C for 1 h. The resultant suspension was allowed to cool to rt and then concentrated in vacuo to give **35**.

Step 2: Pd/C (9 mg, ~40% w/w of **35**) was added to a stirred solution of the residue of **35** from the previous step and formalin (37% aqueous HCHO, 0.05 mL, 0.73 mmol) in degassed MeOH (2 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite (eluent MeOH), then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 200:1) gave **36** as a colorless oil (11 mg, 69%): $[\alpha]_D^{25}$ −10.6 (*c* 0.2, $CHCl_3$); IR ν_{max} 2954, 2928, 2870, 2857, 1602, 1500, 743; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.6, C(5′)H_3), 1.24−1.44 (7H, m, C(1′)H_A, C(2′)H_2, C(3′)H_2, C(4′)H_2), 1.55−1.63 (1H, m, C(1′)H_B), 1.82−1.93 (2H, m, C(3)H_2), 2.65 (1H, app dt, *J* 16.1, 4.2, C(4)H_A), 2.76−2.84 (1H, m, C(4)H_B), 2.92 (3H, s, N*Me*), 3.23 (1H, app dq, *J* 8.6, 4.2, C(2)*H*), 6.52 (1H, d, *J* 7.9, C(8)*H*), 6.58 (1H, app td, *J* 7.4, 1.0, C(6)*H*), 6.97 (1H, d, *J* 7.4, C(5)*H*), 7.07 (1H, app t, *J* 7.4, C(7)*H*); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(5′)), 22.8 (*C*(4′)), 23.7 (*C*(4)), 24.6 (*C*(3)), 25.9 (*C*(3′)), 31.3 (*C*(1′)), 32.2 (*C*(2′)), 38.1 (N*Me*), 59.1 (*C*(2)), 110.5 (*C*(8)), 115.3 (*C*(6)), 122.0 (*C*(4a)), 127.2 (*C*(7)), 128.8 (*C*(5)), 145.5 (*C*(8a)); *m/z* (ESI$^+$) 218 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{24}N^+$ ([M + H]$^+$) requires 218.1903; found 218.1903.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00672.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) The currently preferred scientific name of this tree is *Angostura trifoliata*. The authors would like to thank Dr. Ben Jones, Arboretum Curator, University of Oxford, Harcourt Arboretum, for this information.

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