The Hancock Alkaloids Angustureine, Cuspareine, Galipinine and Galipeine: A Review of Their Isolation, Synthesis and Spectroscopic Data

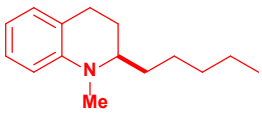
Prof. Stephen G. Davies,* Dr. Ai M. Fletcher,

Dr. Paul M. Roberts, and Dr. James E. Thomson

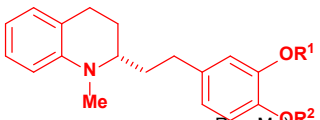
Department of Chemistry, Chemistry Research Laboratory,

University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

TOC Entry



(*R*)-(−)-Angustureine



(*S*)-(−)-Cuspareine (R_1 = R_2 = -CH$_2$-)
(*S*)-(−)-Galipinine (R_1 = Me; R_2 = H)
(*S*)-(−)-Galipeine (R_1 = R_2 = Me)

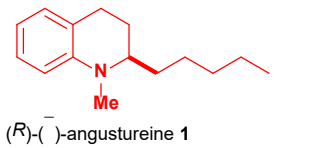
Hancock Alkaloids

The isolation, methods for synthesis, and spectroscopic data for angustureine, cuspareine, galipinine and galipeine are presented.

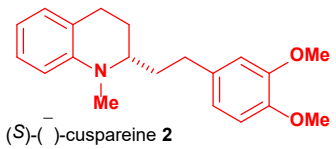
ABSTRACT: A review of the isolation, reported methods for the synthesis (to the end of 2018), and spectroscopic data of angustureine, cuspareine, galipinine, and galipeine, members of the Hancock family of alkaloids based upon a 2-substituted *N*(1)-methyl-1,2-3,4-tetrahydroisolquinoline scaffold, is presented.

Introduction

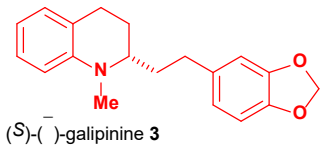
The Hancock alkaloids are a family of natural products isolated from the trunk bark (called angostura) of the shrubby Venezuelan tree *Galipea officinals* Hancock (*Angostura trifoliata* or the Angostura tree). It is a common misconception that Angostura bitters contain angostura (they do not, although the bark is present in a number of other aromatic bitters); both in fact take their names from the Venezuelan city of Angostura (which was renamed Ciudad Bolívar in 1846). Analysis of the alkaloid content of the trunk bark has been the subject of investigations dating back over 125 years,[1] although it was not until the publication a series of reports at the end of the 1990s and early 2000s by Jacquemond-Collet *et al.*[2–5] that four of the Hancock alkaloids in particular were propelled to the attention of the synthetic community. These four alkaloids, all of which are based around a 2-substituted *N*(1)-methyl-1,2,3,4-tetrahydroisoquinoline core, were named angustureine **1**, cuspareine **2**, galipinine **3**, and galipeine **4** (Figure 1).[2,3,6] It is interesting that the isolation of cuspareine **2** from angostura in fact first occurred early in the 20th century[7,8] (albeit the structure of the alkaloid was not deduced until 1950);[9] the alkaloid went largely unnoticed,[10,11] however, until its re-isolation was reported by Jacquemond-Collet *et al.* in their seminal work.[2] The interest in these alkaloids is presumably related to their chirality (they occur naturally in non-racemic form), coupled with a relatively simple structure; they have thus been adopted as benchmark targets to validate or showcase the utility of a developed synthetic methodology and, to date, their synthesis has been a feature of in excess of fifty reports (essentially all within the last twenty years).



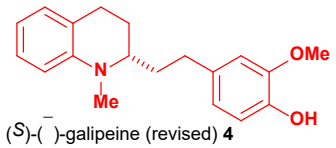
(*R*)-(−)-angustureine **1**



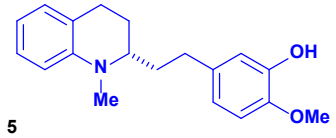
(*S*)-(−)-cuspareine **2**



(*S*)-(−)-galipinine **3**



(*S*)-(−)-galipeine (revised) **4**



5

Figure 1. Structures of the naturally occurring isomers of the Hancock alkaloids (*R*)-(−)-angustureine **1**, (*S*)-(−)-cuspareine **2**, (*S*)-(−)-galipinine **3** and (*S*)-(−)-galipeine **4** (revised structure). For reference, the originally assigned (erroneous) structure **5** of (*S*)-(−)-galipeine is also included.

Our own involvement with these alkaloids began in 2011 when we reported the development of a chiral aniline equivalent for conjugate addition, and an approach to (*R*)-(−)-angustureine **1** using this reagent.[12] We subsequently became aware of anomalies and discrepancies in the spectroscopic data reported for the alkaloids, in particular with respect to those for galipeine **4** and purported synthetic samples thereof. We acquired copies of the ^{1}H and ^{13}C NMR spectra recorded for the samples of the alkaloids **1**–**4** isolated from the natural source by Jacquemond-Collet *et al.*, which allowed us to correct the reported spectroscopic data for all of these alkaloids.[13,14] We developed an independent synthetic route to the alkaloids and on the basis of these studies, the structure of galipeine **4** was duly corrected, as it was originally erroneously assigned as the regioisomer **5** (Figure 1). Given the interest and popularity of these alkaloids as synthetic targets, which continues unabated,[15] we herein compile the corrected ^{1}H and ^{13}C NMR spectroscopic data for **1**–**4** alongside all of their total syntheses reported to the end of 2018[15,16] (many more formal syntheses, typically of the noralkaloids, have also been reported but are not included in this review). It is our hope that the material in the sections which follow will enable facile comparisons to be made between the major routes and tactics employed to facilitate the synthesis of these alkaloids, as well as providing a complete reference resource for their corrected ^{1}H and ^{13}C NMR spectroscopic data.

Discussion

Methods for the Synthesis of the Hancock Alkaloids

Considering the interest in the Hancock alkaloids **1**–**4**, it is perhaps unsurprising that a number of different approaches to them have been devised. Given their relatively simple structures, however, there is much commonality in many of these approaches. The four most popular synthetic routes are: (1) reduction of a 2-substituted quinolone **6** to the corresponding 1,2,3,4-tetrahydroquinoline **7**; (2) conversion of quinolone **8** to a 2-substituted 1,2-dihydroquinoline **9** via 1,2-addition of a nucleophile; (3) aza-conjugate addition to an α,β-unsaturated carbonyl compound **10**; (4) amination of a chiral, secondary alcohol **12** using the Mitsunobu reaction with a suitable nitrogen nucleophile (Figure 2). In the sections which follow, all of the reported routes to the Hancock alkaloids **1**−**4** are delineated. Syntheses are categorised according to the step in which the requisite nitrogen-bearing stereogenic centre is formed; in most cases this is also the key step around which the particular synthesis is designed.

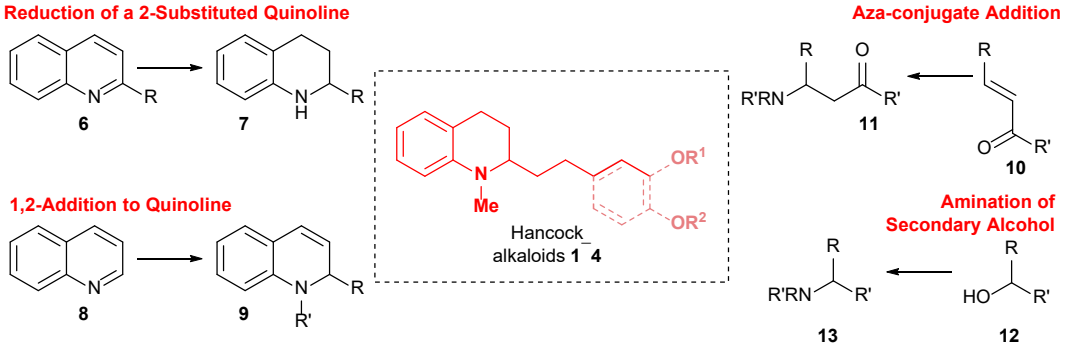
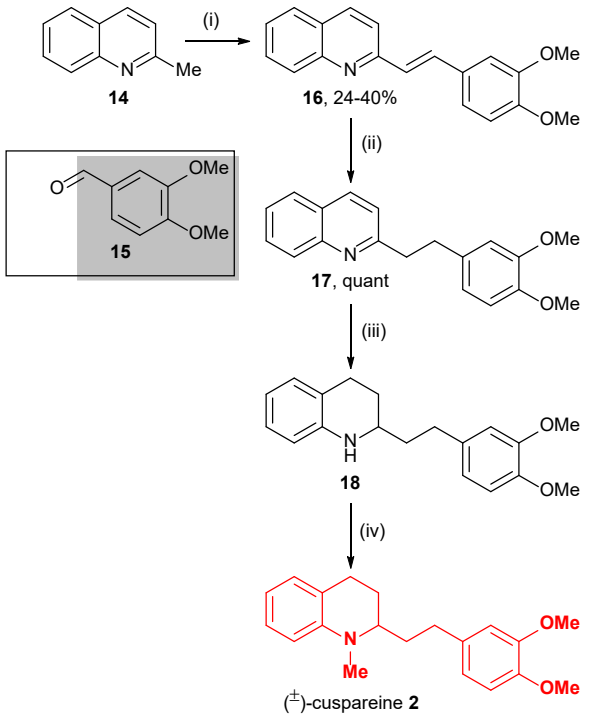


Figure 2. Summary of the most common routes to the Hancock alkaloids angustureine **1**, cuspareine **2**, galipinine **3** and galipeine **4**.

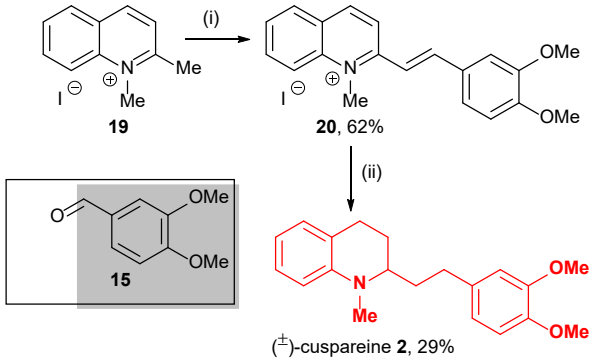
Reduction of a 2-Substituted Quinoline. The first reports of the synthesis of (±)-cuspareine **2** used the hydrogenation of a 2-substituted quinoline **6** to give the corresponding 2-substituted 1,2,3,4-tetrahydroquinoline **7**, and this basic approach has subsequently proven to be the most popular method to facilitate the synthesis of **1**–**4**. Schläger and Leeb[9] used the condensation of quinaldine **14** with piperonal **15** to give 2-substituted quinoline **16** in 24–40% yield, which underwent sequential hydrogenations (mediated by Pd/C and then PtO_2) to give (±)-norcuspareine **18**.[17] A final *N*-methylation (MeI/NaOMe) gave a sample of (±)-cuspareine **2**, confirming the structure that they had proposed for the alkaloid on the basis of degradation studies performed on a natural sample,[9] although no yields were given for the last two steps (Scheme 1). Staněk[10] later reported the related condensation of *N*-methylquinaldinium iodide **19** with piperonal **15** to give **20** in 62% yield. Hydrogenation of **20** then delivered (±)-cuspareine **2** directly, in 29% yield (Scheme 2). Subsequently, Terashima *et al.*[11] prepared **16** from 2-bromoquinoline **21** and 3,4-dimethoxy-β-bromostyrene **22**. Hydrogenation of **16** promoted by PtO_2 gave (±)-norcuspareine **18** in 75% yield, with subsequent *N*-methylation of **18** (NaH then MeI) providing (±)-cuspareine **2** in 80% yield (Scheme 3).

Scheme 1.[a]



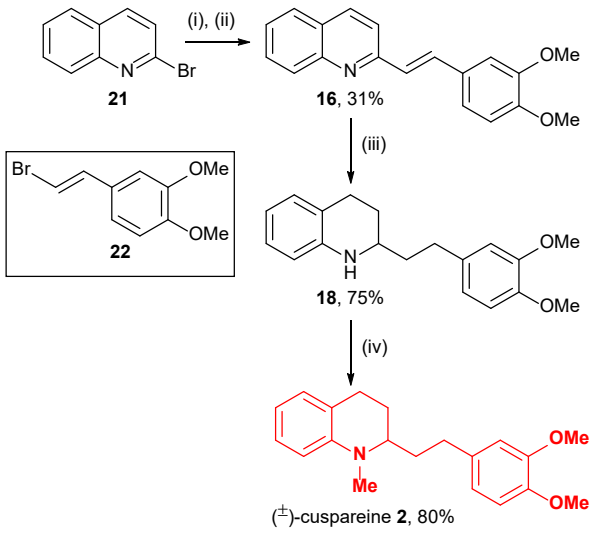
[a]Reagents and Conditions: (i) **15**, $ZnCl_2$, *n*-BuOH, 117 °C, 6 h; (ii) H_2, Pd/C, AcOH; (iii) H_2, PtO_2, AcOH, rt, 75 min; (iv) MeI, NaOMe.

Scheme 2.[a]



[a]Reagents and Conditions: (i) **15**, morpholine, EtOH, reflux, 1 h; (ii) H_2, PtO_2, EtOH.

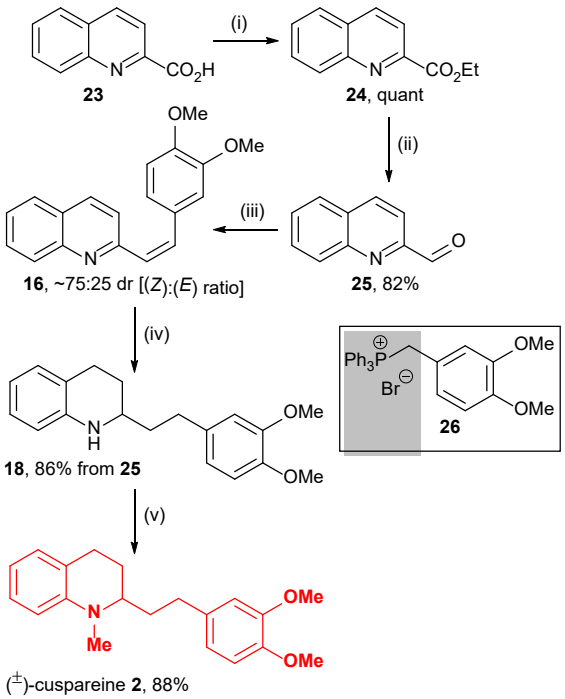
Scheme 3.[a]



[a]Reagents and Conditions: (i) BuLi, Et_2O, −70 °C, then 9-BBN-OMe, rt; (ii) $Pd(PPh_3)_4$, **15**, KOH, Bu_4NBr, PhH, reflux, 10 h; (iii) H_2, PtO_2, EtOH, rt; (iv) NaH, THF, 0 °C, 30 min, then MeI, 0 °C, 30 min, then rt, 1 h.

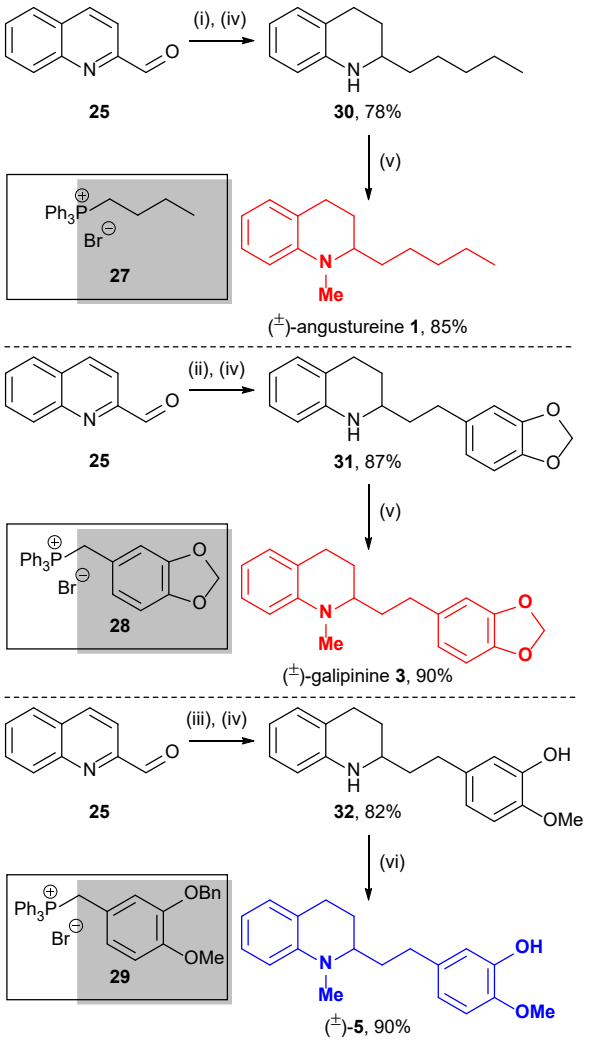
Diaz-Muñoz *et al.*[18] used Wittig olefination of aldehyde **25** (derived from quinaldic acid **23** in 82% yield in two steps) with phosphorane **26** in a biphasic CH_2Cl_2/H_2O mixture to construct 2-substituted quinoline **16** in a more efficient manner. Then, as before, hydrogenation of **16** promoted by PtO_2 gave norcuspareine **18** in 86% yield from **25**, and ensuing *N*-methylation of **18** (K_2CO_3/MeI) gave (±)-cuspareine **2** in 88% yield (Scheme 4). Application to the other members of the Hancock alkaloid family was also reported: use of analogous procedures to effect the olefination of **25** using phosphoranes **27** and **28** was followed by hydrogenation to give the racemic noralkaloids **30** and **31**, in 78% and 87% yield from **25**, respectively. Subsequent *N*-methylation of **30** and **31** gave (±)-angustureine **1** and (±)-galipinine **3**, in 85% and 90% yield, respectively. Meanwhile, olefination of **25** with phosphorane **29** was followed by hydrogenation, which was accompanied by hydrogenolytic removal of the *O*-benzyl group to give **32** in 82% yield. Ensuing reductive *N*-methylation then gave (±)-**5**, the originally reported (erroneous) structure of galipeine, in 90% yield (Scheme 5).

Scheme 4.[a]



[a]Reagents and Conditions: (i) EtI, K_2CO_3, DMF, 60 °C, 18 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 90 min; (iii) **26**, NaOH, CH_2Cl_2, H_2O, rt, 3 h; (iv) H_2, PtO_2, MeOH, rt, 8 h; (v) MeI, K_2CO_3, DMF, rt, 24 h.

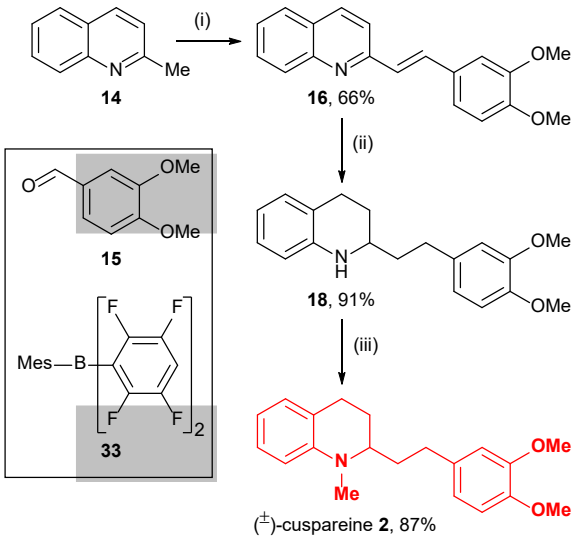
Scheme 5.[a]



[a]Reagents and Conditions: (i) **27**, KO^{t}Bu, CH_2Cl_2, ^{t}BuOH, reflux, 24 h; (ii) **28**, NaOH, CH_2Cl_2, H_2O, rt, 3 h; (iii) **29**, NaOH, CH_2Cl_2, H_2O, rt, 3 h; (iv) H_2, PtO_2, MeOH, rt, 8 h; (v) MeI, K_2CO_3, DMF, rt, 24 h; (vi) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 1 h.

Soós *et al.*[19] reported an alternative method for hydrogenation of **16** promoted by a Lewis acid using the concept of frustrated Lewis pairs (FLP). In this case, condensation of quinaldine **14** with piperonal **15** gave **16** in 66% yield, and then treatment of **16** with hydrogen in the presence of mesitylbis(2,3,5,6-tetrafluorophenyl)borane **33** gave (±)-norcuspareine **18** in 91% yield. Subsequent *N*-methylation (MeI, dioxane, 80 °C) provided (±)-cuspareine **2** in 87% yield (Scheme 6).

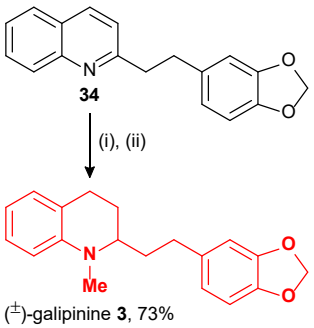
Scheme 6.[a]



[a]Reagents and Conditions: (i) **15**, $ZnCl_2$, 150 °C, 18 h; (ii) H_2, **33**, PhMe, 105 °C, 17 h; (iii) MeI, dioxane, 80 °C, 2 h. Mes = mesityl (2,4,6-trimethylphenyl).

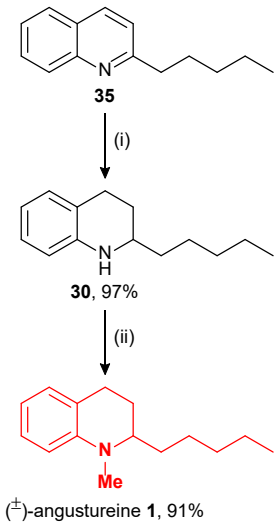
Alternative catalyst systems to effect such reductions continue to be developed, and for example Beller *et al.*[20] reported hydrogenation of a range of quinolines to the corresponding 1,2,3,4-tetrahydroquinolines using cobalt oxide/cobalt nanoparticles featuring nitrogen-doped graphene layers on alumina (Co_3O_4-Co/NGr@α-Al_2O_3), which they employed in a synthesis of (±)-galipinine **3** (Scheme 7). Beller *et al.*[21] later reported the use of supported iron-based materials modified by a nitrogen-doped carbon matrix to effect the same process, which they used in a synthesis of (±)-angustureine **1**. In this case, initial hydrogenation of 2-pentylquinoline **35** promoted by the catalyst Fe(1)/**L4**(4.5)@C-800 to give norangustureine **30** was followed by a novel cobalt-catalysed reductive *N*-methylation with formic acid as the methylating agent (Scheme 8).

Scheme 7.[a]



[a]Reagents and Conditions: (i) H_2, Co_3O_4-Co/NGr@α-Al_2O_3, PhMe, 120 °C, 48 h; (ii) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 1 h.

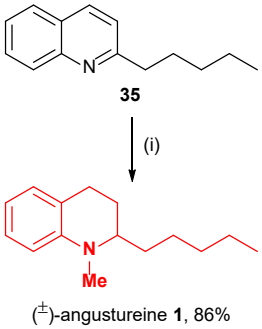
Scheme 8.[a]



[a]Reagents and Conditions: (i) H_2, Fe(1)/**L4**(4.5)@C-800, ^{i}PrOH, H_2O, 140 °C, 72 h; (ii) H_2, HCO_2H, $Co(BF_4)_2{\cdot}6H_2O$, Triphos(*p*-anisole), 1,4-dioxane, 100 °C, 24 h.

Meanwhile, Liu, Han, *et al.*[22] developed a method for one-pot reduction and *N*-methylation of 2-substituted quinolone derivatives, which they used in a synthesis of (±)-angustureine **1**: thus, treatment of 2-pentylquinoline **32** with $Ru(acac)_3$, Triphos and $MeSO_3H$ in THF under an atmosphere comprising a mixture of CO_2 and H_2 gave (±)-angustureine **1** directly, in 86% yield (Scheme 9).

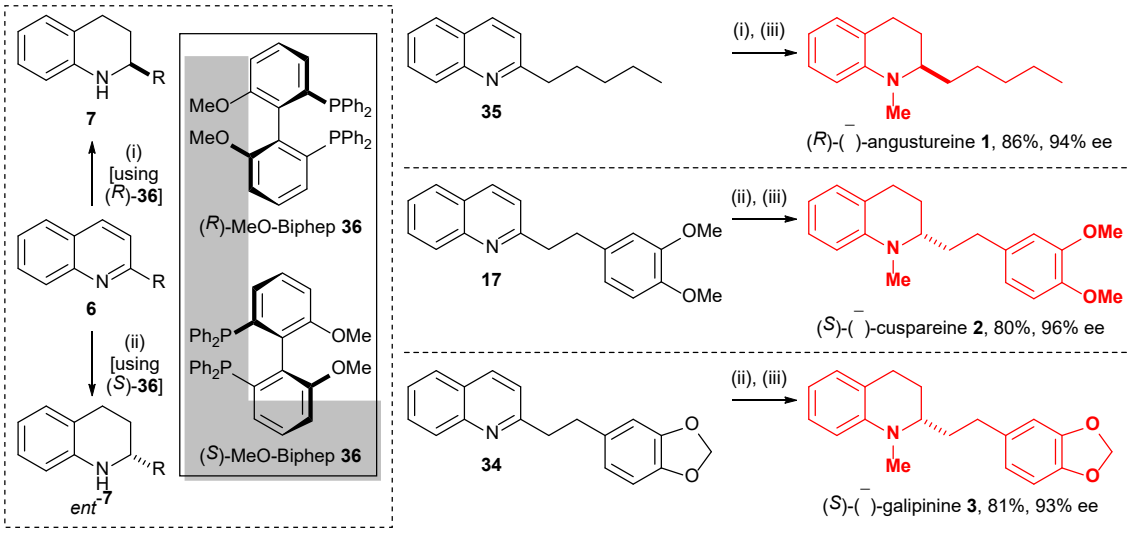
Scheme 9.[a]



[a]Reagents and Conditions: (i) H_2, CO_2, Ru (acac)$_3$, Triphos, $MeSO_3H$, THF, 160 °C, 16 h.

Zhou *et al.*[23] were first to demonstrate the use of enantioselective hydrogenation of a 2-substituted quinoline **6** to give the corresponding enantiopure 2-substituted 1,2,3,4-tetrahydroquinoline **7** in the synthesis of the Hancock alkaloids. Their method used $(IrCodCl)_2$ in conjunction with the appropriate enantiomer of the MeO-Biphep ligand **36** as a catalyst, and iodine as an activating agent. Thus, the requisite substrates **17**, **34** and **35** were hydrogenated enantioselectively to give the corresponding noralkaloids (**18**, **30** and **31**) in 86–92% yield and 93–96% ee; subsequent reductive *N*-methylations of **18**, **30** and **31** then provided (*R*)-(−)-angustureine **1**, (*S*)-(−)-cuspareine **2** and (*S*)-(−)-galipinine **3** (Scheme 10).

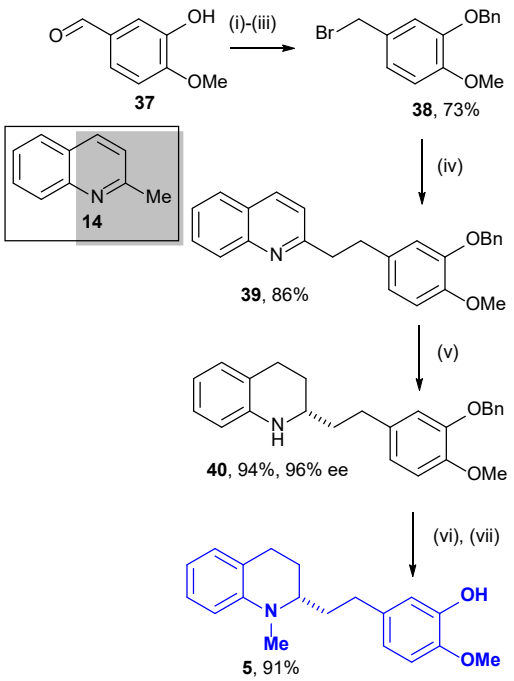
Scheme 10.[a]



[a]Reagents and Conditions: (i) H_2, $(IrCodCl)_2$, (*R*)-MeO-Biphep **36**, I_2, PhMe, rt, 15 h; (ii) H_2, $(IrCodCl)_2$, (*S*)-MeO-Biphep **36**, I_2, PhMe, rt, 15 h; (iii) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 1 h.

Zhou *et al.*[24] also applied this protocol to the synthesis of **5**, the originally reported (erroneous) structure of galipeine. In this synthesis, coupling of quinaldine **14** with bromide **38** (the later prepared from isovanillin **37** in three steps) gave the requisite 2-substituted quinoline **39** in 86% yield. Enantioselective hydrogenation of **39** gave **40** in 94% yield and 96% ee. Subsequent reductive *N*-methylation of **40** was followed by an additional hydrogenolysis step (to effect cleavage of the *O*-benzyl group) to give **5** in 91% yield (Scheme 11).

Scheme 11.[a]

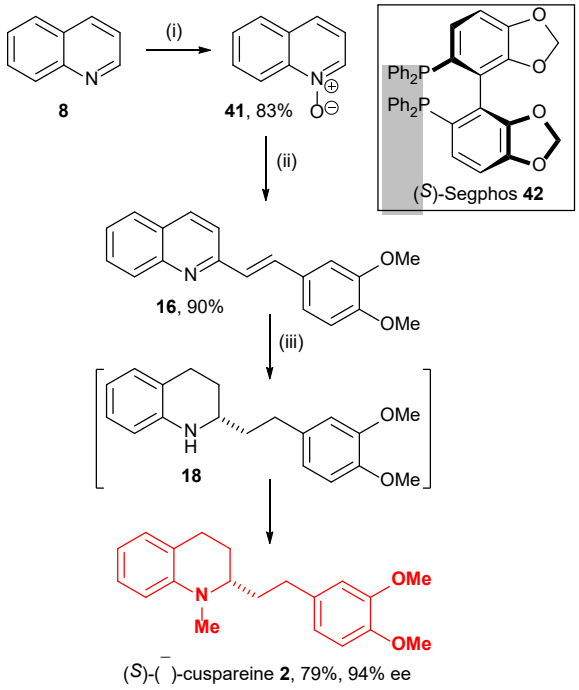


[a]Reagents and Conditions: (i) BnCl, KI, $NaHCO_3$, MeCN, 60 °C, 10 h; (ii) $NaBH_4$, MeOH, 0 °C, 15 min, then rt, 2 h; (iii) PBr_3, pyridine, Et_2O, reflux, 2 h; (iv) **14**, BuLi, Et_2O, 0 °C, 30 min, then add **38**, rt; (v) H_2, $(IrCodCl)_2$, (*S*)-MeO-Biphep **36**, I_2, PhMe, rt, 15 h; (vi) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 1 h; (vii) H_2, Pd/C, EtOAc, AcOH, rt, 10 h.

Bower *et al.*[25] later applied this approach to the enantioselective hydrogenation of 2-substituted quinolines to the corresponding 2-substituted 1,2,3,4-tetrahydroquinolines in a synthesis of (*S*)-(−)-

cusapreine **2**, wherein it was combined with in situ reductive *N*-methylation. In their synthesis, **16** was prepared upon reaction of quinoline *N*-oxide **41** with 3,4-dimethoxystyrene, a transformation which is thought to proceed via 1,3-dipolar cycloaddition followed by rearomatisation and dehydration. Hydrogenation of **16** using a modified condition set was followed by introduction of formalin to the reaction flask, delivering (*S*)-(−)-cuspareine **2** in 79% yield and 94% ee (Scheme 12).

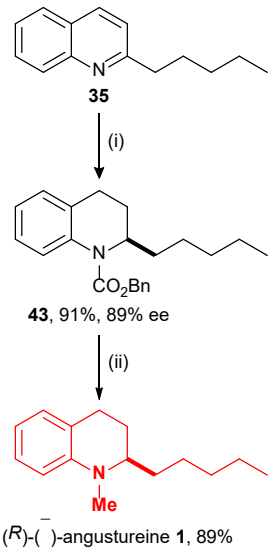
Scheme 12.[a]



[a]Reagents and Conditions: (i) *m*-CPBA, CH_2Cl_2, rt; (ii) 3,4-dimethoxystyrene, $TsOH·H_2O$, DMSO, H_2O, 140 °C, 24 h; (iii) H_2, $(IrCodCl)_2$, (*S*)-SegPhos **42**, I_2, PhH, rt, 16 h, then add HCHO (37% aq), MeOH.

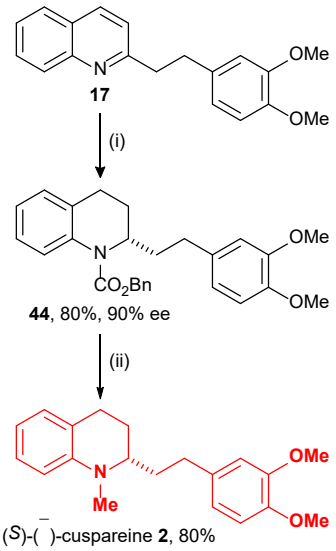
Zhou *et al.*[26] showed that benzyl choroformate was an alternative activator in this hydrogenation protocol, and thus hydrogenation of 2-pentyl quinoline **35** in the presence of $(IrCodCl)_2$, (*R*)-Segphos **42**, benzyl chloroformate and Li_2CO_3 in THF gave **43** in 91% yield and 89% ee. Subsequent treatment of **43** with $LiAlH_4$ effected reduction of the carbamate functionality to furnish (*R*)-(−)-angustureine **1** in 89% yield (Scheme 13). A directly analogous sequence applied to **17** [but using (*S*)-Segphos **42**] gave (*S*)-(−)-cusapreine **2** in 64% overall yield and 90% ee (Scheme 14).

Scheme 13.[a]



[a]Reagents and Conditions: (i) H_2, $(IrCodCl)_2$, (*R*)-SegPhos **42**, $ClCO_2Bn$, Li_2CO_3, THF, rt, 15 h; (ii) $LiAlH_4$, Et_2O, rt.

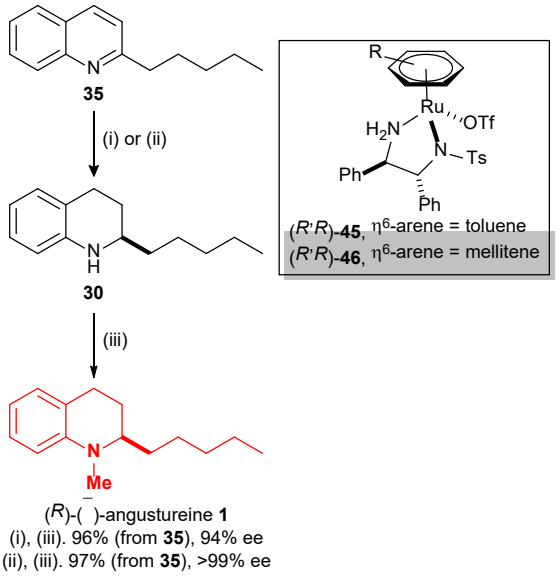
Scheme 14.[a]



[a]Reagents and Conditions: (i) H_2, $(IrCodCl)_2$, (*S*)-SegPhos **42**, $ClCO_2Bn$, Li_2CO_3, THF, rt, 15 h; (ii) $LiAlH_4$, Et_2O, rt.

Fan *et al.*[27,28] demonstrated that several Ru(OTf)(η^6-arene)(TsDpen) complexes were capable of effecting the hydrogenation of a range of quinolines to the corresponding 1,2,3,4-tetrahydroquinolines, which they employed in syntheses of (*R*)-(−)-angustureine **1**. Hydrogenation of **35** using catalyst (*R*,*R*)-**45** (under solvent free conditions) gave norangustureine **30** in 94% ee, which upon reductive methylation gave (*R*)-(−)-angustureine **1** in 96% overall yield. Use of catalyst (*R*,*R*)-**46** (in MeOH) similarly provided **30** and after reductive *N*-methylation (*R*)-(−)-angustureine **1** was duly isolated in 97% overall yield and >99% ee (Scheme 15).

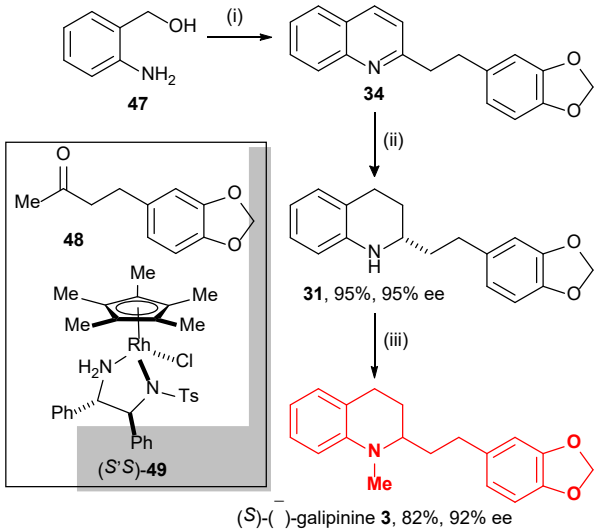
Scheme 15.[a]



[a]Reagents and Conditions: (i) H_2, (*R*,*R*)-**45**, rt, 72 h; (ii) H_2, (*R*,*R*)-**46**, MeOH, rt, 48 h; (iii) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 2 h.

The use of a similar catalyst system to effect the transfer hydrogenation of a range of quinolines coupled with a novel method for *N*-methylation using DMSO as the methyl source was demonstrated by Xiao *et al.*[29] in a synthesis of (*S*)-(−)-galipinine **3**. Reaction of **47** with ketone **48** in the presence of $Pd(OAc)_2$ gave 2-substituted quinoline **34**, which upon asymmetric transfer hydrogenation using (*S*,*S*)-**49** gave norgalipinine **31** in 95% yield and 95% ee. *N*-Methylation of **31** mediated by DMSO then provided (*S*)-(−)-galipinine **3** in 82% yield and 92% ee (Scheme 16). This method for *N*-methylation was also applied to racemic norangustureine **30** as part of this study, thus providing (±)-angustureine **1** in 86% yield.

Scheme 16.[a]

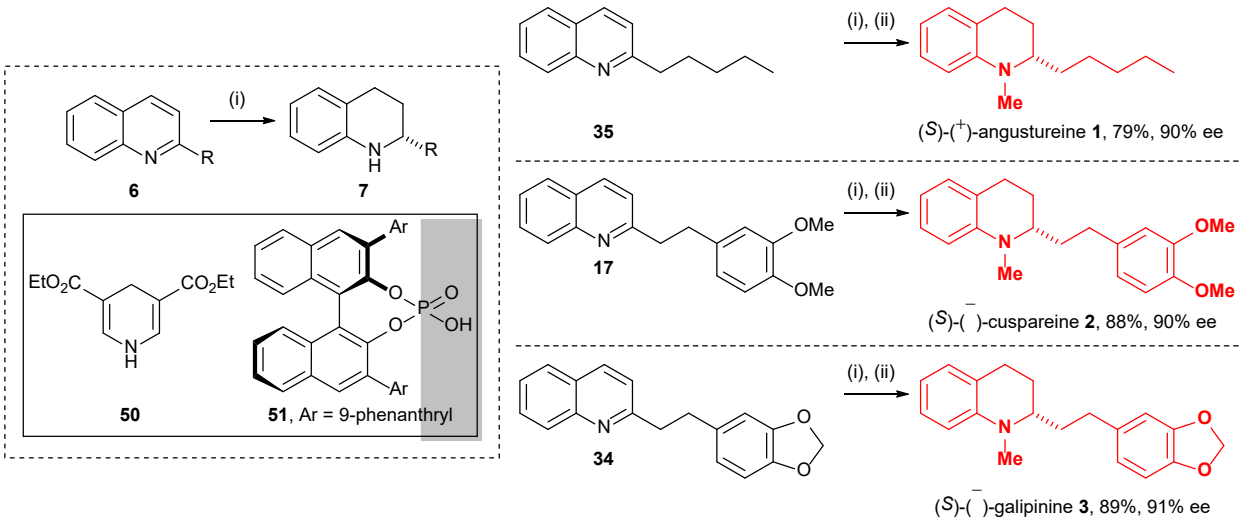


[a]Reagents and Conditions: (i) **48**, $Pd(OAc)_2$, KOH, PhMe, reflux, 24 h; (ii) (*S*,*S*)-**49**, HCO_2Na, NaOAc, AcOH, H_2O (pH 5), 40 °C, 12 h; (iii) DMSO, HCO_2H, Et_3N, 150 °C, 12 h.

A distinctly different, transition metal free method to effect the enantioselective transfer hydrogenation of a range of 2-substituted quinolines **6** to give the corresponding 2-substituted 1,2,3,4-tetrahydroquinolines **7** was reported by Rueping *et al.*[30] using the Hantzsch dihydropyridine **50** in

conjunction with chiral Brønsted acid **51**. The utility of this process was demonstrated by its use as the key step in the synthesis of Hancock alkaloids: in these synthesis, asymmetric transfer hydrogenation of the requisite substrates **17**, **34** and **35** gave the corresponding noralkaloids (**18**, **30** and **31**), which upon reductive *N*-methylation furnished (*S*)-(+)-angustureine **1** in 79% overall yield and 90% ee from **35**, (*S*)-(−)-cuspareine **2** in 88% overall yield and 90% ee from **17**, and (*S*)-(−)-galipinine **3** in 89% overall yield and 91% ee from **34** (Scheme 17).

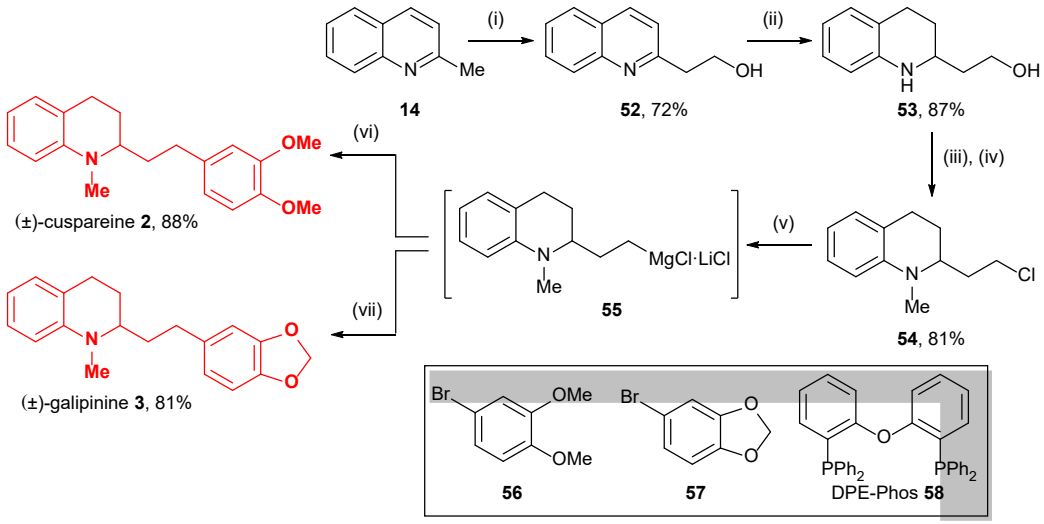
Scheme 17.[a]



[a]Reagents and Conditions: (i) **50**, **51**, PhH, 60 °C, 12 h; (ii) HCHO, $NaBH_4$, AcOH.

Knochel *et al.*[31] have reported the single example of reduction of a 2-substituted quinoline **6** to the corresponding 2-substituted 1,2,3,4-tetrahydroquinoline scaffold **7** applied to the synthesis of the Hancock alkaloids not reliant upon hydrogenation or transfer hydrogenation. In their synthesis, reaction of quinaldine **14** with paraformaldehyde gave **52** in 72% yield (based on returned starting material), and reduction of **52** was accomplished using $NaBH_4$ and $NiCl_2$ in MeOH, delivering 2-substituted 1,2,3,4-tetrahydroquinoline **53** in 87% yield. Reductive *N*-methylation and treatment with $SOCl_2$ gave **54** in 81% overall yield, the precursor for the key step that their synthesis was in fact designed to showcase: use of a nickel-catalysed cross-coupling reaction of an aminoalkylzinc bromide with an aryl bromide. Thus, treatment of **54** with Mg and LiCl gave Turbo Grignard **55** which upon treatment with $ZnBr_2$ and then aryl bromide **56**, DPE-Phos **58** and $Ni(acac)_2$ in a THF/NMP mixture, furnished (±)-cuspareine **2** in 88% yield. Despite this method only delivering the alkaloid in racemic form, it does allow late-stage diversification, as shown by coupling of **55** with aryl bromide **57** under the same conditions to furnish (±)-galipinine **3** in 81% yield (Scheme 18).

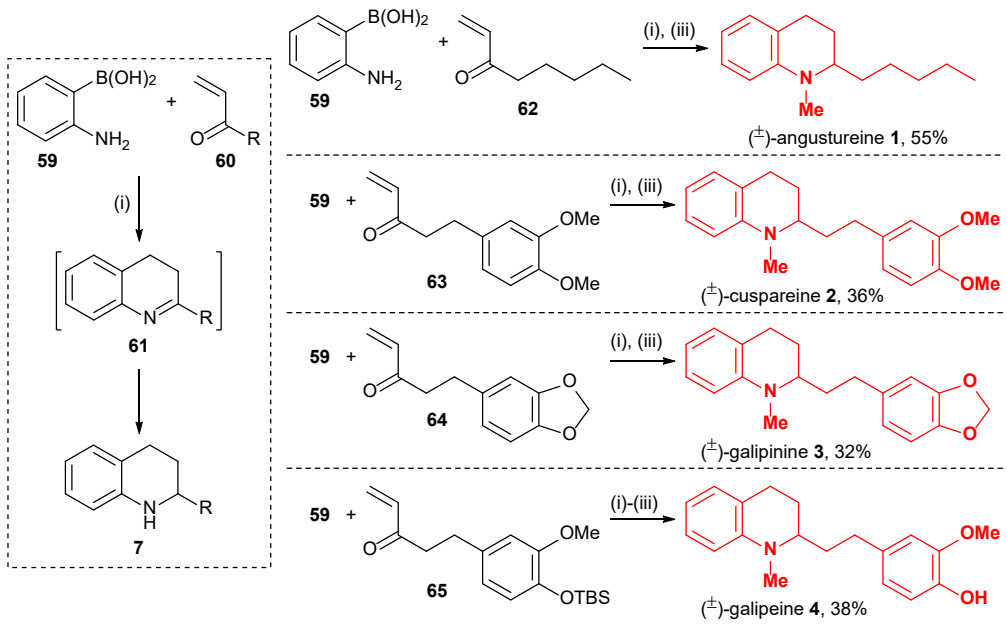
Scheme 18.[a]



[a]Reagents and Conditions: (i) paraformaldehyde, dioxane, H_2O, 110 °C, 20 h; (ii) $NaBH_4$, $NiCl_2$, MeOH, 0 °C to 25 °C, 90 min; (iii) HCHO, $NaBH_3CN$, AcOH, CH_2Cl_2, 25 °C, 16 h; (iv) $SOCl_2$, CH_2Cl_2, 25 °C, 2 h; (v) Mg, LiCl, DIBAL-H (3 mol%), THF, reflux, 2 h; (vi) $ZnBr_2$, THF, NMP, rt, 15 min, then **56**, DPE-Phos **58**, $Ni(acac)_2$, 25 °C, 18 h; (vii) $ZnBr_2$, THF, NMP, rt, 15 min, then **57**, DPE-Phos **58**, $Ni(acac)_2$, 25 °C, 22 h.

Although not a reduction of a 2-substituted quinoline **6** to the corresponding 2-substituted 1,2,3,4-tetrahydroquinoline **7**, Turner, Marsden, *et al.*[32] have recently disclosed a related protocol involving a rhodium-catalysed conjugate addition of *ortho*-aminophenylboronic acid **59** to an α,β-unsaturated keteone **60** followed by in situ imine formation to give a 2-substituted 3,4-dihydroquinoline **61**, which is then able to undergo reduction to the corresponding racemic 2-substituted 1,2,3,4-tetrahydroquinoline **7**.[17,33] Application of this protocol to α,β-unsaturated ketones **62**, **63** and **64** gave the noralkaloids **18**, **30** and **31**, which were subsequently *N*-methylated (K_2CO_3/MeI) to yield (±)-angustureine **1** in 55% yield from **62**, (±)-cuspareine **2** in 36% yield from **63**, and (±)-galipinine **3** in 28% yield from **65**. An analogous procedure using α,β-unsaturated ketone **65**, incorporating an extra step to effect *O*-desilylation, furnished (±)-galipeine **4** in 38% yield from **65** (Scheme 19).

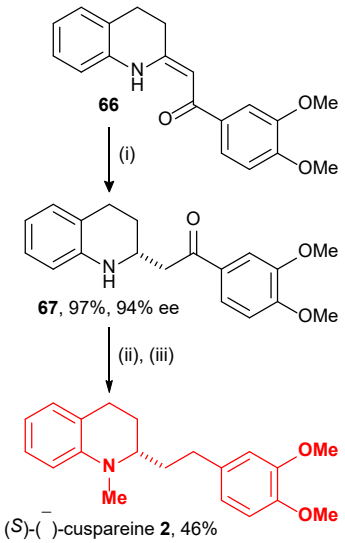
Scheme 19.[a]



[a]*Reagents and conditions:* (i) $[Rh(cod)Cl]_2$, aq KOH, PhMe, 90 °C, 16 h, then $NaBH(OAc)_3$, rt, 1 h; (ii) TBAF, THF, rt, 16 h; (iii) MeI, K_2CO_3, THF, 70 °C, 20 h.

Hydrogenation of an Exocylcic Enamine. Zhou *et al.*[34] have demonstrated the use of their iridium-catalysed enantioselective hydrogenation protocol to effect the reduction of a range of exocyclic enamines and have applied this methodology in a synthesis of (*S*)-(−)-cuspareine **2**. Hydrogenation of **66** in the presence of $(IrCodCl)_2$, (*S*)-MeO-Biphep **36** and iodine gave **67** in 97% yield and 94% ee. Reduction of the ketone functionality within **67** using Et_3SiH in the presence of TFA to give norcuspareine **18** was followed by reductive *N*-methylation to give (*S*)-(−)-cuspareine **2** in 46% yield (Scheme 20).

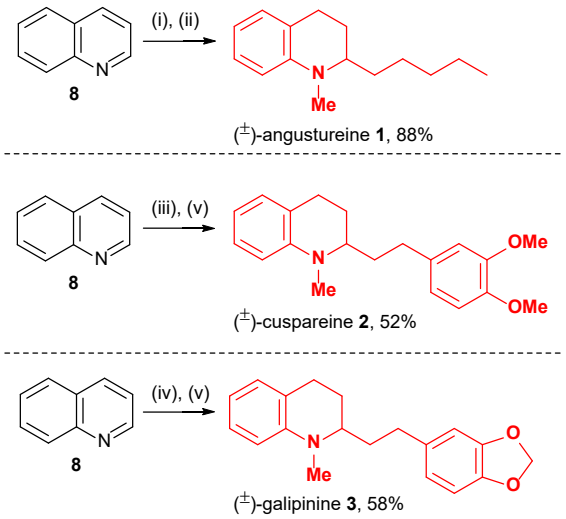
Scheme 20.[a]



[a]Reagents and Conditions: (i) H_2, $(IrCodCl)_2$, (*S*)-MeO-Biphep **36**, I_2, PhMe, rt, 16 h; (ii) Et_3SiH, TFA, rt, 24 h; (iii) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 30 min.

1,2-Addition to Quinoline. Rather than effect reduction of a 2-substituted quinoline **6** to the corresponding 2-substituted 1,2,3,4-tetrahydroquinoline derivative **7** in one step, an alternative approach to the Hancock alkaloids starts from quinoline **8** itself, and effects a 1,2-addition process to introduce functionalisation to C(2), so giving the corresponding 2-substituted-1,2-dihydroquinoline **9** with concomitant formation of the C(2)-stereogenic centre; further reduction and other manipulations then give the target alkaloids. Evans *et al.*[35] reported the simplest application of this methodology to facilitate a rapid synthesis of the Hancock alkaloids in racemic form. Addition of the requisite alkyllithium reagent to quinoline **8** and quenching with MeI was followed by hydrogenolysis of the resultant 1,2-dihydroquinoline derivatives to give the corresponding Hancock alkaloids: (±)-angustureine **1** in 88% overall yield from **8**, (±)-cuspareine **2** in 52% overall yield from **8**, and (±)-galipinine **3** in 58% overall yield from **8** (Scheme 21).

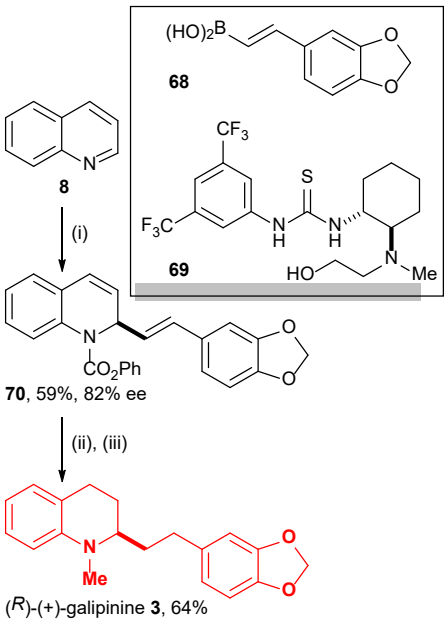
Scheme 21.[a]



[a]Reagents and Conditions: (i) pentyllithium, THF, 0 °C, 30 min, then MeI, 2 h; (ii) H_2, Pd/C, EtOAc, rt, 24 h; (iii) (*E*)-3,4-dimethylstyryllithium, THF, rt, 10 min, then MeI, 0 °C, 2 h; (ii) (*E*)-3,4-methylenedioxystyryllithium, THF, rt, 10 min, then MeI, 0 °C, 2 h; (iv) H_2, Pd/C, EtOH, rt, 72 h.

Other approaches in this class have sought to effect the 1,2-addition process in an enantioselective manner. Takemoto *et al.*[36] reported a method to effect enantioselective addition of a range of styrylboronic acid derivatives to a range of quinoline derivatives (Petasis-type reaction), which they applied to the synthesis of (*R*)-(+)-galipinine **3**. Treatment of quinoline **8** with phenyl chloroformate, (*E*)-3,4-methylenedioxystyrylboronic acid **68** and chiral thiourea catalyst **69** gave 1,2-dihydroquinoline derivative **70** in 59% yield and 82% ee. Hydrogenation of **70** was followed by treatment with $LiAlH_4$ to effect reduction of the carbamate functionality, giving (*R*)-(+)-galipinine **3** in 64% yield (Scheme 22).

Scheme 22.[a]

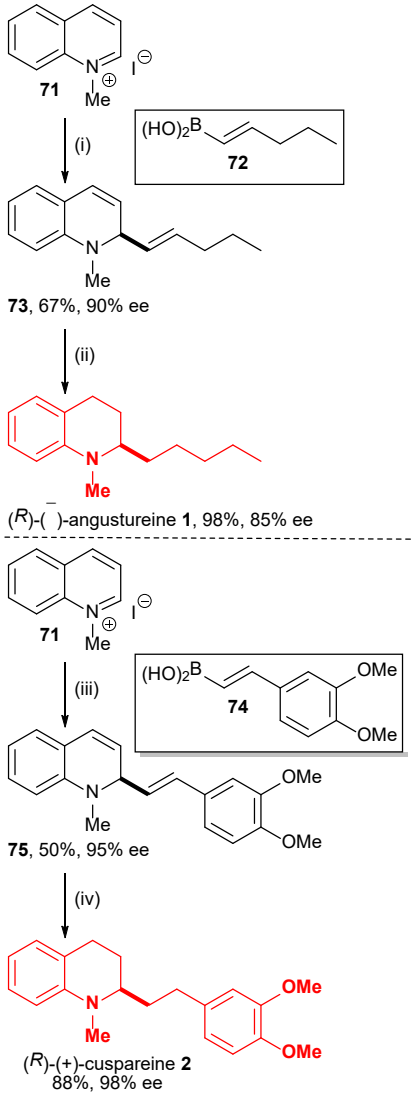


[a]Reagents and Conditions: (i) PhOCOCl, **68**, **69**, $NaHCO_3$, H_2O, CH_2Cl_2, −78 °C, 24 h; (ii) H_2, Pd/C, MeOH, 20 °C, 12 h; (iii) $LiAlH_4$, THF, rt, 12 h.

The related rhodium-catalysed enantioselective addition of a range of aryl- and vinylboronic acids to *N*-alkylquinolinium iodides was reported by Wei, Wang, *et al.*[37] who applied this transformation to enable

the synthesis of Hancock alkaloids. Under their optimised conditions, reaction of *N*-methylquinolinium iodide **71** with (*E*)-1-pentenylboronic acid **72** gave 1,2-dihydroquinoline derivative **73** in 67% yield and 90% ee. Catalytic hydrogenation of **73** gave (*R*)-(−)-angustureine **1** in 98% yield and 85% ee. A related two-step procedure using (*E*)-3,4-dimethoxystyrylboronic acid **74** gave (*R*)-(+)-cuspareine **2** in 44% overall yield and 95% ee from **71** (Scheme 23).

Scheme 23.[a]

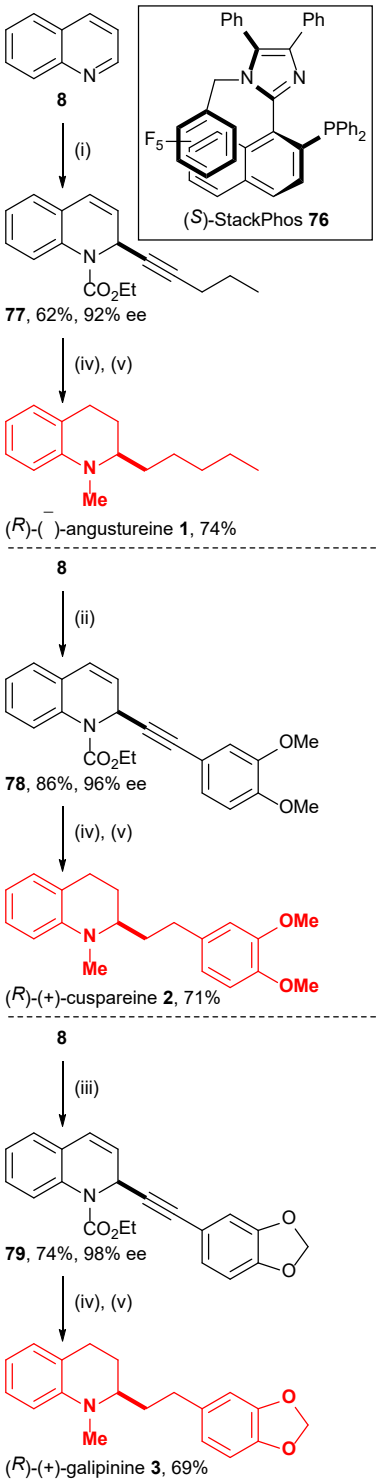


Reagents and conditions: (i) **72**, $(RhCodCl)_2$, (*S*)-SegPhos **42**, $AgBF_4$, $K_3PO_4 \cdot 3H_2O$, MeCN, 45 °C, 12 h; (ii) H_2, Pd/C, EtOAc, 40 °C, 24 h; (iii) **74**, $(RhCodCl)_2$, (*S*)-SegPhos **42**, $AgBF_4$, $K_3PO_4 \cdot 3H_2O$, MeCN, 45 °C, 12 h; (iv) $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 48 h.

Aponick *et al.*[38] developed an enantioselective copper-catalysed alkynylation of quinolines, which were again activated towards the addition by acylation (using ethyl chloroformate in this case), which they showcased in a synthesis of the Hancock alkaloids. Treatment of quinoline **8** with ethyl chloroformate, *n*-propylacetylene, CuBr and (*S*)-StackPhos **76** gave 1,2-dihydroquinoline derivative **77** in 62% yield and 92% ee. Catalytic hydrogenation was followed by reduction of the carbamate functionality using $LiAlH_4$ to give (*R*)-(−)-angustureine **1** in 74% yield. Similarly, use of 3,4-dimethoxyphenylacetylene in a directly analogous protocol gave (*R*)-(+)-cuspareine **2** in 61% yield overall yield and 96% ee from **8**, whilst employing 3,4-

methylenedioxyphenylacetylene gave (*R*)-(+)-galipinine **3** in 51% overall yield and 98% ee from **8** (Scheme 24).

Scheme 24.[a]

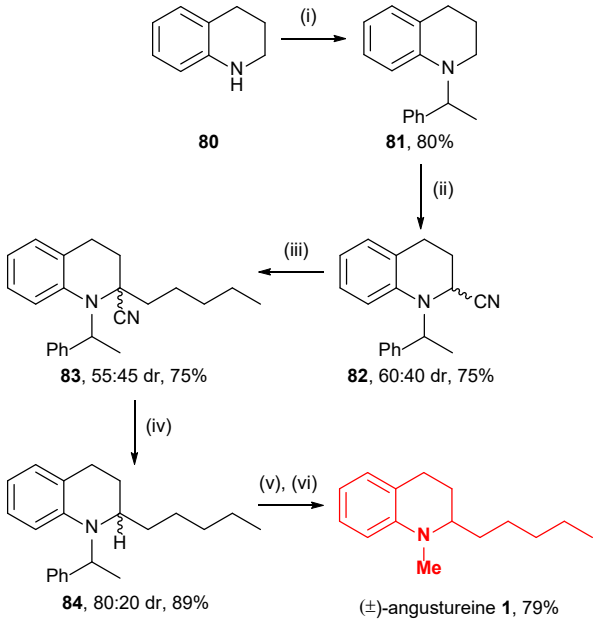


[a]*Reagents and conditions:* (i) $ClCO_2Et$, *n*-propylacetylene, CuBr, (*S*)-StackPhos **76**, $^iPr_2NEt$, CH_2Cl_2, −20 °C, 19 h; (ii) $ClCO_2Et$, 3,4-dimethoxyacetylene, CuBr, (*S*)-StackPhos **76**, $^iPr_2NEt$, CH_2Cl_2, 0 °C to rt, 23 h; (iii) $ClCO_2Et$, 3,4-methylenedioxyacetylene, CuBr, (*S*)-StackPhos **76**, $^iPr_2NEt$, CH_2Cl_2, −20 °C, 22 h; (iv) H_2, Pd/C, EtOH, EtOAc, rt, 16 h; (v) $LiAlH_4$, THF, 55 °C, 3 h.

C(2)-Functionalisation of 1,2,3,4-Tetrahydroquinoline. Two approaches to Hancock alkaloids (in racemic form) beginning from 1,2,3,4-tetrahydroquinoline **80** and proceeding via C(2)-functionalisation to introduce the requisite side-chain have been reported. Hurvois *et al.*[39] effected electrochemical functionalisation to introduce a nitrile functionality to C(2), which then permitted further alkylation.

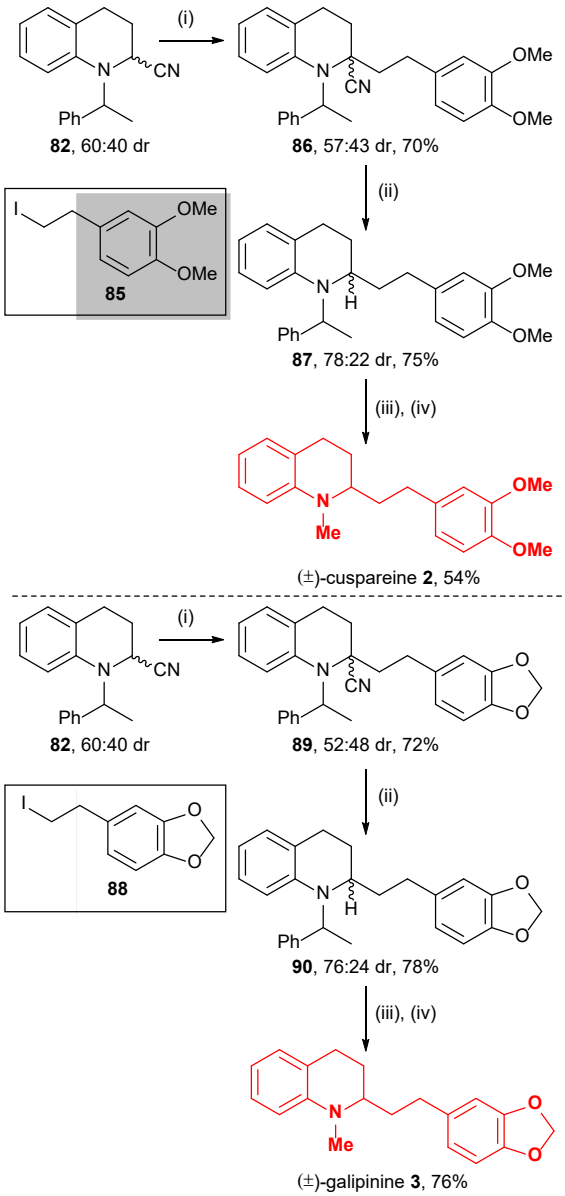
Treatment of 1,2,3,4-tetrahydroquinoline **80** with BuLi then α-methylbenzyl bromide gave **81** in 80% yield. Electrolysis of **81** in MeOH containing LiOAc (as a supporting electrolyte), NaOMe (to facilitate proton loss from the intermediate radical cation), and NaCN (as a trapping agent) gave **82** as a 60:40 mixture of diastereoisomers in 75% combined yield. Treatment of **82** with LDA then 1-iodopentane gave **83** as a 55:45 mixture of diastereoisomers in 75% combined yield. Removal of the cyano group from **83** was then achieved using $NaBH_4$ in EtOH, which gave **84** as an 80:20 mixture of diastereoisomers in 89% combined yield. Hydrogenolysis of **84** followed by *N*-methylation (K_2CO_3/MeI) of the intermediate noralkaloid **30** furnished (±)-angustureine **1** in 79% yield (Scheme 25). A similar sequence of reactions applied to **82** using **85** as the electrophile led to (±)-cuspareine **2** in 28% overall yield from **82**, whilst use of **88** as the electrophile led to (±)-galipinine **3** in 43% overall yield from **82** (Scheme 26).

Scheme 25.[a]



[a]*Reagents and conditions:* (i) BuLi, THF, −80 °C to −20 °C, 3 h, then α-methylbenzyl bromide, −80 °C to 20 °C, 4 h; (ii) LiOAc, Na, NaCN, MeOH, electrolysis; (iii) LDA, THF, −80 °C to −20 °C, 3 h, then 1-iodopentane, −80 °C to −20 °C, 3 h; (iv) $NaBH_4$, EtOH, rt, 12 h, then reflux, 3 h; (v) H_2, Pd/C, MeOH, EtOAc, rt, 48 h; (vi) MeI, K_2CO_3, THF, reflux, 12 h.

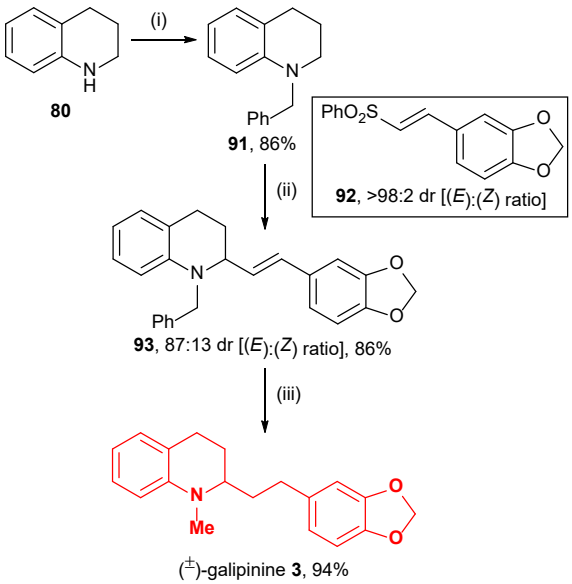
Scheme 26.[a]



[a]*Reagents and conditions:* (i) LDA, THF, −80 °C, to −20 °C, 3 h, then **85**, −80 °C to −20 °C, 12 h; (ii) LDA, THF, −80 °C, to −20 °C, 3 h, then **88**, −80 °C to −20 °C, 12 h; (iii) $NaBH_4$, EtOH, rt, 12 h, then reflux, 3 h; (iii) H_2, Pd/C, MeOH, EtOAc, rt, 48 h; (iv) MeI, K_2CO_3, THF, reflux, 12 h.

MacMillan *et al.*[40] have employed photoredox catalysis to effect α-vinylation via C−H activation of a range of amines, and have applied this method as the key step in a synthesis of (±)-galipinine **3**. *N*-Benzylation of 1,2,3,4-tetrahydroquinoline **80** gave **91** in 86% yield, and then coupling of **91** with vinyl sulfone **92** under photoredox conditions gave **93** as an 87:13 mixture of olefin isomers in 86% combined yield. One-pot hydrogenolysis and reductive *N*-methylation furnished (±)-galipinine **3** in 94% yield (Scheme 27).

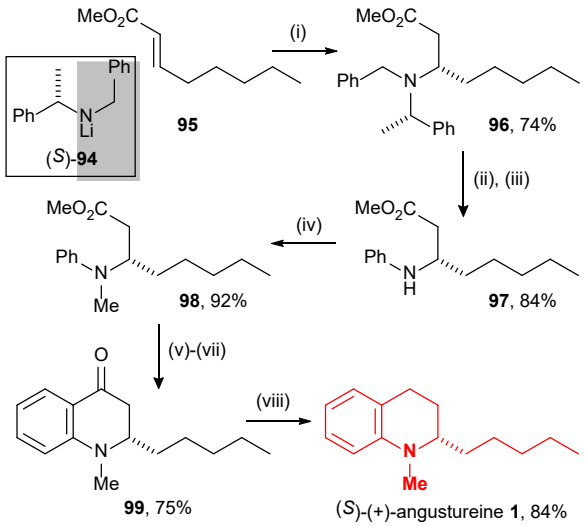
Scheme 27.[a]



[a]*Reagents and conditions:* (i) BnCl, K_2CO_3, MeOH, reflux, 5 h; (ii) **92**, $[IrAr_2(bbbp)]^+[PF_6]^-$, CsOAc, DCE, *hν*, rt, 34 h; (iii) H_2, HCHO (37% aq), Pd/C, MeOH, rt, 38 h. Ar = 2-(2′,4′-difluorophenyl-5-trifluoromethyl)phenyl. bbbp = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

Aza-conjugate Addition. Ma *et al.*[41] reported a synthesis of (*S*)-(+)-angustureine **1** using the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **94** as a chiral ammonia equivalent as the key step to construct the requisite stereogenic centre of the target. Thus, conjugate addition of (*S*)-**94** to α,β-unsaturated methyl ester **95** gave the corresponding β-amino ester **96** in 74% yield. Hydrogenolytic *N*-debenzylation of **96** was followed by copper-catalysed *N*-arylation to give **97** in 84% overall yield. *N*-Methylation upon treatment of **97** with MeI and AgO gave **98** in 92% yield, and was followed by intermolecular Friedel-Crafts-type reaction (sequential ester hydrolysis, activation of the resultant carboxylic acid functionality as the corresponding acyl chloride, and then treatment with $AlCl_3$) to give **99** in 75% overall yield. Hydrogenolytic reduction of the carbonyl functionality within **99** then gave (*S*)-(+)-angustureine **1** in 84% yield (Scheme 28).

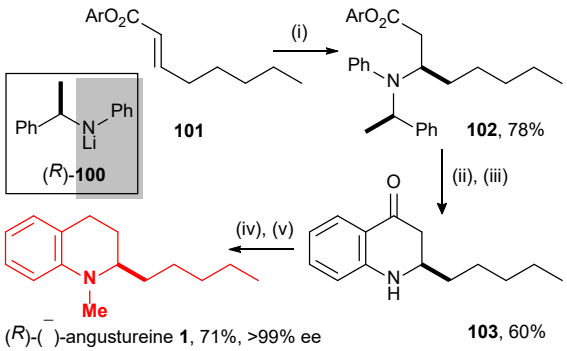
Scheme 28.[a]



[a]*Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **94**, THF, −78 °C, 2 h; (ii) H_2, Pd/C, AcOH, 40 °C, 48 h; (iii) PhI, CuI, K_2CO_3, DMF, 110 °C, 48 h; (iv) MeI, AgO, DMF, rt, 3 h, then 60 °C; (v) NaOH, MeOH, H_2O, 60 °C, 2 h; (vi) $SOCl_2$, CH_2Cl_2, rt, 2 h; (vii) $AlCl_3$, CH_2Cl_2, rt, 24 h; (viii) H_2, Pd/C, MeOH, AcOH, rt, overnight.

Davies *et al.*[12] later developed lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **100** as a chiral aniline equivalent for conjugate addition which was used in a related but more step-economical synthesis of (*R*)-(−)-angustureine **1**. Conjugate addition of **100** to α,β-unsaturated *p*-methoxyphenyl ester **101** gave the corresponding β-amino ester **102** in 78% yield. Ester hydrolysis gave the corresponding carboxylic acid, which upon treatment with PPA furnished **103** in 60% yield (presumably, intramolecular Fridel-Crafts-type reaction was followed by loss of the *N*-α-methylbenzyl group from the vinylogous amide under the acidic conditions of the reaction). Reduction of **103** with $LiAlH_4$ was followed by treatment of the resultant with MeI and K_2CO_3 to give (*R*)-(−)-angustureine **1** in 71% overall yield and >99% ee (Scheme 29).

Scheme 29.[a]

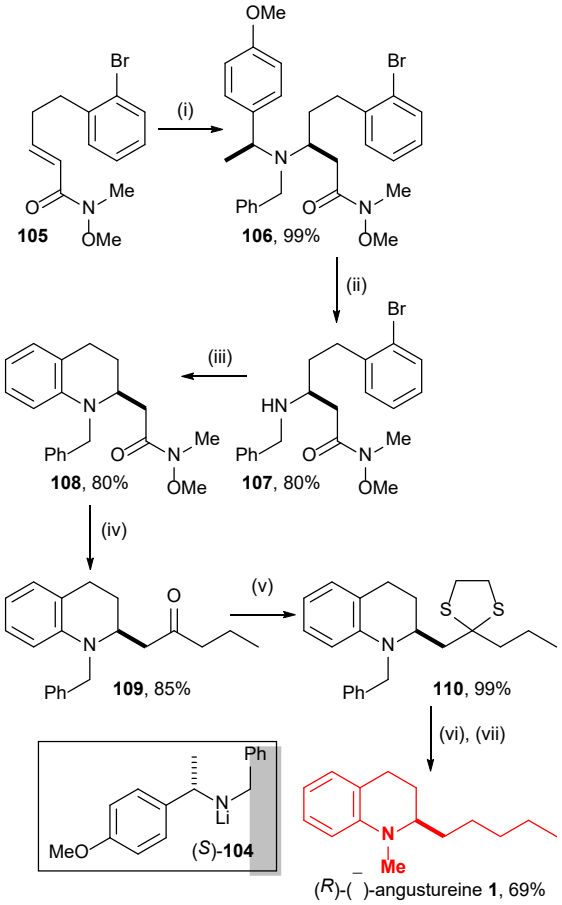


[a]*Reagents and conditions:* (i) lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **100**, THF, −78 °C, 2 h; (ii) LiOH, THF, H_2O, 40 °C, 3 h; (iii) PPA, 100 °C, 16 h; (iv) $LiAlH_4$, THF, reflux, 16 h; (viii) MeI, K_2CO_3, THF, reflux, 16 h. Ar = *p*-methoxyphenyl.

This cyclisation method did not prove applicable to the synthesis of the remaining members of the Hancock alkaloid family and therefore Davies *et al.*[13,14] developed an alternative approach to enable access to all of the family members. Application of the revised synthesis to (*R*)-(−)-angustureine **1** began with conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **104** to α,β-unsaturated Weinreb amide **105**, which gave β-amino amide **106** in 99% yield and >95:5 dr. Treatment of **106** with HCO_2H and Et_3SiH effected removal of the *N*-α-methyl-*p*-methoxybenzyl group to give **107** in 80% yield, with subsequent Buchwald-Hartwig coupling giving tetrahydroquinoline **108** in 80% yield. Treatment of **108** with propyllithium gave the corresponding ketone **109** after work-up. The carbonyl group was reduced to a methanediyl group by initial conversion to dithiane **110**, followed by treatment with Raney-Ni, and the *N*-benzyl group was removed upon hydrogenolysis in the presence of formalin, which effected reductive *N*-methylation in situ to give (*R*)-(−)-angustureine **1** in 69% yield (Scheme 30). Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **104** to α,β-unsaturated Weinreb amide **102** gave the enantiomeric the β-amino amide *ent*-**106**, which was elaborated to *ent*-**108**. Addition of the requisite aryllithium reagent followed by reduction of the carbonyl group and one-pot *N*-debenzylation and *N*-

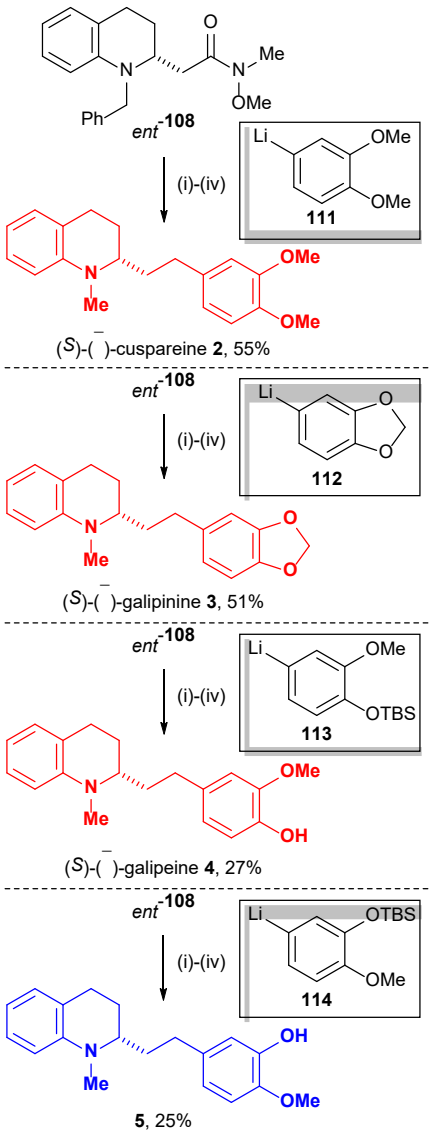
methylation gave the remainder of the tetrad, *viz.* (*S*)-(−)-cuspareine **2**, (*S*)-(−)-galipinine **3** and (*S*)-(−)-galipeine **4**. A sample of **5**, the originally reported (erroneous) structure of galipeine, was also prepared using this method (Scheme 31).

Scheme 30.[a]



[a]*Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **104**, 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; (iv) *n*-PrLi, THF, −78 °C, 1.5 h; (v) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, AcOH, rt, 16 h; (vi) Raney-Ni, EtOH, THF, 80 °C, 1 h; (vii) H_2, HCHO (37% aq), Pd/C, MeOH, rt, 24 h.

Scheme 31.[a]

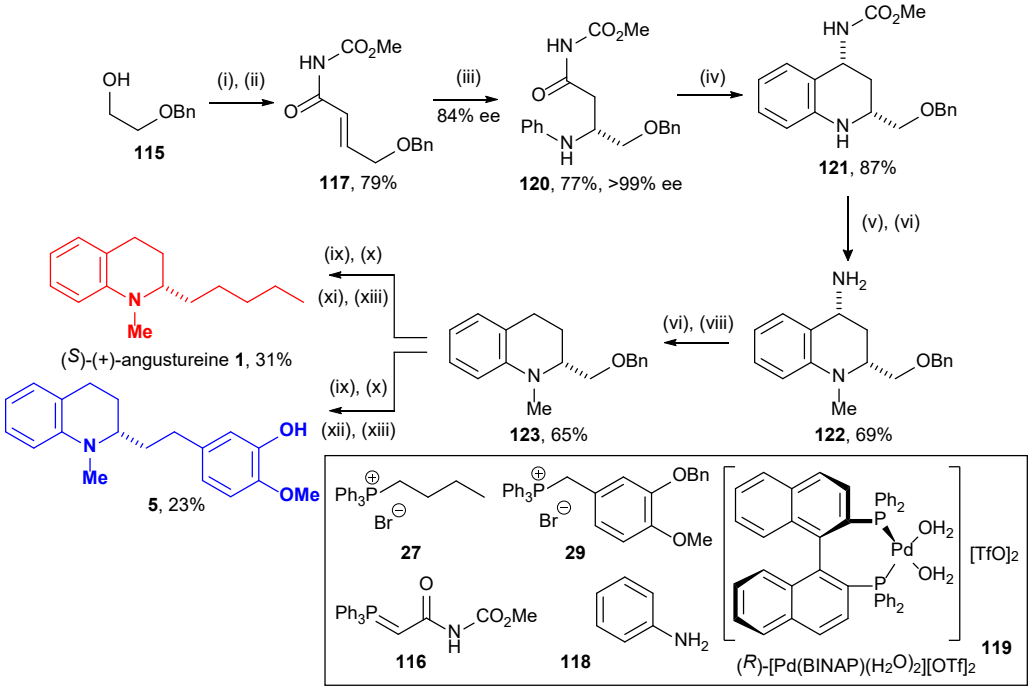


[a]*Reagents and conditions:* (i) ArLi (**111**–**114**), THF, −78 °C, 1.5 h; (ii) $LiAlH_4$, THF, reflux, 16 h; (iii) TFA, Et_3SiH, rt, 16 h; (iv) H_2, HCHO (37% aq), Pd/C, MeOH, rt, 24 h.

Hii *et al.*[42] reported a catalytic asymmetric aza-conjugate addition of aniline as the stereodefining step in syntheses of members of the Hancock alkaloid family. Swern oxidation of monoprotected diol **115** followed by olefination of the resultant aldehyde with ylide **116** gave the requisite α,β-unsaturated carbonyl derivative **117** in 74% yield. Treatment of **117** with aniline **118** in the presence of catalyst **119** in PhMe gave the corresponding adduct **120** in 84% ee, which was isolated in 77% yield and >99% ee after enantiomeric enrichment by iterative crystallisations. Cyclisation of **120** to the corresponding 1,2,3,4-tetrahydroquinoline derivative **121** was achieved (in 87% yield) upon treatment with $NaBH_4$ in the presence of $MgCl_2$. Reductive *N*-methylation followed by removal of the carbamate functionality then provided **122** in 69% yield. The 4-amino functionality within **122** was then removed via initial conversion to the corresponding 4-keto derivative followed by reduction with $LiAlH_4$ in the presence of $AlCl_3$, giving **123** in 65% yield. Hydrogenolytic removal of the *O*-benzyl group from **123** followed by oxidation to the corresponding aldehyde, Wittig olefination with the ylide derived from **27**, and final hydrogenation of the resultant mixture

of olefins gave (*S*)-(+)-angustureine **1** in 31% yield from **123**. This sequence of reactions was also performed using **29** as the ylide precursor; in this case hydrogenolysis of the *O*-benzyl protecting group also occurred in the final step, giving **5**, the originally reported (erroneous) structure of galipeine, in 23% yield from **123** (Scheme 32). A racemic sample of **123** was also subjected to the final reaction sequence using **28** as the ylide precursor, which furnished (±)-galipinine **3** in 22% yield from **123**.

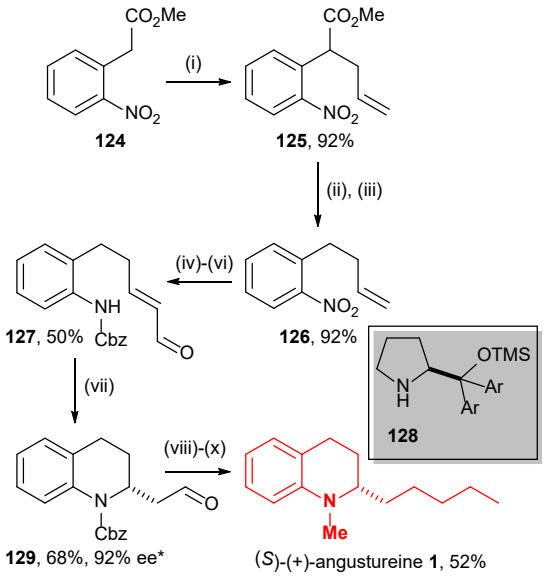
Scheme 32.[a]



[a]*Reagents and conditions:* (i) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h; (ii) **116**, CH_2Cl_2, rt, 16 h; (iii) **118**, **119**, PhMe, 50 °C, 38 h; (iv) $NaBH_4$, $MgCl_2{\cdot}6H_2O$, EtOH, THF, 0 °C, 30 min; (v) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, 5 °C, 1 h; (vi) TMSI, MeCN, rt, 18 h; (vii) 4-formyl-1-methylpyridinium benzenesulfonate, CH_2Cl_2, DMF, rt, 1 h, then DBU, 1 h, then oxalic acid (sat aq), 16 h; (viii) $LiAlH_4$, $AlCl_3$, THF, Et_2O, reflux; (ix) H_2, Raney-Ni, EtOH, THF, reflux; (x) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h; (xi) **27**, KO^{t}Bu, THF, 0 °C, 16 h; (xii) **29**, KO^{t}Bu, THF, 0 °C, 16 h; (xiii) H_2, Pd/C, EtOH, THF, rt, 16 h.

An intramolecular enantioselective, organocatalytic aza-conjugate addition was developed by Fustero *et al.*[43] and deployed as the key step in a synthesis of (*S*)-(+)-angustureine **1**. Allylation of the enolate derived from methyl 2-(*o*-nitrophenyl)acetate **124** gave **125** in 92% yield and was followed by ester hydrolysis and decarboxylation to give **126** in 92% yield. Reduction of **126** using Zn in AcOH and treatment of the resultant primary amine with CbzCl was followed by cross-metathesis with acrolein mediated by Hoveyda-Grubbs II catalyst to give **127**, the precursor to the intramolecular aza-conjugate addition reaction, in 50% yield from **126**. Treatment of **127** with L-proline derivative **128** gave the 2-substituted 1,2,3,4-tetrahydroquinoline **129** in 68% yield and 92% ee (determined for the corresponding primary alcohol, formed upon treatment of the crude reaction mixture with $NaBH_4$), with subsequent Wittig olefination, reduction of the carbamate functionality with $LiAlH_4$ and catalytic hydrogenation giving (*S*)-(+)-angustureine **1** in 52% yield (Scheme 33).

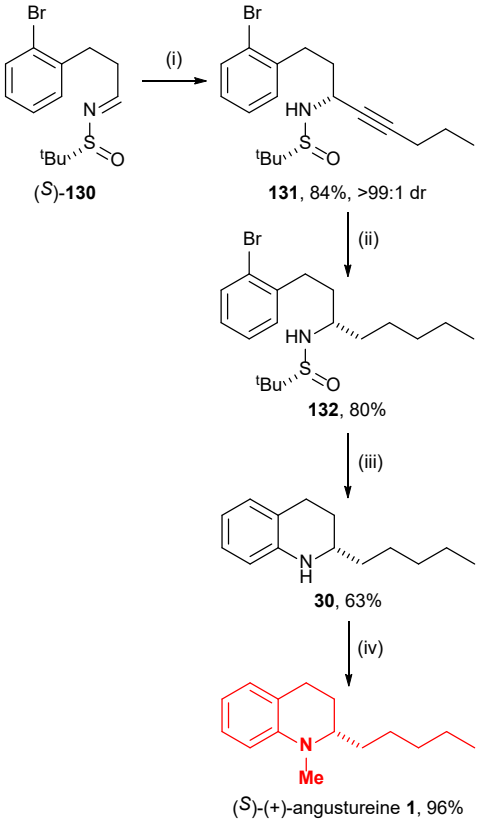
Scheme 33.[a]



[a]*Reagents and conditions:* (i) allyl iodide, K_2CO_3, 18-crown-6, MeCN, reflux, 8 h; (ii) NaOH (1M aq), dioxane, rt, 3 h; (iii) K_2CO_3, DMF, 50 °C, 45 min; (iv) Zn, AcOH, rt, 5 h; (v) CbzCl, K_2CO_3, dioxane, rt, 1 h; (vi) acrolein, Grubbs-Hoveyda II, CH_2Cl_2, rt, 12 h; (vii) **128**, $PhCO_2H$, $CHCl_3$, −30 °C, 24 h; (viii) $[Ph_3P(CH_2)_2Me]^+[Br]^-$, NaHMDS, PhMe, rt, 3 h; (ix) $LiAlH_4$, Et_2O, rt, 3 h; (x) H_2, Pd/C, EtOAc, rt, 12 h. *Enantiomeric excess was determined for the corresponding primary alcohol, formed upon treatment of the crude reaction mixture with $NaBH_4$. Ar = 3,5-(bistrifluoromethyl)phenyl.

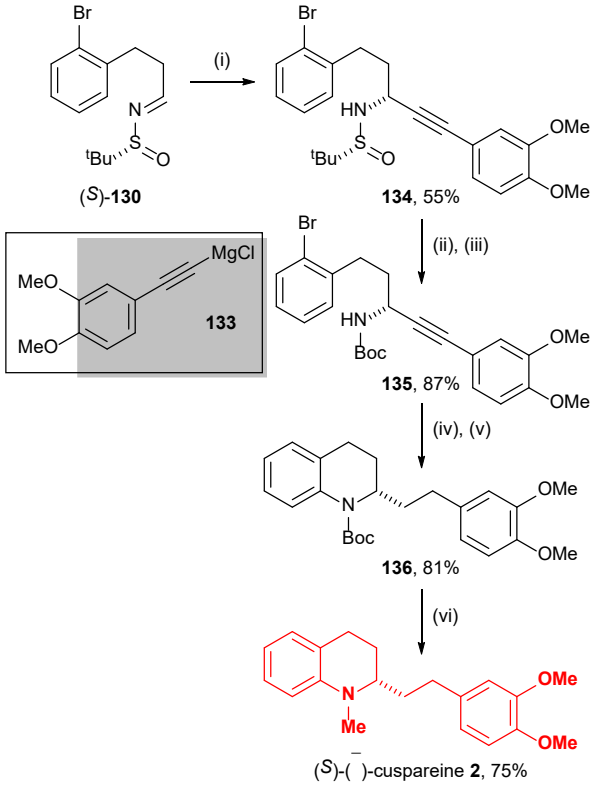
Nucleophilic Addition to a *tert*-Butylsulfinylimine. The C(2)-stereogenic centre of the Hancock alkaloids has been generated upon addition of a range of carbanion equivalents to the enantiomers of *tert*-butylsulfinylimine **130**, derived from condensation of 3-(*o*-bromophenyl)propanal with the requisite enantiomer of *tert*-butylsulfinimide. Wang *et al.*[44] were first to report a synthesis of this type, using alkynyl Grignard reagents as nucleophiles. Addition of $Me(CH_2)_2C{\equiv}CMgCl$ to (*S*)-**130** gave **131** in 84% yield and >99:1 dr. Hydrogenation over PtO_2 effected reduction of the alkyne moiety to give **132** in 80% yield and then subsequent intramolecular Buchwald-Hartwig coupling was accompanied by loss of the *tert*-butylsulfinyl group, giving norangustureine **30** in 63% yield. Reductive *N*-methylation of **30** then furnished (*S*)-(+)-angustureine **1** in 96% yield (Scheme 34). A similar strategy was used to enable the synthesis of (*S*)-(−)-cuspareine **2** from (*S*)-**130**; in the key step in this case, addition of alkynyl Grignard reagent **133** to *tert*-butylsulfinylimine (*S*)-**130**, gave **134** in 55% yield (Scheme 35).

Scheme 34.[a]



[a]*Reagents and conditions:* (i) $Me(CH_2)_2C{\equiv}CMgCl$, CH_2Cl_2, −78 °C, 2 h, then −78 °C to rt, overnight; (ii) H_2, PtO_2, EtOH, rt, 5 h; (iii) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, PhMe, 100 °C, overnight; (iv) HCHO (30% aq), $NaBH_3CN$, AcOH, MeCN, rt, 90 min.

Scheme 35.[a]

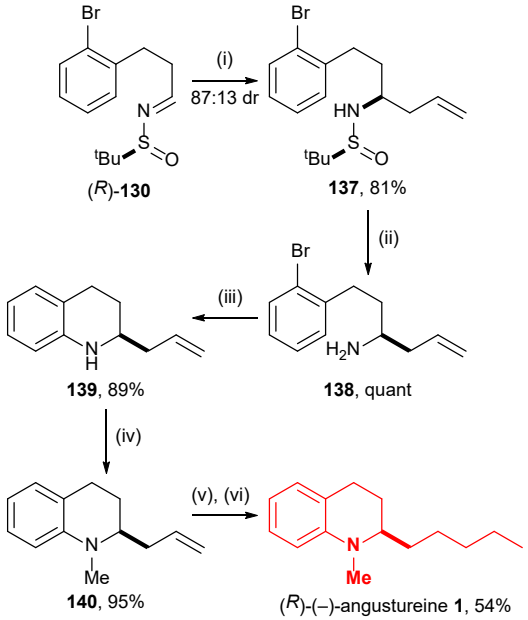


[a]*Reagents and conditions:* (i) **133**, CH_2Cl_2, −78 °C, 2 h, then −78 °C to rt, overnight; (ii) HCl (2 M, aq), MeOH, rt, 4 h; (iii) Boc_2O, $NaHCO_3$, CH_2Cl_2, rt, overnight; (iv) H_2, PtO_2, EtOH, rt, 5 h; (v) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, PhMe, 100 °C, overnight; (vi) $LiAlH_4$, THF, reflux, 5 h.

Foubelo, Yus, *et al.*[45] effected the diastereoselective indium-mediated allylation of *tert*-butylsulfinylimine (*R*)-**130** in a synthesis of (*R*)-(−)-angustureine **1**. Treatment of (*R*)-**130** with allyl bromide

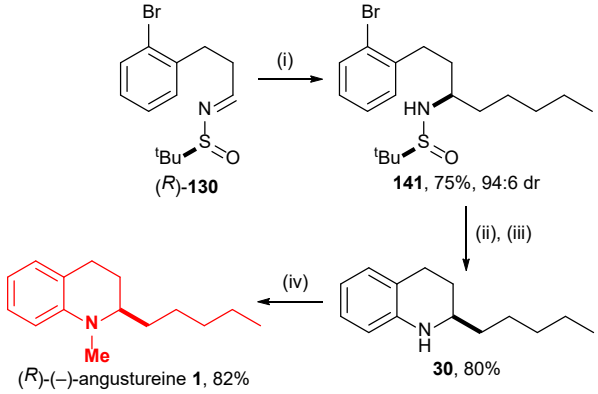
and indium powder gave **137** in 87:13 dr, which was isolated in 81% yield after chromatography. Removal of the *tert*-butylsulfinyl group was achieved quantitatively upon treatment of **137** with 6 M aq HCl to give **138**, and then intramolecular Buchwald-Hartwig coupling of **138** gave 2-allyl-1,2,3,4-tetrahydroquinoline **139** in 89% yield. Reductive *N*-methylation of **139** gave **140** in 95% yield, and then cross-metathesis with *cis*-hexene promoted by Hoveyda-Grubbs catalyst followed by hydrogenation gave (*R*)-(−)-angustureine **1** in 54% yield (Scheme 36). Foubelo, Yus, *et al.*[46] went on to develop an improved approach to (*R*)-(−)-angustureine **1** which used the addition of pentylmagnesium bromide to *tert*-butylsulfinylimine (*R*)-**130** to give **141** in 94:6 dr, which was isolated in 75% yield. Sequential hydrolysis of the *tert*-butylsulfinyl group, intramolecular Buchwald-Hartwig coupling, and final reductive *N*-methylation then gave (*R*)-(−)-angustureine **1** (Scheme 37). A directly analogous sequence of reactions, but using Grignard reagent **142** and the enantiomeric *tert*-butylsulfinylimine (*S*)-**130**, gave access to (*S*)-(−)-cuspareine **2** in 17% overall yield from (*S*)-**130** (Scheme 38).

Scheme 36.[a]



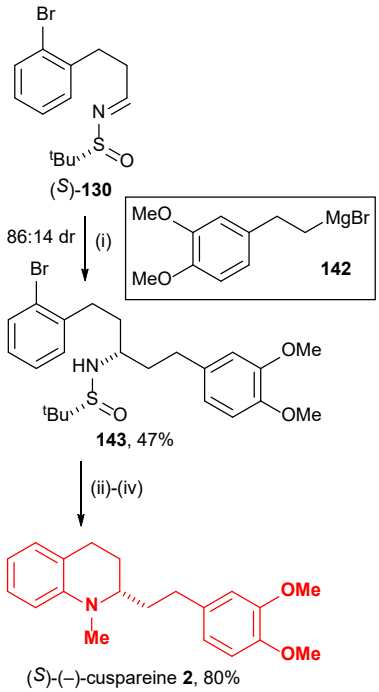
[a]*Reagents and conditions:* (i) In powder, NaBr (sat, aq), 23 °C, 48 h; (ii) HCl (6 M, aq), THF, rt, 1 h; (iii) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, PhMe, 110 °C, 21 h; (iv) paraformaldehyde, $NaBH_3CN$, AcOH, MeCN, 23 °C, 16 h; (v) *cis*-3-hexene, Hoveyda-Grubbs, CH_2Cl_2, 40 °C, 3 h; (vi) H_2, Pd/C, MeOH, 23 °C, 12 h.

Scheme 37.[a]



[a]*Reagents and conditions:* (i) $Me(CH_2)_4MgBr$, PhMe, rt, 4 h; (ii) HCl (6 M, aq), THF, 20 °C, 1 h; (iii) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, PhMe, 115 °C, 20 h; (iv) paraformaldehyde, $NaBH_3CN$, AcOH, MeCN, 20 °C, 15 h.

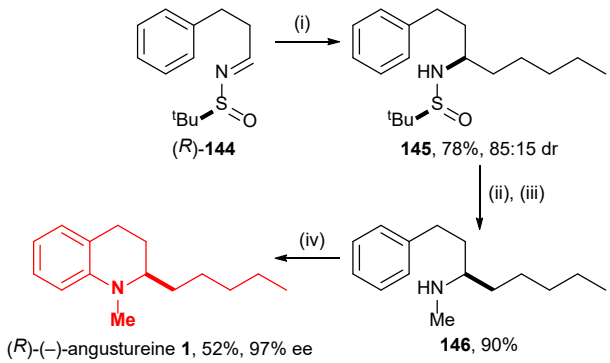
Scheme 38.[a]



[a]*Reagents and conditions:* (i) **142**, PhMe, rt, 4 h; (ii) HCl (6 M, aq), THF, 20 °C, 1 h; (iii) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, PhMe, 115 °C, 20 h; (iv) paraformaldehyde, $NaBH_3CN$, AcOH, MeCN, 20 °C, 15 h.

An alternative method to effect this type of cyclisation, reliant on a radical-mediated C−H activation, was developed by Marsden *et al.*[47] and deployed in an asymmetric synthesis of (*R*)-(−)-angustureine **1**. Addition of propylmagnesium bromide to *tert*-butylsulfinylimine (*R*)-**144** [derived from the condensation of hydrocinnamaldehyde with (*R*)-*tert*-butylsulfinylamine] gave **145** in 78% yield and 85:15 dr. *N*-Methylation (LiHMDS then MeI) followed by acidic removal of the *N*-*tert*-butylsulfinyl group gave **146** in 90% yield. Treatment of **146** with NCS in CH_2Cl_2 in the dark followed by introduction of $MeSO_3H$ to the reaction flask and irradiation with UV light gave (*R*)-(−)-angustureine **1** in 52% yield and 97% ee (Scheme 39). Both steps of the cyclisation procedure have also successfully been carried out in flow with similar overall efficiency.[48]

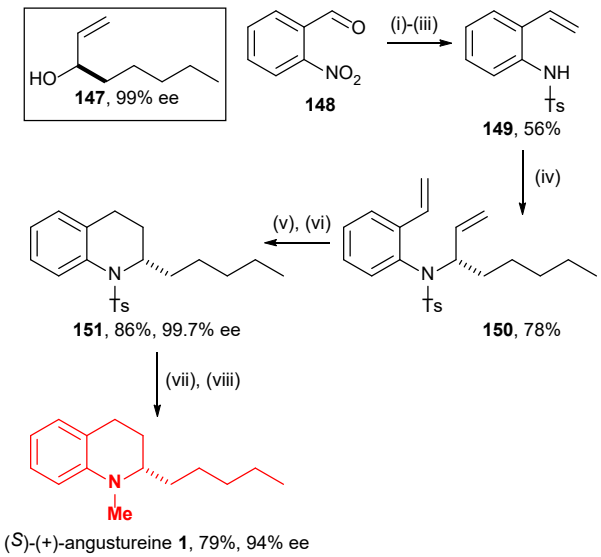
Scheme 39.[a]



[a]*Reagents and conditions:* (i) $C_5H_{11}MgBr$, THF, −78 °C, 2 h; (ii) LiHMDS, THF, 0 °C, 1 h, then MeI, rt, 2 h; (iii) HCl (3 M, MeOH), rt, 1 h; (iv) NCS, CH_2Cl_2, rt, 30 min, then $MeSO_3H$, UV light, rt, 3 h.

Amination of a Secondary Alcohol. Amination of secondary alcohol **12** to give the corresponding amine **13** with inversion of configuration, by means of a Mitsunobu reaction with a suitable nitrogen nucleophile, has been used to generate the C(2)-stereogenic centre of the Hancock alkaloids. In most examples of this strategy, the reaction proceeds in an intermolecular sense, with the 2-substituted 1,2,3,4-tetrahydroquinoline scaffold then being constructed in a subsequent ring-closing process. Arisawa, Nishida, *et al.*[49] were first to report this approach in the synthesis of (*S*)-(+)-angustureine **1**. Wittig olefination of 2-nitrobenzaldehyde **148** was followed by reduction of the nitro functionality and tosylation of the resultant amino functionality to give **149** in 56% overall yield. The key step, amination of the commercially available, enantiopure allylic alcohol **147** (99% ee) using aniline derivative **149** in a Mitsunobu reaction gave **150** in 78% yield. Subsequent ring-closing metathesis of **150** using Grubbs II catalyst followed by catalytic hydrogenation over PtO_2 gave 2-propyl 1,2,3,4-tetrahydroquinoline derivative **151** in 86% overall yield and 99.7% ee. Removal of the *N*-tosyl group from **151** was accomplished using sodium anthracenide and was followed by *N*-methylation of the intermediate noralkaloid **30** to give (*S*)-(+)-angustureine **1** in 79% yield overall yield and 94% ee (Scheme 40).

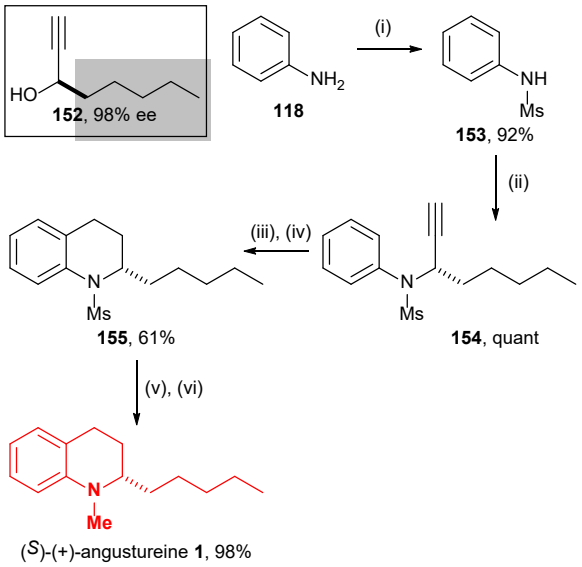
Scheme 40.[a]



[a]*Reagents and conditions:* (i) $[Ph_3PMe]^+[Br]^-$, KHMDS, THF, rt, 1 h; (ii) Zn powder, AcOH, rt, overnight; (iii) TsCl, pyridine, CH_2Cl_2, rt, 1 h; (iv) **147**, DEAD, PPh_3, THF, rt, 2 h; (v) Grubbs II, CH_2Cl_2, 50 °C, 1 h; (vi) H_2, PtO_2, MeOH, rt, 12 h; (vii) sodium anthracenide, DME, −65 °C, 10 min; (viii) MeI, K_2CO_3, THF, reflux, 10 h.

A similar strategy to (*S*)-(+)-angustureine **1** was subsequently reported by Ryu.[50] Initial *N*-mesylation of aniline **118** gave **153** in 92% yield. Amination of the commercially available, enantiopure propargylic alcohol **152** (98% ee) with **153** via the Mitsunobu reaction gave **154** in quantitative yield. Catalytic intramolecular hydroarylation of **154** was accomplished using $PtCl_4$, with ensuing catalytic hydrogenation over Pd/C giving 2-propyl-1,2,3,4-tetrahydroquinoline derivative **155** in 61% overall yield. Exchange of the *N*-mesyl group for an *N*-methyl group gave (*S*)-(+)-angustureine **1** in 98% overall yield (Scheme 41).

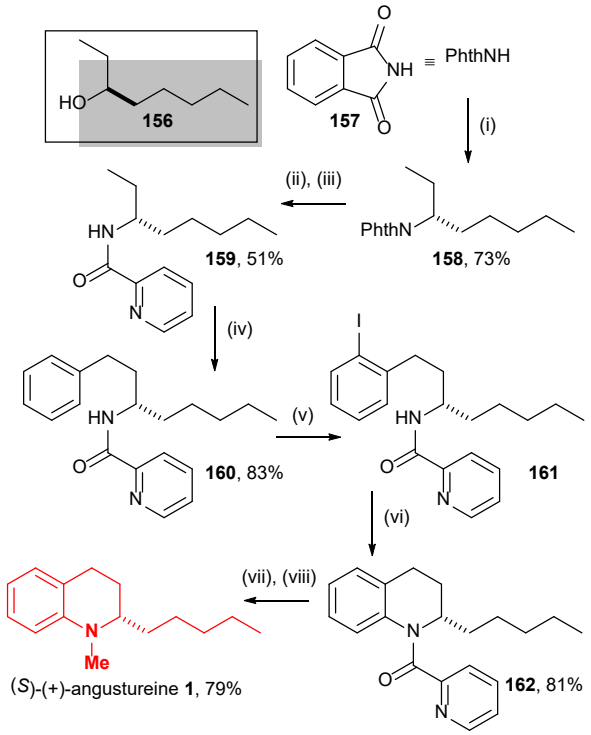
Scheme 41.[a]



[a]*Reagents and conditions:* (i) MsCl, pyridine, CH_2Cl_2, 0 °C, 1 h; (ii) **152**, DEAD, PPh_3, THF, rt, 1 h; (iii) $PtCl_4$, DCE, 70 °C, 2 h; (iv) H_2, Pd/C, EtOH, rt, 3 h; (v) Red-Al, PhMe, 80 °C, 30 min; (vi) MeI, K_2CO_3, THF, reflux, 24 h.

Chen *et al.*[51] developed a method for the construction of 1,2,3,4-tetrahydroquinolines from a range of amines via sequential C−H functionalisations, which they deployed in a synthesis of (*S*)-(+)-angustureine **1**. The precursor for their key synthetic sequence was prepared via initial Mitsunobu reaction of commercially available, enantiopure 3-octanol **156** with phthalimide **157** (PhthNH), which gave **158** in 73% yield. An *N*-protecting group swap via hydrazinolysis of **158** and acylation of the resultant free amino functionality gave *N*-picolinamide **159** in 51% overall yield. Palladium-mediated functionalisation of a γ-C−H bond enabled arylation, giving **160** in 83% yield. Then, treatment of **160** with NIS and $HBF_4{\cdot}OEt_2$ effected iodination of an *ortho*-C−H bond to give **161** and subsequent copper-mediated, intramolecular *N*-arylation gave 2-pentyl 1,2,3,4-tetrahydroquinoline derivative **162** in 81% overall yield. Removal of the *N*-picolinamide functionality from **162** was achieved upon treatment with $LiBEt_3H$ and the resultant noralkaloid **30** was *N*-methylated (K_2CO_3/MeI) to give (*S*)-(+)-angustureine **1** in 79% yield (Scheme 42).

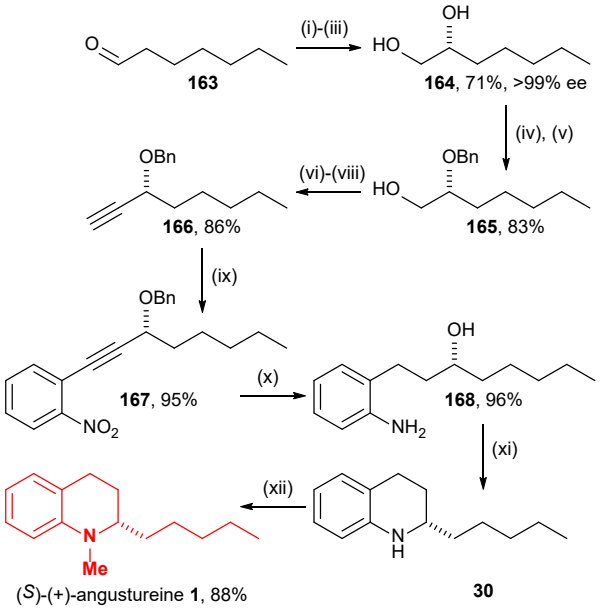
Scheme 42.[a]



[a]*Reagents and conditions:* (i) **156**, DEAD, PPh_3, THF, rt, overnight; (ii) $NH_2NH_2{\cdot}H_2O$, MeOH, rt, overnight; (iii) picolinic acid, EDCI, HOBt, $^iPr_2NEt$, CH_2Cl_2, rt, overnight; (iv) PhI, $Pd(OAc)_2$, $(BnO)_2P(O)OH$, Ag_2CO_3, LiCl, *tert*-amyl alcohol, PhMe, 110 °C, 24 h; (v) NIS, $HBF_4{\cdot}OEt_2$, TFA, CH_2Cl_2, 0 °C, 4 h; (vi) CuI, CsOAc, DMSO, 90 °C, 20 h; (vii) $LiBEt_3H$ THF, 0 °C, 2 h; (viii) MeI, K_2CO_3, THF, 80 °C, overnight.

Pandey *et al.*[52] reported an intramolecular variant of this Mitsunobu approach, in which formation of the requisite nitrogen-bearing stereogenic centre necessarily occurred in concert with the formation of the 2-substituted 1,2,3,4-tetrahydroquinoline scaffold. Enantioselective α-aminoxylation of heptanal **163** upon treatment with PhNO and L-proline to give an intermediate α-aminoxylaldehyde was followed by sequential reduction of the aldehyde moiety with $NaBH_4$ and cleavage of the N−O bond with $CuSO_4$ to give diol **164** in 71% overall yield and >99% ee. Chemoselective *O*-benzyl protection of the secondary hydroxyl group within **164** was achieved via initial conversion to the corresponding 1,2-benzylidene acetal followed by treatment with DIBAL-H, giving **165** in 83% overall yield. Swern oxidation of the primary hydroxyl group was followed by Corey-Fuchs reaction to give the terminal alkyne **166** in 86% overall yield. Sonogashira coupling of **166** with 1-iodo-2-nitrobenzene gave **167** in 95% yield, which was followed by exposure of **167** to H_2 in the presence of Pd/C, resulting in one-pot reduction of the nitro group and alkyne functionality, and cleavage of the *O*-benzyl protecting group to give amino alcohol **168** in 96% yield. Treatment of **168** with DEAD and PPh_3 effected intramolecular Mitsunobu reaction, with attendant inversion of configuration, to give norangustureine **30**, which was immediately subjected to reductive *N*-methylation to give (*S*)-(+)-angustureine **1** in 88% yield (Scheme 43).

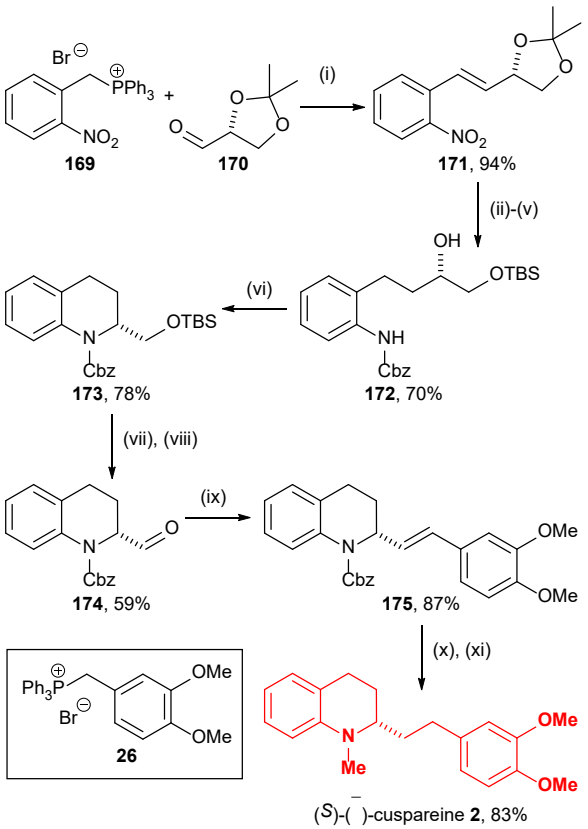
Scheme 43.[a]



[a]*Reagents and conditions:* (i) PhNO, L-proline, DMSO, rt, 12 h; (ii) $NaBH_4$, MeOH, 0 °C, 15 min; (iii) $CuSO_4 \cdot 5H_2O$, MeOH, 0 °C to rt, 12 h; (iv) $PhCH(OMe)_2$, PPTS, PhH, reflux, 1 h; (v) DIBAL-H, CH_2Cl_2, −40 °C to rt, 2 h; (vi) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C, 2 h; (vii) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min; (viii) BuLi, THF, −78 °C to rt, 3 h; (ix) 1-iodo-2-nitrobenzene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, reflux, 3 h; (x) H_2, Pd/C, EtOAc, rt, 24 h; (xi) DEAD, PPh_3, CH_2Cl_2, rt, 12 h; (xii) HCHO (37% aq), $NaBH_3CN$, AcOH, MeCN, rt, 10 h.

Basaveswara Rao, Akula, *et al.*[53] also demonstrated an intramolecular variant of this approach. In their synthesis, the precursor alcohol **172** was assembled from *O*-isopropylidene glyceraldehyde **170** and in the key step, exposure of **172** to DIAD and PPh_3 resulted in intramolecular Mitsunobu reaction to give 2-substituted 1,2,3,4-tetrahedroquinoline derivative **173** in 78% yield. A further series of transformations, including use of a Wittig reaction with phosphorane **26** to complete assembly of the C(2)-side chain, then gave (*S*)-(−)-cuspareine **2** (Scheme 44).

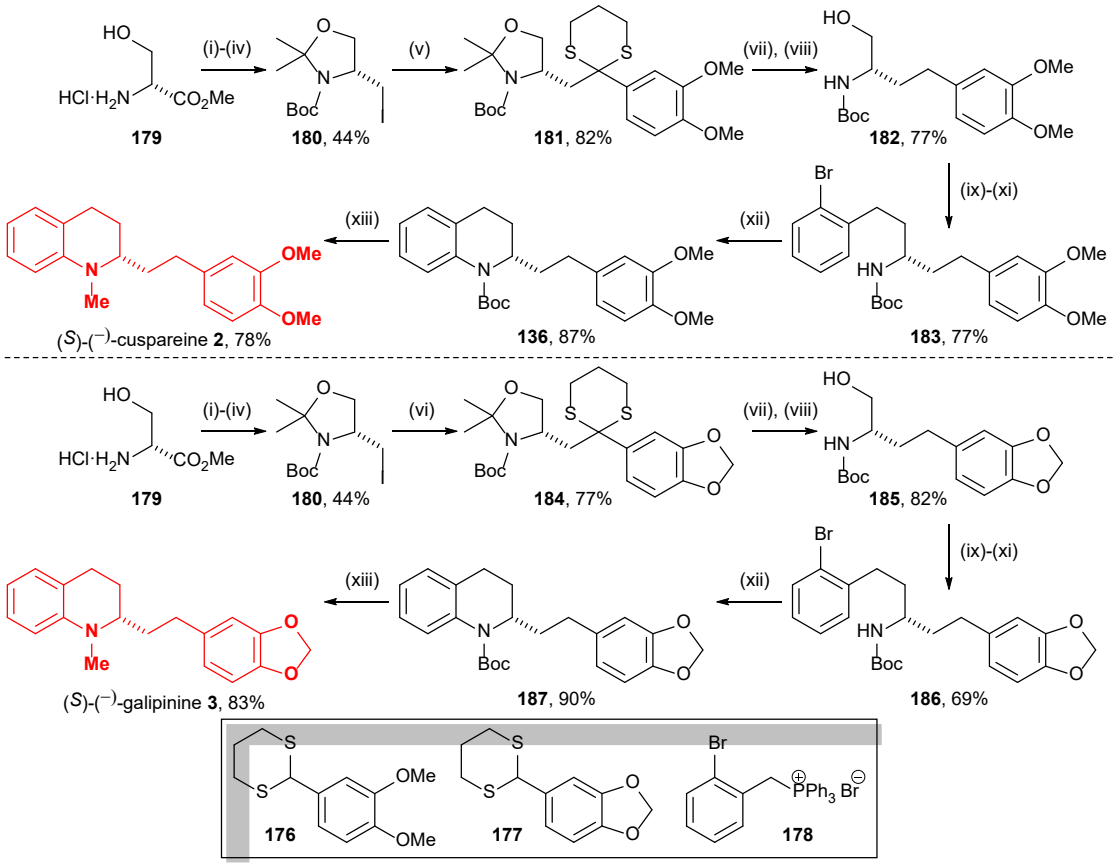
Scheme 44.[a]



[a]*Reagents and conditions:* (i) K_2CO_3, MeCN, rt, 12 h; (ii) H_2, Pd/C, MeOH, rt, 4 h; (iii) CbzCl, DIPEA, CH_2Cl_2, 0 °C, 1 h; (iv) $(CO_2H)_2$, MeCN, H_2O, rt, 14 h; (v) TBSCl, imidazole, THF, 0 °C, 2 h; (vi) DIAD, PPh_3, pyridine, THF, 15 °C, 2 h; (vii) $SnCl_2$, EtOH, H_2O, rt, 12 h; (viii) DMP, CH_2Cl_2, rt, 2 h; (ix) **26**, K_2CO_3, MeCN, rt, 12 h; (x) $[NH_4][HCO_2]$, Pd/C, MeOH, 60 °C, 16 h; (xi) MeI, DIPEA, DMF, 0 °C, 16 h.

Chiral Pool Synthesis from D-Serine. Rampanicker *et al.*[54] used D-serine derived iodide **180** as a common starting material from which both (*S*)-(−)-cuspareine **2** and (*S*)-(−)-galipinine **3** were prepared. In this synthesis, C(2) of each of the targets and *all* the atoms which are connected to them are derived from the chiral pool starting material. D-Serine methyl ester hydrochloride **179** was converted into iodide **180** in four steps and 44% overall yield, involving *N*-Boc protection, *N*,*O*-acetonide protection, ester reduction and Appel reaction. Then, treatment of **180** with the anion of 1,3-dithiane derivative **176** furnished **181** in 82% yield. Reduction of the dithiane moiety was then followed by removal of the *N*,*O*-acetonide functionality using TFA in MeOH to give **182** in 77% yield. Sequential oxidation with IBX, Wittig olefination of the resultant aldehyde with the ylide derived from **178** and hydrogenation of the resultant mixture of olefins gave **183** in 77% yield. Intramolecular palladium-catalysed Buchwald-Hartwig coupling gave 2-substituted 1,2,3,4-tetrahydroquinoline derivative **136** in 87% yield, and reduction of the *N*-Boc group with $LiAlH_4$ furnished (*S*)-(−)-cuspareine **2** in 78% yield. A directly analogous sequence of reactions starting from iodide **180** and employing 1,3-dithiane derivative **177** was used to prepare (*S*)-(−)-galipinine **3** in 33% overall yield (Scheme 45).

Scheme 45.[a]

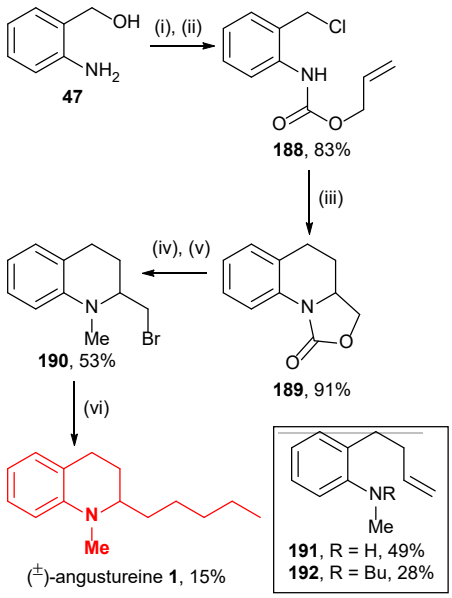


[a]*Reagents and conditions:* (i) Boc_2O, Et_3N, THF, 20 °C, 12 h, then 50 °C, 2 h; (ii) DMP, TsOH, CH_2Cl_2, 20 °C, 48 h; (iii) $LiAlH_4$, THF, 20 °C, 12 h; (iv) PPh_3, I_2, imidazole, PhMe, 20 °C, 24 h; (v) **176**, BuLi, THF, −20 °C, 2 h; (vi) **177**, BuLi, THF, −20 °C, 2 h; (vii) $NiCl_2·6H_2O$, $NaBH_4$, MeOH, THF, 0 °C to 30 °C; (viii) TFA, MeOH, 0 °C; (ix) IBX, DMSO, 30 °C, 5 h; (x) **178**, KO^{t}Bu, CH_2Cl_2, −10 °C; (xi) H_2, Rh/Al_2O_3, EtOH, 30 °C, 2 h; (xii) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, PhMe, reflux,6 h; (xiii) $LiAlH_4$, THF, reflux.

Aza-xylylene Diels-Alder Reaction. Bräse *et al.*[55] used an intramolecular aza-xylylene Diels-Alder reaction in a synthesis of (±)-angustureine **1**. The precursor **188** was prepared from **47** upon chemoselective *N*-protection using allyl chloroformate and then chlorination using $SOCl_2$, giving **188** in 83% yield. Treatment of **188** with Cs_2CO_3 resulted in formation of **189** in 91% yield, consistent with base-promoted 1,4-elimination of HCl to give the intermediate aza-xylylene which undergoes intramolecular Diels-Alder cycloaddition with the pendant olefin. Reduction of **189** with $LiAlH_4$ and then sequential treatment with MsCl and LiBr gave the corresponding bromide **190** in 53% yield. Treatment of **190** with BuLi in the presence of CuI resulted in formation of (±)-angustureine **1**, albeit in only 15% yield. This is consistent with metal-halogen exchange to generate the corresponding carbanion, which reacts with in situ generated BuBr (the side product of metal-halogen exchange) to give **1**. The low yield of this process was due to the competitive formation of **191** and **192**, the result of ring-opening of the intermediate carbanion as the major pathway to give the corresponding metallated amide anion as the driving force, which is then either trapped upon work-up to give **191**, or reacts with BuBr to give **192** (Scheme 46). Although this is a relatively inefficient method for the preparation of (±)-angustureine **1**, it is instructive to compare it to the approach of

Knochel *et al.*[31] (Scheme 18) which involves the Turbo Grignard reagent **55** (i.e., a homologated form of the carbanion derived from **190**, the homologue **55** not being susceptible to ring-opening in the same way).

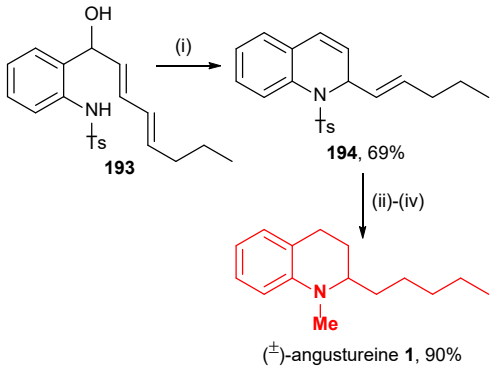
Scheme 46.[a]



[a]*Reagents and conditions:* (i) allyl chloroformate, pyridine, CH_2Cl_2, rt, 7 h; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, rt, 5 h; (iii) Cs_2CO_3, CH_2Cl_2, rt, 72 h; (iv) $LiAlH_4$, THF, reflux, 4.5 h; (v) MsCl, Et_3N, THF, −40 °C, 90 min, then LiBr, 30 min, then rt, 4 h; (vi) BuLi, $CuBr{\cdot}SMe_2$, Et_2O, −78 °C to rt.

Transition-metal Catalysed *N*-Allylation. Transition-metal catalysed *N*-allylation of an aniline derivative via S_N1'-type reaction of a suitable electrophilic partner has been used to good effect in the synthesis of Hancock alkaloids. Chan *et al.*[56] were first to report an intramolecular, gold-catalysed variant of this reaction: treatment of **193** with $AuCl_3$ in combination with $AgSbF_6$ gave 2-substituted 1,2-dihydroquinoline derivative **194** in 69% yield. Subsequent and sequential hydrogenation over Pd/C, removal of the *N*-tosyl group, and reductive *N*-methylation then furnished (±)-angustureine **1** in 90% overall yield (Scheme 47).

Scheme 47.[a]

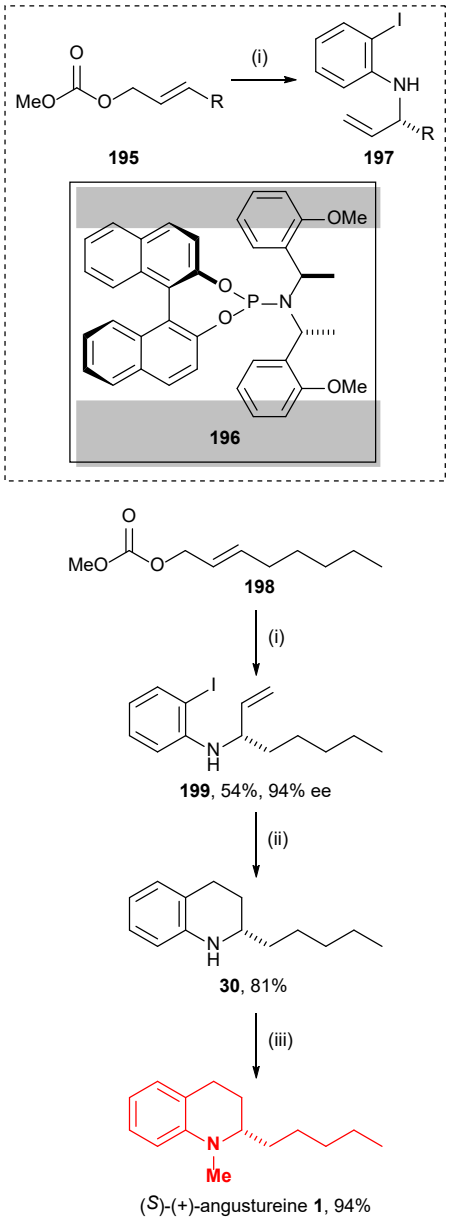


[a]*Reagents and conditions:* (i) $AuCl_3$, $AgSbF_6$, PhMe, reflux, 6 h; (ii) H_2, Pd/C, MeOH, rt, 3 h; (iii) Mg, MeOH, rt, 18 h; (iv) MeI, K_2CO_3, THF, reflux, 12 h.

Subsequent applications of this approach employed iridium catalysis with chiral ligands to impart enantioselectivity to an intermolecular process. Satyanarayana, Helmchen, *et al.*[57] demonstrated the

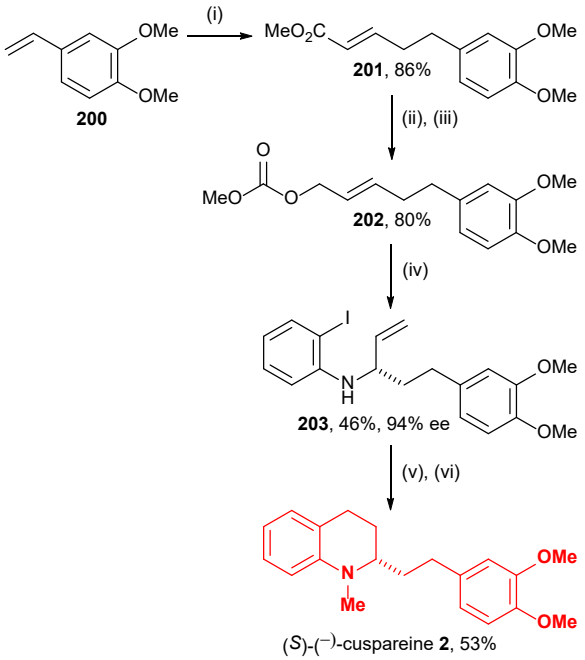
enantioselective S_N1'-type substitution of a range of aliphatic, allylic carbonates **195** upon treatment with *o*-iodoaniline in the presence of $(IrCodCl)_2$, ligand **196** and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in THF, and this method was applied in the synthesis of (*S*)-(+)-angustureine **1**. Thus, S_N1'-type substitution of allylic carbonate **198** by *o*-iodoaniline gave **199** in 54% yield and 94% ee. Hydroboration of **199** with 9-BBN and then treatment of the intermediate trialkylborane with $Pd(dppf)Cl_2$, $AsPh_3$ and Cs_2CO_3 in DMF/H_2O resulted in intramolecular Suzuki coupling to give norangustureine **30** in 81% yield. Reductive *N*-methylation then gave (*S*)-(+)-angustureine **1** in 94% yield (Scheme 48). This protocol also proved applicable in the synthesis of (*S*)-(−)-cuspareine **2**, with the requisite allylic carbamate **202** being prepared from 3,4-dimethoxystyrene **200** upon application of the tandem hydroboration/Suzuki coupling using methyl (*E*)-3-iodoacrylate as the coupling partner, followed by reduction of the ester functionality with DIBAL-H and treatment of the resultant allylic alcohol with methyl chloroformate. A directly analogous sequence of reactions as used in the synthesis of (*S*)-(+)-angustureine **1** was then applied to **202**, furnishing (*S*)-(−)-cuspareine **2** in 24% overall yield from **202** (Scheme 49).

Scheme 48.[a]



[a]*Reagents and conditions:* (i) *o*-iodoanoline, $(IrCodCl)_2$, **196**, TBD, THF, 50 °C, 5 h, 45 min; (ii) 9-BBN, THF, 70 °C, 10 min, then $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, H_2O, 80 °C, 20 h; (iii) paraformaldehyde, $NaBH_3CN$, AcOH, MeCN, rt, 17 h.

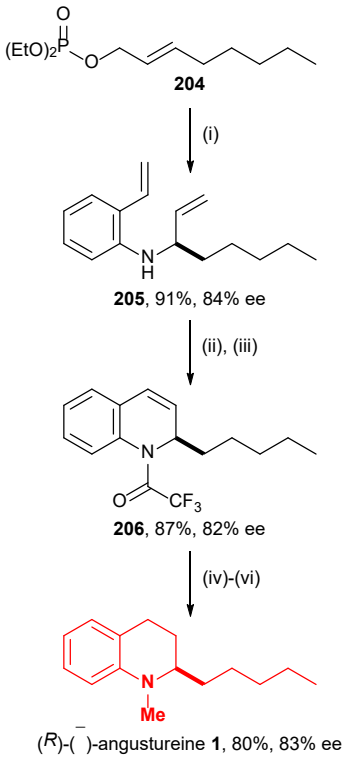
Scheme 49.[a]



[a]*Reagents and conditions:* (i) 9-BBN, THF, 70 °C, 10 min, then methyl (*E*)-3-iodoacrylate, $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, H_2O, rt, 16 h; (ii), DIBAL-H, THF, −78 °C, 3 h; (iii) $ClCO_2Me$, pyridine, CH_2Cl_2, 0 °C to rt, 30 min; (iv) *o*-iodoanoline, $(IrCodCl)_2$, **196**, TBD, THF, 50 °C, 6 h; (v) 9-BBN, THF, 70 °C, 10 min, then $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, H_2O, 80 °C, 24 h; (vi) paraformaldehyde, $NaBH_3CN$, AcOH, MeCN, rt, 16 h.

A variation on this procedure was subsequently developed by You *et al.*[58] and applied in a synthesis of (*R*)-(−)-angustureine **1**. Treatment of allylic phosphonate **204** with *o*-vinylaniline in the presence of $(IrDbcotCl)_2$, ligand **196** and K_3PO_4 in THF gave **205** in 91% yield and 84% ee. Treatment of **205** with trifluoroacetic anhydride followed by RCM with Zhan-1B catalyst gave **206** in 87% overall yield and 82% ee. Sequential catalytic hydrogenation of **206** over Pd/C, removal of the amide functionality using K_2CO_3 in MeOH and H_2O, and *N*-methylation of the resultant noralkaloid **30** (K_2CO_3/MeI) gave (*R*)-(−)-angustureine **1** in 85% overall yield and 83% ee (Scheme 50).

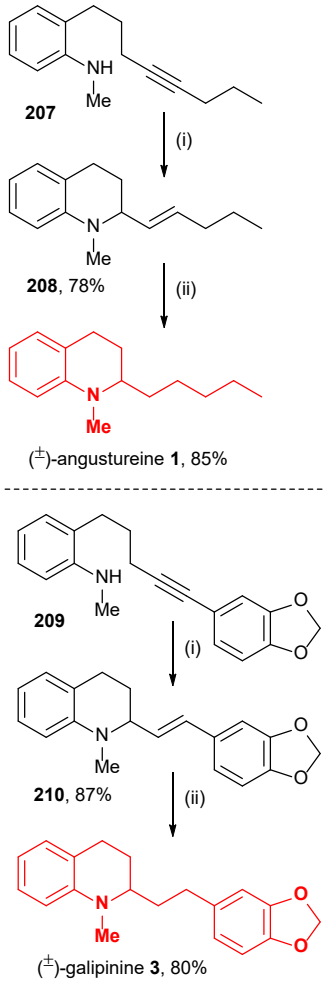
Scheme 50.[a]



[a]*Reagents and conditions:* (i) *o*-vinylaniline, $(IrDbcotCl)_2$, **196**, K_3PO_4, THF, 50 °C; (ii) TFAA, Et_3N, CH_2Cl_2, 0 °C, 30 min; (iii) Zhan-1B, PhMe, 80 °C, 12 h; (iv) H_2, Pd/C, MeOH, rt; (v) K_2CO_3, MeOH, H_2O, 50 °C, 16 h; (vi) MeI, K_2CO_3, THF, reflux, 10 h. Dbcot = dibenzo[*a*,*e*]cyclooctatetraene.

Transition-metal Catalysed Cyclisation of an Amino Alkyne. Yamamoto *et al.*[59] reported a palladium-catalysed cyclisation of a range of amino alkynes which resulted in formation of the corresponding 1,2,3,4-tetrahydroquinoline derivatives, which they employed as a key step in the synthesis of (±)-angustureine **1** and (±)-galipinine **3**. The requisite amino alkyne precursors **207** and **209** were prepared in nine steps from *o*-iodoaniline. Treatment of amino alkyne **207** with $Pd(PPh_3)_4$ and $PhCO_2H$ resulted in cyclisation to 2-substituted 1,2,3,4-tetrahydroquinoline derivative **208** in 78% yield, with subsequent hydrogenation giving (±)-angustureine **1** in 85% yield. An analogous two-step sequence applied to amino alkyne **209** gave (±)-galipinine **3** in 70% overall yield (Scheme 51). The development of an enantioselective variant of this protocol was also evaluated, which proceeded in modest yield and enantioselectivity: use of $Pd_2(dba)_3 \cdot CHCl_3$ in conjunction with (*R*,*R*)-Renorphos as a catalyst system to effect the cyclisation of amino alkyne **207** gave 2-substituted 1,2,3,4-tetrahydroquinoline derivative **208** in 48% yield and 52% ee, which upon hydrogenation allowed preparation of an enantiomerically enriched sample of (*R*)-(−)-angustureine **1** in 85% yield.

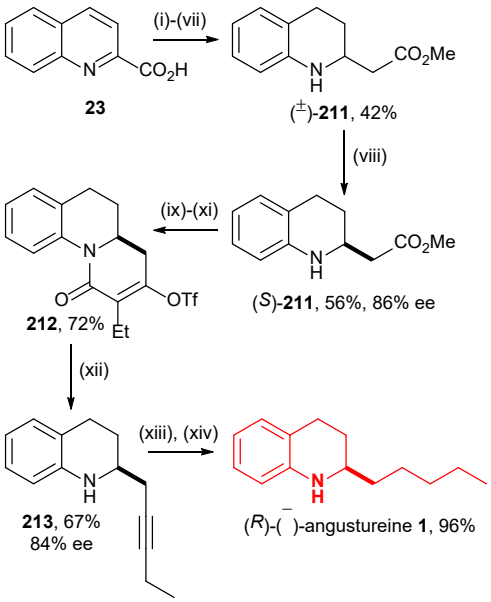
Scheme 51.[a]



[a]*Reagents and conditions:* (i) $Pd(PPh_3)_4$, $PhCO_2H$, PhMe, 120 °C, 24 h; (ii) H_2, Pd/C, MeOH, rt, 12 h.

Resolution Protocols. Several methods to effect the asymmetric synthesis of Hancock alkaloids reliant on resolution of an intermediate have been developed. Dudley *et al.*[60] initially demonstrated this approach in their synthesis of (*R*)-(−)-angustureine **1**, which was in fact designed to demonstrate a formal alkynylation protocol of a β-amino ester. Quinaldinic acid **23** was converted to (±)-**211** in 42% overall yield over seven steps (hydrogenation, esterification, reduction to the corresponding alcohol, Appel reaction, iodide displacement using cyanide ion, nitrile hydrolysis, and final esterification). Resolution of (±)-**211** upon treatment with Novozym® in THF (containing 5% H_2O) gave (*S*)-**211** in 56% yield and 86% ee.[61] Sequential treatment of (*S*)-**211** with α-bromobutanoyl bromide, then ^tBuMgCl, and finally Tf_2O and Et_3N gave **212** in 72% yield. Conversion of **212** to the acetylene **213** was achieved upon treatment with MeLi, furnishing **213** in 67% yield and 84% ee. Catalytic hydrogenation of **213** and then *N*-methylation (MeI/K_2CO_3) of the intermediate noralkaloid **30** gave (*R*)-(−)-angustureine **1** in 96% yield (Scheme 52).

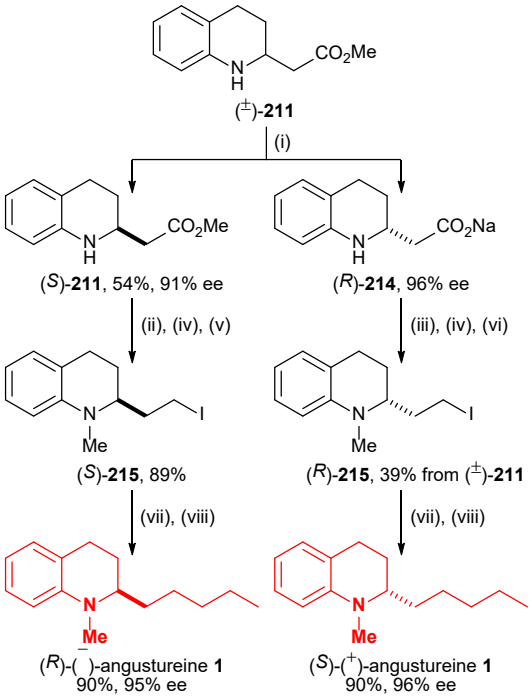
Scheme 52.[a]



[a]*Reagents and conditions:* (i) H_2, PtO_2, MeOH, rt; (ii) $SOCl_2$, MeOH, rt, overnight; (iii) $LiAlH_4$, THF, rt, 3.5 h; (iv) PPh_3, I_2, imidazole, PhMe, MeCN, 0 °C, 15 min, then rt, 30 min; (v) NaCN, DMF, 80 °C, 10 h; (vi) HCl (conc, aq), reflux, 4 h; (vii) $SOCl_2$, MeOH, reflux, 5 h; (viii) Novozym® 435, THF (containing 5% H_2O), 30 °C, 72 h; (ix) α-bromobutanoyl bromide, CH_2Cl_2, DMAP, 60 °C; (x) ^{t}BuMgCl, THF, 60 °C, 2 h; (xi) Tf_2O, Et_3N, CH_2Cl_2, −78 °C, 1 h; (xii) MeLi, PhMe, rt, 30 min; (xiii) H_2, Pd/C, CH_2Cl_2, rt, 3 h; (xiv) MeI, K_2CO_3, acetone, rt, overnight.

Diaz *et al.*[62] subsequently reported an alternative method for the elaboration of the enantiomers of **211**, obtained via the same enzymatic kinetic resolution, into the corresponding enantiomers of angustureine **1**. In this study, resolution of (±)-**211** upon treatment with Novozym® in THF (containing 5% H_2O) gave (*S*)-**211** in 54% yield and 91% ee. Treatment of (*S*)-**211** with MeI and K_2CO_3 was followed by reduction of the ester functionality using $LiAlH_4$ and Appel reaction of the resultant primary alcohol to give iodide (*S*)-**215** in 89% yield. Treatment of (*S*)-**215** with allylmagnesium bromide and then catalytic hydrogenation gave (*R*)-(−)-angustureine **1** in 90% yield. An analogous sequence of reactions applied to the residue from the resolution [containing the sodium carboxylate (*R*)-**214**, the product of the selective hydrolysis of (*R*)-**211**, in 96% ee] delivered (*S*)-(+)-angustureine **1** in 35% overall yield from (±)-**211**, and in 96% ee (Scheme 53).

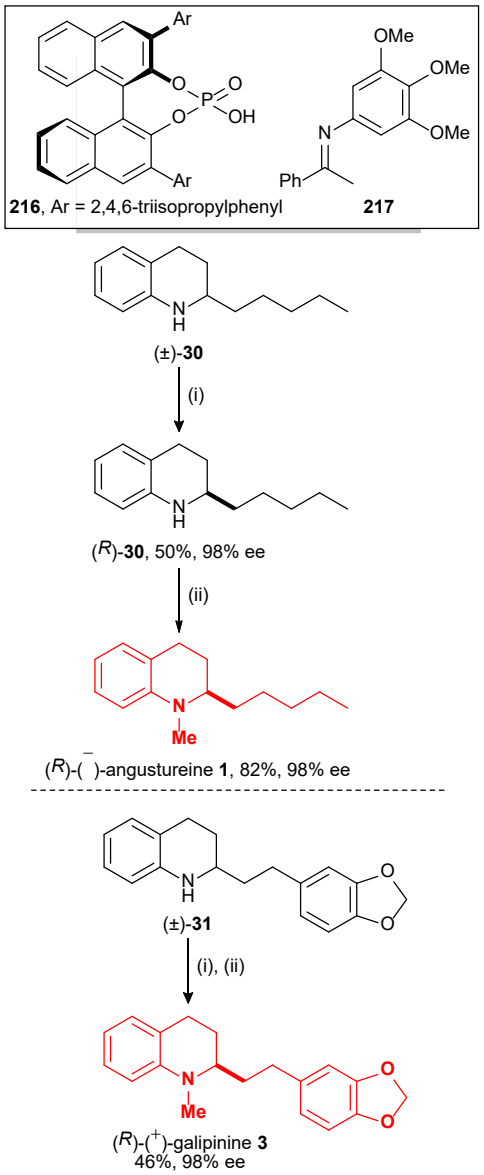
Scheme 53.[a]



[a]*Reagents and conditions:* (i) Novozym® 435, THF (containing 5% H_2O), 30 °C, 72 h; (ii) MeI, K_2CO_3, acetone, 50 °C, 48 h; (iii) MeI, K_2CO_3, DMF, 60 °C, 48 h; (iv) $LiAlH_4$, THF, reflux, 4 h; (v) PPh_3, I_2, imidazole, PhMe, MeCN, 0 °C, 2 h; (vi) PPh_3, I_2, CH_2Cl_2, 0 °C, 1 h; (vii) allylmagnesium bromide, THF, reflux, 4 h; (viii) H_2, Pd/C, MeOH, rt, 20 h.

Akiyama *et al.*[63] developed a kinetic resolution of a range of 2-substituted 1,2,3,4-tetrahydroquinoline derivatives using hydrogen transfer to imine **217**. Thus, treatment of racemic norangustureine (±)-**30** with chiral phosphoric acid **216** in the presence of imine **217** gave (*R*)-**30** in 50% yield and 98% ee. Subsequent *N*-methylation (MeI/K_2CO_3) gave (*R*)-(−)-angustureine **1** in 82% yield and 98% ee. An analogous two-step procedure applied to racemic norgalipinine (±)-**31** gave (*R*)-(+)-galipinine **3** in 46% overall yield and in 98% ee (Scheme 54).

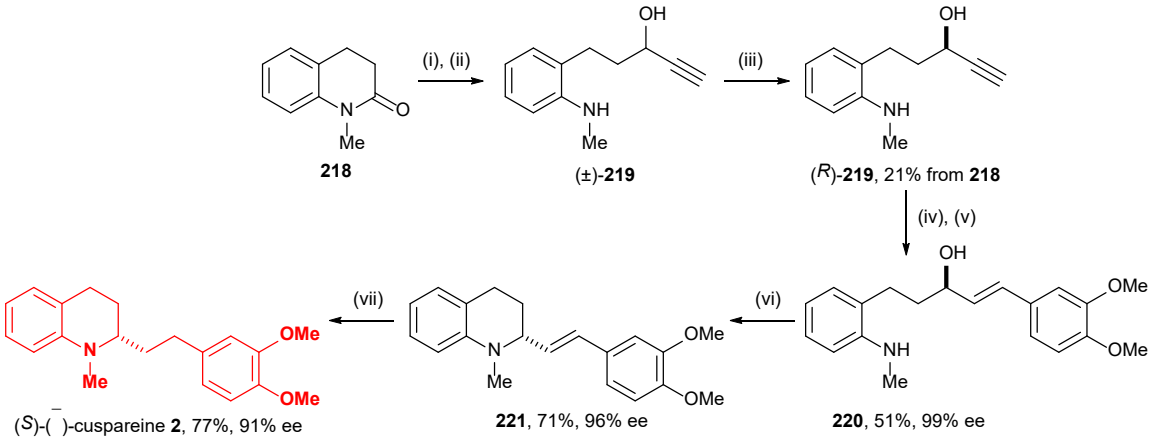
Scheme 54.[a]



[a]*Reagents and conditions:* (i) **216**, **217**, 5 Å MS, PhMe, 110 °C, 72 h; (ii) MeI, K_2CO_3, THF, 65 °C, 22 h.

Orthaber, Samec, *et al.*[64] have recently reported resolution of (±)-**219** as a precursor to an intramolecular variant of the Tsuji-Trost reaction and have used this approach to assemble (*S*)-(−)-cuspareine **2**. This method, proceeding with retention of configuration, is complementary to the approaches involving a Mitsunobu reaction, which proceed with inversion of configuration. Treatment of *N*(1)-methyldihydroquinolin-2(1*H*)-one **218** with propylnylmagnesium bromide followed by treatment of the resultant with $NaBH_4$ gave racemic alcohol (±)-**219**. Resolution of (±)-**219** using CAL-B and vinyl acetate gave (*R*)-**219** in 21% yield from **218**. Sonogashira-type coupling and subsequent reduction of the acetylene functionality to the corresponding olefin using $LiAlH_4$ gave **220** in 51% yield and 99% ee. Treatment of **220** with $[Pd(allyl)Cl]_2$ and BiPhePhos in the presence of AgOTf in toluene effected the Tsuji-Trost type cyclisation with little erosion of stereochemical integrity and the requisite 2-substituted 1,2,3,4-tetrahydroquinoline derivative **221** was isolated in 71% yield and 96% ee. Hydrogenation of **221** then gave (*S*)-(−)-cuspareine **2** in 77% yield and 91% ee (Scheme 55).

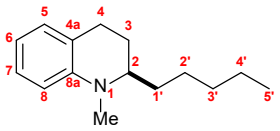
Scheme 55.[a]



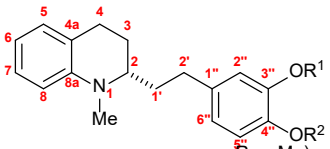
[a]*Reagents and conditions:* (i) HC≡CMgBr, THF, 0 °C to rt, 16 h; (ii) $NaBH_4$, EtOH, 0 °C, 2 h; (iii) CAL-B, vinyl acetate, PhMe, 35 °C, 5 h; (iv) 4-iodoveratrole, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 50 °C, 2 h; (v) $LiAlH_4$, THF, rt, 5 h; (vi) $[Pd(allyl)Cl]_2$, BiPhePhos, AgOTf, PhMe, rt, 16 h; (vii) H_2,Pd/C, EtOH, rt, 2 h.

Corrected ^{1}H and ^{13}C NMR Spectroscopic Data for the Alkaloids

We are grateful to Professor Nicolas Fabre, a member of the team justly credited with isolating angustureine **1**, galipinine **3** and galipeine **4** from angostura, and providing characterisation data for cuspareine **2** for the first time, for providing us with copies of the original ^{1}H and ^{13}C NMR spectra of all of these alkaloids.[65] Unfortunately, some transcriptional errors from the original spectra occurred when the data were first reported. We have validated, and corrected as necessary, both the ^{1}H and ^{13}C NMR spectroscopic data for all of the original samples of these alkaloids.[13,14] In addition to correction of transcriptional errors, it should also be noted that much of the ^{13}C NMR data reported for cuspareine was unfortunately transposed with that of galipinine. The reference frequencies for each of the spectra (for ^{1}H NMR, $CHCl_3$, 7.26 ppm; for ^{13}C NMR, $CDCl_3$, 77.16 ppm)[66,67] have also been corrected. These compiled data for **1**–**4** represent the first source of independently verified, accurate data for the natural samples of the alkaloids (Table 1 and Table 2).



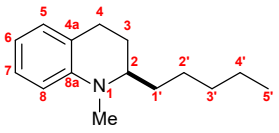
(*R*)-(−)-Angustureine **1**



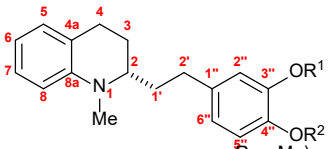
(*S*)-(−)-Cuspareine **2** (R_1 = R_2 = -CH$_2$-)
(*S*)-(−)-Galipinine **3** (R_1 = Me; R_2 = H)
(*S*)-(−)-Galipeine **4** (R_1 = H; R_2 = Me)
5 (R_1 = R_2 = Me)

proton #[a]	Angustureine	Cuspareine	Galipinine	Galipeine	5
NMe	3.04 (3H, s)	2.92 (3H, s)	2.93 (3H, s)	2.91 (3H, s)	2.90 (3H, s)
2-H	3.35 (1H, d)	3.29 (1H, m)	3.31 (1H, m)	3.28 (1H, m)	3.27 (1H, m)
3-H_2	2.01 (2H, m)	1.94 (3H, m)[b]	1.92 (3H, m)[b]	1.92 (3H, m)[b]	1.92 (3H, m)[b]
4-H_A	2.78 (1H, m)	2.63 (2H, m)[b]	2.68 (4H, m)[b]	2.68 (2H, m)[b]	2.66 (2H, m)[b]
4-H_B	2.94 (1H, m)	2.83 (1H, m)	2.68 (4H, m)[b]	2.84 (1H, m)	2.84 (1H, ddd)
5-H	6.97 (1H, d)	6.99 (1H, d)	6.99 (1H, d)	6.98 (1H, d)	6.98 (1H, d)
6-H	6.58 (1H, td)	6.60 (1H, t)	6.68 (5H, m)[b]	6.59 (1H, td)	6.59 (1H, td)
7-H	7.07 (1H, t)	7.10 (1H, t)	7.11 (1H, t)	7.08 (1H, t)	7.08 (1H, td)
8-H	6.65 (1H, d)	6.54 (1H, d)	6.68 (5H, m)[b]	6.53 (1H, d)	6.52 (1H, d)
1′-H_A	1.49 (7H, m)[b]	1.76 (1H, m)	1.70 (1H, m)	1.72 (1H, m)	1.71 (1H, m)
1′-H_B	1.73 (1H, m)	1.94 (3H, m)[b]	1.92 (3H, m)[b]	1.90 (3H, m)[b]	1.92 (3H, m)[b]
2′-H_A	1.49 (7H, m)[b]	2.50 (1H, m)	2.68 (4H, m)[b]	2.52 (1H, m)	2.49 (1H, ddd)
2′-H_B	1.49 (7H, m)[b]	2.63 (2H, m)[b]	2.68 (4H, m)[b]	2.70 (2H, m)[b]	2.66 (2H, m)[b]
3′-H_2	1.49 (7H, m)[b]	-	-	-	-
4′-H_2	1.49 (7H, m)[b]	-	-	-	-
5′-H_3	1.04 (3H, m)	-	-	-	-
2″-H	-	6.75 (3H, m)[b]	6.68 (5H, m)[b]	6.67 (2H, m)[b]	6.77 (2H, m)[b]
5″-H	-	6.75 (3H, m)[b]	6.68 (5H, m)[b]	6.82 (1H, m)	6.77 (2H, m)[b]
6″-H	-	6.75 (3H, m)[b]	6.68 (5H, m)[b]	6.67 (2H, m)[b]	6.66 (1H, dd)
OMe	-	3.85 (3H, s)	-	3.87 (3H, s)	3.87 (3H, s)
OMe	-	3.88 (3H, s)	-	-	-
OCH_2O	-	-	5.92 (2H, s)	-	-
OH	-	-	-	5.47 (1H, s)	5.56 (1H, s)

Table 1. Corrected ^{1}H NMR data for the natural samples of (*R*)-(−)-angustureine **1**, (*S*)-(−)-cuspareine **2**, (*S*)-(−)-galipinine **3** and (*S*)-(−)-galipeine **4**. Data for a synthetic sample of **5**, the originally assigned (erroneous) structure of galipeine, is also included for comparison. The reference frequency employed ($CHCl_3$) is δ_H = 7.26 ppm. Mid-points of all multiplets are given. [a]Assignments based on a more detailed spectroscopic analysis of synthetic samples of these alkaloids. [b]Overlapping signals.



(*R*)-(−)-Angustureine **1**



(*S*)-(−)-Cuspareine **2** (R_1 = R_2 = Me)
(*S*)-(−)-Galipinine **3** (R_1 = Me; R_2 = H)
(*S*)-(−)-Galipeine **4** (R_1 = H; R_2 = Me)
5 (R_1 = R_2 = -CH$_2$-)

carbon #[a]	Angustureine 1	Cuspareine 2	Galipinine 3	Galipeine 4	5
NMe	38.0	38.3	38.1	38.2	38.2
2	59.0	58.6	58.3	58.5	58.3
3	24.5	24.5	24.4	24.5	24.5
4	23.6	23.7	23.6	23.7	23.7
4a	121.8	121.9	121.8	121.8	121.9
5	128.7	128.8	128.7	128.8	128.8
6	115.3	115.5	115.5	115.5	115.5
7	127.1	127.3	127.2	127.3	127.2
8	110.4	110.7	110.7	110.7	110.7[c]
8a	145.4	145.4	145.4	145.4	145.5
1′	31.2	33.2	33.2	33.3	33.0
2′	32.1	32.1	32.1	32.2	31.6
3′	25.8	-	-	-	-
4′	22.8	-	-	-	-
5′	14.1	-	-	-	-
1″	-	134.8	135.9	134.1	135.5
2″	-	111.7	108.8	110.9	114.6
3″	-	147.3[b]	145.7[b]	146.5	145.6
4″	-	149.0[b]	147.6[b]	143.8	144.9
5″	-	111.4	108.2	114.4	110.7[c]
6″	-	120.2	121.0	120.9	119.7
OMe	-	56.0	-	56.1	56.1
OMe	-	56.1	-	-	-
OCH_2O	-	-	100.8	-	-

Table 2. Corrected ^{13}C NMR data for the natural samples of (*R*)-(−)-angustureine **1**, (*S*)-(−)-cuspareine **2**, (*S*)-(−)-galipinine **3** and (*S*)-(−)-galipeine **4**. Data for a synthetic sample of **5**, the originally assigned (erroneous) structure of galipeine, is also included for comparison. The reference frequency employed ($CDCl_3$) is δ_C = 77.16 ppm. [a]Assignments based on a more detailed spectroscopic analysis of synthetic samples of these alkaloids. [b]These resonances may be transposed; they were not unambiguously distinguishable. [c]Two resonances are discernible for these carbons in the ^{13}C NMR spectrum (appearing at δ_C 110.68 ppm and δ_C 110.74 ppm).

Specific Rotation Data for the Alkaloids: Angustureine the Odd One Out?

Specific rotation data were obtained by Jacquemond-Collet *et al.* for the natural samples of the alkaloids, isolated from angostura, which established them all to be non-racemic: for angustureine **1**, $[\alpha]_D$ −7.16; for cuspareine **2**, $[\alpha]_D$ −22.8 (*c* 0.0135 in $CHCl_3$); for galipinine **3**, $[\alpha]_D$ −33.4 (*c* 0.0055 in $CHCl_3$), and for galipeine **4** {$[\alpha]_D$ −13.6}. The temperature at which these values were recorded was not reported and unfortunately neither was the concentration not the solvent in the cases of angustureine **1** and galipeine **4** (although Professor Fabre was "*almost sure that the solvent was chloroform*"). Nonetheless, the collected synthetic endeavours towards these alkaloids have unambiguously established the absolute configurations and signs of the specific rotations of both enantiomeric forms of all four of the alkaloids: (*R*)-angustureine **1**, (*S*)-cuspareine **2**, (*S*)-galipinine **3** and (*S*)-galipeine **4** have uniformly negative sign of their specific rotation values when measured in a range of common organic solvents ($CHCl_3$, CH_2Cl_2, MeOH and EtOH) at a range

of temperatures (generally between 15 °C and 25 °C), with complementary, uniformly positive sign of specific rotation values reported for (*S*)-angustureine **1**, (*R*)-cuspareine **2**, (*R*)-galipinine **3** and (*R*)-galipeine **4** (see the Supporting Information). On this basis the absolute configurations of the naturally occurring enantiomeric forms of the alkaloids have been assigned as (*R*)-(−)-angustureine **1**, (*S*)-(−)-cuspareine **2**, (*S*)-(−)-galipinine **3** and (*S*)-(−)-galipeine **4**. It is interesting, therefore, that apparently only three of the naturally occurring enantiomers of the four alkaloids share the same absolute configuration, with angustureine **1** being different. Whilst the biosynthesis of these alkaloids (originating from the same organism) is not definitively known, a common biosynthetic pathway has previously been postulated, with which the apparent non-homochirality of the four alkaloids would seem somewhat incongruous. It remains of interest, therefore, to unambiguously verify the signs of the specific rotations of the naturally occurring forms of the alkaloids. This would require their re-extraction from the natural source, from Venezuela, although at the present time this has proven impossible to obtain, despite our best efforts.

Conclusion

In conclusion, the Hancock alkaloids angustureine, cuspareine, galipinine and galipeine have been employed as targets of a significant number of investigations, and the basic 2-substituted 1,2,3,4-tetrahydroquinoline scaffold which is common to all four has been constructed in a number of different ways. These simple alkaloids have held the attention of the synthetic community for over 20 years and interest in them shows no sign of abating. It is hoped that the organisation of material presented in this review will prove informative for planning other future synthetic endeavours to these compounds, and that the compilation of independently verified and corrected ^{1}H and ^{13}C NMR spectroscopic data will provide a useful reference resource.

Corresponding Author

*Email: steve.davies@chem.ox.ac.uk.

http://research.chem.ox.ac.uk/steve-davies.aspx

ORCID

Stephen G. Davies: 0000-0003-3181-8748.

Notes

The authors declare no competing financial interest.

Keywords

Alkaloids

Synthetic Methods

Total Synthesis

Chirality

Angustureine

Cuspareine

Galipinine

Galipeine

Hancock

References and Notes

[1] For instance, see: (a) W. G. Körner, C. Böhringer, *Ann. Chim.* **1883**, 201 [alternatively, see: *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2305]; (b) W. G. Körner, C. Böhringer, *Gazz. Chim. Ital.* **1883**, *13*, 363 [alternatively, see: *J. Chem. Soc., Abstr.* **1884**, *46*, 341–342].

[2] J. H. Rakotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, I. Fourasté, C. Moulis, *Planta Med.* **1998**, *64*, 762–763.

[3] I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fourasté, C. Moulis, *Phytochemistry* **1999**, *51*, 1167–1169.

[4] I. Jacquemond-Collet, J.-M. Bessière, S. Hannedouche, C. Bertrand, I. Fourasté, C. Moulis, *Phytochem. Anal.* **2001**, *12*, 312–319.

[5] I. Jacquemond-Collet, F. Benoit-Vical, Mustofa, A. Valentin, E. Stanislas, M. Mallié, I. Fourasté, *Planta Med.* **2002**, *68*, 68–69.

[6] The isolation of cusapreine and galipinine from angostura was also subsequently independently reported by Houghton *et al.*, although the latter was named by them as allocuspareine (a name which has not been propagated in the literature); see: P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, M. Yates, *Planta Med.* **1999**, *65*, 250–254.

[7] J. Tröger, O. Müller, *Arch. Pharm.* **1910**, *248*, 1–22.

[8] J. Tröger, H. Runne, *Arch. Pharm.* **1911**, *249*, 174–208.

[9] J. Schläger, W. Leeb, *Monatsch. Chem.* **1950**, *81*, 714–724.

[10] J. Staněk, *Monatsh. Chem.* **1957**, *88*, 250–252.

[11] M. Ishikura, I. Oda, M. Terashima, *Heterocycles* **1985**, *23*, 2375–2386.

[12] S. A. Bentley, S. G. Davies, J. A. Lee, P. M. Roberts, J. E. Thomson, *Org. Lett.* **2011**, *13*, 2544–2547.

[13] S. G. Davies, A. M. Fletcher, I. T. T. Houlsby, P. M. Roberts, J. E. Thomson, *J. Org. Chem.* **2017**, *82*, 10673–10679.

[14] S. G. Davies, A. M. Fletcher, I. T. T. Houlsby, P. M. Roberts, J. E. Thomson, D. Zimmer, *J. Nat. Prod.* **2018**, *81*, 2731–2742.

[15] At the time of submission, the Hancock alkaloids have already been the feature of two further reports appearing in print outside of the time frame of this review; see: (a) R. K. Zhang, K. Chen, X. Huang, L. Wohlschlager, H. Renata, F. H. Arnold, *Nature* **2019**, *565*, 67–72 (C-2 functionalisation of 1,2,3,4-tetrahydroquinoline); (b) Y. Pan, Z. Luo, J. Han, X. Xu, C. Chen, H. Zhao, L. Xu, Q. Fan, J. Xiao, *Adv. Synth. Catal.* **2019**, *361*, DOI: 10.1002/adsc.201801447 (reduction of a formamide to the corresponding *N*-methyl amine).

[16] G. D. Muñoz, G. B. Dudley, *Org. Prep. Proc. Int.* **2015**, *47*, 179–206.

[17] In their synthesis of (±)-cuspareine **2**, Schläger and Leeb reported an alternative method to enable the preparation of (±)-norcuspareine **18**, involving hydrogenation of the condensation product of 2-nitrobenzalacetone with piperonal and/or the condensation product of 3,4-dimethoxybenzylideneacetone with 2-nitrobenzaldehyde; in both cases these reactions may proceed via the intermediacy of the corresponding 2-substituted quinoline and/or 2-substituted 3,4-dihydroquinoline; see: Ref 9.

[18] G. Diaz-Muñoz, R. G. Isidorio, I. L. Miranda, G. Nunes de Souza Diaz, M. A. N. Diaz, *Tetrahedron Lett.* **2017**, *58*, 3311–3315.

[19] G. Erős, K. Nagy, H. Mehdi, I. Pápai, P. Nagy, P. Király, G. Tárkányi, T. Soós, *Chem. Eur. J.* **2012**, *18*, 574–585.

[20] F. Chen, A.-E. Surkus, L. He, M.-M. Pohl, J. Radnik, C. Topf, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 11718–11724.

[21] B. Sahoo, C. Kreyenschulte, G. Agostini, H. Lund, S. Bachmann, M. Scalone, K. Junge, M. Beller, *Chem. Sci.* **2018**, *9*, 8134–8141.

[22] Z. He, H. Liu, Q. Qian, L. Lu, W. Guo, L. Zhang, B. Han, *Sci. China Chem.* **2017**, *60*, 927–933.

[23] W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.

[24] P.-Y. Yang, Y.-G. Zhou, *Tetrahedron: Asymmetry* **2004**, *15*, 1145–1149.

[25] G. E. M. Crisenza, E. M. Dauncey, J. F. Bower, *Org. Biomol. Chem.* **2016**, *14*, 5820–5825.

[26] S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2006**, *45*, 2260–2263.

[27] Z.-J. Wang, H.-F. Zhou, T.-L. Wang, Y.-M. He, Q.-H. Fan, *Green Chem.* **2009**, *11*, 767–769.

[28] T.-L. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891.

[29] X. Jiang, C. Wang, Y. Wei, D. Xue, Z. Liu, J. Xiao, *Chem. Eur. J.* **2014**, *20*, 58–63.

[30] M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686.

[31] L. Melzig, T. Dennenwaldt, A. Gavryushin, P. Knochel, *J. Org. Chem.* **2011**, *76*, 8891–8906.

[32] S. C. Cosgrove, S. Hussain, N. J. Turner, S. P. Marsden, *ACS Catal.* **2018**, *8*, 5570–5573.

[33] Turner, Marsden, *et al.* also developed a procedure to effect the enzymatic resolution of 2-substituted 1,2,3,4-tetrahydroquinolines, which worked efficiently for norcuspareine **17** (90% ee) and **27** (>99% ee), thus constituting a formal synthesis of (*R*)-(+)-cuspareine **2** and (*R*)-(+)-**5**. However, this procedure was less efficient when applied to norangustureine **25** (47% ee), norgalipinine **26** (70% ee) and norgalipeine (70% ee).

[34] X.-B. Wang, D.-W. Wang, S.-M. Lu, C.-B. Yu, Y.-G. Zhou, *Tetrahedron: Asymmetry* **2009**, *20*, 1040–1045.

[35] A. O'Byrne, P. Evans, *Tetrahedron* **2008**, *64*, 8067–8072.

[36] Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687.

[37] Y. Wang, Y. Liu, D. Zhang, H. Wei, M. Shi, F. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 3776–3780.

[38] M. Pappoppula, F. S. P. Cardoso, B. O. Garrett, A. Aponick, *Angew. Chem. Int. Ed.* **2015**, *54*, 15202–15206.

[39] S. Shahane, F. Louafi, J. Moreau, J.-P. Hurvois, J.-L. Renaud, P. van de Weghe, T. Roisnel, *Eur. J. Org. Chem.* **2008**, 4622–4631.

[40] A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605.

[41] X.-F. Lin, Y. Li, D.-W. Ma, *Chin. J. Chem.* **2004**, *22*, 932–934.

[42] L. L. Taylor, F. W. Goldberg, K. K. Hii, *Org. Biomol. Chem.* **2012**, *10*, 4424–4432.

[43] S. Fustero, J. Moscardó, D. Jiménez, M. D. Pérez-Carrión, M. Sánchez-Roselló, C. del Pozo, *Chem. Eur. J.* **2008**, *14*, 9868–9872.

[44] B.-L. Chen, B. Wang, G.-Q. Lin, *J. Org. Chem.* **2010**, *75*, 941–944.

[45] J. A. Sirvent, F. Foubelo, M. Yus, *J. Org. Chem.* **2014**, *79*, 1356–1367.

[46] J. A. Sirvent, F. Foubelo, M. Yus, *Heterocycles* **2014**, *88*, 1163–1174.

[47] S. C. Cosgrove, J. M. C. Plane, S. P. Marsden, *Chem. Sci.* **2018**, *9*, 6647–6652.

[48] S. C. Cosgrove, G. E. Douglas, S. A. Raw, S. P. Marsden, *ChemPhotoChem* **2018**, *2*, 851–854.

[49] C. Theeraladanon, M. Arisawa, M. Nakagawa, A. Nishida, *Tetrahedron: Asymmetry* **2005**, *16*, 827–831.

[50] J.-S. Ryu, *Bull. Kor. Chem. Soc.* **2006**, *27*, 631–632.

[51] W. A. Nack, G. He, S.-Y. Zhang, C. Lu, G. Chen, *Org. Lett.* **2013**, *15*, 3440–3443.

[52] Y. Garg, S. Gahalawat, S. K. Pandey, *RSC Adv.* **2015**, *5*, 38846–38850.

[53] M. V. Madhubabu, R. Shankar, T. Krishna, Y. Satish Kumar, Y. Chiranjeevi, C. Muralikrishna, H. Rama Mohan, S. S. More, M. V. Basaveswara Rao, R. Akula, *Tetrahedron: Asymmetry* **2017**, *28*, 1803–1807.

[54] S. Chacko, R. Ramapanicker, *J. Heterocycl. Chem.* **2015**, *52*, 1902–1906.

[55] F. Avemaria, S. Vanderheiden, S. Bräse, *Tetrahedron* **2003**, *59*, 6785–6796.

[56] P. Kothandaraman, S. J. Foo, P. W. H. Chan, *J. Org. Chem.* **2009**, *74*, 5947–5952.

[57] G. Satyanarayana, D. Pflaesterer, G. Helmchen, *Eur. J. Org. Chem.* **2011**, 6877–6886.

[58] K.-Y. Ye, H. He, W.-B. Liu, L.-X. Dai, G. Helmchen, S.-L. You, *J. Am. Chem. Soc.* **2011**, *133*, 19006–19014.

[59] N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 6577–6579.

[60] J. Tummatorn, G. D. Munoz, G. B. Dudley, *Tetrahedron Lett.* **2013**, *54*, 1312–1314.

[61] Nagata *et al.* reported that the resolution of (±)-**208** under the same conditions proceeded to give (*S*)-**208** in 50% yield and 93% ee after 96 h, and that recrystallization of the corresponding (*S*)-camphorsulfonate salt (followed by neutralisation) enriched the enantiomeric purity of (*S*)-**208** to 97.5% ee; see: S. Katayama, N. Ae, R. Nagata, *Tetrahedron: Asymmetry* **1998**, *9*, 4295–4299.

[62] G. Diaz, M. A. N. Diaz, M. A. Reis, *J. Braz. Chem. Soc.* **2013**, *24*, 1497–1503.

[63] K. Saito, H. Miyashita, T. Akiyama, *Chem. Commun.* **2015**, *51*, 16648–16651.

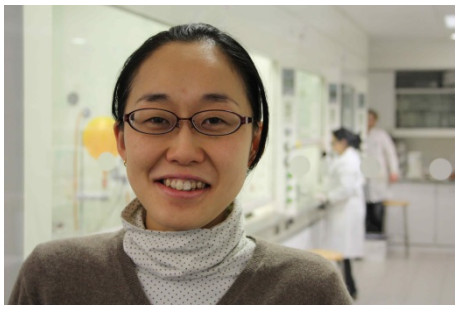
[64] S. Akkarasamiyo, S. Sawadjoon, A. Othaber, J. S. M. Samec, *Chem. Eur. J.* **2018**, *24*, 3488–3498.

[65] Copies of the ^{1}H and ^{13}C NMR spectra of the samples of angustureine **1**, cuspareine **2**, galipinine **3**, and galipeine **4** isolated from angostura are contained within the PhD theses of J. H. Rakotoson and I. Jaquemond-Collet. These documents are held at the Bibliothèque de l'Ecole Nationale Supérieure Agronomique de Toulouse (ENSAT) (J.H.R.) and the Mediathèque de l'Ecole Nationale Supérieure des Ingénieurs en Arts Chimiques et Technologiques de Toulouse (ENSIACET) (I.J.C.) in Toulouse, France.

[66] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512–7515.

[67] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.

Biosketches

	Steve Davies is the fifth Waynflete Professor of Chemistry at the University of Oxford. He has been the recipient of numerous prizes, including the following Royal Society of Chemistry awards: Hickinbottom Fellowship, Corday Morgan Medal and Prize, Award for Organometallic Chemistry, Bader Award, Tilden Lectureship, Award for Stereochemistry, and Perkin Prize for Organic Chemistry. In 2014, he was elected Dr Honoris Causa, University of Salamanca (Spain). He has published more than 600 papers and has research interests ranging from organometallic chemistry, asymmetric synthesis and natural product chemistry to medicinal chemistry and drug discovery.
	Ai Fletcher obtained a B.En. from Keio University, Japan, then moved to the U.K. where she pursued a Ph.D. at Imperial College London under the supervision of Professor Chris Braddock. Since completing her Ph.D. in 2004, she has explored a range of chemistry as a post-doctoral researcher at the University of Regensburg (with Professor Oliver Reiser) and at the University of Bath (with Professor Michael Willis). She joined the group of Professor Steve Davies in Oxford in 2007, where she has been involved with the development of asymmetric synthetic methodology and its application to the total synthesis of natural products.
	Paul Roberts graduated with an M.Chem. from the University of Oxford in 2000, which was followed by a D.Phil. with Professor Steve Davies. In 2005 he took up a post-doctoral position with Professor Davies, and his research interests centre upon the development of new methods for asymmetric synthesis, in particular for the total synthesis of natural products and their analogues.
	Jim Thomson studied chemistry at the University of Oxford where he gained an M.Chem. (2003) and then D.Phil. (2007), working with Professor Steve Davies in the area of β-amino acid organocatalysis. He then took up a post-doctoral position with Professor Davies, as a Junior Research Fellow, and in 2010 was appointed to a Research Fellowship in association with St. Catherine's College, Oxford. His research interests centre upon the development of novel asymmetric transformations and the total synthesis of natural products.