The stereoselective preparation of substituted pyrrolidines using titanium- and zirconium-mediated diene metallabicyclisation methodology: the total synthesis of (−)-α-kainic acid

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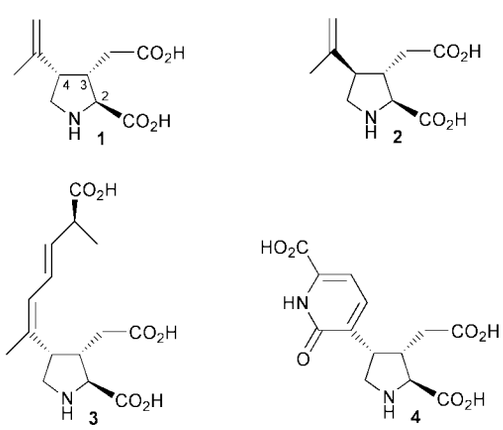
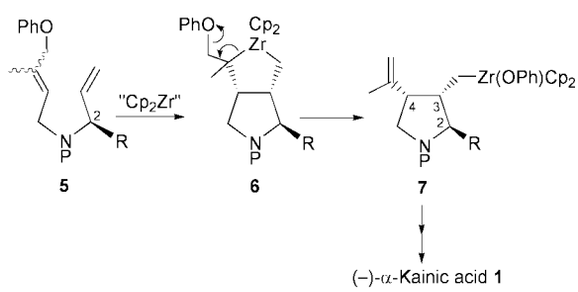
Zirconium- and titanium-mediated diene metallabicyclisation–elimination–functionalisation have been compared, contrasted and utilised for the preparation of 3,4-disubstituted and 2,3,4-trisubstituted pyrrolidines in high yield and excellent stereoselectivity. The zirconium-mediated methodology has been employed as the key step in a partial synthesis of (−)-α-kainic acid starting from D-serine, but the key metallabicyclisation sequence proceeded with poor stereocontrol. By contrast, the total synthesis of (−)-α-kainic acid starting from L-serine was accomplished using a titanium-mediated cyclisation sequence which proceeded with excellent stereocontrol. Novel kainoids and piperidines are also reported.

(−)-α-Kainic acid **1** has a highly functionalised trisubstituted



pyrrolidine skeleton with three contiguous chiral centres.[1] The C-2–C-3 arrangement is *trans* while the C-3–C-4 substituents are in the thermodynamically less favourable *cis*-configuration. (−)-α-Kainic acid **1** was first isolated from the marine algae *Digenea simplex*[2] along with its C-4 epimer α-allokainic acid **2**. In later work, kainic acid was obtained from the marine algae *Centrocerus clavulatum*[3] and from the Corsican moss *Alsidum helminthocorton*.[4] The potent neuroexcitatory activity of kainic acid has generated enormous interest,[1] but it also possesses insecticidal[5] and anthelmintic[6] activity. With the discoveries of the bioactive domoic acid[7] and acromelic acid[8,9] families (*e.g.* domoic acid **3** and acromelic acid A **4**), the synthetic community has been stimulated to design efficient, stereocontrolled routes to 2,3,4-trisubstituted pyrrolidines.[1,10]

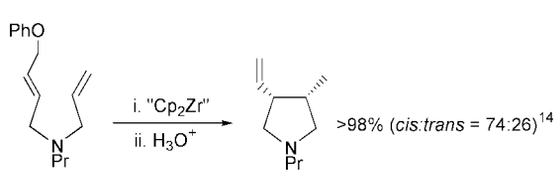
Given our own interest in the kainoid area,[11] and our ongoing research into synthetic applications of zirconium-mediated diene cyclisation reactions,[12] we envisaged a new approach to kainic acid as shown in Scheme 1. Thus, zirconium-mediated metallabicyclisation[13] of dienes **5** should produce metallabicycles **6** which would be expected to undergo rapid β-elimination to generate the archetypal kainoid 4-isopropenyl substituent. This sequence would produce alkylorganometallic reagents **7** which could then be functionalised to



Scheme 1

introduce the requisite 3-carboxymethyl substituent of the kainoids.

Other cyclisation–elimination approaches to the kainoids have been investigated but stereochemical control has been poor.[14] We felt that the approach outlined in Scheme 1 was worthy of study, however, particularly as Takahashi *et al.*[15] had shown that *cis*-3,4-disubstituted pyrrolidines can be formed using the zirconocene metallabicyclisation of 1,6-dienes containing a terminal allylic ether (Scheme 2): it was proposed that



Scheme 2

the intermediate *cis*-3,4-zirconabicycle was kinetically preferred and that equilibration to the *trans*-isomer was minimised by the rapid elimination of the β-phenoxy group.

Despite this encouraging precedent, several questions remained, particularly: (i) will the C-2 substituent affect the efficiency of cyclisation, (ii) will the C-2 substituent direct cyclisation to produce the required 2,3-*trans*-arrangement of substituents and will the 3,4-*cis*-arrangement of substituents predominate, (iii) will cyclisation occur on to the sterically demanding trisubstituted alkene, (iv) will the recently

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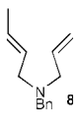
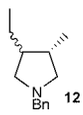
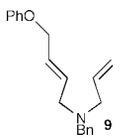
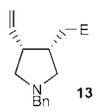
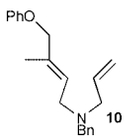
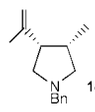
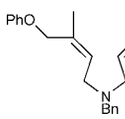
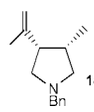
Table 1 Model metallabicyclisation studies

Entry no.	Starting diene	Major product	Electrophile	Zr(II) Yield (%); *cis*:*trans*	Ti(II) Yield (%); *cis*:*trans*
i	 **8**	 **12**	H^+	50; *1*:*1*	—
ii	 **9**	 **13** **a**, E = H; **b**, E = Br; **c**, E = I; **d**, E = CHO	H^+ Br_2 I_2 ^nBuNC	69; *3*:*1* — 81; *3*:*1* 47; *3*:*1*	95; *6*:*1* 67; *6*:*1* 72; *6*:*1* 0
iii	 **10**	 **14**	H^+	59; *10*:*1*	83; *cis* only
iv	 **11**	 **14**	H^+	74; *25*:*1*	85; *cis* only

described[16] titanium(II)-mediated metallabicyclisation methodology be superior to the zirconium procedure illustrated, and (v) will it be possible to elaborate alkylorganometallic reagents **7** to give kainic acid?

Model studies were therefore carried out to assess the viability of this new approach to the kainoids[17] whilst comparing and contrasting the Zr(II) and Ti(II) methodologies for the synthesis of substituted pyrrolidines.

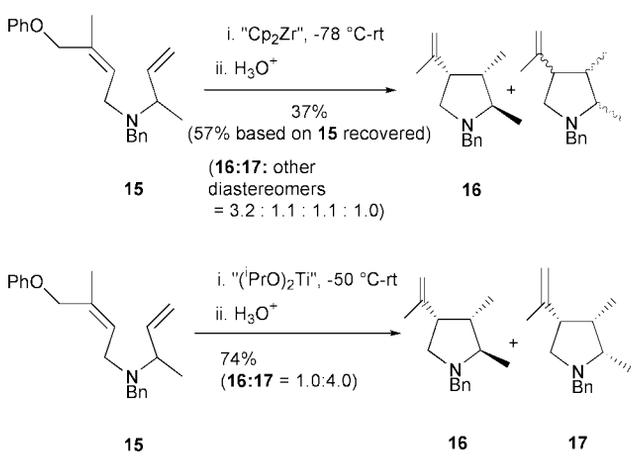
Results and discussion

Cyclisation precursors **8**–**11**, utilised in the model metallabicyclisation studies to investigate C-3–C-4 stereoselectivity (Table 1), were readily prepared by alkylation of *N*-allyl-*N*-benzylamine[18] with the corresponding allyl chloride in the presence of potassium carbonate and catalytic sodium iodide in refluxing acetonitrile.

Initial studies were carried out using Negishi's zirconocene equivalent ($ZrCp_2Cl_2$–2 BuLi).[13] As expected,[13,15] zirconium-mediated cyclisation of (2*E*)-*N*-benzyl-*N*-allylbut-2-en-1-amine **8** (Table 1, entry i) resulted in a 1:1 mixture of *cis*- and *trans*-diastereomers **12** after protonation. However, with diene **9** bearing a phenoxy leaving group (entry ii), zirconium-mediated diene cyclisation–elimination–protonation proceeded smoothly giving **13a** as a 3:1 *cis*:*trans* mixture. It seems likely[15] that elimination occurs before significant equilibration from the kinetically preferred *cis*-metallocycle to the thermodynamically-preferred *trans*-product can occur.[19,20] We next compared the cyclisation–elimination–protonation sequence using the same diene **9**, but employing Sato's titanium procedure [$Ti(OPr^i)_4$–2 ^iPrMgCl][16] as shown in Table 1, entry ii: with this reagent **13a** was obtained in improved yield (95%) and with better stereoselectivity (*cis*:*trans* = 6:1).[17] Furthermore, we were able to trap the alkyl zirconium or titanium organometallic intermediate with electrophiles (entry ii) giving a range of substituted pyrrolidines **13b**–**d**. Of note is that quenching the alkyl zirconium intermediate with *n*-BuNC gives the corresponding aldehyde **13d** as the only product after acidic work up, but no reaction is observed with the corresponding titanium reagent.

Cyclisation of the trisubstituted alkenes **10** and **11** to give **14** was investigated next (Table 1, entries iii and iv) and found to proceed efficiently with a much higher *cis*-selectivity with both reagents, the titanium process occurring with total stereoselectivity. Molecular modelling studies are in progress to explain this enhanced selectivity, but it may be that the elimination to form the C-4 isopropene unit is faster than the elimination to form the monosubstituted alkene (entry ii), hence minimising equilibration.

We next studied the reactions of diene **15** to assess the effect of a C-2 substituent on the metallabicyclisation process (Scheme 3).



Scheme 3

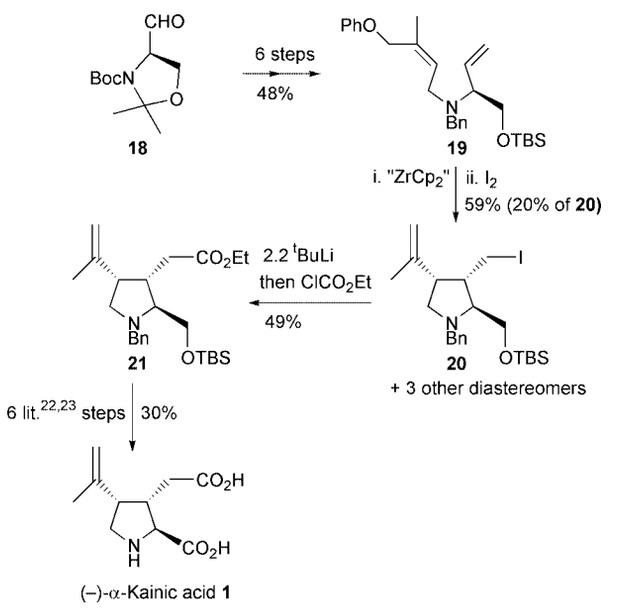
Cyclisation of diene **15** using "$ZrCp_2$" does not proceed with the same efficiency or diastereocontrol as the previous model systems in Table 1. Thus, although the major product **16** had the kainoid configuration, three more diastereomers were also isolated. The low yield and poor stereocontrol could indicate that the C-2 substituent prevents efficient coordination of zirconium to the terminal alkene and that, at least in part, initial zirconium complexation is occurring at the more electron rich trisubstituted alkene.

We next investigated the titanium-mediated cyclisation–elimination reaction of **15**. We were delighted to observe that, in this case, the high C-3–C-4 *cis*-selectivity observed in the earlier model studies was retained, and only the two separable diastereoisomers **16** and **17** were isolated. The stereochemical assignments were confirmed by comparison of the ^{1}H-NMR spectra of **16** and **17** with **13a** and related systems,[15] and by

NOE studies (*e.g.* H-2 and H-4 enhanced by irradiation at H-3). It is not entirely clear why the major product is the *cis*,*cis*-pyrrolidine **17**, although we assume that the smaller size of the titanium reagent allows efficient coordination to the terminal alkene, and it may be that intramolecular nitrogen to titanium coordination is involved. It should be noted that during the course of our studies Sato *et al.* also reported the stereoselective synthesis of a 2,3,4-trisubstituted pyrrolidine *via* titanium-mediated diene metallabicyclisation,[16b] although their system was not suitable for elaboration to produce kainoids.

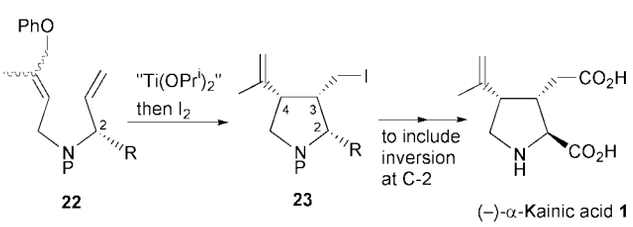
Synthesis of (−)-α-kainic acid

The results detailed in Scheme 3 above indicated that the zirconium-mediated route could be employed to prepare kainoids, although the metallabicyclisation process seemed likely to be inefficient. This was confirmed as part of a formal total synthesis of kainic acid **1** (Scheme 4). Thus, the *R*-Garner aldehyde **18**, readily prepared from D-serine,[21] was converted into diene **19** *via* a straightforward six step sequence (see later). Zirconium-mediated metallabicyclisation–elimination–iodination gave a mixture of diastereomeric products, as expected, with the kainoid precursor **20** predominating. Lithiation followed by ethoxycarbonylation gave adduct **21** which can be converted into kainic acid **1** *via* published[22,23] procedures (6 steps, 30% overall yield).



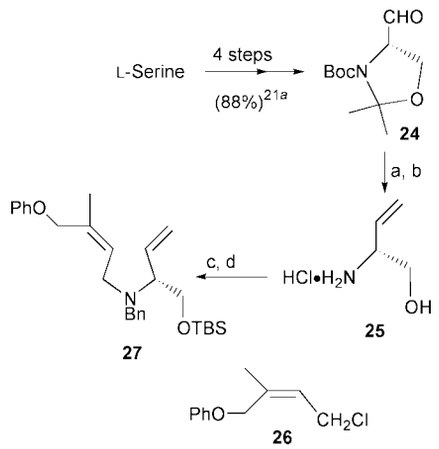
Scheme 4

Thus, a formal total synthesis of kainic acid had been achieved using zirconium methodology but the route was marred by the low stereoselectivity of the metallobicyclisation step. The titanium-mediated process shown in Scheme 3 showed much greater stereoselectivity than the corresponding zirconium reaction, but the major product was a *cis*,*cis*-pyrrolidine. Thus, the original analysis (Scheme 1) needed to be revised as shown in Scheme 5: the enantiomeric C-2 system **22** would be expected to produce mainly the *cis*,*cis*-pyrrolidine **23** with the kainoid C-3–C-4 *cis*-arrangement, subsequent inversion of configuration at C-2 being required to complete the natural product synthesis.



Scheme 5

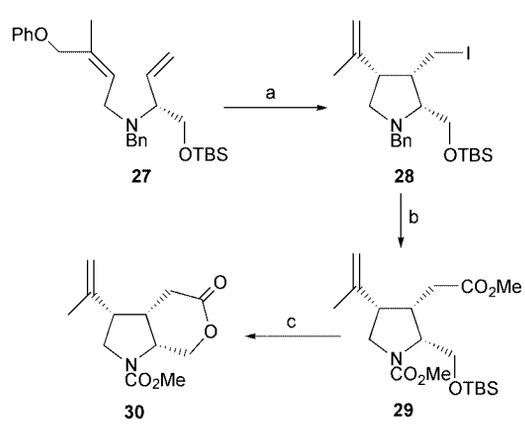
There are published examples of all *cis*-analogues of kainic acid undergoing epimerisation at C-2 to give the kainoid structure.[24] We therefore decided to explore a titanium-mediated metallabicyclisation approach to kainoids. It should be noted that a C-2 inversion strategy requires the use of the *S*-Garner aldehyde **24** as starting material (Scheme 6).



Scheme 6 *Reagents and conditions*: (TBS = $Me_2{}^tBuSi$) (a) $Ph_3P^+CH_3Br^-$, KHMDS, THF, −78 °C to rt (80%); (b) 6 M HCl (100%); (c) (1) PhCHO, Et_3N, Na_2SO_4, DCM, Δ, (2) $NaBH_4$, MeOH, 0 °C, (3) TBSCl, imidazole, DMF (70%); (d) **26**, K_2CO_3, cat. NaI, MeCN (86%).

Thus, L-Serine was converted into the *S*-Garner aldehyde **24** using our improved procedure.[21] Wittig methylenation[21] and acid hydrolysis gave vinylglycinol hydrochloride **25**. Reductive amination using benzaldehyde followed by *O*-silylation furnished a secondary amine which was *N*-alkylated with allyl chloride **26** to produce cyclisation precursor **27** in 60% yield over 4 steps from **24**. Allyl chloride **26** was prepared by Horner–Wadsworth–Emmons elaboration of 2-phenoxyacetone with methyl diethylphosphonoacetate (94%, *E*:*Z* = 2:1) followed by chromatographic separation, reduction of the resulting α,β-unsaturated ester (DIBAL) and chlorination (TsCl, DMAP).

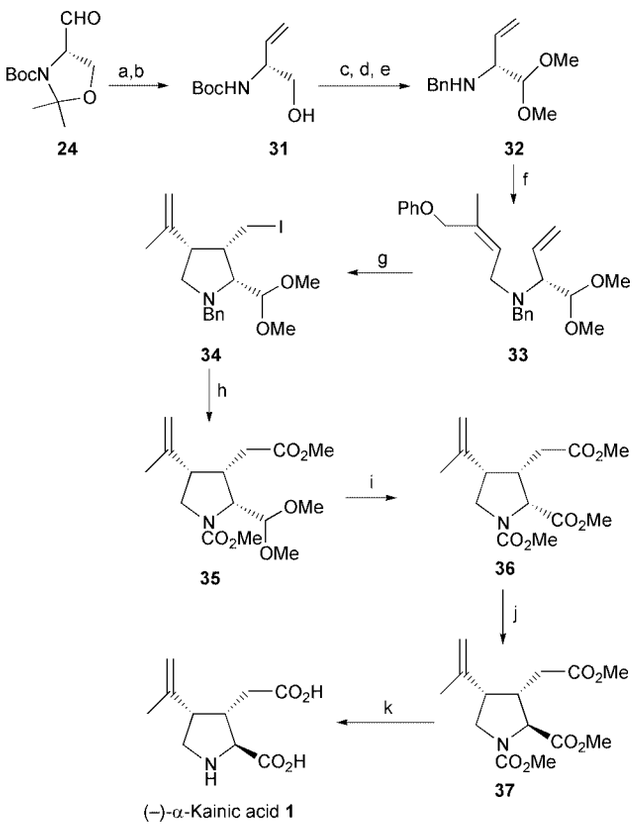
The Ti(II) mediated cyclisation–iodination of **27** was investigated next (Scheme 7) and found to proceed in excellent yield and, in this case, with complete stereoselectivity to give **28** with the expected *cis*,*cis*-geometry. Evidence for the stereochemistry of **28** was obtained by NMR analysis and by lithiation followed by trapping with ethyl chloroformate: the resultant ethyl ester



Scheme 7 *Reagents and conditions*: (a) (1) Ti(O-*i*-Pr)$_4$ + 2 *i*-PrMgCl, Et_2O, −50 °C to rt, (2) I_2, 0 °C (70%); (b) ^{t}BuLi (2.2 eq.), Et_2O, −80 °C then excess $ClCO_2Me$, −80 °C, then Δ, 2 h (71%); (c) cat. TsOH, MeOH, rt (100%).

displayed different NMR characteristics to the known[22] C-2 epimer **21**. Lithium–halogen exchange and quenching with excess methyl chloroformate followed by heating gave the ester with concomitant *N*-benzyl cleavage–urethane formation to produce **29** in 71% overall yield (*N*-benzyl protection can be retained if the reaction is quenched at low temperature). The next task was to convert the C-2 substituent into a carboxylic acid derivative prior to epimerisation. Unfortunately, and perhaps unsurprisingly, cleavage of the TBS group resulted in facile cyclisation between the C-2 and C-3 side chains to produce lactone **30**. Numerous attempts (including cyanide addition to iodide **28** and Jones' oxidation of lactone **30**) were made to overcome this problem but without success.

Therefore it was decided to carry out the metallabicyclisation sequence with the C-2 substituent protected as a masked aldehyde (Scheme 8). The requisite diene **33** was prepared from the



Scheme 8 *Reagents and conditions*: (a) $Ph_3P^+CH_3Br^-$, KHMDS, THF, −78 °C (80%); (b) Dowex (H^+) resin, aq. MeOH (93%); (c) Dess–Martin oxidation; (d) HCl–MeOH; (e) PhCHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$ (31% for 3 steps); (f) **26**, K_2CO_3, cat. NaI, MeCN, Δ (88%); (g) (1) $Ti(O\text{-}i\text{-}Pr)_4$, 2-*i*-PrMgCl, Et_2O, −50 °C to rt, (2) I_2, 0 °C [56% (78% based on recovered **35**)]; (h) (1) ^{t}BuLi (2.2 eq.), Et_2O, −80 °C, then excess $ClCO_2Me$, −80 °C, (2) excess $ClCO_2Me$, $ClCH_2CH_2Cl$, Δ, 2 h (61%); (i) Jones' oxidation then CH_2N_2 (65%); (j) LiHMDS (2.5 eq.), THF, 0 °C then MeOH (80%); (k) NaOH–MeOH, Δ (70%).

S-Garner aldehyde **24** by Wittig methylenation and oxazolidine cleavage to give the Boc protected vinylglycinol **31**.[25] Dess–Martin oxidation produced a very unstable aldehyde which was immediately subjected to *N*-Boc deprotection–acetal formation to give an amino acetal which was reductively aminated with benzaldehyde to give **32** in 31% yield over 3 steps. The ee of this amine was shown to be 93% by comparison with racemic material using HPLC on a chiral column [Chiralpak AS, 1:99 ^{i}PrOH–hexane, R_t 324 s (*vs.* 287 s)]. Alkylation with allyl chloride **26** gave diene **33** in 88% yield.

Ti(II)-mediated cyclisation–iodination gave, again, the *cis*,*cis*-pyrrolidine **34** as the only cyclised product in 56% yield (78% based on recovered diene **33**). Lithium–halogen exchange and quenching with excess methyl chloroformate gave **35** in 61% overall yield. Jones' oxidation cleaved the acetal and oxidised the resulting aldehyde to produce the corresponding acid which was treated with diazomethane to produce ester **36**. Compound **36** is a protected derivative of the so-called β-kainic acid: the titanium methodology provides a very convenient and stereoselective route to these compounds which are reported to have interesting anti-convulsant properties.[26]

Epimerisation of **36** at C-2 was successfully achieved using LiHMDS (2.5 eq.) and quenching with MeOH.[24a] Using this procedure, complete conversion into the epimeric ester **37** was observed [TLC (SiO_2: EtOAc–light petroleum, 1:2) **36**, R_f 0.30; **37**,[27] R_f 0.31]. Saponification of **37** was accompanied by *N*-deprotection giving (−)-α-kainic acid **1**, which was spectroscopically consistent with authentic material and corresponded well in terms of polarimetry {$[\alpha]_D$ −15.2 (*c* 0.95, H_2O); lit.[23] $[\alpha]_D$ −15.0 (*c* 0.5, H_2O)} and mp (mp 244–247 °C dec.; lit.[23] mp 237–243 °C dec.).

Synthesis of novel pyrrolidines and piperidines

Having succeeded with two syntheses of kainic acid, we attempted to extend the diene-cyclisation methodology to produce novel C-4 substituted pyrrolidines and disubstituted piperidines. The results are summarised in Table 2.

In an attempt to extend the methodology to novel analogues of acromelic acid A **4**, the metallabicyclisation reactions of the cyclohexyl substituted diene **38** were studied (Table 2, entry i). Again the zirconium- and titanium-mediated cyclisation processes proceeded well with excellent *cis*-selectivity to give the novel cyclohexenyl product **39** after protonation. We had hoped to produce the corresponding aryl analogue **41** by metallabicyclisation–elimination–aromatisation of diene **40** (entry ii). Unfortunately, no cyclised product was isolated from either the zirconium or titanium-mediated protocols.

We also carried out a preliminary study to look at piperidine synthesis using metallabicyclisation.[15,16,19] Cyclisation–protonation of diene **42** using "$ZrCp_2$" gave a mixture of *cis*- and *trans*-**43** and **44** but excellent *cis*-selectivity was again observed using the titanium methodology (entry iii). Finally (entry iv), the metallabicyclisation of diene **45** prepared from (*R*)-2-methylbenzylamine using the titanium methodology gave complete *cis*-C-3–C-4 diastereoselectivity but no asymmetric induction (as expected from earlier enyne studies by Sato *et al.*[16b]).

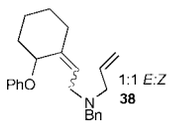
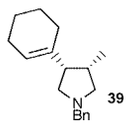
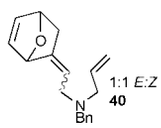
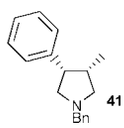
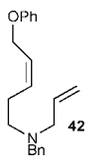
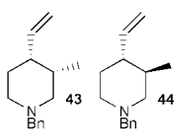
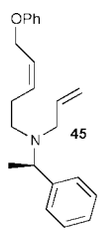
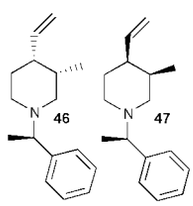
Conclusions

In conclusion, we have developed a new enantioselective synthesis of (−)-α-kainic acid **1** which has as its cornerstone a totally stereoselective titanium-mediated diene metallabicyclisation process. The total synthesis is high yielding (3.5% in 12 steps from commercially available material). This new route contrasts to other cyclisation–elimination approaches to the kainoids where stereochemical control has been poor,[14] and although our procedure does require epimerisation at C-2 to obtain the kainoid structure, it also provides a potential route to β-kainoids. In addition, kainoid analogues with a range of different substituents at C-3 and C-4 are available *via* this route. From a general methodological viewpoint, the new procedure for the stereoselective preparation of *cis*-3,4-di- and *cis*,*cis*-2,3,4-trisubstituted pyrrolidines and *cis*-3,4-disubstituted piperidines is noteworthy.

Experimental

NMR spectra were recorded on JEOL GX-270 or Bruker AMX 400 instruments. Tetramethylsilane (TMS) or $CDCl_3$–$CHCl_3$ was used as the internal standard and *J* values are in Hz. Carbon spectra were verified using DEPT experiments. Melting points were recorded on a Electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared (IR)

Table 2 Related metallabicyclisation studies

Entry no.	Starting diene	Major product(s) after H^+	Zr(II) Yield (%); *cis*:*trans*	Ti(II) Yield (%); *cis*:*trans*
i	 1:1 *E*:*Z* **38**	 **39**	50 10:1	52 *cis* only (**39**)
ii	 1:1 *E*:*Z* **40**	 **41**	(No **41** observed)	(No **41** observed)
iii	 **42**	 **43** **44**	59 1.0:1.4	58 *cis* only (**43**)
iv	 **45**	 **46** **47**	(No **46** or **47** observed)	63 *cis* only 1:1 mixture of diastereomers (**46** and **47**)

spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high resolution mass spectra (HRMS) were recorded on a Micromass Autospec spectrometer. Elemental analyses were carried out at the University of Newcastle. Chromatography is medium pressure flash chromatography and was performed using Matrex silica 60 (70–200) with the eluent specified. Where necessary, ether and THF were distilled from sodium–benzophenone ketyl, and DCM from calcium hydride, immediately before use. Light petroleum is the fraction bp 40–60 °C which was redistilled before use. Except where specified, all reagents were purchased from commercial sources and were used without further purification.

(2*E*)-*N*-Allyl-*N*-benzylbut-2-en-1-amine 8

To (2*E*)-*N*-allylbut-2-en-1-amine[28] (100 mg, 0.90 mmol) and K_2CO_3 (249 mg, 1.80 mmol) in MeCN (10 mL) was added BnBr (0.12 mL, 1.00 mmol) and the reaction was stirred overnight under N_2. The solvent was evaporated *in vacuo* and the residue was taken up in Et_2O (20 mL) and water (20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with light petroleum–EtOAc (15:1) to afford the *title compound* **8** (86 mg, 48%) as a colourless oil; R_f 0.40 (light petroleum–EtOAc, 9:1); ν_{max} cm^{-1} 2918, 2791, 1449, 1118, 968, 917, 697; δ_H (270 MHz, $CDCl_3$) 1.70 (3H, d, *J* 6.0, CH_3), 3.00–3.15 (4H, m, 2 × CH_2CH=CH), 3.55 (2H, s, CH_2Ph), 5.10–5.25 (2H, m, CH=CH_2), 5.45–5.70 (2H, m, CH=$CHCH_3$), 5.85–5.95 (1H, m, CH=CH_2), 7.15–7.28 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$), 17.9 (CH_3), 55.5 (CH_2), 56.3 (CH_2), 57.4 (CH_2), 117.3 (CH_2), 126.7, 127.6, 128.1, 128.3, 128.9 (5 × CH), 136.0 (CH), 139.5 (C); *m*/*z* (CI) 202 (MH^+, 100%); HRMS (CI) [MH^+] $C_{14}H_{20}N$ requires 202.1600. Found: 202.1596 (2.1 ppm error).

cis- and *trans*-1-Benzyl-3-ethyl-4-methylpyrrolidine 12

To zirconocene dichloride (123 mg, 0.42 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.34 mL, 0.84 mmol) under N_2 and stirred for 1 h, followed by addition of diene **8** (100 mg, 0.49 mmol) in THF (5 mL). The reaction was allowed to warm up to rt and stirred for a further 2 h. The reaction was quenched with MeOH (5 mL) and was stirred for a further 1 h before dilution with Et_2O (30 mL). The organic layer was separated, washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a colourless oil. Purification by flash column chromatography eluting with CH_2Cl_2–MeOH (9:1) gave the *title compound* **12** as an inseparable pair of diastereomers (50 mg, 50%, 1:1) as a colourless oil; R_f 0.15 (EtOAc); ν_{max} cm^{-1} 2957, 2874, 1454; δ_H (270 MHz, $CDCl_3$, *cis* + *trans*) 0.85–1.10 (6H, 2 × m, CH_3), 1.10–2.35 (6H, m, CH_3CH_2 + 2 × NCH_2CH), 2.65–2.80 + 2.95–3.10 (2 × 1H, m, $CHCH$), 3.51–3.72 (2H, m, NCH_2Ph), 7.09–7.34 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$, *cis* + *trans*) 12.8 + 13.1 (CH_3), 14.6 + 19.6 (CH_3), 22.4 + 27.4 (CH_2), 34.1 + 38.7 (CH), 42.3 + 48.1 (CH), 59.9, 60.4, 60.8, 61.1, 62.3, 62.6 (6 × CH_2), 126.7 (CH), 128.1 (CH), 128.8 (CH), 139.4 (C); *m*/*z* (EI) 203 (MH^+, 100%); HRMS (EI) [M^+] $C_{14}H_{21}N$ requires 203.1674. Found 203.1681 (3.6 ppm error).

(2*E*)-*N*-Allyl-*N*-benzyl-4-phenoxybut-2-en-1-amine 9

To *N*-allyl-*N*-benzylamine[18] (200 mg, 1.36 mmol), K_2CO_3 (376 mg, 2.72 mmol) and NaI (40 mg, 0.27 mmol) in MeCN (10 mL) was added [(1*E*)-3-chloroprop-1-enyloxy]benzene[29] (248 mg, 1.36 mmol) and the reaction was refluxed overnight under N_2. The solvent was evaporated and the residue was taken up in Et_2O (20 mL) and water (20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with light petroleum–EtOAc (9:1) to afford the *title compound* **9** (300 mg, 75%) as a colourless oil; R_f 0.25 (light petroleum–EtOAc, 9:1) (Found: C 81.6, H 7.8, N 4.8. $C_{20}H_{23}NO$ requires C 81.9, H 7.9, N 4.8%); ν_{max} cm^{-1} 3063, 3027, 2797, 1599, 1495, 1241, 753; δ_H (270 MHz, $CDCl_3$) 3.18 (2H, d, *J* 6.3, NCH_2CH), 3.21 (2H, d, *J* 4.5, NCH_2CH), 3.67 (2H, s, CH_2Ph), 4.60–4.66 (2H, d, *J* 3.9, CH_2OPh), 5.20–5.33 (2H, m, CH=CH_2), 5.89–6.04 (3H, m, CH=CH, CH=CH_2), 6.97–7.11 (3H, m, Ar-*H*), 7.29–7.48 (7H,

m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 55.0, 56.5, 57.6 (3 × CH_2), 68.1 (CH_2), 114.8 (CH), 117.5 (CH_2), 120.7 (CH), 126.8, 128.0, 128.1, 128.9, 129.4, 131.7, 135.7 (7 × CH), 139.3 (C), 159.5 (C); *m*/*z* (CI) 294 (MH^+, 100%); HRMS (CI) [MH^+] $C_{20}H_{24}NO$ requires 294.1858. Found 294.1860 (0.8 ppm error).

cis- and *trans*-1-Benzyl-3-methyl-4-vinylpyrrolidine 13a

Zirconium procedure. To zirconocene dichloride (110 mg, 0.38 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 0.47 mL, 0.75 mmol) under N_2 and stirred for 1 h followed by addition of diene **9** (100 mg, 0.34 mmol) in THF (2 mL). The reaction was allowed to warm up to rt and stirred for a further 4.5 h. The reaction was quenched with 2 M HCl (2 mL) and stirred for 10 min followed by dilution with Et_2O (30 mL) and 30%NaOH (10 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:1) to afford the *title compounds* **13a** as an inseparable mixture of 2 diastereomers (47 mg, 69%, 3:1) as a colourless oil; R_f 0.20 (light petroleum–EtOAc, 3:1); ν_{max} cm^{-1} 2957, 2785, 1639, 1454, 910, 735; δ_H (270 MHz, $CDCl_3$, *cis*) 0.89 (3H, d, *J* 7.0, C*H*$_3$), 2.01 (1H, apparent t, *J* 9.1, CH_3(CH)CHC*H*$_2$), 2.18–2.51 (3H, m, CH_3(C*H*)C*H*C*H*$_2$), 2.95–3.06 (2H, m, NC*H*$_2$CH-(CH)CH), 3.56–3.68 (2H, m, NC*H*$_2$Ph), 4.90–5.01 (2H, m, CH=C*H*$_2$), 5.70–5.88 (1H, m, C*H*=CH_2), 7.20–7.34 (5H, m, Ar-*H*); δ_H (270 MHz, $CDCl_3$, *trans*) 1.01 (3H, d, *J* 6.8, C*H*$_3$), 1.88–2.02 (1H, m, CH_3(CH)CHC*H*$_2$), 2.18–2.51 (3H, m, CH_3(C*H*)C*H*C*H*$_2$), 2.75–2.82 (2H, m, NC*H*$_2$CH(CH)CH), 3.56–3.68 (2H, m, NC*H*$_2$Ph), 4.90–5.01 (2H, m, CH=C*H*$_2$), 5.70–5.88 (1H, m, C*H*=CH_2), 7.20–7.34 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$, *cis*) 15.6 (CH_3), 35.2 (CH), 45.6 (CH), 59.5, 60.7, 62.2 (3 × CH_2), 115.1 (CH_2), 126.8, 128.1, 128.8, 138.7 (4 × CH), 139.3 (C); δ_C (67.9 MHz, $CDCl_3$, *trans*) 17.9 (CH_3), 39.1 (CH), 51.2 (CH), 59.9, 61.7, 60.8 (3 × CH_2), 114.1 (CH_2), 126.8, 128.1, 128.8, 139.3 (4 × CH), 140.8 (C); *m*/*z* (EI) 210 (MH^+, 30%); HRMS (EI) [M^+] $C_{14}H_{19}N$ requires 201.1518. Found 201.1520 (1.0 ppm error).

Titanium procedure. To diene **9** (100 mg, 0.34 mmol) in dry Et_2O at −50 °C under N_2 and stirred was added Ti(O-*i*-Pr)$_4$ (126 μL, 0.43 mmol) then *i*-PrMgCl (2.0 M in Et_2O, 0.41 mL, 0.82 mmol) and the reaction was allowed to warm to rt. The reaction was stirred for 30 min then quenched with MeOH (2 mL) and stirred for 2 min followed by dilution with Et_2O (50 mL) and washing with sat. $NaHCO_3$ (20 mL) then 1 M NaOH (10 mL). The combined aqueous layers were re-extracted with Et_2O (30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:9) to afford the *title compounds* **13a** as an inseparable mixture of 2 diastereomers (65 mg, 95%, 6:1) as a colourless oil. The spectroscopic data matched those reported above.

cis- and *trans*-1-Benzyl-3-(bromomethyl)-4-vinylpyrrolidine 13b

Titanium procedure. To diene **9** (250 mg, 0.85 mmol) in dry Et_2O (8 mL) at −50 °C under N_2 was added Ti(O-*i*-Pr)$_4$ (315 μL, 1.08 mmol) then *i*-PrMgCl (2.0 M in Et_2O, 1.03 mL, 1.06 mmol) and stirred at that temperature for 10 min before being allowed to warm slowly to rt. The reaction was stirred for 1 h then cooled to 0 °C and bromine [408 mg in Et_2O (4 mL), 2.55 mmol] was added. The reaction was stirred for 30 min then quenched with MeOH (2 mL) and stirred for 2 min followed by dilution with Et_2O (50 mL) and washing with sat. $NaHCO_3$ (20 mL) then 1 M NaOH (10 mL). The combined aqueous layers were re-extracted with Et_2O (30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:9) to afford the *title compounds* **13b** as an inseparable mixture of 2 diastereomers (159 mg, 67%, 6:1); R_f 0.20 (EtOAc–light petroleum, 1:9); ν_{max} cm^{-1} 2791, 1494, 1453, 1227, 917; δ_H (270 MHz, $CDCl_3$, *cis*) 2.35–3.70 (10H, m, N(C*H*$_2$Ph)C*H*$_2$C*H*(C*H*$_2$)C*H*(CH)C*H*$_2$), 4.95–5.12 (2H, m, CH=C*H*$_2$), 5.65–5.82 (1H, m, C*H*=CH_2), 7.21–7.35 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$, *cis*) 34.8 (CH_2), 43.7 (CH), 45.4 (CH), 59.2 (2 × CH_2), 60.0 (CH_2), 117.3 (CH_2), 127.2 (CH), 128.3 (CH), 128.8 (CH), 136.1 (CH), 138.2 (C); *m*/*z* (CI) 280, 282 (MH^+ 100%); HRMS (CI) [MH^+] $C_{14}H_{19}N^{79}Br$ requires 280.0701. Found 280.0702 (0.3 ppm error).

cis- and *trans*-1-Benzyl-3-(iodomethyl)-4-vinylpyrrolidine 13c

Zirconium procedure. To zirconocene dichloride (120 mg, 0.41 mmol) in THF (5 mL) at −78 °C under N_2 was added *n*-BuLi (1.6 M in hexanes, 0.51 mL, 0.82 mmol) and the reaction stirred for 1 h followed by addition of diene **9** (100 mg, 0.34 mmol) in THF (2 mL) and allowed to warm slowly to rt. The reaction was stirred for 1 h then cooled to 0 °C and iodine [173 mg in THF (2 mL), 0.68 mmol] was added. The reaction was stirred for 30 min then quenched with MeOH (2 mL) and stirred for 2 min followed by dilution with Et_2O (50 mL) and washing with sat. $NaHCO_3$ (20 mL) then 1 M NaOH (10 mL). The combined aqueous layers were re-extracted with Et_2O (30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:9→1:4) to afford the *title compounds* **13c** as an inseparable mixture of 2 diastereomers (90 mg, 81%, 3:1) as a colourless oil, R_f 0.30 (EtOAc–light petroleum, 1:9); ν_{max} cm^{-1} 2786, 1493, 1185, 915, 698; δ_H (270 MHz, $CDCl_3$, *cis*) 2.29 (1H, dd, *J* 9.2, 7.8, C*H*$_2$I), 2.41 (1H, dd, *J* 9.2, 6.3, C*H*$_2$I), 2.68–3.21 (6H, m, NC*H*$_2$C*H*(CH$_2$)C*H*-(CH)C*H*$_2$), 3.64 (2H, apparent d, *J* 2.8, NC*H*$_2$Ph), 5.06–5.13 (2H, m, CH=C*H*$_2$), 5.68–5.81 (1H, m, C*H*=CH_2), 7.21–7.35 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$, *cis*) 8.0 (CH_2), 44.3 (CH), 46.0 (CH), 59.6 (CH_2), 60.2 (CH_2), 61.1 (CH_2), 117.2 (CH_2), 127.0 (CH), 128.3 (CH), 128.7 (CH), 136.2 (CH), 138.6 (C); *m*/*z* (CI) 328 (MH^+, 100%); HRMS (CI) [MH^+] $C_{14}H_{19}NI$ requires 328.0562. Found 328.0569 (2.2 ppm error).

Titanium procedure. To diene **9** (400 mg, 1.36 mmol) in dry Et_2O (8 mL) at −50 °C under N_2 was added Ti(O-*i*-Pr)$_4$ (0.50 mL, 1.72 mmol) then *i*-PrMgCl (2.0 M in Et_2O, 1.64 mL, 3.28 mmol) and allowed to warm slowly to rt. The reaction was stirred for 1 h then cooled to 0 °C and iodine [1.035 g in Et_2O (4 mL), 2.55 mmol] was added. The reaction was stirred for 30 min then quenched with MeOH (2 mL) and stirred for 2 min followed by dilution with Et_2O (50 mL) and washing with sat. $NaHCO_3$ (20 mL) then 1 M NaOH (10 mL). The combined aqueous layers were re-extracted with Et_2O (30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:9) to afford the *title compounds* **13c** as an inseparable mixture of 2 diastereomers (320 mg, 72%, 6:1); the spectroscopic data matched those reported above.

cis- and *trans*-1-Benzyl-4-vinylpyrrolidin-3-ylacetaldehyde 13d

Zirconium procedure. To zirconocene dichloride (120 mg, 0.41 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 0.51 mL, 0.82 mmol) under N_2 and stirred for 1 h followed by addition of diene **9** (100 mg, 0.34 mmol) in THF (2 mL). The reaction was allowed to warm up to rt and stirred for a further 1 h. *n*-BuNC (40 mg, 0.38 mmol) was added at 0 °C and the reaction was heated to 45 °C for 3 h followed by quenching with 50% AcOH (2 mL) at −78 °C to rt and stirring for 10 min. 30% NaOH (5 mL) was added along with Et_2O

(20 mL) and the organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil which was purified by flash column chromatography eluting with EtOAc to afford the *title compounds* **13d** as an inseparable mixture of 2 diastereomers (36 mg, 47%, 3:1) as a colourless oil, R_f 0.10 (light petroleum–EtOAc, 1:1); ν_{max} cm^{-1} 2923, 1721, 1640, 1029, 734; δ_H (270 MHz, $CDCl_3$, *cis*) 2.11 (1H, dd, *J* 9.0, 7.5, CH_2CHO), 2.24–2.56, 2.70–2.95 (4H + 3H, 2 × m, NCH_2CH(CH_2)CH(CH)CH_2), 3.56 (2H, s, NCH_2Ph), 4.90–4.97 (2H, m, CH=CH_2), 5.62–5.72 (1H, m, CH=CH_2), 7.14–7.24 (5H, m, Ar-*H*), 9.65 (1H, s, CHO); δ_C (67.9 MHz, $CDCl_3$, *cis*) 35.5 (CH), 44.6 (CH), 45.1 (CH_2), 59.1, 59.1, 60.3 (3 × CH_2), 116.7 (CH_2), 127.2, 128.3, 128.8, 128.9 (4 × CH), 137.9 (C), 201.8 (C); δ_C (67.9 MHz, $CDCl_3$, *trans*) 38.4 (CH), 48.1 (CH), 49.0 (CH_2), 59.1, 59.2, 60.1 (3 × CH_2), 115.7 (CH_2), 127.1, 128.8, 138.5 (4 × CH), 139.3 (C), 201.6 (C); *m*/*z* (CI) 230 (MH^+, 25%); HRMS (CI) [MH^+] $C_{15}H_{20}NO$ requires 230.1545. Found: 230.1540 (2.1 ppm error).

(2*E*)-*N*-Allyl-*N*-benzyl-3-methyl-4-phenoxybut-2-en-1-amine 10

To *N*-allyl-*N*-benzylamine[18] (251 mg, 1.71 mmol), K_2CO_3 (394 mg, 2.85 mmol) and NaI (43 mg, 0.28 mmol) in MeCN (10 mL) was added {[(2*E*)-4-chloro-2-methylbut-2-enyl]oxy}benzene (280 mg, 1.42 mmol) and the reaction was refluxed overnight under N_2. Work-up as for amine **9** followed by purification by flash column chromatography eluting with light petroleum–EtOAc (9:1) afforded the *title compound* **10** (354 mg, 81%) as a colourless oil; R_f 0.20 (light petroleum–EtOAc, 9:1); ν_{max} cm^{-1} 2919, 2802, 1598, 1494, 1241, 735, 692; δ_H (270 MHz, $CDCl_3$) 1.70 (3H, s, CH_3), 3.05 (2H, d, *J* 6.3, NCH_2CH), 3.11 (2H, d, *J* 6.5, NCH_2CH), 3.54 (2H, s, NCH_2Ph), 4.41 (2H, s, CH_2OPh), 5.11–5.20 (2H, m, CH=CH_2), 5.69 (1H, t, *J* 6.5, CH_2CH=CR_2), 5.81–5.95 (1H, m, CH=CH_2), 6.90–6.94 (3H, m, Ar-*H*), 7.23–7.31 (7H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 14.1 (CH_3), 50.5, 56.7, 57.8 (3 × CH_2), 73.4 (CH_2), 114.9 (CH), 117.4 (CH_2), 120.7 (CH), 125.8, 126.8, 128.1, 128.9, 129.3, 135.9 (6 × CH), 133.8 (C) 139.3 (C), 158.7 (C); *m*/*z* (CI) 308 (MH^+, 100%); HRMS (CI) [MH^+] $C_{21}H_{26}NO$ requires 308.2014. Found: 308.2014 (0.1 ppm error).

(2*Z*)-*N*-Allyl-*N*-benzyl-3-methyl-4-phenoxybut-2-en-1-amine 11

To *N*-allyl-*N*-benzylamine[18] (90 mg, 0.61 mmol), K_2CO_3 (141 mg, 1.02 mmol) and NaI (15 mg, 0.10 mmol) in MeCN (10 mL) was added allyl chloride **26** (100 mg, 0.51 mmol) and the reaction was stirred overnight under N_2. Work-up as for amine **9** followed by purification by flash column chromatography eluting with light petroleum–EtOAc (7:1) afforded the *title compound* **11** (140 mg, 89%) as a colourless oil; R_f 0.20 (light petroleum–EtOAc, 9:1); ν_{max} cm^{-1} 2918, 2801, 1598, 1495, 1239, 1008, 753, 693; δ_H (270 MHz, $CDCl_3$) 1.86 (3H, d, *J* 1.0, CH_3), 3.06–3.12 (4H, m, 2 × NCH_2CH), 3.56 (2H, s, NCH_2Ph), 4.44 (2H, s, CH_2OPh), 5.11–5.22 (2H, m, CH=CH_2), 5.57 (1H, dt, *J* 7.8, 1.0, CH_2CH=CR_2), 5.88 (1H, ddt, *J* 17.2, 10.2, 6.3, CH=CH_2), 6.85–6.97 (3H, m, Ar-*H*), 7.21–7.34 (7H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 21.5 (CH_3), 50.3 (CH_2), 56.7 (CH_2), 57.8 (CH_2), 66.6 (CH_2), 114.7 (CH), 117.5 (CH_2), 120.7 (CH), 126.8, 128.2, 128.9, 129.4, 135.9 (6 × CH), 134.6 (C), 139.3 (C), 158.9 (C); *m*/*z* (CI) 308 (MH^+, 100%); HRMS (CI) [MNH_4^+] $C_{21}H_{26}NO$ requires 308.2014. Found 308.2008 (2.0 ppm error).

cis-1-Benzyl-3-isopropenyl-4-methylpyrrolidine 14

Titanium procedure. To diene **11** (100 mg, 0.33 mmol) in dry Et_2O at −50 °C under N_2 was added Ti(O-*i*-Pr)$_4$ (118 μL, 0.39 mmol) then *i*-PrMgCl (2.0 M in Et_2O, 0.39 mL, 0.78 mmol) and allowed to warm to rt. The reaction was stirred for 30 min then worked-up as for the preparation of pyrrolidines **13a**. Purification by flash column chromatography eluting with EtOAc–light petroleum (1:1) afforded the *title compound* **14** (60 mg, 85%) as a colourless oil, R_f 0.25 (light petroleum–EtOAc, 3:1); ν_{max} cm^{-1} 2960, 2917, 2787, 1646, 1453, 887, 698; δ_H (270 MHz, $CDCl_3$) 0.81 (3H, d, *J* 7.0, CHCH_3), 1.72 (3H, s, CH_3CR_2), 2.08 (1H, dd, *J* 9.2, 5.6, CH_2CHCH$_3$), 2.38–2.58 (2H, m, CHCH), 2.76–2.87 (2H, m, CH_2CH(CR_2)CH), 3.13 (1H, dd, *J* 9.2, 7.3, CH_2CHCH$_3$), 3.64 (2H, s, NCH_2Ph), 4.66 (1H, br s, CR_2=CH_2), 5.00 (1H, br s, CR_2=CH_2), 7.21–7.35 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 15.9 (CH_3), 23.6 (CH_3), 33.8 (CH), 48.2 (CH), 56.1, 61.1, 62.4 (3 × CH_2), 110.8 (CH_2), 126.8 (CH), 128.2 (CH), 128.7 (CH), 139.5 (C), 144.3 (C); *m*/*z* (CI) 216 (MH^+, 100%); HRMS (CI) [MH^+] $C_{15}H_{22}N$ requires 216.1752. Found: 216.1747 (2.6 ppm error).

(2*Z*)-*N*-Benzyl-3-methyl-*N*-(1-methylprop-2-enyl)-4-phenoxybut-2-en-1-amine 15

(a) To benzylamine (500 mg, 4.66 mmol), K_2CO_3 (612 mg, 4.43 mmol) and NaI (66 mg, 0.44 mmol) in MeCN (10 mL) was added 3-chlorobut-1-ene (401 mg, 4.43 mmol) and the reaction was refluxed overnight under N_2. The solvent was evaporated and the residue was taken up in Et_2O (40 mL) and sat. $NaHCO_3$ (20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with CH_2Cl_2–MeOH (9:1) to afford *N-benzyl-N-(1-methylprop-2-enyl)amine* (100 mg, 14%) as a colourless oil; R_f 0.35 (CH_2Cl_2–MeOH, 9:1) which was fully characterised.

(b) To *N*-benzyl-*N*-(1-methylprop-2-enyl)amine (95 mg, 0.59 mmol), K_2CO_3 (192 mg, 1.18 mmol) and NaI (18 mg, 0.12 mmol) in MeCN (20 mL) was added allyl chloride **26** (116 mg, 0.59 mmol) and the reaction was refluxed overnight under N_2. Work-up as for amine **9** followed by purification by flash column chromatography eluting with light petroleum–EtOAc (20:1) afforded the *title compound* **15** (150 mg, 79%) as a colourless oil; R_f 0.55 (light petroleum–EtOAc, 9:1); ν_{max} cm^{-1} 2970, 1598, 1495, 1238, 1008; δ_H (270 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.8, CH_3CH), 1.82 (3H, s, CH_3CR=CH), 3.12 (2H, m, NCH_2CH), 3.37 (1H, apparent quintet, *J* 6.8, NCH), 3.55 (1H, d, *J* 13.8, NCH_2Ph), 3.61 (1H, d, *J* 13.8, NCH_2Ph), 4.42 (2H, s, CH_2OPh), 5.04–5.15 (2H, m, CH=CH_2), 5.51 (1H, apparent t, *J* 5.9, CH=CR_2), 5.90 (1H, ddd, *J* 17.2, 10.5, 6.8, CH=CH_2), 6.84–6.96 (3H, m, Ar-*H*), 7.16–7.36 (7H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 15.3 (CH_3), 21.5 (CH_3), 46.7 (CH_2), 53.6 (CH_2), 56.2 (CH), 66.7 (CH_2), 114.6 (CH), 115.5 (CH_2), 120.7 (CH), 126.6, 128.1, 128.5, 139.4, 140.2, 140.6 (9 × CH), 158.9 (C); *m*/*z* (CI) 322 (MH^+, 100%); HRMS (CI) [MH^+] $C_{22}H_{28}NO$ requires 322.2171. Found 322.2183 (3.7 ppm error).

2,3-*trans*-3,4-*cis*-1-Benzyl-4-isopropenyl-2,3-dimethylpyrrolidine and 2,3-*cis*-3,4-*cis*-1-benzyl-4-isopropenyl-2,3-dimethylpyrrolidine 16 and 17

Titanium procedure. Diene **15** (75 mg, 0.23 mmol) was treated with Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl according to the general procedure outlined for the cyclisation of diene **9**. Purification by flash column chromatography eluting with EtOAc–light petroleum (1:1) afforded the *title compounds* **16** and **17** as an inseparable mixture of 2 diastereomers (39 mg, 74%, 1:4) as colourless oils; R_f 0.20 (EtOAc–light petroleum, 1:1); ν_{max} cm^{-1} 2965, 1646, 1453, 1376, 697; δ_H (270 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.3, NCH(CH$_3$)CH(CH_3)), 1.08 (3H, d, *J* 6.3, NCH(CH_3)-CH(CH$_3$)), 1.70 (3H, s, CH_3CR=CH_2), 2.17 (1H, apparent quintet, *J* 6.3, NCH(CH$_3$)CH(CH$_3$)), 2.44 (1H, dd, *J* 10.0, 8.7, NCH_2CH), 2.67 (1H, ddd, *J* 9.5, 8.7, 6.3, NCH$_2$CH), 2.90 (1H, apparent quintet, *J* 6.3, NCH), 3.13 (1H, dd, *J* 10.0, 9.5, NCH_2CH), 3.36 (1H, d, *J* 13.8, NCH_2Ph), 3.97 (1H, d, *J* 13.8, NCH_2Ph), 4.58 (1H, br s, CH$_3$CR=CH_2), 4.79 (1H, br s, CH$_3$CR=CH_2), 7.19–7.37 (5H, m, Ar-*H*); δ_C (67.9 MHz,

$CDCl_3$) 9.0 (CH_3), 15.5 (CH_3), 23.1 (CH_3), 39.6 (CH), 47.3 (CH), 53.4 (CH_2), 58.5 (CH_2), 63.2 (CH), 110.4 (CH_2), 128.2 (CH), 128.8 (CH), 129.5 (CH), 144.0 (C), 156.2 (C); *m*/*z* (CI) 230 (MH^+, 100%); HRMS (CI) [MH^+] $C_{16}H_{24}N$ requires 230.1909. Found 230.1912 (1.5 ppm error).

{[(2*Z*)-4-Chloro-2-methylbut-2-enyl]oxy}benzene 26

(a) To diethyl phosphonoacetate (25.85 g, 123 mmol) in THF (250 mL) was added NaH (60%, 4.92 g, 123 mmol) portionwise under N_2 and stirring was continued for 30 min. The reaction mixture was cooled to −15 °C and 1-phenoxyacetone (15.79 g, 17.2 mL, 105 mmol) was added dropwise over 20 min and stirred at −15 °C for a further 30 min. The reaction was quenched with water (150 mL) and diluted with Et_2O (200 mL) and the organic layer was separated and washed with sat. $NaHCO_3$ (100 mL) then 2 M HCl (100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with light petroleum–EtOAc (20:1) to afford methyl (2*Z*)-3-methyl-4-phenoxyybut-2-enoate (6.92 g, 32%) as a colourless oil, R_f 0.25 (light petroleum–EtOAc, 20:1) followed by methyl (2*E*)-3-methyl-4-phenoxybut-2-enoate (13.44 g, 62%) as a colourless oil; R_f 0.10 (light petroleum–EtOAc, 20:1) which were fully characterised.

(b) To the *Z*-α,β-unsaturated ester above (1.00 g, 4.85 mmol) in dry toluene (20 mL) at −78 °C was added DIBAL (1.0 M in toluene, 9.70 mL, 9.70 mmol) and the reaction was stirred for 30 min under N_2. The reaction was quenched by addition of MeOH (10 mL) and allowed to warm to rt. 10% Citric acid (50 mL) and Et_2O (50 mL) were added and the reaction stirred vigorously for 1 h. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was used without purification in the next reaction.

(c) To the crude alcohol in CH_2Cl_2 (100 mL) was added DMAP (1.19 g, 9.70 mmol) then tosyl chloride (1.11 g, 5.81 mmol) followed by stirring overnight. The organic layer was then washed with sat. $NaHCO_3$ (30 mL) and dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a thick yellow gum which was purified by flash column chromatography (pre-adsorbed onto silica) eluting with light petroleum–EtOAc (30:1) to afford the *title compound* **26** (372 mg, 39%) as a colourless oil; R_f 0.40 (light petroleum–EtOAc, 9:1); ν_{max} cm^{-1} 2947, 1598, 1495, 1238, 1008, 754, 691; δ_H (270 MHz, $CDCl_3$) 1.90 (3H, t, *J* 0.7, CH_3), 4.15 (2H, *J* 8.0, CH_2Cl), 4.55 (2H, s, CH_2OPh), 5.61–5.71 (1H, m, $CH{=}CR_2$), 6.89–7.00 (3H, m, Ar-*H*), 7.23–7.33 (2H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 21.4 (CH_3), 39.7 (CH_2), 66.1 (CH_2), 114.6 (CH), 121.1 (CH), 124.6 (CH), 129.5 (CH), 137.7 (C), 158.5 (C); *m*/*z* (CI) 214 (MNH_4^+, 100%); HRMS (CI) [MNH_4^+] $C_{11}H_{17}NOCl$ requires 214.0999. Found 214.0993 (2.5 ppm error).

{[(2*E*)-4-Chloro-2-methylbut-2-enyl]oxy}benzene *E*-26

A similar sequence was employed to convert methyl (2*E*)-3-methyl-4-phenoxybut-2-enoate into *E*-**26**: colourless oil (24% over 3 steps); R_f 0.55 (light petroleum–EtOAc, 9:1); ν_{max} cm^{-1} 2922, 1598, 1495, 1245, 1172, 754; δ_H (270 MHz, $CDCl_3$) 1.76 (3H, t, *J* 0.5, CH_3), 4.08 (2H, *J* 7.8, CH_2Cl), 4.36 (2H, s, CH_2OPh), 5.74 (1H, m, $CH{=}CR_2$), 6.82–6.92 (3H, m, Ar-*H*), 7.15–7.24 (2H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 13.7 (CH_3), 39.9 (CH_2), 72.3 (CH_2), 114.7 (CH), 120.1 (CH), 122.8 (CH), 129.4 (CH), 137.4 (C), 158.9 (C); *m*/*z* (CI) 214 (MNH_4^+, 100%); HRMS (CI) [MNH_4^+] $C_{11}H_{17}NOCl$ requires 214.0999. Found 214.0995 (1.6 ppm error).

N-Benzyl-*N*-[(1*R*)-1-(*tert*-butyl(dimethyl)silyloxymethyl)prop-2-enyl]-*N*-[(2*Z*)-3-methyl-4-phenoxybut-2-enyl]amine 27

(a) (2*R*)-1-Hydroxybut-3-en-2-amine hydrochloride[21a] **25** (550 mg, 4.45 mmol), benzaldehyde (520 mg, 4.90 mmol), triethylamine (540 mg, 5.34 mmol) and Na_2SO_4 (3 g) in CH_2Cl_2 (25 mL) were heated under reflux overnight under N_2. The reaction was then cooled, filtered and concentrated *in vacuo*, taken up in MeOH (20 mL), cooled to 0 °C followed by addition of $NaBH_4$ (242 mg, 4.45 mmol). The reaction was warmed to rt and stirred for a further 1 h. The solvent was then evaporated and the residue was taken up in EtOAc (60 mL) and sat. $NaHCO_3$ (40 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product which was dissolved in DMF (10 mL) along with TBSCl (810 mg, 5.37 mmol), imidazole (664 mg, 9.75 mmol) and was stirred overnight under N_2. The solvent was then evaporated *in vacuo* and the residue was taken up in EtOAc (60 mL) and sat. $NaHCO_3$ (20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with light petroleum–EtOAc (9:1) to afford (2*R*)-*N*-benzyl-1-*tert*-butyl(dimethyl)silyloxybut-3-en-2-amine (900 mg, 70%) as a colourless oil; R_f 0.35 (light petroleum–EtOAc, 9:1); $[a]_D$ −26.6 (*c* 0.98, $CHCl_3$) which was fully characterised.

(b) To (2*R*)-*N*-benzyl-1-*tert*-butyl(dimethyl)silyloxybut-3-en-2-amine (449 mg, 1.54 mmol), K_2CO_3 (426 mg, 3.08 mmol) and NaI (46 mg, 0.30 mmol) in MeCN (30 mL) was added allyl chloride **26** (303 mg, 1.54 mmol) and the reaction was refluxed overnight under N_2. Standard work up as for amine **9** followed by purification by flash column chromatography eluting with light petroleum–EtOAc (30:1) afforded the *title compound* **27** (594 mg, 86%) as a colourless oil; R_f 0.50 (light petroleum–EtOAc, 9:1); $[a]_D$ +1.8 (*c* 0.95, $CHCl_3$) (Found: C 74.5, H 9.2, N, 3.5. $C_{28}H_{41}NO_2Si$ requires C 74.45, H 9.15, N 3.1%); ν_{max} cm^{-1} 2928, 2856, 1598, 1495, 1239, 1102, 837, 753; δ_H (270 MHz, $CDCl_3$) 0.05 (6H, m, $OSi(CH_3)_2C(CH_3)_3$), 0.91 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.86 (3H, d, *J* 1.0, $CH_3CR{=}CH$), 3.14–3.35 (3H, m, NCH_2CH, NC*H*), 3.54 (1H, d, *J* 14.0, NCH_2Ph), 3.72–3.86 (2H, m, OCH_2SiR_3), 3.85 (1H, d, *J* 14.0, NCH_2Ph), 4.45 (2H, s, CH_2OPh), 5.17–5.29 (2H, m, $CH{=}CH_2$), 5.54 (1H, t, *J* 6.0, $CR_2{=}CH$), 5.85 (1H, ddd, *J* 17.2, 9.7, 6.8, $CH{=}CH_2$), 6.87–6.99 (3H, m, Ar-*H*), 7.23–7.40 (7H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) −5.4 (CH_3), −5.4 (CH_3), 18.3 (C), 21.4 (CH_3), 25.9 (CH_3), 47.6 (CH_2), 54.7 (CH_2), 63.2 (CH), 64.7 (CH_2), 66.9 (CH_2), 114.6 (CH), 118.1 (CH_2), 120.7 (CH), 126.6 (CH), 128.1 (CH), 128.4 (CH_2), 128.5 (CH), 129.5 (CH), 133.8 (C), 135.4 (CH), 140.7 (C), 158.9 (C); *m*/*z* (CI) 452 (MH^+, 100%).

(2*R*,3*S*,4*S*)-1-Benzyl-2-[*tert*-butyl(dimethyl)silyloxy-methyl]-3-(iodomethyl)-4-isopropenylpyrrolidine 28

To diene **27** (197 mg, 0.44 mmol) in dry Et_2O (8 mL) at −50 °C under N_2 was added $Ti(O\text{-}i\text{-}Pr)_4$ (164 μL, 0.55 mmol) then *i*-PrMgCl (2.0 M in Et_2O, 0.53 mL, 1.06 mmol) and stirred at that temperature for 10 min before being allowed to warm slowly to rt. The reaction was stirred for 1 h then cooled to 0 °C and iodine [335 mg in Et_2O (4 mL), 1.32 mmol] was added. The reaction was stirred for 30 min then quenched with MeOH (2 mL) and stirred for 2 min followed by dilution with Et_2O (50 mL) and washing with sat. $NaHCO_3$ (20 mL) then 1 M NaOH (10 mL). The combined aqueous layers were re-extracted with Et_2O (30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:25) to afford the *title compound* **28** (148 mg, 70%) as a pale yellow oil; R_f 0.25 (EtOAc–light petroleum, 1:9); $[a]_D$ +40.6 (*c* 0.32, $CHCl_3$); ν_{max} cm^{-1} 2928, 1470, 1255, 1987, 836; δ_H (270 MHz, $CDCl_3$) 0.09 (3H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.09 (3H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.92 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.86 (3H, s, $CH_3CR{=}CH_2$), 2.45 (1H, dd, *J* 9.7, 7.3, CH_2I), 2.76–3.13 (5H, m, $CHCH_2I$, NCH_2CH), 3.42–3.50 (2H, m, NC*H*, NCH_2Ph),

3.74 (1H, dd, *J* 10.7, 7.3, OC*H*$_2$), 3.94 (1H, dd, *J* 10.7, 6.5, OC*H*$_2$), 4.17 (1H, d, *J* 13.6, NC*H*$_2$Ph), 4.90 (1H, br s, CH$_3$-CR=C*H*$_2$), 4.95 (1H, br s, CH$_3$CR=C*H*$_2$), 7.25–7.34 (5H, m, Ar-*H*); δ_C (67.9 MHz, CDCl$_3$) −5.4 (CH$_3$), −5.4 (CH$_3$), 1.7 (CH$_2$I), 18.2 (C), 23.7 (CH$_3$), 26.0 (CH$_3$), 47.5 (CH), 48.0 (CH), 55.6 (CH$_2$), 59.9 (CH$_2$), 63.3 (CH$_2$), 68.7 (CH), 113.7 (CH$_2$), 126.7 (CH), 128.1 (CH), 128.4 (CH), 140.1 (C), 143.4 (C); *m*/*z* (CI) 486 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{22}H_{37}NOSiI$ requires 486.1689. Found 486.1697 (1.6 ppm error).

Methyl [(2*R*,3*S*,4*S*)-1-benzyl-2-[*tert*-butyl(dimethyl)silyloxymethyl]-4-isopropenyl-3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate 29

To alkyl halide **28** (82 mg, 0.169 mmol) in Et$_2$O (5 mL) at −80 °C was added *t*-BuLi (1.7 M in pentane, 0.22 mL, 0.372 mmol) and the reaction was stirred for 3 min under N$_2$. Methyl chloroformate (0.2 mL, 2.54 mmol) was added and the reaction was allowed to warm to rt and the reaction stirred for a further 2 h. Methyl chloroformate (0.2 mL, 2.54 mmol) was added again and the reaction was stirred for 4 h. Methyl chloroformate (0.4 mL, 5.08 mmol) was added again and the reaction was refluxed overnight. The reaction was quenched with triethylamine (2 mL) then sat. NaHCO$_3$ (20 mL) and then diluted with Et$_2$O (30 mL). The organic layer was separated, dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with light petroleum–EtOAc (6:1) to afford the *title compound* **29** (46 mg, 71%) as a colourless oil; R_f 0.20 (light petroleum–EtOAc, 6:1); $[\alpha]_D$ +39.7 (*c* 2.00, CHCl$_3$); ν_{max} cm^{-1} 2953, 1740, 1709, 1449, 1379, 838; δ_H (270 MHz, d^8-toluene, 80 °C) 0.01 (3H, s, OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.02 (3H, s, OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.87 (9H, s, OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.51 (3H, s, C*H*$_3$CR=CH$_2$), 2.08 (1H, dd, *J* 17.0, 7.1, C*H*$_2$CO$_2$Me), 2.20–2.27 (1H, m, C*H*CH$_2$CO$_2$Me), 2.61 (1H, dd, *J* 17.0, 7.0, C*H*$_2$CO$_2$Me), 2.96 (1H, m, NCH$_2$C*H*), 3.12 (1H, apparent t, *J* 10.4, NC*H*$_2$), 3.35 (3H, s, NCO$_2$C*H*$_3$), 3.43–3.52 (4H, m, NC*H*$_2$, CO$_2$C*H*$_3$), 3.77 (2H, apparent d, *J* 5.6, OC*H*$_2$), 4.10–4.20 (1H, m, NC*H*), 4.49 (1H, br s, CH$_3$CR=C*H*$_2$), 4.69 (1H, br s, CH$_3$CR=C*H*$_2$); δ_C (67.9 MHz, d$_8$-toluene, 80 °C) −4.4 (CH$_3$), 19.4 (C), 24.0 (CH$_3$), 27.1 (CH$_3$), 30.7 (CH$_2$), 40.2 (CH), 48.7 (CH), 50.4 (CH$_2$), 51.8 (CH$_3$), 52.7 (CH$_3$), 62.6 (CH$_2$), 63.8 (CH), 113.4 (CH$_2$), 143.8 (C), 156.7 (C), 173.9 (C); *m*/*z* (CI) 386 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{19}H_{36}NO_5Si$ requires 386.2363. Found 386.2377 (3.8 ppm error).

Methyl (3*S*,3a*S*,7a*R*)-3-isopropenyl-5-oxooctahydropyrano-[3,4-*b*]pyrrole-1-carboxylate 30

To ester **29** (39 mg, 0.101 mmol) dissolved in MeOH (6 mL) was added TsOH·H$_2$O (2 mg, 0.01 mmol) and the reaction was stirred for 5 h under N$_2$. The solvent was evaporated and the residue was taken up in EtOAc (20 mL) and sat. NaHCO$_3$ (10 mL). The organic layer was separated, dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the *title compound* **30** (24 mg, 100%) as a colourless oil; R_f 0.20 (light petroleum–EtOAc, 2:1); $[\alpha]_D$ +32.1 (*c* 1.20, CHCl$_3$); ν_{max} cm^{-1} 2956, 1748, 1703, 1453, 1385; δ_H (270 MHz, CDCl$_3$) 1.75 (3H, s, C*H*$_3$CR=CH$_2$), 2.33–2.38 (2H, m, C*H*$_2$CO$_2$R), 2.78–3.03 (2H, m, NCHC*H*C*H*), 3.24–3.36 (1H, m, NC*H*), 3.67–3.96 (4H, m, NC*H*, NCO$_2$-C*H*$_3$), 4.21–4.56 (3H, m, NC*H*C*H*$_2$), 4.73 (1H, br s, CH$_3$CR=C*H*$_2$), 5.03 (1H, br s, CH$_3$CR=C*H*$_2$); *m*/*z* (CI) 240 (MH$^+$, 50%); HRMS (CI) [MH$^+$] $C_{12}H_{18}NO_4$ requires 240.1236. Found 240.1235 (0.2 ppm error).

(2*R*)-*N*-Benzyl-1,1-dimethoxybut-3-en-2-amine 32

(a) *tert*-Butyl (1*R*)-1-(hydroxymethyl)prop-2-enylcarbamate **31**[25] (505 mg, 2.70 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and Dess–Martin periodinane (1.95 g, 4.60 mmol) was added and the reaction stirred for 2 h under N$_2$. The solvent was evaporated and the product triturated with Et$_2$O (20 mL). The solution was filtered and then washed with sat. Na$_2$S$_2$O$_3$. The organic layer was separated, dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the crude aldehyde product as a colourless oil which was used without purification.

(b) HCl–MeOH was prepared by adding AcCl (4 mL) to MeOH (24 mL) at 0 °C and stirring for 10 min under N$_2$. The crude aldehyde from (a) was added and the reaction stirred for 2 h. The solvent was evaporated and the amine was purified by flash column chromatography eluting with CH$_2$Cl$_2$–MeOH–AcOH–H$_2$O (60:15:2:3) to give (2*R*)-1,1-dimethoxybut-3-en-2-amine (200 mg) as a yellow oil, R_f 0.25 (CH$_2$Cl$_2$–MeOH–AcOH–H$_2$O, 60:15:2:3) which gave consistent NMR data but was used without further characterisation.

(c) To (2*R*)-1,1-dimethoxybut-3-en-2-amine (248 mg, 1.89 mmol) and PhCHO (201 mg, 1.89 mmol) in 1,2-dichloroethane (15 mL) was added NaBH(OAc)$_3$ (561 mg, 2.65 mmol) and the reaction was stirred for 2 h under N$_2$. The solvent was evaporated *in vacuo* and the residue was taken up in EtOAc (40 mL) and sat. NaHCO$_3$ (20 mL). The aqueous layer was washed again with EtOAc (40 mL) and the combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc to afford the *title compound* **32** (184 mg, 31% over 3 steps) as a colourless oil; R_f 0.40 (EtOAc) (93% ee by chiral HPLC—see text for details); $[\alpha]_D$ −13.1 (*c* 0.97, CHCl$_3$) (Found: C 70.3, H 8.6, N 6.3. $C_{13}H_{19}NO_2$ requires C 70.6, H 8.65, N 6.3%); ν_{max} cm^{-1} 2832, 1454, 1117, 1064; δ_H (270 MHz, CDCl$_3$) 2.22–2.62 (1H, br, N*H*), 3.34 (1H, dd, *J* 8.3, 6.1, NHC*H*), 3.45 (3H, s, OC*H*$_3$), 3.47 (3H, s, OC*H*$_3$), 3.72 (1H, d, *J* 13.3, NC*H*$_2$Ph), 3.98 (1H, d, *J* 13.3, NC*H*$_2$Ph), 4.39 (1H, d, *J* 6.1, C*H*(OCH$_3$)$_2$), 5.37 (1H, dd, *J* 17.2, 1.7, CH=C*H*$_2$), 5.42 (1H, d, *J* 10.4, 1.7, CH=C*H*$_2$), 5.85 (1H, ddd, *J* 17.2, 10.4, 8.3, C*H*=CH$_2$), 7.34–7.43 (5H, m, Ar-*H*); δ_C (67.9 MHz, CDCl$_3$) 51.2 (CH$_2$), 54.9 (CH$_3$), 55.4 (CH$_3$), 62.7 (CH), 106.8 (CH), 119.3 (CH$_2$), 127.3 (CH), 128.7 (CH), 128.9 (CH), 136.5 (CH), 140.7 (C); *m*/*z* (CI) 222 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{13}H_{20}NO_2$ requires 222.1494. Found 222.1491 (1.5 ppm error).

N-Benzyl-*N*-[(1*R*)-1-(dimethoxymethyl)prop-2-enyl]-*N*-[(2*Z*)-3-methyl-4-phenoxybut-2-enyl]amine 33

To amine **32** (286 mg, 1.36 mmol), K$_2$CO$_3$ (188 mg, 1.36 mmol) and NaI (20 mg, 0.13 mmol) in MeCN (30 mL) was added allyl chloride **26** (268 mg, 1.36 mmol) and the reaction was refluxed for 3 h under N$_2$. Work-up as for amine **9** followed by purification by flash column chromatography eluting with light petroleum–EtOAc (9:1) afforded the *title compound* **33** (436 mg, 88%) as a colourless oil; R_f 0.25 (light petroleum–EtOAc, 9:1); $[\alpha]_D$ +20.1 (*c* 0.98, CHCl$_3$) (Found: C 75.6, H 8.1, N, 3.5. $C_{24}H_{31}NO_3$ requires C 75.6, H 8.2, N 3.7%); ν_{max} cm^{-1} 2932, 1598, 1495, 1239, 1060, 753; δ_H (270 MHz, CDCl$_3$) 1.86 (3H, s, C*H*$_3$CR=CH), 3.07 (1H, dd, *J* 10.5, 7.8, NC*H*$_2$CH), 3.24–3.38 (3H, m, NC*H*$_2$Ph, NC*H*$_2$CH, NC*H*), 3.33 (3H, s, OC*H*$_3$), 3.38 (3H, s, OC*H*$_3$), 3.93 (1H, d, *J* 13.6, NC*H*$_2$Ph), 4.40–4.51 (3H, m, C*H*$_2$OPh, C*H*(OCH$_3$)$_2$), 5.21 (1H, d, *J* 17.2, CH=C*H*$_2$), 5.35 (1H, d, *J* 10.5, CH=C*H*$_2$), 5.53 (1H, apparent t, *J* 7.8, CR$_2$=C*H*), 5.80–5.94 (1H, m, C*H*=CH$_2$), 6.87–6.98 (3H, m, Ar-*H*), 7.23–7.40 (7H, m, Ar-*H*); δ_C (67.9 MHz, CDCl$_3$) 21.4 (CH$_3$), 47.7 (CH$_2$), 53.0 (CH$_3$), 54.6 (CH$_2$), 55.1 (CH$_3$), 62.9 (CH), 66.6 (CH$_2$), 105.7 (CH), 114.6 (CH), 119.7 (CH$_2$), 120.7 (CH), 126.7, 127.9, 128.1, 128.7, 129.4 (5 × CH), 132.2 (CH), 134.3 (C), 140.3 (C), 158.9 (C); *m*/*z* (CI) 382 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{24}H_{32}NO_3$ requires 382.2382. Found 382.2386 (0.9 ppm error).

(2*R*,3*S*,4*S*)-1-Benzyl-2-(dimethoxymethyl)-3-(iodomethyl)-4-isopropenylpyrrolidine 34

To diene **33** (166 mg, 0.436 mmol) in dry Et$_2$O (8 mL) at −50 °C

under N_2 was added Ti(O-*i*-Pr)$_4$ (162 μL, 0.545 mmol) then *i*-PrMgCl (2.0 M in Et_2O, 0.52 mL, 1.046 mmol) and the reaction was allowed to warm to rt. The reaction was stirred for 2 h then cooled to 0 °C and iodine [332 mg in Et_2O (4 mL), 1.307 mmol] was added. The reaction was stirred for 30 min then quenched with MeOH (2 mL) and stirred for 2 min followed by dilution with Et_2O (50 mL) and washing with sat. $NaHCO_3$ (20 mL) then 1 M NaOH (10 mL). The combined aqueous layers were re-extracted with Et_20 (30 mL). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:9) to afford the *title compound* **34** and starting diene **33** as an inseparable mixture (2:1) (148 mg, 56% **34**; 78% based on recovered starting diene); R_f 0.25 (EtOAc–light petroleum, 1:9); ν_{max} cm^{-1} 2930, 1598, 1495, 1112, 1073; δ_H (270 MHz, $CDCl_3$) 1.86 (3H, s, CH_3CR=CH_2), 2.45 (1H, apparent t, *J* 7.0, NCH_2CH), 2.69 (1H, apparent q, *J* 7.0, NCH$_2$C*H*), 2.84 (1H, apparent quintet, *J* 7.0, C*H*CH$_2$I), 3.03–3.13 (3H, m, CHCH_2I, NC*H*, NCH_2-CH), 3.20–3.40 (2H, m, CHCH_2I, NCH_2Ph), 3.45 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 4.37 (1H, d, *J* 13.8, NCH_2Ph), 4.53 (1H, d, *J* 6.8, C*H*(OCH$_3$)$_2$), 4.81 (1H, br s, CH$_3$CR=CH_2), 4.94 (1H, br s, CH$_3$CR=CH_2), 7.10–7.31 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$) 0.41 (CH_2), 23.4 (CH_3), 46.6, 46.9 (2 × CH), 53.6 (CH_3), 54.1 (CH_2), 54.7 (CH_3), 60.2 (CH_2), 68.3 (CH), 105.2 (CH), 113.0 (CH_2), 120.2 (CH), 127.7 (CH), 128.9 (CH), 139.8 (C), 142.2 (C); *m*/*z* (CI) 416 (MH$^+$, 20%); HRMS (CI) [MH$^+$] $C_{18}H_{27}NO_2I$ requires 416.1087. Found 416.1089 (0.6 ppm error).

Methyl [(2*R*,3*S*,4*S*)-2-(dimethoxymethyl)-4-isopropenyl-3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate 35

To alkyl iodide **34** (62.4 mg, 0.150 mmol) contaminated with diene **33** (28.6 mg, 0.075 mmol) in Et_2O (4.5 mL) at −80 °C was added *t*-BuLi (1.7 M in pentane, 0.195 mL, 0.331 mmol) and the reaction was stirred for 3 min under N_2. Methyl chloroformate (0.2 mL) was added and the reaction was warmed to rt and stirred for 48 h. The solvent was concentrated *in vacuo* and the residue was taken up in Et_2O (40 mL) and sat. $NaHCO_3$ (10 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:9) to afford the recovered diene **33** (28.6 mg, 0.075 mmol). Further elution with EtOAc–light petroleum (1:4→1:1) afforded the *title compound* along with the unreacted *N*-benzyl analogue. The crude mixture was then dissolved in 1,2-dichloroethane (2 mL) and methyl chloroformate (0.2 mL) was added and the reaction was heated at reflux for 2 h. The solvent was concentrated *in vacuo* and the residue was taken up in Et_2O (40 mL) and sat. $NaHCO_3$ (20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:2) to afford the *title compound* **35** (29 mg, 61%) as a colourless oil; R_f 0.10 (EtOAc–light petroleum, 1:4); $[\alpha]_D$ +34.5 (*c* 0.20, $CHCl_3$); ν_{max} cm^{-1} 2925, 1737, 1703, 1450, 1385; δ_H (270 MHz, $CDCl_3$) 1.73 (3H, s, CH_3CR=CH_2), 2.16 (1H, dd, *J* 17.2, 6.1, CH_2CO$_2$R), 2.60–2.70 (1H, m, C*H*CH$_2$CO$_2$R), 2.92 (1H, dd, *J* 17.2, 6.8, CH_2CO$_2$R), 3.17 (1H, apparent quintet, *J* 6.8, NCH$_2$C*H*), 3.32 (1H, apparent t, *J* 10.9, NCH_2), 3.41 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.63 (3H, s, CO$_2$CH_3), 3.66–3.79 (1H, m, NCH_2), 3.71 (3H, s, CO$_2$CH_3), 4.08 (1H, dd, *J* 7.0, 4.1, NC*H*), 4.68 (1H, br s, CH$_3$CR=CH_2), 4.91 (2H, br s, CH$_3$CR=CH_2, C*H*(OCH$_3$)$_2$); δ_C (67.9 MHz, $CDCl_3$) 23.2 (CH_3), 30.5 (CH_2), 37.7 (CH), 47.5 (CH), 48.8 (CH_2), 51.3 (CH_3), 52.4 (CH_3), 56.3 (CH_3), 58.0 (CH_3), 62.3 (CH), 105.6 (CH), 112.9 (CH_2), 142.0 (C), 155.9 (C), 173.9 (C); *m*/*z* (CI) 316 (MH$^+$, 10%); HRMS (CI) [MH$^+$] $C_{15}H_{26}NO_6$ requires 316.1760. Found 316.1761 (0.3 ppm error).

Dimethyl [(2*R*,3*S*,4*S*)-4-isopropenyl-3-(2-methoxy-2-oxoethyl)-pyrrolidine-1,2-dicarboxylate 36

To acetal **35** (24 mg, 0.076 mmol), in acetone (5 mL) at 0 °C was added Jones' reagent (0.8 mL) under N_2. The reaction was stirred at the same temperature for 2 h then quenched with propan-2-ol (2 mL). The reaction was diluted with Et_2O (25 mL) and water (5 mL). The aqueous layer was re-extracted with Et_2O (2 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude acid as a colourless oil. The crude product was taken up in MeOH (8 mL), cooled to 0 °C, excess ethereal diazomethane was added and the reaction stirred for 15 min. The excess diazomethane was blown off with N_2 and the solvent was concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:2) to afford the *title compound* **36** (14.8 mg, 65%) as a colourless oil; R_f 0.30 (EtOAc–light petroleum, 1:2); $[\alpha]_D$ +32.8 (*c* 0.60, $CHCl_3$); ν_{max} cm^{-1} 2954, 1754, 1707, 1450, 1386, 1203; δ_H (270 MHz, $CDCl_3$, mixture of rotamers) 1.74 (3H, s, CH_3CR=CH_2), 2.17–2.27 (1H, m, CH_2CO$_2$CH$_3$), 2.37–2.50 (1H, m, CH_2CO$_2$CH$_3$), 2.79–2.88 (1H, m, NCHC*H*), 3.18–3.25 (1H, m, NCH$_2$C*H*), 3.41–3.60 (1H, m, NCH_2), 3.64 (3H, s, CO$_2$CH_3), 3.66 (0.5 × 3H, s, CO$_2$CH_3), 3.68 (0.5 × 3H, s, CO$_2$CH_3), 3.70 (0.5 × 3H, s, CO$_2$CH_3), 3.72 (0.5 × 3H, s, CO$_2$CH_3), 3.70–3.79 (1H, m, NCH_2), 4.45 (1H, apparent t, *J* 6.3, NC*H*), 4.70 (0.5H, br s, CH$_3$CR=CH_2), 4.73 (0.5H, br s, CH$_3$CR=CH_2), 4.98 (1H, br s, CH$_3$CR=CH_2); δ_C (67.9 MHz, $CDCl_3$, mixture of rotamers) 22.7 (CH_3), 29.4, 29.6 (CH_2), 38.2, 39.4 (CH), 47.2, 47.3 (CH), 47.9, 48.0 (CH_2), 51.7 (CH_3), 52.0, 52.1 (CH_3), 52.7 (CH_3), 62.7, 62.9 (CH), 113.4, 113.7 (CH_2), 140.5, 140.6 (C), 155.2, 155.6 (C), 170.5, 170.8 (C), 172.6 (C); *m*/*z* (CI) 300 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{14}H_{22}NO_6$ requires 300.1447. Found 300.1447 (0.0 ppm error).

Dimethyl [(2*S*,3*S*,4*S*)-4-isopropenyl-3-(2-methoxy-2-oxoethyl)-pyrrolidine-1,2-dicarboxylate 37

To ester **36** (25 mg, 0.083 mmol) in THF (2 mL) at 0 °C was added LiHMDS (1.0 M in THF, 206 μL, 0.206 mmol) and the reaction was stirred for 1 h under N_2. MeOH (0.5 mL) was added and the reaction was diluted with Et_2O (15 mL) and $NaHCO_3$ (5 mL). The organic layer was separated, washed with 2 M HCl then dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a colourless oil which was purified by flash column chromatography eluting with EtOAc–light petroleum (1:2) to afford the *title compound* **37** (19.7 mg, 80%) as a colourless oil; R_f 0.31 (EtOAc–light petroleum, 1:2); $[\alpha]_D$ −24.4 (*c* 0.25, $CHCl_3$) {lit.[27] $[\alpha]_D$ −23.8 (*c* 1.07, $CHCl_3$)}; HRMS (CI) [MH$^+$] $C_{14}H_{22}NO_6$ requires 300.1447. Found 300.1447 (0.0 ppm error).

The spectroscopic data were fully consistent with those reported.[27]

(−)-α-Kainic acid 1

To ester **37** (30.0 mg, 0.100 mmol) in MeOH (1 mL) was added 40% NaOH (1 mL) and the solution was refluxed for 2 h. The mixture was cooled and diluted with CH_2Cl_2 (5 mL) and water (10 mL). The aqueous layer was filtered through 2 separate ion exchange columns [Amberlite IRA-45 (OH$^-$), H_2O then 1 M HCO_2H, and then Amberlite CG-120 (H$^+$), H_2O] to give a white solid which was recrystallised from H_2O to give **1** (21.0 mg, 70%) as white needles, mp 244–247 °C (decomp.) [lit.[23] mp 237–243 °C (decomp.)]; $[\alpha]_D$ −15.2 (*c* 0.95, H_2O) {lit.[23] $[\alpha]_D$ −15.0 (*c* 0.5, H_2O)}; HRMS (EI) [M$^+$] $C_{10}H_{15}NO_4$ requires 213.1000. Found 213.0994 (2.8 ppm error).

The spectroscopic data were fully consistent with those reported.[30]

cis-1-Benzyl-3-(cyclohex-1-en-1-yl)-4-methylpyrrolidine 39

Titanium procedure. Dienes **38** (50 mg, 0.144 mmol) were treated with Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl according to the general procedure outlined for the cyclisation of diene **9**. Purification by column chromatography eluting with MeOH–CH_2Cl_2 (1:9) afforded the *title compound* **39** (19 mg, 52%) as a colourless oil; R_f 0.20 (MeOH–CH_2Cl_2, 1:9); ν_{max} cm^{-1} 2922, 1494, 1453, 1373; δ_H (270 MHz, $CDCl_3$) 0.80 (3H, d, *J* 7.3, C*H*$_3$), 1.48–1.70 and 1.75–2.05 (8H, m, $CH_2CH_2CH_2CH_2$), 2.19 (1H, dd, *J* 9.7, 5.6, NC*H*$_2$CH), 2.43 (1H, m, CH_3CH), 2.62 (1H, apparent t, *J* 8.7, NC*H*), 2.77 (1H, apparent q, *J* 8.7, NCH_2CH), 2.92 (1H, dd, *J* 8.7, 6.5, NC*H*), 3.21 (1H, dd, *J* 9.7, 7.3, NC*H*), 3.74 (2H, br s, NC*H*$_2$Ph), 5.36 (1H, br s, CH_2CH=CR_2), 7.24–7.41 (5H, m, Ar-H); δ_C (67.9 MHz, $CDCl_3$) 15.7 (CH_3), 22.6, 22.6, 25.2, 29.4 (4 × CH_2), 34.0 (CH), 47.9 (CH), 55.2, 60.8, 61.9 (3 × CH_2), 122.2 (CH), 127.4, 128.4, 129.1, 129.3 (3 × CH + C), 135.5 (C); *m*/*z* (CI) 256 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{18}H_{26}N$ requires 256.2065. Found 256.2061 (1.6 ppm error).

cis-1-Benzyl-3-methyl-4-vinylpiperidine 43

Titanium procedure. Diene **42** (79 mg, 0.257 mmol) was treated with Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl according to the general procedure outlined for the cyclisation of diene **9**. Purification by column chromatography eluting with light petroleum–EtOAc (4:1→1:1) afforded the *title compound* **43** (32 mg, 58%) as a colourless oil; R_f 0.25 (light petroleum–EtOAc, 4:1); ν_{max} cm^{-1} 2933, 1638, 1453; δ_H (270 MHz, d_8-toluene, 80 °C) 0.92 (3H, d, *J* 7.0, C*H*$_3$), 1.45–1.55 and 1.57–1.70 and 1.71–1.82 (3H, m, $NCH_2CH_2CRHCR_2H$), 2.01–2.18 (3H, m, RC*H*$_2$N(Bn)-C*H*$_2$R), 2.36 (1H, ddd, *J* 11.2, 5.6, 1.2, NC*H*$_2$CH$_2$R), 2.57 (1H, apparent q, *J* 5.3, $NCH_2CH_2CR_2H$), 3.29 (1H, d, *J* 12.3, NC*H*$_2$Ph), 3.37 (1H, d, *J* 12.3, NC*H*$_2$Ph), 4.90–5.02 (2H, m, CRH=C*H*$_2$), 5.81 (1H, ddd, *J* 17.5, 10.4, 7.0, CR*H*=CH$_2$), 6.98–7.30 (5H, m, Ar-*H*); δ_C (67.9 MHz, $CDCl_3$, *cis*) 14.6 (CH_3), 27.9 (CH_2), 33.5 (CH), 42.6 (CH), 52.2 and 58.9 (2 × CH_2), 63.3 (CH_2), 114.2 (CH_2), 126.7 (CH), 128.1 (CH), 128.9 (CH), 138.9 (C), 140.4 (CH); *m*/*z* (CI) 216 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{15}H_{22}N$ requires 216.1752. Found 216.1751 (0.7 ppm error).

(3*S*,4*R*)-3-Methyl-1-[(1*R*)-1-phenylethyl]-4-vinylpiperidine and (3*R*,4*S*)-3-methyl-1-[(1*R*)-1-phenylethyl]-4-vinylpiperidine 46 and 47

Diene **45** (100 mg, 0.312 mmol) was treated with Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl according to the general procedure outlined for the cyclisation of diene **9**. Purification by column chromatography eluting with light petroleum–EtOAc (4:1) afforded the *title compounds* **46** and **47** as an inseparable pair of diastereomers (45 mg, 63%, 1:1) as a colourless oil; R_f 0.25 (light petroleum–EtOAc, 4:1); ν_{max} cm^{-1} 2973, 1639, 1452; δ_H (270 MHz, d_8-toluene, 80 °C) 1.16 (1.5H, d, *J* 6.8, NCH_2CRHCH_3), 1.18 (1.5H, d, *J* 7.0, NCH_2CRHCH_3), 1.48 (1.5H, d, *J* 6.8, $CHCH_3$), 1.49 (1.5H, d, *J* 6.8, $CHCH_3$), 1.61–2.08 (3H, m, $NCH_2CH_2CRHCR_2H$), 2.25–2.36 (3H, m, RC*H*$_2$N(CHR)-C*H*$_2$R), 2.59–2.72 (1H, m, NC*H*$_2$CR$_2$H), 2.81 (0.5H, m, C*H*CH=CH$_2$), 2.94 (0.5H, m, C*H*CH=CH$_2$), 3.50 (0.5H, q, *J* 6.8, NC*H*), 3.53 (0.5H, q, *J* 6.8, NC*H*), 5.13–5.24 (2H, m, CH=C*H*$_2$), 5.97–6.13 (1H, m, C*H*=CH$_2$), 7.23–7.55 (5H, m, Ar-*H*); δ_C (67.9 MHz, d_8-toluene, 80 °C) 15.1 and 15.4 (CH_3), 19.9 and 20.3 (CH_3), 29.3 and 29.4 (CH_2), 35.2 (CH), 44.5 (CH), 50.7 and 51.0 (CH_2), 57.2 and 58.1 (CH_2), 65.8 and 66.0 (CH), 114.9 (CH_2), 127.9, 128.9 and 129.5 (3 × CH), 142.3 and 142.4 (CH), 146.5 (C); *m*/*z* (CI) 230 (MH$^+$, 100%); HRMS (CI) [MH$^+$] $C_{16}H_{24}N$ requires 230.1909. Found 230.1903 (2.5 ppm error).

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