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Rapid synthesis of the tetrahydroquinoline alkaloids: angustureine, cuspareine and galipinine

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ABSTRACT

A one-pot method for the preparation of 1,2-substituted dihydroquinolines is described. This method features the C-2 addition of a range of organolithium reagents to quinoline followed by the in-situ addition of an electrophile. Standard palladium-catalysed hydrogenation, of the resultant 1,2-disubstituted dihydroquinoline adducts, generates the corresponding 1,2-disubstituted tetrahydroquinoline. A series of such compounds have been synthesised including the natural products; (±)-angustureine **1**, cuspareine **2** and galipinine **3**.

1. Introduction

Tetrahydroquinoline derivatives continue to attract interest due to their importance as synthetic intermediates and as the key structural element in several natural products. One such family of optically active 1-methyl-2-alkyl tetrahydroquinolines **1**–**4** (Fig. 1) has recently been isolated from *Galipea officinalis* Hancock, a Venezuelan shrubby tree.[1] A preparation made from this tree, commonly called angostura, is acclaimed in the area of folk medicine principally to combat fevers.[1,2] This study also demonstrated that individual members of the family of natural products, particularly galipinine **3**, exhibit promising activities against the malaria disease causing parasite, *Plasmodium falciparum*.[1a]

Over the years several synthetic routes have been devised for the preparation of this type of 2-substituted tetrahydroquinoline.[3] Asymmetric approaches have, more recently, been described for the preparation of **1**, **2** and **3**, which have enabled the absolute stereochemistry of the single stereogenic centre present in the naturally occurring compounds to be determined.[4] We envisaged that such 1,2-disubstituted tetrahydroquinoline alkaloids could be readily synthesised by the reaction of quinoline **5** with an organometallic reagent, followed by the addition of an alkyl halide electrophile. It has long been appreciated that π-poor aromatic heterocycles, such as **5**, are susceptible to nucleophilic addition.[5] Additionally, it has recently been shown that such adducts may undergo efficient in-situ alkylation, on addition of an external electrophile.[6] Subsequent palladium-catalysed hydrogenation of the dihydroquinoline product of this reaction would generate the desired 1,2-disubstituted tetrahydroquinoline structural motif.

2. Results and discussion

As illustrated in Scheme 1, in order to investigate the feasibility of this sequence for the synthesis of **1**–**4** we began by exploring a range of suitable organometallic reagents. Thus, a solution of quinoline **5** in THF[†] was treated with the various organolithium reagents[‡] followed by addition of the appropriate electrophile. The nucleophilic C-2 addition step was monitored by TLC and on consumption of the starting material **5** the electrophile was directly added to the solution of the lithium anilide.

In the case of aqueous ammonium chloride (entry 1), in addition to the expected dihydroquinoline a small amount of the re-oxidised 2-butylquinoline **13** was also observed. Subsequent treatment of this mixture under standard reduction conditions gave a separable mixture of 2-butyltetrahydroquinoline **6** (84%) and **13** (14%). Similarly, the use of methyliodide gave good yields of the adduct **7** following the three-step reaction sequence (entry 2). Use of benzyl bromide (entry 3) gave good conversion forming the corresponding

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[†] The use of diethylether for this one-pot process in the place of THF proved, in some instances, to be problematic due to the insolubility of the intermediate lithium anilide in this solvent.

[‡] Addition of *n*-butylmagnesium chloride to **5** under these conditions does not proceed to completion; see also Ref. 6a.

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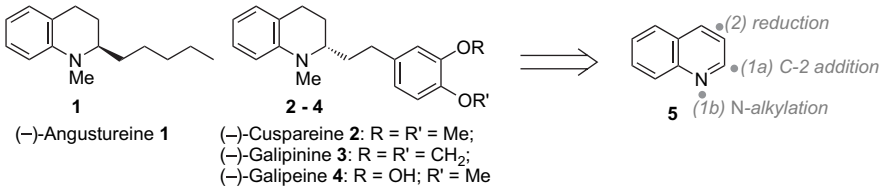


Figure 1. Representative tetrahydroquinoline natural products **1**–**4** and their retrosynthesis based on the one-pot C-2 nucleophilic addition—*N*-alkylation of quinoline **5**.

dihydroquinoline, however, on hydrogenolysis significant cleavage of the *N*-benzylic bond was also observed, forming **6** (36%) in addition to the *N*-benzyl target compound **8** (55%). Attempts to optimise this reaction further by altering the catalyst loading and reaction times were not successful. The use of 1-bromo-2-methylpropane (entry 4) made a significant difference to the overall efficiency of the one-pot procedure. The desired 1,2-adduct, **9**, was only isolated in 17% overall yield and in addition **6** (22%) and 2-butylquinoline **13** (51%) were separated following purification by flash column chromatography. This finding is presumably explained by the diminished reactivity of this particular alkylating reagent. The use of alternative, commercially available, organolithium reagents, *t*-BuLi, MeLi and PhLi (entries 5–7), gave the products from the hoped-for reaction sequence. In the case of *t*-BuLi (entry 5) it was necessary to conduct the reaction initially at −78 °C in order to minimise its non-productive reaction with the solvent. Also of note was the observation that adduct **12** was isolated in reasonable yield (69%) indicating that, in this instance, in contrast to entry 3, benzylic carbon–nitrogen bond cleavage did not significantly occur (entry 7).

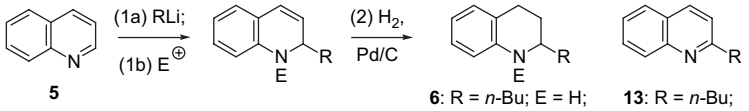
Having verified the versatility of the method, we desired to employ this approach for the synthesis of the naturally occurring 1,2-dialkyltetrahydroquinoline compounds **1**–**3**. In the case of angustureine **1** (Scheme 1, entry 8), *n*-pentyllithium was generated from *n*-pentylbromide and lithium metal in pentane.[7] This reagent was then added to quinoline **5** in THF under nitrogen at 0 °C. Following complete formation of the 2-substituted anilide, methyliodide was added. As above, the resultant dihydroquinoline was then converted to angustureine **1** in 90% yield (three-steps) following palladium-catalysed hydrogenation.

The construction of cuspareine **2** and galipinine **3** presented a greater challenge since the requisite organometallic precursor was not commercially available. Our approach to these compounds was based on a report by Lee et al.[8] and using this method *trans*-vinyl bromides **17** and **19** were prepared in approximately 50% yields from the respective, commercially available, cinnamic acids **15** and **16** (Scheme 2).

Although the preparation of **17** and **19**, under the conditions indicated, proved to be *E*-stereoselective, in our hands we observed the formation of a more polar by-product. On analysis these impurities proved to be compounds **18** and **20**, which presumably arise from the further conversion of the *trans*-vinyl bromides **17** and **19** under the reaction conditions.[9] This hypothesis was corroborated by the observation that a purified sample of **17** underwent efficient conversion to **18** under identical reaction conditions.

Lithiation of vinyl bromides **17** and **19** was achieved using *tert*-butyllithium in diethylether at −78 °C. In relation to this lithium-bromide exchange process it was found to be important to use 2 equiv of *t*-BuLi in order to minimise formation of protonated styrene by-products. Subsequent addition of the lithium species to quinoline **5** in THF at room temperature gave the anilide, which, on addition of methyliodide gave **21** and **22**. Flash column chromatography was employed to remove excess quinoline **5** and the resulting dihydroquinoline adducts were each reduced with hydrogen (1 atm) using palladium as a catalyst. In relation to this transformation, it was found that under these conditions the endocyclic, dihydroquinoline, double bond undergoes conversion significantly more rapidly than the exocyclic, styrenyl alkene. In this manner (±)-**2** and (±)-**3** were formed in 52% and 58% yields, respectively, over the four-steps.

Based on the report by Alexakis and co-workers,[6a] we briefly investigated whether the inclusion of the diamine, (−)-sparteine, influenced the one-pot process in an asymmetric sense. This was investigated for the synthesis of galipinine **3** in two approaches; firstly (−)-sparteine was pre-mixed with quinoline **5** in THF before



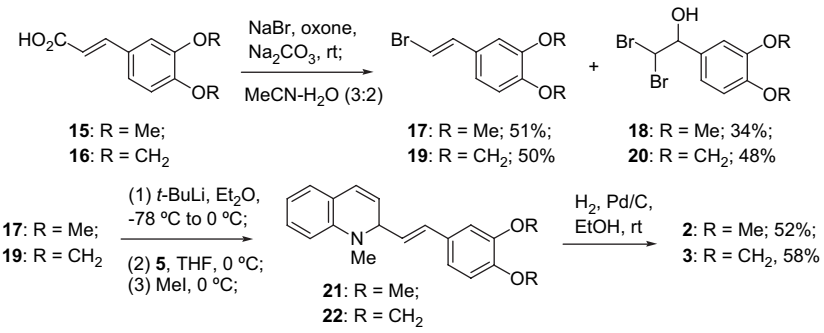
6: R = *n*-Bu; E = H;
7: R = *n*-Bu; E = Me;
8: R = *n*-Bu; E = Bn;
9: R = *n*-Bu; E = *i*-Bu;
10: R = *t*-Bu; E = Me;
11: R = Me; E = Me;
12: R = Ph; E = Me;
1: R = *n*-Pent; E = Me

13: R = *n*-Bu;
14: R = *n*-Pent

Entry	R	E	Product (%)[a]
1	*n*-Bu	H ($NH_4Cl_{(aq)}$)	**6** (84%); **13** (14%)
2	*n*-Bu	Me (MeI)	**7** (86%)
3	*n*-Bu	Bn (BnBr)	**8** (55%); **6** (36%)
4	*n*-Bu	*i*-Bu (*i*-BuBr)	**9** (17%); **6** (22%); **13** (51%)
5[b]	*t*-Bu	Me (MeI)	**10** (84%)
6	Me	Me (MeI)	**11** (67%)
7	Ph	Me (MeI)	**12** (69%)
8	*n*-Pent	Me (MeI)	**1**(90%); **14** (6%)

Cond. (1a) RLi (1.5 - 2 equiv.), THF, 0 °C; (1b) E⊕, 0 °C; (2) H_2, Pd/C (10 mol%), EtOH;
[a]Isolated yield over 3-steps following purification by flash column chromatography;
[b]*t*-BuLi was added at -78 ºC and then warmed to 0 °C

Scheme 1.



Scheme 2.

addition of the vinyl lithium reagent derived from **19** at 0 °C. Methyliodide was then added and the reaction finally quenched. In this case **3** was obtained in 20% ee[§] following reduction. In an alternative process (−)-sparteine was initially added to the vinyl bromide **19** at −78 °C, which was then treated with *t*-BuLi. Subsequent addition to quinoline **5** ultimately provided an enantiomeric excess of 13% ee for **3**. In both these unoptimised examples preferential formation of the unnatural (+)-isomer of **3** occurred.

In conclusion, we have developed an efficient three-step, two-pot procedure for the synthesis of racemic 1,2-dialkyl substituted tetrahydroquinolines. Typically these compounds were obtained in moderate to good overall yields and the examples chosen represent the versatility of this reaction with regards to both the organolithium reagent and the electrophile. This approach has been successfully applied to the synthesis of the tetrahydroquinoline alkaloids, angustureine **1**, cuspareine **2** and galipinine **3** featuring the use of functionalised, styryl organometallic species that have not been described previously.

3. Experimental

3.1. General

Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone prior to use. Quinoline **5** was dried over $MgSO_4$ and distilled under reduced pressure (15 mmHg) prior to use. All other reagents were obtained from commercial sources and used without further purification.

3.2. General procedure for the one-pot C-2 addition—N-functionalisation of quinoline 5

Under nitrogen at 0 °C a solution of quinoline **5** (0.30 mL, 2.54 mmol, 1 equiv) in THF (20 mL) was treated with the appropriate organolithium reagent (3.81 mmol, 1.5 equiv). Stirring was continued for 0.5 h whereupon TLC analysis indicated the consumption of starting material. The electrophile (5.08 mmol, 2 equiv) was then added dropwise and stirring maintained for 2 h. Saturated aqueous NH_4Cl (20 mL) and dichloromethane (20 mL) were added and the resultant aqueous layer was further extracted with dichloromethane (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude dihydroquinoline product was dissolved in EtOH (20 mL) and 10% w/w Pd/C (270 mg, ca. 10 mol %) was added before the mixture was stirred under H_2 (ca. 1 atm) for 24 h. The reaction mixture was then filtered through Celite, washing with EtOAc (2×20 mL) and the solvent removed under reduced pressure. Purification, finally, by flash column chromatography afforded the desired 1,2-disubstituted tetrahydroquinoline.

3.3. 2-Butyl-1,2,3,4-tetrahydroquinoline 6

Following the above procedure, quinoline **5** (0.30 mL, 2.54 mmol) was converted into **6** (401 mg, 84%) with a 1.6 M solution of *n*-BuLi in hexanes (2.40 mL, 3.81 mmol) and quenching with a saturated aqueous ammonium chloride solution (20 mL). The *title compound* was isolated after flash column chromatography (cyclohexane–EtOAc; 19:1) as a yellow oil. R_f=0.5 (cyclohexane–EtOAc; 19:1); ν_{max} (neat/cm^{-1}) 3016, 2927, 2857, 1605, 1491, 1352, 1310, 1273, 1126, 1077, 927, 829, 746, 659; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, J=7.0 Hz, CH_3), 1.33–1.40 (4H, m, CH_2), 1.47–1.52 (2H, m, CH_2), 1.54–1.64 (1H, m, CH_2-3), 1.94–1.99 (1H, m, CH_2-3), 2.69–2.84 (2H, m, CH_2-4), 3.20–3.26 (1H, m, CH-2), 3.75 (1H, br s, NH), 6.46 (1H, dd, J=1.0, 8.5 Hz, ArH), 6.59 (1H, dd, J=1.0, 7.5 Hz, ArH), 6.93–7.00 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.8 (CH_2), 26.4 (CH_2), 27.9 (CH_2), 28.1 (CH_2), 36.4 (CH_2), 51.6 (CH), 114.0 (CH), 116.9 (CH), 121.4 (C), 126.7 (CH), 129.2 (CH), 144.7 (C); HRMS calcd for $C_{13}H_{20}N$ (M+1) requires 190.1596; found 190.1587. Further elution gave 2-butylquinoline **13** (67 mg, 14%) as a yellow oil;[10] R_f=0.3 (cyclohexane–EtOAc; 19:1); ν_{max} (neat/cm^{-1}) 3196, 3053, 2954, 2823, 1602, 1561, 1504, 1460, 1309; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, J=7.5 Hz, CH_3), 1.46 (2H, sex, J=7.5 Hz, CH_2), 1.76–1.84 (2H, m, CH_2), 2.98 (2H, t, J=8.0 Hz, CH_2), 7.30 (1H, d, J=8.5 Hz, ArH), 7.40–7.46 (1H, m, ArH), 7.66–7.70 (1H, m, ArH), 7.77 (1H, dd, J=1.0, 8.5 Hz, ArH), 8.03–8.07 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.7 (CH_2), 32.2 (CH_2), 39.1 (CH_2), 121.4 (CH), 125.6 (CH), 126.7 (C), 127.5 (CH), 128.8 (CH), 129.3 (CH), 136.2 (CH), 147.9 (C), 163.1 (C); HRMS calcd for $C_{13}H_{16}N$ (M+1) requires 186.1283; found 186.1282.

3.4. 1-Methyl-2-butyl-1,2,3,4-tetrahydroquinoline 7

Following the above procedure, quinoline **5** (0.30 mL, 2.54 mmol) was converted into **7** (444 mg, 86%) with a 1.6 M solution of *n*-BuLi in hexanes (2.40 mL, 3.81 mmol) and subsequent reaction with methyliodide (0.32 mL, 5.08 mmol). The *title compound* was isolated after flash column chromatography (cyclohexane–EtOAc; 19:1) as a yellow oil. R_f=0.8 (cyclohexane–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 3066, 2930, 2929, 2870, 2799, 1603, 1578, 1500, 1452, 1380, 1334, 1274, 1215, 1091, 1051; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, J=6.5 Hz, CH_3), 1.29–1.53 (5H, m, CH_2), 1.66–1.72 (1H, m, CH_2), 1.91–1.98 (2H, m, CH_2-3), 2.73 (1H, ddd, app. dt, J=4.0, 16.5 Hz, CH_2-4), 2.84–2.92 (1H, m, CH_2-4), 3.00 (3H, s, CH_3), 3.28–3.33 (1H, m, CH-2), 6.60 (1H, d, J=7.5 Hz, ArH), 6.66 (1H, t, J=7.5 Hz, ArH), 7.04 (1H, d, J=7.5 Hz, ArH), 7.25 (1H, t, J=7.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.9 (CH_2), 23.5 (CH_2), 24.4 (CH_2), 28.3 (CH_2), 30.9 (CH_2), 37.9 (CH_3), 58.9 (CH), 110.3 (CH), 115.1 (CH), 121.8 (C), 127.0 (CH), 128.6 (CH), 145.3 (C); HRMS calcd for $C_{14}H_{22}N$ (M+1)

[§] The enantiomeric excess was determined by chiral HPLC according to Ref. 4c.

requires 204.1752; found 204.1743; Anal. Calcd for $C_{14}H_{12}N$: C, 82.70; H, 10.41; N, 6.89%; found: C, 82.42; H, 10.26; N, 6.76%.

3.5. 1-Benzyl-2-butyl-1,2,3,4-tetrahydroquinoline 8

Following the above procedure, quinoline **5** (0.30 mL, 2.54 mmol) was converted into **8** (390 mg, 55%) with a 1.6 M solution of *n*-BuLi in hexanes (2.40 mL, 3.81 mmol) and subsequent reaction with benzyl bromide (0.61 mL, 5.08 mmol). The *title compound* was isolated after flash column chromatography (cyclohexane–EtOAc; 19:1) as a yellow oil. R_f=0.4 (cyclohexane–EtOAc; 19:1); ν_{max} (neat/cm^{-1}) 3025, 2928, 2858, 1602, 1498, 1454, 1212, 1174, 1064, 926; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH_3), 1.16–1.35 (5H, m, CH_2), 1.47–1.64 (1H, m, CH_2), 1.93–2.00 (2H, m, CH_2-3), 2.70 (1H, dt, J=4.0, 16.0 Hz, CH_2-4), 2.84–2.90 (1H, m, CH_2-4), 2.92 (2H, s, CH_2), 3.32–3.37 (1H, m, CH-2), 6.38 (1H, d, J=8.0 Hz, ArH), 6.55 (1H, t, J=8.0 Hz, ArH), 6.93 (1H, t, J=8.0 Hz, ArH), 7.00 (1H, d, J=8.0 Hz, ArH), 7.17–7.20 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.8 (CH_2), 23.6 (CH_2), 24.2 (CH_2), 28.3 (CH_2), 31.7 (CH_2), 37.9 (CH_2), 57.8 (CH), 111.4 (CH), 115.3 (CH), 121.6 (C), 127.0 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 141.8 (C), 144.5 (C); HRMS calcd for $C_{20}H_{26}N$ (M+1) requires 280.2065; found 280.2054. On further elution **6** (171 mg, 36%) was also isolated whose data corresponded with that reported above.

3.6. 1-*iso*-Butyl-2-butyl-1,2,3,4-tetrahydroquinoline 9

Following the above procedure, quinoline **5** (0.30 mL, 2.54 mmol) was converted into **9** (107 mg, 17%) on treatment with a 1.6 M solution of *n*-BuLi in hexanes (2.40 mL, 3.81 mmol) and subsequent reaction with *iso*-butyl bromide (0.55 mL, 5.08 mmol). The *title compound* was isolated after flash column chromatography (cyclohexane–EtOAc; 19:1) as a yellow oil. R_f=0.6 (cyclohexane–EtOAc; 19:1); ν_{max} (neat/cm^{-1}) 3019, 2952, 2865, 1499, 1344, 1254, 1212, 1098, 1057, 1002, 910; δ_H (400 MHz, $CDCl_3$) 0.89–0.97 (9H, m, CH_3), 1.21–1.47 (5H, m, CH_2), 1.51–1.60 (1H, m, CH_2), 1.89–1.94 (2H, m, CH_2-3), 2.04–2.12 (1H, m, CH), 2.64–2.70 (2H, m, CH_2-4, CH_2), 2.82–2.91 (1H, m, CH_2-4), 3.25–3.30 (1H, m, CH-2), 3.40 (1H, dd, J=4.5, 18.5 Hz, CH_2), 6.51 (1H, d, J=8.0 Hz, ArH), 6.55 (1H, t, J=8.0 Hz, ArH), 6.99 (1H, d, J=8.0 Hz, ArH), 7.04 (1H, t, J=8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 22.9 (CH_2), 23.1 (CH_2), 23.7 (CH_2), 26.6 (CH), 28.4 (CH_2), 30.7 (CH_2), 58.4 (CH), 58.5 (CH_2), 110.8 (CH), 114.5 (CH), 121.0 (C), 126.8 (CH), 129.2 (CH), 144.3 (C); HRMS calcd for $C_{17}H_{28}N$ (M+1) requires 246.2222; found 246.2215. Further elution gave initially **6** (139 mg, 29%) then **13** (240 mg, 51%) whose data was as above.

3.7. 1-Methyl-2-*tert*-butyl-1,2,3,4-tetrahydroquinoline 10

Following the above procedure, quinoline **5** (0.30 mL, 2.54 mmol) was converted into **10** (434 mg, 84%) on treatment with a 1.7 M solution of *tert*-butyllithium in pentane (2.24 mL, 3.81 mmol, 1.5 equiv) at −78 °C. The reaction mixture was warmed to 0 °C over 1.5 h and methyliodide (0.32 mL, 5.08 mmol) was added. Following hydrogenation as described the *title compound* was isolated by flash column chromatography (cyclohexane–EtOAc; 99:1) as a yellow oil. R_f=0.6 (cyclohexane–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 3017, 2956, 2904, 2795, 1683, 1601, 1578, 1503, 1500, 1368, 1320, 1272, 1212, 1095, 1043, 930, 744; δ_H (400 MHz, $CDCl_3$) 0.97 (9H, s, CH_3), 1.85 (1H, app. septet, J=7.5 Hz, CH_2-3), 2.13–2.18 (1H, m, CH_2-3), 2.70 (1H, dd, J=5.0, 16.7 Hz, CH_2-4), 2.85–2.94 (1H, m, CH_2-4), 3.00 (1H, dd, J=2.5, 5.5 Hz, CH-2), 3.14 (3H, s, CH_3), 6.60 (2H, app. t, J=7.5 Hz, ArH), 6.97 (1H, d, J=7.5 Hz, ArH), 7.11 (1H, t, J=7.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 22.9 (CH_2), 24.8 (CH_2), 28.6 (CH_3), 38.3 (C), 43.8 (CH_3), 67.7 (CH), 111.4 (CH), 115.0 (CH), 121.8 (C), 126.8 (CH), 128.8 (CH), 146.7 (C); HRMS calcd for $C_{14}H_{22}N$ (M+1) requires 204.1752; found 204.1743; Anal. Calcd for $C_{14}H_{12}N$: C, 82.70; H, 10.41; N, 6.89%; found: C, 82.47; H, 10.28; N, 6.63%.

3.8. 1,2-Dimethyl-1,2,3,4-tetrahydroquinoline 11[3a]

Following the above procedure, quinoline **5** (0.30 mL, 2.54 mmol) was converted into **11** (274 mg, 67%) on treatment with a 1.6 M solution of MeLi in diethylether (2.40 mL, 3.81 mmol). The *title compound* was isolated after flash column chromatography (cyclohexane–EtOAc; 19:1) as a yellow oil. R_f=0.5 (cyclohexane–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 3067, 3019, 2965, 2930, 2870, 2846, 2826, 1668, 1603, 1576, 1499, 1479, 1455, 1373, 1328, 1305, 1275, 1216, 1162, 1137, 1121, 1084, 1048, 1034; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, J=6.5 Hz, CH_3), 1.73–1.81 (1H, m, CH_2-3), 1.94–2.06 (1H, m, CH_2-3), 2.66–2.74 (1H, m, CH_2-4), 2.80–2.87 (1H, m, CH_2-4), 2.91 (3H, s, CH_3), 3.41–3.50 (1H, m, CH-2), 6.55–6.63 (2H, m, ArH), 6.98 (1H, d, J=7.5 Hz, ArH), 7.10 (1H, t, J=7.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 17.6 (CH_3), 23.8 (CH_2), 28.1 (CH_2), 37.0 (CH_3), 53.8 (CH), 110.6 (CH), 115.4 (CH), 122.6 (C), 127.1 (CH), 128.5 (CH), 145.4 (C); HRMS calcd for $C_{11}H_{16}N$ (M+1) requires 162.1283; found 162.1286.

3.9. 1-Methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 12

According to the general procedure quinoline **5** (0.30 mL, 2.54 mmol) in THF (20 mL) was treated with a 1.8 M solution of phenyllithium in di-*n*-butylether (2.11 mL, 3.81 mmol). Methyliodide (0.32 mL, 5.08 mmol, 2 equiv) was then added. The crude product (636 mg) was then dissolved in EtOH (20 mL), 10% w/w Pd/C (270 mg, ca. 10 mol %) was added and the reaction was stirred under H_2 (ca. 1 atm) for 24 h. Purification by flash column chromatography (cyclohexane–EtOAc; 99:1) afforded **12** (391 mg, 69%) as a white solid. R_f=0.6 (cyclohexane–EtOAc; 9:1); mp 98–99 °C [lit. mp 102 °C (MeOH–H_2O)];[11] ν_{max} (neat/cm^{-1}) 3027, 2928, 2894, 2834, 1882, 1600, 1577, 1499, 1448, 1379, 1341, 1311, 1222, 1176, 1129, 1073; δ_H (400 MHz, $CDCl_3$) 1.99–2.08 (1H, m, CH_2-3), 2.17–2.28 (1H, m, CH_2-3), 2.60–2.69 (2H, m, CH_2-4), 4.51 (1H, t, J=4.5 Hz, CH-2), 6.68 (2H, app. quartet, J=7.5 Hz, ArH), 7.01 (1H, d, J=7.5 Hz, ArH), 7.16–7.37 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 24.2 (CH_2), 30.1 (CH_2), 37.7 (CH_3), 63.2 (CH), 109.9 (CH), 115.5 (CH), 122.6 (C), 126.5 (CH), 126.8 (CH), 127.3 (CH), 128.3 (CH), 128.4 (CH), 144.3 (C), 146.1 (C); HRMS calcd for $C_{16}H_{18}N$ (M+1) requires 224.1439; found 224.1429.

3.10. *n*-Pentyllithium[7]

At room temperature, under nitrogen, 1-bromopentane (1.5 mL, 12.1 mmol, 1 equiv) was added dropwise over ca. 10 min to small pieces of lithium foil (176 mg, 25.4 mmol, 2.1 equiv) rapidly stirred in pentane (20 mL). The mixture was stirred at room temperature for 1.5 h and used directly.

3.11. 1-Methyl-2-pentyl-1,2-dihydroquinoline

Under nitrogen at 0 °C a solution of quinoline **5** (0.57 mL, 4.80 mmol, 1 equiv) in THF (20 mL) was treated with the above *n*-pentyllithium solution (10 mL, ca. 6.05 mmol, 1.25 equiv) and stirred for 0.5 h. TLC analysis indicated consumption of starting material. Methyliodide (0.70 mL, 11.24 mmol, 2.3 equiv) was added dropwise and stirring was maintained for 2 h. Saturated aqueous NH_4Cl (20 mL) and dichloromethane (20 mL) were added and the resultant aqueous layer was further extracted with dichloromethane (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (cyclohexane–EtOAc; 9:1) afforded the dihydroquinoline (923 mg, 89%) as a yellow oil. R_f=0.7 (cyclohexane–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 3065, 3038, 2928, 2857, 1642, 1598, 1497; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t,

J=6.5 Hz, CH_3), 1.23–1.36 (6H, m, CH_2), 1.45–1.52 (1H, m, CH_2), 1.62–1.69 (1H, m, CH_2), 2.90 (3H, s, CH_3), 4.03–4.06 (1H, m, CH-2), 5.69 (1H, dd, J=5.5, 9.5 Hz, CH-3), 6.38 (1H, d, J=9.5 Hz, CH-4), 6.43 (1H, d, J=7.5 Hz, ArH), 6.59 (1H, t, J=7.5 Hz, ArH), 6.88 (1H, dd, J=1.5, 7.5 Hz, ArH), 7.09 (1H, dt, J=1.5, 7.5 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 23.8 (CH_2), 32.1 (CH_2), 33.9 (CH_2), 36.4 (CH_3), 60.7 (CH), 109.8 (CH), 116.1 (CH), 121.8 (C), 125.2 (CH), 125.7 (CH), 126.7 (CH), 129.0 (CH), 145.3 (C); HRMS calcd for $C_{15}H_{20}N$ (M−1) requires 214.1596; found 214.1585. Further elution gave 2-pentylquinoline **14**[12] (55 mg, 6%) as a yellow oil. R_f=0.6 (cyclohexane–EtOAc; 9:1); δ_H (400 MHz, $CDCl_3$) 0.78 (3H, t, J=7.0 Hz, CH_3), 1.22–1.30 (4H, m, CH_2), 1.67 (2H, pent, J=7.5 Hz, CH_2), 2.85 (2H, t, J=7.5 Hz, CH_2), 7.16 (1H, d, J=8.5 Hz, CH-3), 7.34 (1H, t, J=8.0 Hz, ArH), 7.55 (1H, t, J=8.0 Hz, ArH), 7.63 (1H, d, J=8.0 Hz, ArH), 7.92 (1H, d, J=8.5 Hz, CH-4), 7.94 (1H, d, J=8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.5 (CH_2), 29.5 (CH_2), 31.7 (CH_2), 39.2 (CH_2), 121.3 (CH), 125.6 (CH), 126.6 (C), 127.4 (CH), 128.7 (CH), 129.3 (CH), 136.2 (CH), 147.7 (C), 163.0 (C); HRMS calcd for $C_{14}H_{18}N$ (M+1) requires 200.1439; found 200.1430.

3.12. 1-Methyl-2-pentyl-1,2,3,4-tetrahydroquinoline (angustureine) 1[1b,4b]

A mixture of 1-methyl-2-pentyl-1,2-dihydroquinoline (923 mg, 4.29 mmol, 1 equiv) and 10% w/w Pd/C (250 mg, ca. 5 mol %) in EtOAc (25 mL) was stirred under hydrogen (ca. 1 atm) for 24 h. The reaction mixture was filtered through Celite and washed with EtOAc (2×25 mL). Solvent removal under reduced pressure gave angustureine **1** (920 mg, 99%) as a yellow oil. R_f=0.5 (cyclohexane–EtOAc; 19:1); ν_{max} (neat/cm^{-1}) 3022, 2931, 2859, 1602, 1500; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, t, J=7.0 Hz, CH_3), 1.27–1.48 (7H, m, CH_2), 1.60–1.67 (1H, m, CH_2), 1.90–1.94 (2H, m, CH_2-3), 2.69 (1H, ddd, app. dt, J=4.5, 16.5 Hz, CH_2-4), 2.84 (1H, ddd, J=7.0, 10.5, 16.5 Hz, CH_2-4), 2.96 (3H, s, CH_3), 3.24–3.28 (1H, m, CH-2), 6.56 (1H, d, J=7.5 Hz, ArH), 6.61 (1H, t, J=7.5 Hz, ArH), 6.99 (1H, d, J=7.5 Hz, ArH), 7.11 (1H, t, J=7.5 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 23.7 (CH_2), 24.6 (CH_2), 25.8 (CH_2), 31.3 (CH_2), 32.1 (CH_2), 38.0 (CH_3), 59.0 (CH), 110.5 (CH), 115.3 (CH), 122.0 (C), 127.1 (CH), 128.7 (CH), 145.5 (C); HRMS calcd for $C_{15}H_{24}N$ (M+1) requires 218.1909; found 218.1898.

3.13. *trans*-4-(2-Bromovinyl)-1,2-dimethoxybenzene 17[9]

trans-(3,4-Dimethoxy)cinnamic acid **15** (1.25 g, 6.00 mmol, 1 equiv), sodium bromide (1.85 g, 18.00 mmol, 3 equiv), sodium carbonate (0.63 g, 6.00 mmol, 1 equiv) and oxone (3.69 g, 6.00 mmol, 1 equiv) were dissolved in acetonitrile (60 mL) and H_2O (40 mL) and the reaction stirred for 3 h. EtOAc (50 mL) was added. The resultant organic layer was separated and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (cyclohexane–EtOAc; 15: 1) afforded the *title compound* **17** (741 mg, 51%) as a white solid; mp 48–50 °C; R_f=0.5 (cyclohexane–EtOAc; 2:1); ν_{max} (neat/cm^{-1}) 3075, 3002, 2957, 2935, 2909, 2835, 1603, 1578, 1514, 1461, 1441, 1418, 1329, 1264, 1246, 1205, 1190, 1158, 1140, 1026, 941, 855, 813, 773; δ_H (300 MHz, $CDCl_3$) 3.89 (3H, s, CH_3), 3.91 (3H, s, CH_3), 6.63 (1H, d, J=14.0 Hz, CH), 6.80–6.87 (3H, m, ArH), 7.03 (1H, J=14.0, CH); δ_C (100 MHz, $CDCl_3$) 55.7 (CH_3), 55.8 (CH_3), 104.2 (CH), 108.5 (CH), 111.1 (CH), 119.3 (CH), 128.9 (C), 136.7 (CH), 149.0 (C), 149.2 (C); HRMS cacld for $C_{10}H_{11}O_2Br$ requires 241.9942; found 241.9946. Further elution gave 2,2-dibromo-1-(3,4-dimethoxyphenyl)ethanol **18** (702 mg, 34%) as a white solid; mp 42–43 °C; R_f=0.4 (cyclohexane–EtOAc; 2:1); ν_{max} (neat/cm^{-1}) 3482, 3004, 2960, 2936, 2837, 2599, 1717, 1677, 1595, 1515, 1463, 1420, 1341, 1265, 1237, 1141, 1094, 1080, 1025, 962; δ_H (300 MHz, $CDCl_3$) 3.87 (3H, s, CH_3), 3.89 (3H, s, CH_3), 4.98 (1H, d, J=5.0, CH), 5.76 (1H, d, J=5.0 Hz, CH), 6.83–6.86 (1H, m, ArH), 6.93–6.96 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 52.3 (CH), 55.9 (CH_3), 56.0 (CH_3), 78.8 (CH), 109.8 (CH), 110.8 (CH), 119.6 (CH), 130.4 (C), 149.0 (C), 149.5 (C); HRMS calcd for $C_{10}H_{12}O_3Br_2Na$ (M+Na) requires 360.9051; found 360.9045.

3.14. *trans*-5-(2-Bromovinyl)benzo[*d*][1,3]dioxole 19[13]

trans-3-Benzo[1,3]dioxol-5-yl-acrylic acid **16** (1.15 g, 6.00 mmol, 1 equiv), sodium bromide (1.85 g, 18.00 mmol, 3 equiv), sodium carbonate (0.63 g, 6.00 mmol, 1 equiv) and oxone (3.69 g, 6.00 mmol, 1 equiv) were dissolved in acetonitrile (60 mL) and H_2O (40 mL) and the reaction stirred for 3 h. EtOAc (50 mL) was added and the aqueous and organic layers were separated. The aqueous layer was further extracted with EtOAc (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (cyclohexane–EtOAc; 15: 1) afforded the *title compound* **19** (681 mg, 50%) as a white solid; mp 39–42 °C; R_f=0.7 (cyclohexane–EtOAc; 2:1); ν_{max} (neat/cm^{-1}) 3074, 3011, 2896, 2779, 2694, 2601, 2443, 2361, 2205, 2045, 1855, 1612, 1586, 1503, 1489, 1446, 1351, 1250, 1212, 1184, 1122, 1101, 1039, 930, 859, 820, 795, 770, 739, 713, 682, 634, 602, 568, 529; δ_H (400 MHz, $CDCl_3$) 5.96 (2H, s, CH_2), 6.59 (1H, d, J=14.0 Hz, CH), 6.74–6.75 (2H, m, ArH), 6.80–6.81 (1H, m, ArH), 7.00 (1H, d, J=14.0 Hz, CH); δ_C (100 MHz, $CDCl_3$) 101.2 (CH_2), 104.5 (CH), 105.4 (CH), 108.4 (CH), 120.9 (CH), 130.3 (C), 136.7 (CH), 147.7 (C), 148.1 (C); HRMS cacld for $C_9H_7O_2Br$ requires 225.9629; found 225.9621. Further elution gave 1-benzo[1,3]dioxol-5-yl-2,2-dibromoethanol **20**[14] (933 mg, 48%) as a yellow oil. R_f=0.4 (cyclohexane–EtOAc; 2:1); ν_{max} (neat/cm^{-1}) 3482, 3076, 3006, 2901, 1730, 1681, 1604, 1504, 1489, 1445, 1357, 1248, 1143, 1096, 1038, 931; δ_H (400 MHz, $CDCl_3$) 4.94 (1H, d, J=5.0 Hz, CH), 5.72 (1H, d, J=5.0 Hz, CH), 5.98 (2H, s, CH_2), 6.80 (1H, d, J=8.0 Hz, ArH), 6.87 (1H, dd, J=1.5, 8.0 Hz, ArH), 6.92 (1H, d, J=1.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 55.1 (CH), 78.7 (CH), 101.3 (CH_2), 107.2 (CH), 108.1 (CH), 120.8 (CH), 131.7 (C), 147.7 (C), 148.0 (C); Anal. Calcd for $C_9H_8O_3Br_2$: C, 33.37; H, 2.49%; found, C, 33.78; H, 2.56%.

3.15. 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1-methyl-1,2,3,4-tetrahydroquinoline (cuspareine) 2[2,4c]

trans-4-(2-Bromovinyl)-1,2-dimethoxybenzene **17** (1.00 g, 4.10 mmol, 1 equiv) was dissolved in diethylether (30 mL) under nitrogen at −78 °C. To this a 1.7 M solution of *tert*-butyllithium in pentane (4.80 mL, 8.20 mmol, 2 equiv) was added and the reaction stirred for 1 min. This solution was then added dropwise to quinoline **5** (0.48 mL, 4.10 mmol, 1 equiv) dissolved in THF (30 mL) under nitrogen at room temperature. Stirring was maintained at room temperature for 10 min, then the reaction was brought to 0 °C and methyliodide (0.51 mL, 8.20 mmol, 2 equiv) was added dropwise. Stirring was maintained for 2 h. Saturated aqueous NH_4Cl (50 mL) and dichloromethane (50 mL) were added and the resultant aqueous layer was further extracted with dichloromethane (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Excess quinoline **5** was removed by flash column chromatography (cyclohexane–EtOAc; 30:1). The crude product **21** was then dissolved in EtOH (80 mL) and 10% w/w Pd/C (435 mg, ca. 10 mol %) was added, the reaction was stirred under H_2 (ca. 1 atm) for 72 h. The reaction mixture was then filtered through Celite and washed with EtOAc (2×50 mL). The solvent was removed under reduced pressure and purification by flash column chromatography (cyclohexane–EtOAc; 99:1) afforded the *title compound* **2** (664 mg, 52%) as a yellow oil. R_f=0.5 (cyclohexane–EtOAc; 2:1); ν_{max} (neat/cm^{-1})

2933, 2838, 1601, 1508, 1456, 1331, 1262, 1148, 1029, 931, 851, 806, 745, 631; δ_H (600 MHz, $CDCl_3$) 1.75–1.82 (1H, m, CH_2-3′), 1.94–2.02 (3H, m, CH_2-3, CH_2-3′), 2.56–2.61 (1H, m, CH_2-4′), 2.69–2.76 (2H, m, CH_2-4, CH_2-4′), 2.87–2.93 (1H, m, CH_2-4), 2.96 (3H, s, CH_3), 3.31–3.35 (1H, m, CH_2-2), 3.88 (3H, s, CH_3), 3.91 (3H, s, CH_3), 6.58 (1H, d, J=7.5 Hz, ArH), 6.59 (1H, t, J=7.5 Hz, ArH), 6.76–6.78 (2H, m, ArH), 6.83–6.85 (1H, m, ArH), 7.03 (1H, d, J=7.5 Hz, ArH), 7.13–7.15 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 23.5 (CH_2), 24.3 (CH_2), 31.8 (CH_2), 33.0 (CH_2), 38.0 (CH_3), 55.7 (CH_3), 55.8 (CH_3), 58.3 (CH), 110.5 (CH), 111.3 (CH), 111.6 (CH), 115.3 (CH), 120.0 (CH), 121.6 (C), 127.0 (CH), 128.6 (CH), 134.6 (C), 145.2 (C), 147.2 (C), 148.8 (C); HRMS calcd for $C_{20}H_{26}NO_2$ (M+1) requires 312.1964; found 312.1961.

3.16. 2-(2-Benzo[1,3]dioxol-5-ylethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (galipinine) 3[2,4c]

trans-5-(2-Bromovinyl)benzo[*d*][1,3]dioxole **19** (1.00 g, 4.40 mmol, 1 equiv) was dissolved in diethylether (30 mL) under nitrogen and brought to −78 °C. To this a 1.7 M solution of *tert*-butyllithium in pentane (5.20 mL, 8.80 mmol, 2 equiv) was added and the reaction stirred for 1 min. This solution was then added dropwise to quinoline (0.52 mL, 4.40 mmol, 1 equiv) dissolved in THF (30 mL) under nitrogen at room temperature. Stirring was maintained at room temperature for 10 min, then the reaction was brought to 0 °C and methyliodide (0.55 mL, 8.80 mmol, 2 equiv) was added dropwise. Stirring was maintained for 2 h. Saturated aqueous NH_4Cl (50 mL) and dichloromethane (50 mL) were added and the resultant aqueous layer was further extracted with dichloromethane (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Unreacted quinoline **5** was removed by flash column chromatography (cyclohexane–EtOAc; 30:1). The dihydroquinoline **22** was then dissolved in EtOH (80 mL) and 10% w/w Pd/C (468 mg, ca. 10 mol %) was added, the reaction was stirred under H_2 (ca. 1 atm) for 72 h. The reaction mixture was filtered through Celite, washed with EtOAc (2×50 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (cyclohexane–EtOAc; 99:1) afforded the *title compound* **3** (754 mg, 58%) as a yellow oil. R_f=0.6 (cyclohexane–EtOAc; 2:1); ν_{max} (neat/cm^{-1}) 2931, 2891, 1602, 1508, 1443, 1331, 1244, 1094, 1039, 932, 859, 806, 746; δ_H (500 MHz, $CDCl_3$) 1.67–1.74 (1H, m, CH_2-3′), 1.85–1.97 (3H, m, CH_2-3, CH_2-3′), 2.48–2.54 (1H, m, CH_2-4′), 2.61–2.71 (2H, m, CH_2-4, CH_2-4′), 2.80–2.87 (1H, m, CH_2 CH_2-4), 2.91 (3H, s, CH_3), 3.25–3.29 (1H, m, CH_2-2), 5.92 (2H, s, CH_2), 6.53 (1H, d, J=7.5 Hz, ArH), 6.59 (1H, t, J=7.5 Hz, ArH), 6.63 (1H, dd, J=1.5, 8.0 Hz, ArH), 6.68 (1H, d, J=1.5 Hz, ArH), 6.72 (1H, d, J=8.0 Hz, ArH), 6.97 (1H, d, J=7.5 Hz, ArH), 7.08 (1H, t, J=7.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 23.5 (CH_2), 24.3 (CH_2), 31.9 (CH_2), 33.1 (CH_2), 38.0 (CH_3), 58.1 (CH), 100.7 (CH_2), 108.1 (CH), 108.6 (CH), 110.6 (CH), 115.4 (CH), 120.8 (CH), 121.7 (C), 127.0 (CH), 128.6 (CH), 135.8 (C), 145.2 (C), 145.6 (C), 147.6 (C); HRMS calcd for $C_{19}H_{22}NO_2$ (M+1) requires 296.1651; found 296.1637.

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