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**PAPER**

# Asymmetric synthesis of 2-alkyl-substituted tetrahydroquinolines by an enantioselective aza-Michael reaction†

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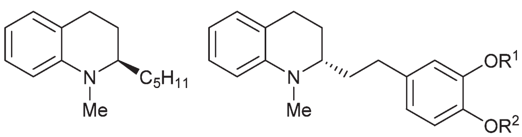
An optically active tetrahydroquinoline intermediate (**5**) was prepared in 8 steps from monoprotected ethylene glycol, using a Pd-catalysed aza-Michael reaction to induce chirality. This can be transformed into three *Galipea* alkaloids (angustureine, galipeine and cuspareine). The proximity of a benzyloxy group is found to exert profound effects in several steps of the synthesis.

## Introduction

Angustureine (**1**), galipeine (**2**), ~~galipinine~~ (**3**) and ~~cuspareine~~ (**4**) constitute a family of anti-malaria and cytotoxic tetrahydroquinoline alkaloids extracted from the bark of a Venezuelan tree (*Galipea officinalis* Hancock) (Fig. 1).[1–4] Asymmetric synthesis of these natural products was first achieved by Zhou *et al.* by catalytic hydrogenation of the corresponding 2-alkyl substituted quinolines, where up to 97% ee was attained.[5,6] The reduction can also be effected by a non-metal catalyst in 90–91% ee, but this requires an excess of Hantzsch ester (2.4 eq.) as the hydride source.[7] In comparison, other attempts to access these compounds by catalytic methodologies had been less efficient; these include Pd-catalysed asymmetric intramolecular alkyne hydroamination,[8] nucleophilic addition of arylboronic acids to quinolines catalysed by chiral thioureas,[9] and more recently, Ir-catalysed allylic substitution by an amine.[10] In all cases, reaction scope was rather limited, prolonged reaction times were required, and product yields and/or selectivity were modest, even at high catalyst loadings (≥10 mol%).




(*R*)-(-)-**1**

$R^1$ = H, $R^2$ = Me, (*S*)-(-)-**2**
$R^1$ = $R^2$ = Me, (*S*)-(-)-**3**
$R^1$-$R^2$ = -$CH_2$-, (*S*)-(-)-**4**

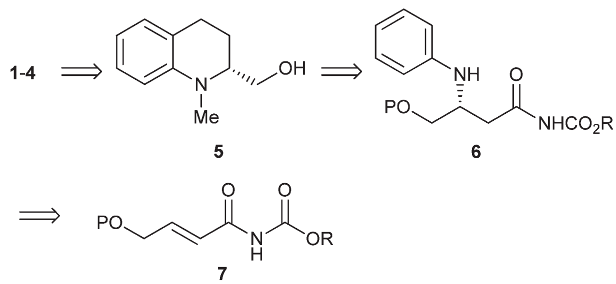
**Fig. 1** 2-Alkyl tetrahydroquinoline alkaloids isolated from *Galipea officinalis* Hancock.

Herein, we will describe the synthesis of these alkaloids from an optically pure tetrahydroquinoline intermediate (**5**), derived from an aza-Michael adduct prepared by the enantioselective addition of aniline to **7** (Scheme 1).[11] In this approach, the stereogenic centre is installed by a non-hydrogenative step, allowing the 2-substituent to be defined in the last step of the synthesis.

## Results and discussion

### Preparation of Michael acceptors (Scheme 2)

Following published procedures, ethylene glycol was desymmetrised by using two different *O*-protecting groups (benzyl and *tert*-butyldiphenylsilyl).[12,13] Oxidation of **8a–b** under Swern conditions furnished protected β-hydroxy aldehydes **9a** and **9b**, respectively. Initial attempts to subject these compounds to the Horner–Wadsworth–Emmons olefination reaction, using phosphonate carbamates **10a–b** and DBU, afforded low yields of the expected products (Table 1, entries 1–3). Attributing this to the instability of the aldehyde under basic conditions, the reaction




**Scheme 1** Retrosynthetic scheme for the synthesis of the *Galipea* alkaloids *via* an aza-Michael reaction.

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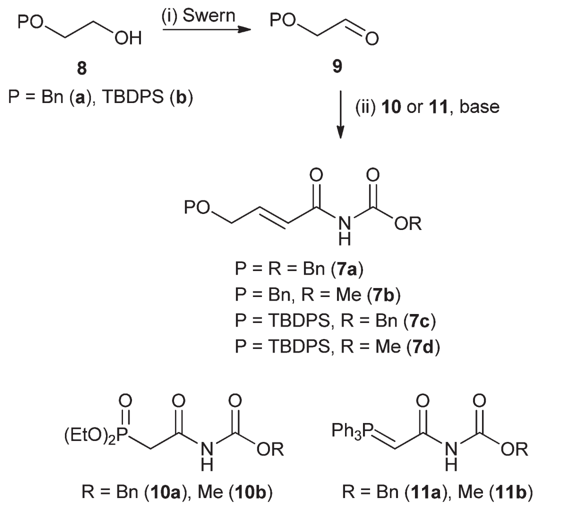


**Scheme 2** Preparation of Michael acceptors by tandem oxidation and olefination reactions.

**Table 1** Preparation of Michael acceptors **7a–d** (Scheme 2, step ii)[a]

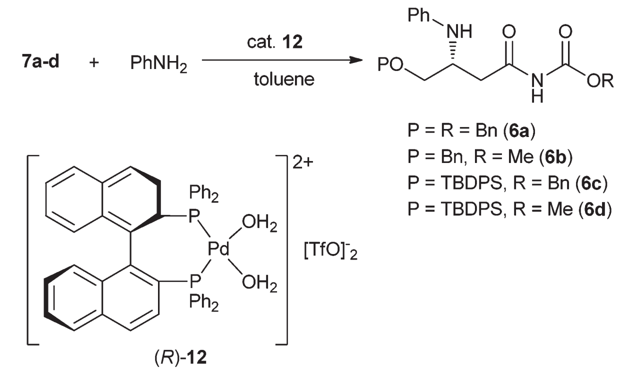
| Entry | Reactant | P-reagent | Product | Olefination conditions | Yield[b]/% |
|---|---|---|---|---|---|
| 1 | **9a** | **10a** | **7a** | DBU | 23 |
| 2 | **9b** | **10a** | **7c** | DBU | 20 |
| 3 | **9b** | **10b** | **7d** | DBU | 21 |
| 4 | **9a** | **10a** | **7a** | i-PrEt$_2$N, LiCl | 44 |
| 5 | **9a** | **10b** | **7b** | i-PrEt$_2$N, LiCl | 42 |
| 6 | **9b** | **10a** | **7c** | i-PrEt$_2$N, LiCl | 32 |
| 7 | **9b** | **10b** | **7d** | i-PrEt$_2$N, LiCl | 45 |
| 8 | **9a** | **11a** | **7a** | — | 53[c] |
| 9 | **9a** | **11b** | **7b** | — | 75[c] |
| 10 | **9a** | **11b** | **7b** | — | 79[d,e] |

[a] See Experimental section for reaction conditions. [b] Isolated yield after column chromatography. [c] Mixture of *E* : *Z* isomers (*ca.* 3.5 : 1). [d] DMP utilised in the oxidation step. [e] *E*-isomer only.

was repeated under Masamune–Roush modified conditions (Hünig's base/LiCl),[14] but this led only to a marginal improvement (entries 4–7). By using phosphonium ylides **11a** and **11b**, the products were attained in acceptable yields as a mixture of *E*/*Z* isomers (*ca.* 3.5 : 1, entries 8 and 9). Although the selectivity was somewhat compromised, the isomers can be separated by column chromatography, and the reaction can be used to furnish the Michael acceptors on a multigram scale. In a further attempt to improve the efficiency of this process, a tandem one-pot oxidation–olefination procedure was performed by using DMP as the oxidant and **11b**. In this case, the exclusive formation of the *E*-isomer can be achieved in 79% yield over two steps (entry 10).

### Pd-catalysed enantioselective aza-Michael reactions

The addition of aniline to the series of Michael acceptors **7a–d** was initially performed in toluene in the presence of (*R*)-BINAP-complex **12** as a chiral Lewis acid catalyst (Scheme 3).



**Scheme 3** Aza-Michael addition reactions.

Due to their lower solubility, reactions of the TBDPS derivatives were performed at 50 °C and higher dilutions. Interestingly, the addition is highly dependent on the *O*-protecting group employed on the Michael acceptors: while the addition of aniline to **7a** and **7b** was complete within 18 h to give the expected products in moderate ee values (Table 2, entries 1 and 2), reactions with **7c** and **7d** were incomplete even after three days (entries 3 and 4). Compounded by their low solubility, and difficulty in the separation of the enantiomers by chiral HPLC, further work with the silyl-protected substrates **7c** and **7d** was consequently abandoned.

Previously, we have found that the coordination of the *N*-nucleophile to the metal centre can have a significant inhibitory effect on the conjugate addition.[11b] With this in mind, the addition of aniline was examined at different concentrations of **7a** between 1–0.075 M. As expected, an increase in dilution led to a marked improvement to the enantioselectivity without compromising the reaction yield (entries 5–9). Further improvement was achieved by slow addition of the nucleophile *via* a programmable syringe pump (entries 10 and 11), to afford good enantioselectivities of 81 and 84% for adducts **6a** and **6b**, respectively.

Finally, products **6a–b** can be rendered enantiomerically pure by recrystallisation from toluene–cyclohexane, whereby optically pure material can be recovered from the mother liquor.

### Synthesis of the common intermediate 5

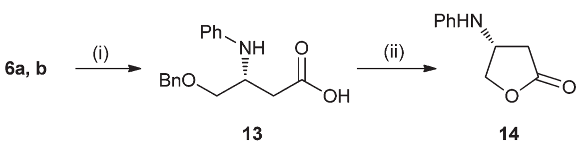
The tetrahydroquinoline **5** has been previously synthesised by an aza-Diels–Alder reaction as a racemic mixture, and shown to be a viable intermediate for the synthesis of *Galipea* alkaloids.[15,16] In this work, electrophilic cyclisations of *N*-aryl amino acids to 4-keto tetrahydroquinoline were attempted initially under Friedel–Crafts conditions,[17] or by using the Brønsted acid PPA.[18] Application of these procedures to **13**, however, led to highly capricious reaction mixtures, from which a small amount of the lactone **14** can be isolated (Scheme 4), *i.e.* the *O*-benzyl protecting group is unstable under these acidic conditions.

The formation of the heterocycle was ultimately achieved by a reductive cyclization of **6a** to afford 4-amino-2-substituted tetrahydroquinoline **15** as the *syn* isomer (Scheme 5).[11a,19] Methylation of **15** at N-1, followed by deprotection of N-2, furnished compound **17**, which was subjected to transamination using Rapoport's reagent[20] to the 4-keto derivative **18**. Finally,

**Table 2** Optimisation of the aza-Michael reaction (Scheme 5)[a]

| Entry | Substrate | Product | Dilution[b]/M | Time | Conversion[c]/% | ee[d]/% |
|---|---|---|---|---|---|---|
| 1 | **7a** | **6a** | 0.3 | 16 | 100 | 69 |
| 2 | **7b** | **6b** | 0.4 | 16 | 100 | 61 |
| 3 | **7c** | **6c** | 0.2 | 71 | 93 | ND |
| 4 | **7d** | **6d** | 0.2 | 71 | 78 | ND |
| 5 | **7a** | **6a** | 1 | 16 | 96 | 39 |
| 6 | | | 0.6 | 16 | 98 | 58 |
| 7 | | | 0.3 | 16 | 98 | 67 |
| 8 | | | 0.2 | 16 | 95 | 74 |
| 9 | | | 0.075 | 16 | 97 | 76 |
| 10 | **7a** | **6a** | [e] | 17 | 96 | 81 |
| 11 | **7b** | **6b** | [e] | 18 | 96 | 84 |

[a] General reaction condition: catalyst (*R*)-**12** (0.015 mmol, 5 mol%), **10a–d** (0.3 mmol, 1 eq.), aniline (0.3 mmol, 1 eq.), toluene, 50 °C. [b] With respect to substrate **10a–d**. [c] Determined by $^1$H NMR. [d] Determined by chiral HPLC. [e] Slow addition of aniline (see Experimental section).



**Scheme 4** Attempted electrophilic cyclisation. (i) 1 M aq. KOH; (ii) either: (a) chlorination followed by $AlCl_3$, or (b) PPA.

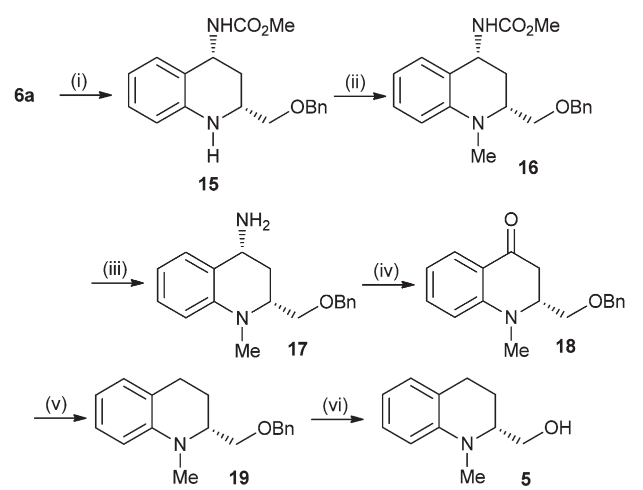
complete reduction using $LiAlH_4$, facilitated by $AlCl_3$,[21] furnished the key intermediate **19**.

Unexpectedly, the *O*-benzyl protecting group of **5** proved to be inert to most hydrogenation protocols, including the use of 10% Pd/C and a number of hydrogen sources ($H_2$ and 1,4-cyclohexadiene). Ultimately, nickel sponge proved to be an efficient catalyst,[22,23] affording slow but clean conversion of **19** to the intermediate **5**.[24]

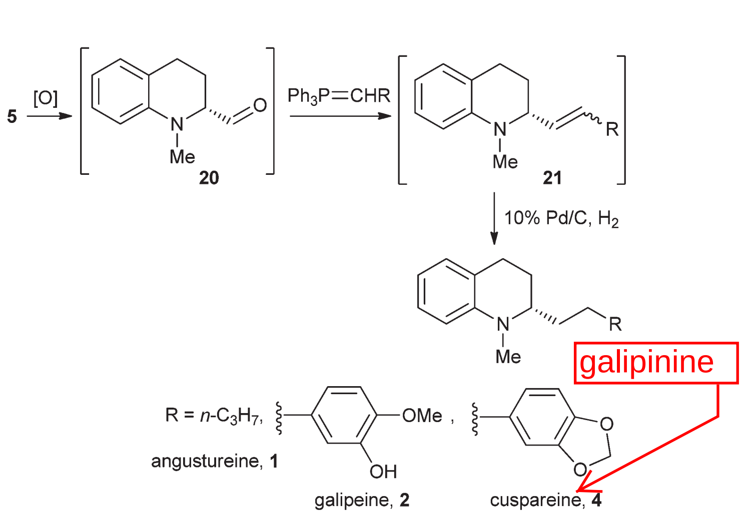
## Synthesis of three *Galipea* alkaloids

Finally, the tetrahydroquinoline **5** was transformed into the *Galipea* alkaloids by a sequence of oxidation–Wittig–reduction reactions (Scheme 6), performed in tandem without isolation or purification of the intermediates **20** (unstable) or **21** (mixture of *E*/*Z* isomers). Overall yields of 44, 32 and 31% (over three steps) were obtained for the synthesis of angustureine (**1**), galipeine (**2**) and cuspareine (**4**), respectively. The benzylic phosphonium salts **22a** and **22b** required for the Wittig reaction were prepared from commercially available alcohols (Scheme 7). For the synthesis of galipeine, the phenolic moiety was masked as a benzyloxy group in **22b**, which was removed in the subsequent catalytic hydrogenation step.

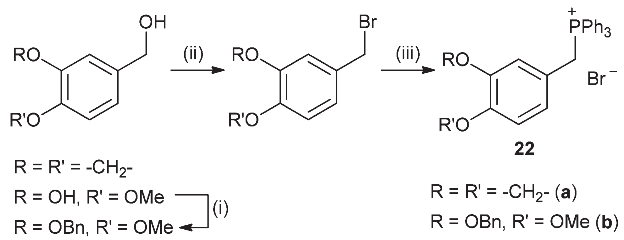
From our previous work, it was expected that the *R*-enantiomer of the key intermediate **5** will be preferentially formed by employing (*R*)-BINAP ligated catalyst **12**.[11a,b] Assuming that the stereochemistry is preserved in subsequent reactions, this will produce the opposite and natural enantiomeric forms of alkaloids **1** and **2**, respectively. Indeed, this was verified by comparing their spectroscopic and optical rotatory data with reported values (Table 3). As noted previously,[25] the optical rotation of the enantiomerically pure sample of galipeine **2** is considerably larger than that reported for the natural isomer.



**Scheme 5** Transformation of the Michael adduct to **5**: (i) $MgCl_2$, $NaBH_4$, EtOH–THF, −10 °C, 87%; (ii) HCHO, $NaCNBH_3$, AcOH–$CH_3CN$, 0 °C, 88%; (iii) TMSI, $CH_3CN$, 78%; (iv) a. 4-formyl-1-methylpyridinium benzenesulfonate, DBU, DCM–DMF, rt; b. oxalic acid, 75%; (v) $LiAlH_4$, $AlCl_3$, THF, 87%; (vi) RANEY® Ni, $H_2$, EtOH–THF, reflux, 71%.




**Scheme 6** Transformation of **5** to *Galipea* alkaloids.

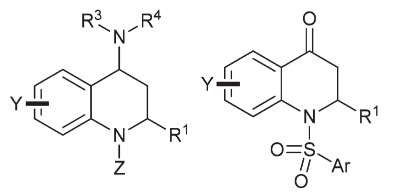



**Scheme 7** Preparation of phosphonium salts used in the Wittig reaction in Scheme 6: (i) BnBr, $K_2CO_3$, acetone, reflux; (ii) $PBr_3$, $CH_2Cl_2$; (iii) $PPh_3$, toluene.

**Table 3** Synthesis and optical properties of compounds **1**, **2** and **4**[a]

| Entry | Product | Yield[b]/% | Obs. $[\alpha]_D$ [c] | Lit. $[\alpha]_D^{20}$ |
|---|---|---|---|---|
| 1 | **1** | 44 | +7.5 | −7.16[d] |
| 2 | **2** | 32 | −27.0 | −13.6[d], −26.1[e] |
| 3 | **4** | 31 | —[f] | −33.4[1] |

[a] Reaction procedures are described in the Experimental section. [b] Isolated yield after column chromatography, over two steps. [c] Recorded in $CHCl_3$. [d] Optical rotation reported of the natural product.[2,26] [e] Optical rotation reported of **2** obtained by asymmetric synthesis (96% ee).[25] [f] Performed only with *rac*-**5**.



I II

**Fig. 2** Biologically active tetrahydroquinoline derivatives.

## Conclusions

Synthesis of *Galipea* alkaloids **1**, **2** and **4** was achieved *via* a catalytic aza-Michael reaction in 12 steps.[27] The proximity of the *O*-benzyl group in **7a** presented unexpected effects in several steps of the synthesis. Most crucially, the failure of the electrophilic cyclisation necessitated a rather circuitous route to the quinolone **18** (steps i–iv, Scheme 5). Nevertheless, the additional steps provide novel enantiomerically pure tetrahydroquinoline derivatives (Fig. 2) that are important pharmacophores, for which there are few synthetic methods.[28] For very recent examples, 4-amino-substituted tetrahydroquinolines **I** are found to be non-steroidal selective androgen receptor modulators[29] and bromodomain inhibitors,[30,31] while quinolin-4-one derivatives **II** have also been reported to have potent binding affinity for 5-HT6 serotonin receptors.[32] Further applications of the catalytic asymmetric aza-Michael reaction for the synthesis of such highly functionalised tetrahydroquinolines are currently in progress.

## Experimental

### General experimental conditions

$^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on Bruker AVANCE machines operating at 400 and 100 MHz, respectively. Chemical shifts are reported in $\delta$ (ppm), referenced to TMS. Multiplicity is abbreviated to s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Melting points were recorded using an Electrothermal Gallenhamp apparatus, and were uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 100 series FT-IR spectrometer, fitted with a beam-condensing ATR accessory. Chiral HPLC was performed on Gilson and Hewlett Packard HPLC systems, each equipped with variable wavelength UV detectors, using chiral HPLC columns (250 × 4.6 mm). Mass spectrometry and elemental analyses were performed by the relevant technical support units at Imperial College and London Metropolitan University, respectively.

All reactions with air- or moisture-sensitive materials were carried out under $N_2$ using standard Schlenk techniques. Anhydrous solvents were dried by passing through molecular sieves under $N_2$ in purification towers. Unless otherwise stated, all chemical reagents and precursors were procured from commercial sources and used without purification. The following compounds were prepared by following literature procedures: 2-(benzyloxy)ethanol (**8a**),[12] 2-(2,2-dimethyl-1,1-diphenylpropoxy)ethanol (**8b**),[13] benzyl (**10a**) and methyl (**10b**) 2-(diethoxyphosphoryl)acetylcarbamates.[10]

### Synthesis of phosphonium ylides, 11a–b

$PPh_3$ (38.4 g, 146 mmol) was added to benzyl 2-chloroacetylcarbamate (27.8 g, 122 mmol) in THF (300 mL). The reaction was heated to reflux until complete consumption of starting material occurred (TLC). The reaction mixture was cooled to room temperature, whereupon the phosphonium salt precipitated, which was collected by filtration.

*(2-(Benzyloxycarbonylamino)-2-oxoethyl)triphenyl-phosphonium chloride* was collected as a white solid (45.5 g, 76%); mp 147–149 °C; $\nu_{max}/cm^{-1}$ 2870, 1778, 1437, 1109, 687; $\delta_H$: 12.25 (1H, s, NH), 7.85–7.70 (10H, m, ArH), 7.61–7.55 (5H, m, ArH), 7.40–7.19 (5H, m, ArH), 5.44 (2H, d, $J$ = 14.0 Hz, $PCH_2$), 5.11 (2H, s, $OCH_2Ph$); $\delta_C$: 163.0, 150.6, 135.1, 135.0, 134.0 (d, $J$ = 11 Hz), 130.3 (d, $J$ = 13 Hz), 128.6, 128.4, 128.1, 117.9 (d, $J$ = 89 Hz), 67.0, 33.5 (d, $J$ = 58 Hz); $m/z$ (HRMS-ESI) 454.1568 ($[M - Cl]^+$ $C_{28}H_{25}NO_3P$ requires 454.1572), 326 (6), 224 (15).

*(2-(Methoxycarbonylamino)-2-oxoethyl)triphenyl-phosphonium chloride* was similarly obtained from methyl 2-chloroacetylcarbamate as a white solid (39 g, 78%); mp 184–186 °C; $\nu_{max}/cm^{-1}$ 3090, 2060, 2890, 3830, 2770, 1780, 1620, 1530, 1440; $\delta_H$: 12.25 (1H, br. s, NH), 7.83–7.70 (9H, m, Ar-H), 7.55–7.65 (6H, m, Ar-H), 5.45 (2H, d, $J$ = 16.0 Hz, $PCH_2$), 3.62 (3H, s, $OCH_3$); $\delta_C$: 163.1 (d, $J$ = 4 Hz), 151.2, 135.1, 134.0 (d, $J$ = 10 Hz), 130.2 (d, $J$ = 13 Hz), 118.0 (d, $J$ = 88 Hz), 52.7, 33.4 (d, $J$ = 58 Hz); $m/z$ (HRMS-ESI) 378.1253 ($[M - Cl]^+$ $C_{22}H_{21}NO_3P$ requires 378.1259), 326 (4), 303 (6).

KOtBu (9.92 g, 88.2 mmol) was added slowly in several portions to a suspension of the phosphonium salt (21.6 g, 44.1 mmol) in THF (150 mL) at −5 °C. The solid phosphonium carbamate salt gradually dissolved during the addition, and the resultant homogeneous reaction mixture was stirred for 1 h. $CH_2Cl_2$ (300 mL) and $H_2O$ (150 mL) were then added.

The aqueous layer was extracted with $CH_2Cl_2$ (200 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The ylide is used directly in the following reactions without further purification.

### Preparation of the Michael acceptors by a typical tandem oxidation–Wittig reaction

Under a $N_2$ atmosphere, DMSO (29.5 mL, 0.415 mol) was added to a solution of oxalyl chloride (18.1 mL, 0.207 mol) in $CH_2Cl_2$ (600 mL) over 20 min, at −78 °C. The reaction was stirred for 10 min, followed by the addition of a solution of **8a** (21.0 g, 0.138 mol) in $CH_2Cl_2$ (10 mL) over 10 min. After stirring for a further 30 min, $NEt_3$ (91 mL, 0.650 mol) was added over 20 min. The reaction was allowed to warm to room temperature, diluted with $Et_2O$ (600 mL) and filtered through a pad of $MgSO_4$. The filtrate was concentrated under vacuum to yield the aldehyde **9a** as an unstable yellow oil, to which a solution of the ylide (0.415 mol, 1 eq.) in $CH_2Cl_2$ was immediately added. The solution was stirred for 16 h, before it was concentrated under vacuum to give the olefinated product as a mixture of *E* and *Z* isomers, separable by column chromatography.

### (*E*)-Benzyl 4-(benzyloxy)-but-2-enoylcarbamate, 7a

White solid purified by column chromatography (1.0 g, 61%). $R_f$ = 0.3 (EtOAc–*n*-hexane, 3 : 2), *E*-isomer; mp 98–100 °C; $\nu_{max}$/cm$^{-1}$ 3260, 1747, 1650, 1510; $\delta_H$: 7.76 (1H, br s, N*H*), 7.44–7.29 (10H, m, Ar-H), 7.15 (1H, dt, *J* = 3.9, 15.5 Hz, $CH_2CH$), 7.06 (1H, br d, *J* = 15.5 Hz, C*H*CO), 5.22 (2H, s, $CO_2CH_2$), 4.60 (2H, s, $OCH_2Ar$), 4.23 (2H, dd, *J* = 1.6, 3.9 Hz, $CH_2CH$); $\delta_C$: 165.3, 151.4, 146.1, 137.7, 135.0, 128.7, 128.6, 128.5, 128.4, 127.9, 127.8, 121.2, 72.8, 68.8, 67.9; *m*/*z* (HRMS-ESI) 326.1387 ($MH^+$, $C_{19}H_{20}NO_4$ requires 326.1392), 243 (78), 91 (100). *Z*-isomer $R_f$ = 0.35: mp 72–75 °C; $\delta_H$: 8.26 (1H, br. s, NH), 7.50–7.26 (10H, m, Ar-H), 6.73 (1H, br. d, *J* = 11.7 Hz, C*H*CO), 6.60 (1H, dt, *J* = 4.5, 11.7 Hz, $CH_2CH$), 5.22 (2H, s, $CO_2CH_2$), 4.67 (2H, dd, *J* = 2.2, 4.5 Hz, $CH_2CH$), 4.57 (2H, s, $OCH_2Ar$); $\delta_C$: 165.6, 151.6, 150.5, 137.9, 135.0, 128.7, 128.6, 128.5, 128.4, 127.9, 127.8, 119.5, 72.9, 69.3, 67.9.

### (*E*)-Methyl 4-(benzyloxy)-but-2-enoylcarbamate, 7b

White solid purified by column chromatography (12.2 g, 74%). $R_f$ = 0.28 (EtOAc–*n*-hexane, 3 : 2); mp 83–85 °C; $\nu_{max}$/cm$^{-1}$ 3250, 1770, 1650, 1200; $\delta_H$: 8.66 (1H, s, NH), 7.39–7.25 (5H, m, Ar-H), 7.14 (1H, dt, *J* = 4.2, 15.4 Hz, $CH_2CH$), 7.01 (1H, br d, *J* = 15.4 Hz, C*H*CO), 4.57 (2H, s, $OCH_2Ar$), 4.21 (2H, dd, *J* = 1.8, 4.2 Hz, $CH_2CH$), 3.77 (3H, s, $OCH_3$); $\delta_C$: 165.8, 152.2, 145.9, 137.7, 128.5, 127.8, 127.7, 121.5, 72.8, 68.8, 53.1; *m*/*z* (HRMS-ESI) 250.1078 ($MH^+$, $C_{13}H_{16}NO_4$ requires 250.1079) 158 (38), 143 (78), 91 (100).

### (*E*)-Benzyl 4-(*tert*-butyldiphenylsilyloxy)-but-2-enoylcarbamate, 7c

White solid purified by recrystallisation from EtOAc–*n*-hexane (0.5 g, 32%); mp 93–95 °C; $\nu_{max}$/cm$^{-1}$ 3261, 1750, 1655, 1216; $\delta_H$: 7.79–7.65 (5H, m, Ar-H and NH), 7.52–7.35 (11H, m, Ar-H), 7.23 (1H, d, *J* = 15.2 Hz, CHCO), 7.17 (1H, br. d, *J* = 15.2 Hz, $CH_2CH$), 5.25 (2H, s, $OCH_2Ar$), 4.45–4.40 (2H, m, $OCH_2CH$), 1.13 (9H, s, $CH_3$); $\delta_C$: 165.6, 151.4, 148.8, 135.5, 135.1, 133.0, 130.1, 128.7, 128.6, 128.4, 127.8, 119.8, 67.9, 63.3, 26.7, 19.3; *m*/*z* (EI) 473.2026 ($M^+$ $C_{28}H_{31}NO_4Si$ requires 473.2022) 256 (4), 199 (100).

### (*E*)-Methyl 4-(*tert*-butyldiphenylsilyloxy)but-2-enoylcarbamate, 7d

White solid purified by recrystallisation from EtOAc–*n*-hexane (0.41 g, 45%); mp 134–136 °C; $\nu_{max}$/cm$^{-1}$ 3169, 1746, 1655, 1540, 1230; $\delta_H$: 7.69 (4H, dd, *J* = 1.3, 7.7 Hz, Ar-H), 7.62 (1H, br. s, NH), 7.51–7.36 (6H, m, Ar-H), 7.23 (1H, d, *J* = 15.2 Hz, C*H*CO), 7.16 (1H, dt, *J* = 2.7, 15.2 Hz, $CH_2CH$), 4.45–4.38 (2H, m, $OCH_2CH$), 3.83 (3H, s, $OCH_3$), 1.12 (9H, s, $CH_3$); $\delta_C$: 165.8, 152.2, 148.9, 135.5, 132.9, 129.9, 127.8, 119.7, 63.2, 53.1, 26.7, 19.3; *m*/*z* (HRMS-ESI) 398.1790 ($MH^+$ $C_{22}H_{28}NO_4Si$ requires 398.1788), 256 (10), 199 (100).

### Methods for the aza-Michael reaction

Method A (substrate screening): A Radley's reaction tube was charged with a stir bar and (*R*)-**12**, placed under vacuum for 30 min and then flushed with $N_2$ before toluene was added. The reaction tube was placed in the heating block and the temperature was adjusted to 50 °C using a thermostat. The Michael acceptor and aniline were added, and the reaction was monitored by $^1H$ NMR spectroscopy. Upon completion, the reaction mixture was evaporated to dryness and the residue was purified by column chromatography.

Method B (slow addition): A round-bottomed flask was charged with (*R*)-**12** (0.35 g, 0.329 mmol) and the Michael acceptor (6.58 mmol). Dry toluene (20 mL) was added and the mixture was heated to 50 °C to afford a clear solution. To this, a solution of aniline (0.6 mL, 6.58 mmol) in toluene (15 mL) was added slowly using a syringe pump, over 20 h. The reaction mixture was stirred at 50 °C for an additional 18 h, cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography.

### (*R*)-(+)-Benzyl 4-(benzyloxy)-3-(phenylamino)-butanoylcarbamate, 6a

Obtained as a light brown oil after column chromatography, $R_f$ = 0.38 ($Et_2O$–*n*-pentane, 1 : 1); $[\alpha]_D^{25}$ +3.5° (*c* = 1.3, $CH_2Cl_2$, 85% ee); Daicel Chiralpak AD-H, 1 : 9 IPA–*n*-hexane, 1.0 mL min$^{-1}$, $t_R$ = 28.7 (major), 33.9 (minor) min; $\nu_{max}$/cm$^{-1}$ 3380, 3280, 1750, 1660, 1210; $\delta_H$: 7.90 (1H, br. s, N*H*CO), 7.45–7.29 (10H, m, Ar-H), 7.19 (2H, dd, *J* = 7.3, 7.8 Hz, Ar-H), 6.76 (1H, t, *J* = 7.3 Hz, Ar-H), 6.66 (2H, d, *J* = 7.8 Hz, Ar-H), 5.19 (2H, s, $CO_2CH_2$), 4.54 (2H, s, $OCH_2Ar$), 4.16 (2H, br. s, ArN*H* and C*H*), 3.71–3.57 (2H, m, $OCH_2CH$), 3.18–3.00 (2H, m, $CH_2CO$); $\delta_C$: 172.3, 151.3, 146.5, 137.9, 134.9, 129.4, 128.7, 128.4, 128.4, 127.8, 127.7, 118.3, 114.1, 73.3, 70.9, 67.9, 50.0, 37.9; *m*/*z* (HRMS-EI) 418.1898 ($M^+$, $C_{25}H_{26}N_2O_4$ requires 418.1893) 310 (35), 297 (100), 189 (89), 146 (92), 104 (82), 77 (75); Anal.

Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69%. Found: C, 71.71; H, 6.16; N, 6.79%.

**(*R*)-(+)-Methyl 4-(benzyloxy)-3-(phenylamino)butanoyl-carbamate, 6b**

Purified by column chromatography, $R_f$ = 0.33 ($Et_2O$–*n*-pentane, 2 : 1); $[\alpha]_D^{25}$ +4.2° (*c* = 1.2, $CHCl_3$, 97% ee); Daicel Chiralpak AD-H, 2 : 98 IPA–*n*-hexane, 1.0 mL $min^{-1}$, $t_R$ = 22.3 (major), 25.5 (minor) min; $\nu_{max}/cm^{-1}$ 3260, 3180, 1755, 1600; $\delta_H$: 7.92 (1H, br s, N*H*CO), 7.41–7.30 (5H, m, Ar-H), 7.19 (2H, dd, *J* = 7.4, 7.8 Hz, Ar-H), 6.76 (1H, t, *J* = 7.4 Hz, Ar-H), 6.67 (2H, d, *J* = 7.8 Hz, Ar-H), 4.54 (2H, s, OC$H_2$Ar), 4.09–4.23 (2H, br. m, ArN*H* and C*H*), 3.77 (3H, s, $OCH_3$), 3.59–3.68 (2H, m, $OCH_2$), 2.99–3.15 (2H, m, $CH_2CO$); $\delta_C$: 172.4, 152.0, 145.6, 137.9, 129.4, 128.4, 127.8, 127.7, 118.3, 114.1, 73.3, 70.9, 53.0, 50.1, 37.9; *m*/*z* (HRMS-EI) 342.1581 ($M^+$, $C_{19}H_{22}N_2O_4$ requires 342.1580), 310 (15), 221 (69), 189 (48), 146 (100), 104 (41), 91 (60).

A sample of optically active **6b** (4.12 g, 84% ee) was suspended in EtOAc (6 mL) and heated to reflux. Hexane was then added dropwise until the solution started to turn cloudy (~18 mL). The mixture was cooled to room temperature, whereupon white needle-like crystals were formed, which were collected by filtration (2.04 g, 70% ee). The filtrate was evaporated to give optically enriched material (2.04 g, >99% ee). This process was repeated with the less optically pure product. Overall, the optically pure product was obtained can be recovered in 77% yield and >99% ee, as a yellow oil.

**Benzyl 4-(*tert*-butyldiphenylsilyloxy)-3-(phenylamino)-butanoylcarbamate, 6c**

Purified as a yellow oil after column chromatography, $R_f$ = 0.30 ($Et_2O$–*n*-pentane, 3 : 2); separation of enantiomers by chiral HPLC was not possible, $\nu_{max}/cm^{-1}$ 2960, 2940, 2870, 1780, 1700, 1610, 1500; $\delta_H$: 7.85 (1H, br. s, CON*H*), 7.69–7.57 (4H, m, Ar-H), 7.49–7.31 (11H, m, Ar-H), 7.14 (1H, dd, *J* = 7.3, 7.8, Ar-H), 6.74 (1H, t, *J* = 7.3 Hz, Ar-H), 6.54 (2H, d, *J* = 7.8, Ar-H), 5.20 (2H, s, OC$H_2$Ar), 4.17 (1H, br. s, ArN*H*), 4.06–3.98 (1H, br. m, CH), 3.82 (1H, dd, *J* = 4.8, 10.2 Hz, OSiC$H_2$), 3.77 (1H, dd, *J* = 3.1, 10.2 Hz, SiOC$H_2$), 3.17 (1H, dd, *J* = 6.4, 16.2 Hz, CHC$H_2$CO), 3.08 (1H, dd, *J* = 5.6, 16.2, CHC$H_2$CO), 1.09 (9H, $CH_3$); $\delta_C$: 135.6, 135.6, 135.0, 133.1, 133.0, 129.9, 129.8, 129.4, 128.7, 128.5, 127.9, 127.8, 118.2, 114.1, 67.8, 64.5, 51.5, 37.8, 26.9, 19.3; *m*/*z* (HRMS-ESI) 567.2668 ($MH^+$, $C_{34}H_{38}N_2O_4Si$ requires 567.2679), 537 (8), 496 (10).

**Methyl 4-(*tert*-butyldiphenylsilyloxy)-3-(phenylamino)-butanoylcarbamate, 6d**

Obtained as a yellow oil after column chromatography. $R_f$ = 0.34 (EtOAc–*n*-hexane, 2 : 3); separation of enantiomers by chiral HPLC was not possible; $\nu_{max}/cm^{-1}$ 2960, 2940, 2870, 1770, 1700, 1610, 1500, 1210, 1110; $\delta_H$: 8.11 (1H, br. s, N*H*CO), 7.71–7.60 (4H, m, Ar-H), 7.52–7.33 (6H, m, Ar-H), 7.17 (2H, dd, *J* = 7.3, 7.8 Hz, Ar-H1), 6.76 (1H, t, *J* = 7.3 Hz, Ar-H), 6.59 (2H, d, *J* = 7.8 Hz, Ar-H), 4.17 (1H, br. s, ArN*H*), 3.85 (1H, dd, *J* = 4.9, 10.2 Hz, $OCH_2$), 3.82–3.75 (5H, m, $OCH_3$ and $OCH_2$), 3.18 (1H, dd, *J* = 6.6, 16.2 Hz, $OCH_2$), 3.11 (1H, dd, *J* = 5.6, 16.2 Hz, C$H_2$CO), 1.12 (9H, s, $CH_3$); $\delta_C$: 172.7, 152.1, 146.6, 135.6, 135.5, 133.1, 133.0, 129.9, 129.8, 129.4, 127.8, 127.7, 118.3, 114.1, 64.5, 53.0, 51.6, 37.8, 26.9, 19.3; *m*/*z* 490.2292 ($M^+$, $C_{28}H_{34}N_2O_4Si$ requires 490.2288), 433 (25), 340 (27), 316 (92), 221 (90), 146 (100).

**4-(Benzyloxy)-3-(phenylamino)butanoic acid, 13**

To a solution of the carbamate **6a** or **6b** (2.9 mmol) in MeOH (30 mL) was added 1 M aq. KOH (29 mL, 29 mmol). The resultant solution was stirred at room temperature for 1 hour, before it was evaporated. $H_2O$ (30 mL) was added to the residue and the aqueous layer was washed with $Et_2O$ (2 × 30 mL), before it was acidified to pH 4 by the addition of 1 M aq. HCl. The acidic solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to give the acid as a yellow oil (0.58 g, 70%); $\nu_{max}/cm^{-1}$ 3400, 3050, 2920, 2850, 1710, 1600, 1500; $\delta_H$: 7.45–7.29 (5H, m, Ar-H), 7.22 (2H, dd, *J* = 7.4, 8.0 Hz, Ar-H), 6.81 (1H, t, *J* = 7.4 Hz, Ar-H), 6.71 (2H, d, *J* = 8.0 Hz, Ar-H), 4.55 (2H, s, OC$H_2$Ar), 4.00 (1H, m, NHC*H*), 3.62 (2H, close AB, $OCH_2$), 2.74 (2H, dd, *J* = 2.6, 6.5 Hz, C$H_2$CO), OH and NH signals were broadened due to fast exchange; $\delta_C$: 176.1, 146.0, 137.8, 129.5, 128.5, 127.9, 127.7, 119.1, 114.9, 73.4, 70.4, 50.9, 36.0; *m*/*z* (HRMS-ESI) 286.1432 ($MH^+$, $C_{17}H_{20}NO_3$ requires 286.1443), 268 (10), 198 (8).

**4-(Methyl(phenyl)amino)dihydrofuran-2(3*H*)-one, 14**

Yellow oil; $\nu_{max}/cm^{-1}$ 2933, 1773, 1597; $\delta_H$: 7.39 (1H, m, ArH), 7.34–7.26 (2H, m, ArH), 6.91 (2H, m, ArH), 4.69 (1H, m, CH), 4.54 (1H, dd, *J* = 7.0, 10.0 Hz, $OCH_2$), 4.38 (1H, dd, *J* = 4.0, 10.0 Hz, $OCH_2$), 2.84–2.76 (4H, m, $NCH_3$ and $CH_2CO$), 2.63 (1H, dd, *J* = 4.5, 18.0 Hz, $CH_2CO$); $\delta_C$: 175.7, 149.6, 129.3, 119.9, 116.3, 71.1, 56.2, 33.4, 39.1; *m*/*z* (EI) 191 ($M^+$, 95%), 132 (100); (HRMS-EI) 191.0943 ($M^+$, $C_{11}H_{13}NO_2$ requires 191.0946).

**(2*R*,4*R*)-(−)-(2-Benzyloxymethyl-1,2,3,4-tetrahydroquinolin-4-yl)-carbamic acid methyl ester, 15**

To a stirred solution of **6a** (6.5 g, 19 mmol) dissolved in ethanol–THF (1 : 1, 65 mL) was added $NaBH_4$ (0.5 g, 13 mmol) at −10 °C. A solution of $MgCl_2·6H_2O$ (4.0 g, 20 mmol) in $H_2O$ (10 mL) was slowly added, maintaining the temperature below 0 °C. When the addition was complete, the reaction was allowed to continue at 0 °C for 30 min, before it was quenched by addition of $CH_2Cl_2$ (80 mL), 1 M aq. HCl (80 mL) and citric acid (9 g, 47 mmol). The biphasic layer was stirred at room temperature for 4 h. The organic layer was separated, before the addition of $H_2O$ (100 mL), followed by another portion of citric acid (5.5 g, 28 mmol). After stirring at room temperature for 45 min, the organic layer was separated, dried over $MgSO_4$ and concentrated under vacuum. The volatiles remaining in the residue was displaced by co-distillation with hexane under reduced pressure, to give the 2,4-disubstituted tetrahydroquinoline as an off-white solid (5.4 g, 87%); mp 90–92 °C; $[\alpha]_D^{25}$ −13.5° ($c$ = 0.7, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3370, 3330, 2950, 2940, 2860, 1710, 1520, 1470, 1240, 1090; $\delta_H$: 7.47–7.29 (5H, m, Ar-H), 7.19 (1H, dd, $J$ = 1.6, 7.7 Hz, Ar-H), 7.05 (1H, dt, $J$ = 1.6, 7.7 Hz, Ar-H), 6.70 (1H, dt, $J$ = 1.2, 7.7 Hz, Ar-H), 6.54 (1H, dd, $J$ = 1.2, 7.7 Hz, Ar-H), 5.12–5.00 (2H, m, H-4 and N*H*CO), 4.59 (2H, s, OC*H*$_2$Ar), 4.41 (1H, br. s, ArNH), 3.78–3.69 (4H, m, $OCH_3$ and H-2), 3.57 (1H, dd, $J$ = 3.3, 9.1, CHC*H*$_2$O), 3.40 (1H, t, $J$ = 9.1, CHC*H*$_2$O), 2.29–2.09 (1H, m, H-3), 1.55–1.35 (1H, m, H-3′); $\delta_C$: 157.2, 144.5, 137.9, 128.6, 128.4, 127.9, 127.8, 126.9, 121.8, 117.8, 114.7, 74.0, 73.3, 52.2, 50.4, 47.6, 32.7; $m/z$ (HRMS-EI) 326.1620 ($M^+$, $C_{19}H_{22}N_2O_3$ requires 326.1630), 205 (7), 143 (8), 130 (100), 91 (20); Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58%. Found: C, 70.14; H, 6.91; N, 8.68%.

### (2*R*,4*R*)-(+)-Methyl 2-(benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate, 16

A mixture of tetrahydroquinoline **15** (6.2 g, 19 mmol) and formaldehyde (37% w/w solution $H_2O$, 14.2 mL, 0.19 mol) in MeCN (150 mL) was stirred and cooled to 5 °C. $NaCNBH_3$ (3.6 g, 57 mmol) was added portion-wise to the solution, followed by glacial acetic acid (3.8 mL, 66 mmol), maintaining the temperature below 10 °C during the additions. After stirring at 5 °C for a further 30 min, a further portion of glacial acetic acid was added (3.8 mL, 66 mmol). Stirring was continued at 5 °C for another 30 min before $Et_2O$ (400 mL) was added. The organic layer was separated and washed with 1 M aq. KOH (3 × 100 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography to afford the product as an off-white solid (5.7 g, 88%). $R_f$ = 0.35 (EtOAc–*n*-hexane, 1 : 1.5); mp 90–92 °C; $[\alpha]_D^{25}$ +10° ($c$ = 1.1, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3320, 3030, 2920, 1710, 1700, 1520, 1490, 1240, 1210; $\delta_H$: 7.44–7.25 (6H, m, Ar-H), 7.21 (1H, m, Ar-H), 6.72 (1H, t, $J$ = 7.3 Hz, Ar-H), 6.65 (1H, d, $J$ = 8.2 Hz, Ar-H), 5.63 (1H, br. d, $J$ = 7.7 Hz, NH), 4.99–4.85 (1H, m, H-4), 4.53 (2H, s, OC*H*$_2$Bn), 3.85–3.54 (6H, m, CHC*H*$_2$O, H-2 and $OCH_3$), 2.99 (3H, s, $NCH_3$), 2.40–2.28 (1H, m, H-3), 2.28–2.16 (1H, m, H-3′); $\delta_C$: 156.7, 145.9, 137.8, 128.9, 128.4, 127.8, 127.7, 127.6, 122.3, 116.4, 111.5, 73.4, 71.3, 56.8, 51.9, 45.9, 37.8, 32.1; $m/z$ (HRMS-EI) 340.1789 ($M^+$, $C_{20}H_{24}N_2O_3$ requires 340.1787), 219 (19), 187 (6), 144 (100), 91 (15); Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23%. Found: C, 70.74; H, 6.96; N, 8.16%.

### 2-(Benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine, 17

To a solution of the tetrahydroquinoline **16** (1.00 g, 3.00 mmol) in MeCN (20 mL) was added TMSI (1.70 mL, 11.7 mmol). The resultant solution was stirred at room temperature for 18 h. The reaction was quenched by the addition of MeOH (10 mL), and evaporated. $Et_2O$ (20 mL) and 1 M aq. HCl (20 mL) were added to the residue and the aqueous layer was separated. The pH of the solution was adjusted to 12 by the addition of 1 M aq. KOH. It was then extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to dryness. The amine was obtained as a brown oil (0.65 g, 78%); $\nu_{max}/cm^{-1}$ 2920, 1600, 1500, 1450, 1370, 1070; $\delta_H$: 7.38–7.24 (6H, m, Ar-H), 7.20 (1H, t, $J$ = 7.6 Hz, Ar-H), 6.74 (1H, t, $J$ = 7.6 Hz, Ar-H), 6.63 (1H, d, $J$ = 7.6 Hz, Ar-H), 4.58 (1H, d, $J$ = 11.9 Hz, $OCH_2Ph$), 4.51 (1H, d, $J$ = 11.9 Hz, $OCH_2Ph$), 4.14 (1H, apparent triplet, $J$ = 5.5 Hz, H-4), 3.77 (1H, dd, $J$ = 4.6, 9.7 Hz, OC*H*$_2$), 3.70 (1H, dd, $J$ = 5.3, 9.7, OC*H*$_2$), 3.59 (1H, m, H-2), 3.38 (2H, br. s, $NH_2$), 2.98 (3H, s, $NCH_3$), 2.33 (1H, dt, $J$ = 5.5, 13.7 Hz, H-3), 2.08 (1H, dt, $J$ = 5.7, 13.7 Hz, H-3′); $\delta_C$: 145.3, 137.9, 128.5, 128.4, 127.7, 127.6, 127.9, 125.4, 116.4, 111.6, 73.3, 72.2, 57.2, 46.6, 37.7, 34.5; $m/z$ (HRMS-EI) 282.1731 ($M^+$, $C_{18}H_{22}N_2O$ requires 282.1732), 265 (5), 161 (55), 144 (100), 91 (32).

### (*R*)-(−)-2-(Benzyloxymethyl)-1-methyl-2,3-dihydroquinolin-4-(1*H*)-one, 18

4-Formyl-1-methylpyridinium benzenesulfonate (3.7 g, 13 mmol) was added to a solution of the **17** (2.5 g, 8.8 mmol) in $CH_2Cl_2$–DMF (1 : 1, 50 mL). After stirring for 1 h, DBU (3.9 mL, 26 mmol) was added and the resulting dark purple solution was stirred for a further hour at room temperature. The reaction was quenched by the addition of sat. oxalic acid (50 mL) and stirred for a further 16 h. The biphasic mixture was evaporated to dryness and the residue purified by column chromatography to afford the tetrahydroquinolone as a yellow oil (1.85 g, 75%); $R_f$ = 0.40 (EtOAc–*n*-hexane, 1 : 1.5); $[\alpha]_D^{25}$ −88° ($c$ = 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ 2870, 1670, 1600, 1490, 1450, 1350, 1210; $\delta_H$: 7.88 (1H, dd, $J$ = 1.7, 7.8 Hz, Ar-H), 7.42 (1H, m, Ar-H), 7.3 (5H, m, Ar-H), 6.68 (1H, m, Ar-H), 6.65 (1H, d, $J$ = 8.5 Hz, Ar-H), 4.46 (2H, s, $OCH_2Ph$), 3.83 (1H, m, H-2), 3.71 (1H, dd, $J$ = 6.6, 9.5 Hz, OC*H*$_2$), 3.53 (1H, dd, $J$ = 5.9, 9.5 Hz, OC*H*$_2$), 3.11 (3H, s, $NCH_3$), 3.00 (1H, dd, $J$ = 6.6, 16.6 Hz, H-3), 2.73 (1H, dd, $J$ = 2.4, 16.6 Hz, H-3′); $\delta_C$: 192.9, 150.2, 137.8, 135.8, 128.4, 127.7, 127.6, 127.4, 119.0, 116.2, 112.78, 73.4, 68.9, 60.59, 38.9, 38.8; $m/z$ (HRMS-EI) 281.1416 ($M^+$, $C_{18}H_{19}NO_2$ requires 281.1416), 174 (12), 160 (100), 91 (20); Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84%: H, 6.81%: N, 4.98%. Found: C, 76.94%: H, 6.66%: N, 4.85%.

### (*R*)-(−)-2-(Benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinoline, 19

A solution of $LiAlH_4$ (30 mg, 0.75 mmol) in THF (0.75 mL) was added slowly to a vigorously stirred suspension of $AlCl_3$ (60 mg, 0.43 mmol) in $Et_2O$ (1 mL). After 20 min, a solution of the tetrahydroquinolone **18** (60 mg, 0.21 mmol) in THF (1 mL) was added a rate that is sufficient to maintain a gentle reflux. When the reaction was judged to be complete (TLC), the mixture was cooled to 0 °C, whereupon $H_2O$ (5 mL) and $Et_2O$ (3 mL) were added. The $Et_2O$ layer was decanted and the aqueous layer was washed several times with $Et_2O$ until the washings were colourless. The combined organic extracts were dried over $MgSO_4$, filtered, concentrated and purified by column chromatography, to give the tetrahydroquinoline as a colourless oil (50 mg, 87%). $R_f$ = 0.45 (EtOAc–*n*-hexane, 1 : 1), $[\alpha]_D^{25}$ −4.5° ($c$ = 1.4, $CH_2Cl_2$); $\nu_{max}/cm^{-1}$ 2920, 2850, 1720, 1600, 1500, 1380, 1250; $\delta_H$: 7.43–7.30 (5H, m, Ar-H), 7.13 (1H, t,

$J$ = 7.6 Hz, Ar-H), 7.00 (1H, d, $J$ = 7.6 Hz, Ar-H), 6.64 (1H, t, $J$ = 7.6 Hz, Ar-H), 6.58 (1H, d, $J$ = 7.6, Ar-H), 4.60 (1H, d, $J$ = 12.0 Hz, OC$H_2$Ph), 4.52 (1H, d, $J$ = 12.0 Hz, OC$H_2$Ph), 3.65–3.56 (2H, m, C$H_2$O and H-2), 3.53–3.45 (1H, m, C$H_2$O), 3.03 (3H, s, $NCH_3$), 2.82–2.65 (2H, m, H-4), 2.20–2.11 (1H, m, H-3), 1.97–1.85 (1H, m, H-3′); $\delta_C$: 145.1, 138.4, 128.6, 128.4, 127.7, 127.6, 127.2, 121.7, 115.5, 110.3, 73.4, 70.5, 58.2, 38.3, 23.7, 22.9; $m/z$ (HRMS-EI) 267.1620 ($M^+$, $C_{18}H_{21}NO$ requires 267.1623), 146 (100), 131 (8), 91 (8); Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%. Found: C, 80.66; H, 8.02; N, 5.26%.

### (*R*)-(−)-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)-methanol, 5

Ni sponge (4 g) was added to a solution of the tetrahydroquinoline **19** (0.8 g, 3.0 mmol) in a mixture of EtOH and THF (7 : 8 mL). The reaction was heated to reflux under a $H_2$ atmosphere. On completion of the reaction (TLC), the mixture was filtered through celite to remove the catalyst, and the filtrate was evaporated to dryness. The residue was purified by column chromatography, giving the alcohol as a colourless oil (0.37 g, 71%). $R_f$ = 0.4 (EtOAc–hexane, 1 : 1): $[\alpha]_D^{25}$ −16.7° ($c$ = 0.9, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3370, 2940, 2890, 1600, 1510, 1310, 1220, 1040; $\delta_H$: 7.14 (1H, t, $J$ = 7.6 Hz, Ar-H), 7.01 (1H, d, $J$ = 7.6 Hz, Ar-H), 6.71–6.62 (2H, m, Ar-H), 3.77–3.67 (2H, m, C$H_2$OH), 3.44–3.37 (1H, m, H-2), 3.04 (3H, s, $NCH_3$), 2.91–2.64 (2H, m, H-4), 2.14–2.05 (1H, m, H-3), 1.97–1.85 (1H, m, H-3′), 1.65 (1H, br. s, OH); $\delta_C$: 145.5, 128.7, 127.3, 122.5, 116.2, 111.3, 63.3, 60.1, 38.6, 24.3, 23.0; $m/z$ (HRMS-EI) 177.1154 ($M^+$, $C_{11}H_{15}NO$ requires 177.1154); Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90%. Found: C, 74.65; H, 8.46; N, 7.80%.

### Protection of 3-hydroxy-4-methoxy-benzyl alcohol (Scheme 7, step i)

To a mixture of the alcohol (0.50 g, 3.20 mmol) and $K_2CO_3$ (0.67 g, 4.80 mmol) in acetone (30 mL) was added benzyl bromide (0.39 mL, 3.20 mmol). The resultant mixture was heated to reflux under $N_2$ for 4 h. The reaction was then cooled to room temperature and stirred overnight. EtOAc (50 mL) and $H_2O$ (50 mL) were added and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness to give the product as a white solid (0.56 g, 71%); mp 68–70 °C (lit.[33] 65–66 °C); $\nu_{max}/cm^{-1}$ 3360, 2940, 2880, 2840, 1590, 1520, 1420, 1260, 1140; $\delta_H$: 7.47 (2H, d, $J$ = 7.3 Hz, Ar-H), 7.39 (2H, t, $J$ = 7.3 Hz, Ar-H), 7.36–7.28 (1H, m, Ar-H), 6.95 (1H, s, Ar-H), 6.92–6.84 (2H, m, Ar-H), 5.14 (2H, s, OC$H_2$Ar), 4.54 (2H, s, HOC$H_2$), 3.88 (3H, s, $OCH_3$); $\delta_C$: 149.2, 148.3, 137.1, 133.7, 128.6, 127.9, 127.4, 120.0, 113.1, 111.7, 70.9, 65.0, 56.1; $m/z$ (HRMS-EI) 244.1094 ($M^+$, $C_{15}H_{16}O_3$ requires 244.1099), 136 (5), 91 (100), 65 (10).

### Preparation of phosphonium salts 22 from benzyl alcohols (Scheme 7, steps ii and iii)

To the corresponding alcohol (2.00 g, 1.0 eq.) in $CH_2Cl_2$ (30 mL) at −5 °C was added $PBr_3$ (2.0 eq.) dropwise, maintaining the temperature below 0 °C. After 20 min the reaction was allowed to warm to room temperature and stirring was continued for an additional 2 h. The reaction was quenched by the dropwise addition of sat. aq. $NaHCO_3$ (30 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The resultant bromide was then dissolved in toluene (30 mL) and triphenylphosphine (1.0 eq.) was added. The resultant slurry was heated to reflux for 18 h. After cooling to room temperature, the precipitated solid was collected by filtration and recrystallised from EtOH.

### (Benzo-1,3-dioxol-5-ylmethyl) triphenylphosphonium bromide 22a[34]

White solid (5.90 g, 95%); mp 221–223 °C (lit. 227–229 °C);[35] $\delta_H$: 7.83–7.60 (15H, m, Ar-H), 6.65–6.60 (1H, m, Ar-H), 6.58–6.51 (2H, m, Ar-H), 5.88 (2H, s, OC$H_2$), 5.31 (2H, d, $J$ = 13.9 Hz, $CH_2P$); $\delta_C$: 147.7, 135.0, 134.4 (d, $J$ = 10 Hz), 130.1 (d, $J$ = 12 Hz), 125.5 (d, $J$ = 7 Hz), 120.1 (d, $J$ = 9 Hz), 117.8, 111.4, 108.6, 101.3, 30.5 (d, $J$ = 47 Hz); $m/z$ (HRMS-ESI) 397.1353 ($[M - Br]^+$, $C_{26}H_{22}O_2P$ requires 397.1357).

### (3-(Benzyloxy)-4-methoxybenzyl)triphenylphosphonium bromide, 22b

White solid (4.30 g, 92%); mp 223–225 °C; $\delta_H$: 7.84–7.57 (15H, m, Ar-H), 7.28–7.23 (5H, m, Ar-H), 6.85 (1H, s, Ar-H), 6.69 (1H, d, $J$ = 8.3 Hz, Ar-H), 6.63 (1H, d, $J$ = 8.3 Hz, Ar-H), 5.31 (2H, d, $J$ = 13.7 Hz, C$H_2$P), 4.77 (2H, s, OC$H_2$Ph), 3.81 (3H, s, $OCH_3$); $\delta_C$: 149.6, 148.1, 136.7, 134.9, 134.5 (d, $J$ = 10 Hz), 130.1 (d, $J$ = 12 Hz), 128.4, 127.8, 127.6, 124.5 (d, $J$ = 6 Hz), 118.9 (d, $J$ = 9 Hz), 118.4, 116.7 (d, $J$ = 5 Hz), 111.7, 70.7, 55.9, 30.3 (d, $J$ = 48 Hz); $m/z$ (HRMS-ESI) 489.1968 ($[M - Br]^+$, $C_{33}H_{30}O_2P$ requires 489.1983).

### Tandem oxidation–Wittig–reduction reactions of 5 (Scheme 6)

At −78 °C, a solution of DMSO (40 μL, 0.56 mmol) in $CH_2Cl_2$ (0.5 mL) was added to a solution of oxalyl chloride (28 μL, 0.31 mmol) in $CH_2Cl_2$ (1 mL). After stirring for 1 h, a solution of **5** (50 mg, 0.28 mmol) in $CH_2Cl_2$ (0.5 mL) was added dropwise, carefully maintaining the temperature below −60 °C. The reaction was stirred for a further 1 h, before the addition of $NEt_3$ (0.19 mL, 1.4 mmol). The reaction mixture was allowed to warm to room temperature, whereupon it was quenched by the addition of sat. aq. $NH_4Cl$ (2 mL). The organic layer was separated and washed with additional portions of sat. aq. $NH_4Cl$ (3 × 2 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The aldehyde was used immediately in the next step without further purification.

To a solution of the requisite phosphonium salt **22** (0.62 mmol, 2.2 eq.) in THF (2 mL), a solution of $t$-BuOK (63 mg, 0.56 mmol) in THF (0.5 mL) was added at 0 °C. After stirring for 30 min, a solution of the aldehyde in THF (0.5 mL) was added, and the reaction was stirred for 16 h. The solvent was then removed and the residue was purified by flash column chromatography (EtOAc–$n$-hexane, 1 : 9), to give the olefinated product as a mixture of the *E*- and *Z*-isomers. This was dissolved in a mixture of EtOH and THF (0.5 : 0.5 mL), and subjected to hydrogenation for 16 h, under $H_2$ (1 atm) over 10% Pd/C (0.2 g). The Pd/C was removed by filtration through celite, and the solution evaporated to dryness.

#### *ent*-(+)-Angustureine, 1

Purified by column chromatography as a colourless oil (27 mg, 44%). $R_f$ = 0.40 (EtOAc–*n*-hexane, 1 : 100); $[\alpha]_D^{25}$ +7.5° (*c* = 0.4, $CHCl_3$), lit. −7.16 (*c* = 1.0, $CHCl_3$, natural product);[2,26] $\nu_{max}$/cm$^{-1}$ 2930, 2860, 950, 750; $\delta_H$: 7.11 (1H, t, *J* = 7.6 Hz, Ar-H), 6.99 (1H, d, *J* = 7.6 Hz, Ar-H), 6.60 (1H, t, *J* = 7.6 Hz, Ar-H), 6.55 (1H, d, *J* = 7.6 Hz, Ar-H), 3.31–3.19 (1H, m, H-2), 2.95 (3H, s, $NCH_3$), 2.91–2.74 (1H, m, H-4), 2.75–2.63 (1H, m, H-4′), 1.97–1.86 (2H, m, H-3), 1.62 (1H, m, $CH_2$), 1.46–1.26 (10H, m, $CH_2$, and $CH_3$); $\delta_C$: 145.4, 128.6, 127.1, 121.9, 115.2, 110.4, 59.0, 38.0, 32.1, 31.2, 29.7, 25.8, 24.4, 23.6, 22.7; *m/z* (HRMS-ESI) 217.1828 ($M^+$, $C_{15}H_{23}N$ requires 217.1830), 146 (100), 83 (60).

#### (−)-Galipeine, 2

Obtained as a colourless gum (27 mg, 32%) after column chromatography, $R_f$ = 0.28 ($Et_2O$–pentane, 3 : 7); $[\alpha]_D^{25}$ −27° (*c* = 0.7, $CHCl_3$), lit. −26.1 (*c* = 0.44, $CHCl_3$, 96%);[25] $\nu_{max}$/cm$^{-1}$ 3500, 2940, 2850, 1600, 1500, 1280; $\delta_H$: 7.12 (1H, t, *J* = 8.0 Hz, Ar-H), 7.02 (1H, d, *J* = 7.2 Hz, Ar-H), 6.88–6.76 (2H, m, Ar-H), 6.70 (1H, dd, *J* = 2.0, 8.2, Ar-H), 6.63 (1H, t, *J* = 7.2 Hz, Ar-H), 6.57 (1H, d, *J* = 8.0 Hz, Ar-H), 5.61 (1H, br. s, OH), 3.91 (3H, s, $OCH_3$), 3.39–3.23 (1H, m, H-2), 2.94 (3H, s, $NCH_3$), 2.92–2.82 (1H, m, H-4), 2.79–2.60 (2H, m, H-4 and $CH_2$), 2.60–2.46 (1H, m, $CH_2$), 2.04–1.86 (3H, m, $CH_2$ and H-3), 1.84–1.67 (1H, m, $CH_2$); $\delta_C$: 145.5, 145.4, 144.8, 135.4, 128.8, 127.1, 121.8, 119.6, 115.4, 114.5, 110.7, 110.6, 58.2, 56.0, 38.0, 32.9, 31.6, 24.4, 23.6. *m/z* (HRMS-ESI) 298.1796 ($MH^+$, $C_{19}H_{24}NO_2$ requires 298.1807), 194 (2).

#### (±)-Galipinine, 4

Purified by column chromatography as a colourless gum (26 mg, 31%). $R_f$ = 0.31 ($Et_2O$–hexane 1 : 20); $\nu_{max}$/cm$^{-1}$ 2940, 2880, 1610, 1500, 1490, 1450, 1240; $\delta_H$: 7.12 (1H, t, *J* = 7.9 Hz, Ar-H), 7.01 (1H, d, *J* = 7.2 Hz, Ar-H), 6.78–6.62 (4H, m, Ar-H), 6.56 (1H, d, *J* = 7.9, Ar-H), 5.95 (2H, s, $OCH_2$), 3.36–3.26 (1H, m, H-2), 2.95 (3H, s, $NCH_3$) 2.93–2.85 (1H, m, $CH_2$), 2.78–2.60 (2H, m, H-4 and $CH_2$), 2.61–2.46 (1H, m, H-4′), 2.03–1.84 (3H, m, H-3 and $CH_2$), 1.80–1.67 (1H, m, H-3′); $\delta_C$: 147.6, 145.6, 145.4, 135.9, 128.7, 127.1, 121.7, 120.9, 115.4, 110.6, 108.7, 108.2, 100.8, 58.2, 38.1, 33.2, 32.0, 24.4, 23.6. *m/z* (HRMS-ESI) 296.1647 ($MH^+$, $C_{19}H_{22}NO_2$ requires 296.1651).

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