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

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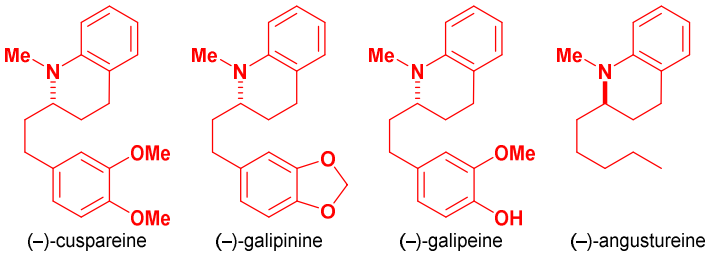


The asymmetric syntheses of all members of the Hancock alkaloid family based upon a 2-substituted *N*-methyl-1,2,3,4-tetrahydroquinoline core is delineated. The conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to 5-(*o*-bromophenyl)-*N*-methoxy-*N*-methylpent-2-enamide is used to generate the requisite C(2)-stereogenic center of the targets, whilst 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.

Introduction

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 non-racemic {$[\alpha]_D^{20}$ −20.4 (*c* 6.8 in EtOH)}.[6] Cuspareine was then largely ignored for over fifty 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 characterisation 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 which 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 (^1H, ^{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 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 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 (sixteen syntheses of cuspareine, fourteen syntheses of galipinine, and twenty-seven syntheses of angustureine reported to date),[16–26] it is incredible that discrepancies between the ^1H 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 fifteen 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 manuscript, 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 our 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]

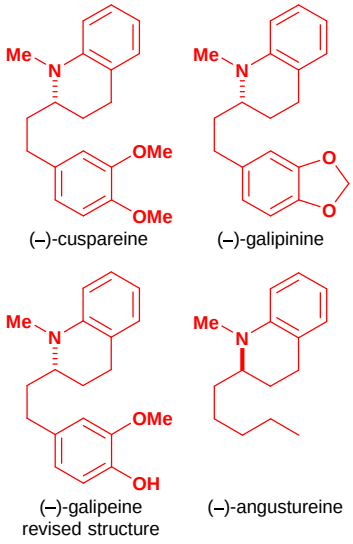


FIGURE 1. Structures (naturally occurring isomers shown).

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 was 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 arylbromide 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).

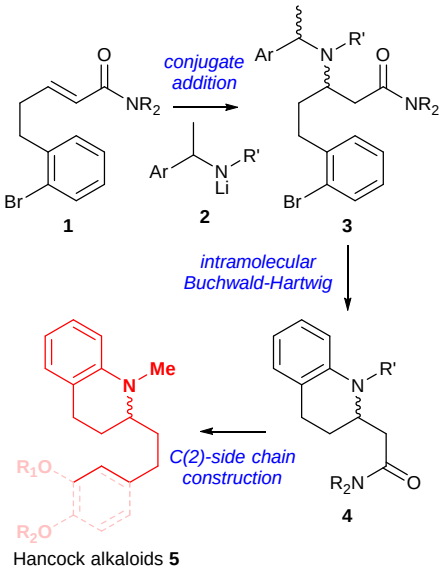
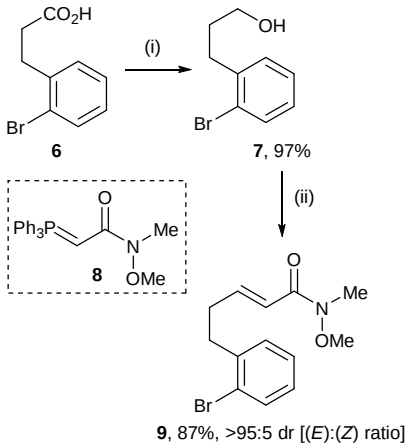


FIGURE 2. Proposed synthesis of the Hancock alkaloids (−)-cuspareine, (−)-galipinine (−)-galipeine and (−)-angustureine.

(−)-Cuspareine, (−)-Galipinine and (−)-Galipeine. The preparation of the three members of the Hancock alkaloid family based upon a *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 then gave **9** as a single diastereoisomer [>95:5 dr, (*E*):(*Z*) ratio] that was isolated in 87% yield; the diagnostic value $^3J_{2,3}$ = 15.4 Hz enabled confident assignment of the geometry of the newly formed olefin functionality (Scheme 1).

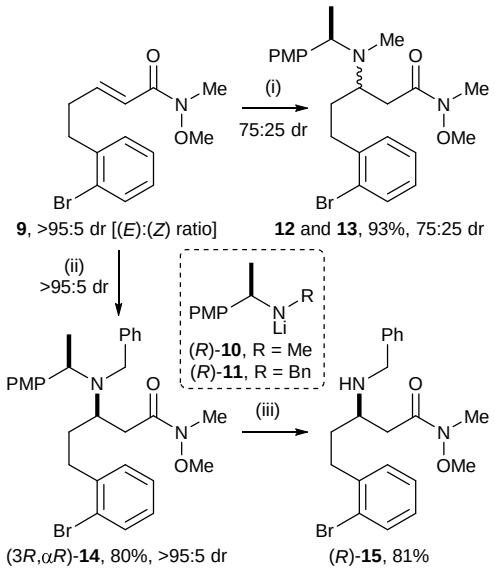
SCHEME 1. Preparation of α, β-Unsaturated Weinreb Amide 9.[a]



[a]Reagents and Conditions: (i) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, 0 °C, 1 h; (ii) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 30 min, then $Ph_3P{=}CHCON(Me)(OMe)$, rt, 16 h.

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 ppm and δ_H 3.14 ppm and those of the minor diastereoisomer **13** at δ_H 2.09 ppm and δ_H 3.17 ppm in the ^{1}H NMR spectrum of the crude reaction mixture; the relative configurations within **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*,α*R*)-**14** as a single diastereoisomer (>95:5 dr), which was isolated in 80% yield. The absolute configuration at the newly formed C(3)-stereogenic center within (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 reaction.[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).

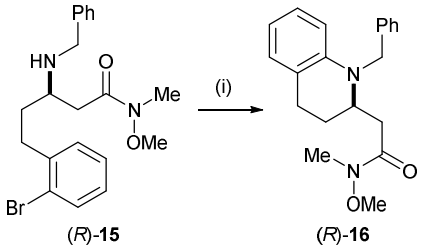
SCHEME 2. Preparation of Enantiopure β-Amino Amides 14 and 15.[a]



[a]Reagents and Conditions: (i) lithium (*R*)-*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**10**, THF, −78 °C, 2 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide (*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]



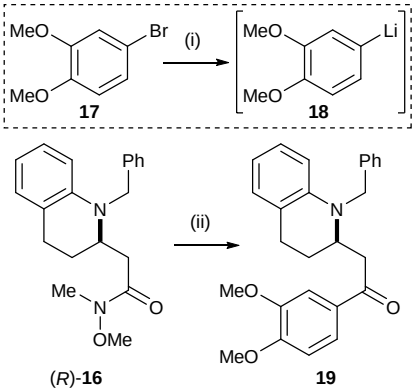
Entry	$Pd(OAc)_2$ mol%	ligand	conversion	yield
1	5	PPh_3	43%	37%
2	15	PPh_3	quant	79%
3	5	XPhos	quant	quant

[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 optimisation (Scheme 4). Initially, 1.0 equiv of *n*-BuLi was added to 1.0 equiv of **17** in 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, 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). The effect of reaction stoichiometry was next investigated in order to promote formation of the desired 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).

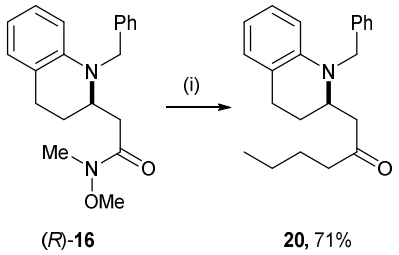
SCHEME 4. Preparation of Ketone 19.[a]



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.

SCHEME 5. Preparation of Ketone 20.[a]



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