ARTICLE

OBC
www.rsc.org/obc

Intramolecular carbolithiation reactions for the preparation of 3-alkenylpyrrolidines

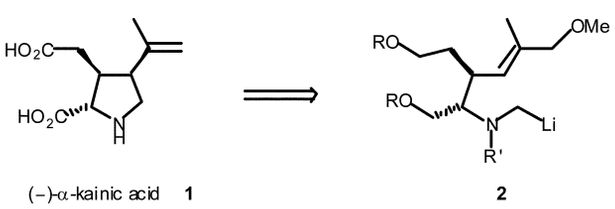
Iain Coldham,* Kathy N. Price and Richard E. Rathmell
School of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD.
E-mail: i.coldham@ex.ac.uk

Received 3rd April 2003, Accepted 1st May 2003
First published as an Advance Article on the web 14th May 2003

Tin–lithium exchange allows the formation of α-amino-organolithium species that undergo anionic cyclization onto allylic ethers to give 3-alkenylpyrrolidines. The methodology has been applied to the synthesis of an advanced intermediate related to the natural product (–)-α-kainic acid.

Introduction

It is well-known that organolithium species undergo ready cyclization onto suitably positioned terminal alkenes.[1] The chemistry provides a convenient and high-yielding synthesis of, in particular, substituted cyclopentanes, tetrahydrofurans and pyrrolidines.[1,2] The cyclization is thought to proceed by way of a chair-shaped transition state and is highly stereoselective. Our work has centred on the use of α-amino-organolithium species, generated by tin–lithium exchange, and results in the formation of cyclic amine products.[3] Cyclization of organolithium species onto an alkene bearing an electron-withdrawing substituent (such as Ph, SPh or $SiMe_3$) is also known.[4] We were attracted to reports that cyclization onto allylic ethers is possible.[5] In this chemistry, displacement of an alkoxide (S_N' addition) takes place to provide a cyclic product with a new alkene group. Such alkenes could be manipulated further or could be present in the desired final product. For example, the natural product (–)-α-kainic acid **1**[6] contains an alkenyl substituent that might be able to be accessed using such anionic cyclization chemistry, for example, from a suitably protected substrate **2** (Scheme 1). This paper outlines in full our work on the simple model system,[7] and our studies on the application of this methodology to a more advanced intermediate, suitable for the preparation of the kainoids and related compounds.



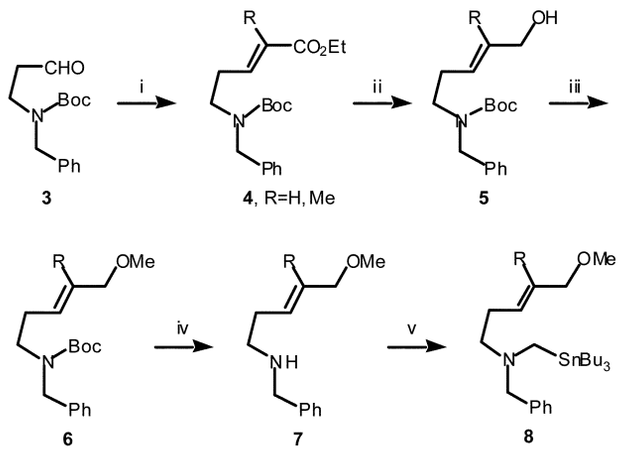
(–)-α-kainic acid **1** **2**

Scheme 1 Retrosynthesis of α-kainic acid.

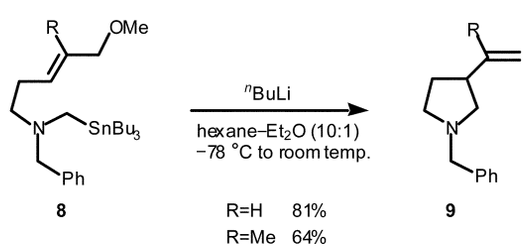
Results and discussion

The simplest substrates to test the methodology are the organolithium species derived from tin–lithium exchange of the stannanes **8** (R = H or Me, Scheme 2). These were prepared from the known aldehyde **3**,[8] using Wittig olefination to give the esters **4** (R = H or Me), reduction with DIBAL-H to give the allylic alcohols **5** and *O*-methylation to the allylic ethers **6**, followed by *N*-Boc deprotection to the secondary amines **7** and *N*-alkylation with *O*-methanesulfonyltributylstannylmethanol.[9]

Treatment of the stannanes **8**, R = H or Me, with *n*-BuLi in hexane–Et_2O (10 : 1) at −78 °C, followed by warming to room temperature gave the pyrrolidine products **9**, R = H or Me (Scheme 3).



Scheme 2 *Reagents and conditions:* i, $Ph_3{=}CHCO_2Et$ or $Ph_3P{=}C(Me)CO_2Et$, THF, 40 °C, R = H 68% or R = Me 72%; ii, DIBAL-H, PhMe, −78 °C, R = H 67%, R = Me 41%; iii, NaH, THF then MeI, R = H 96%, R = Me 71%; iv, TFA, CH_2Cl_2, R = H 96%, R = Me 98%; v, $MsOCH_2SnBu_3$, MeCN, K_2CO_3, R = H 70%, R = Me 50%.

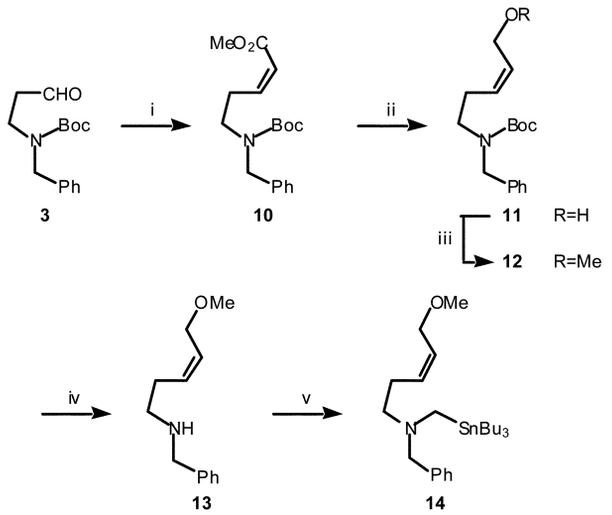


Scheme 3 Cyclization onto an *E*-allylic ether.

Alternatively, the products **9** could be obtained using THF as the solvent, although yields were better in the non-polar solvent system. The successful cyclization to give the product **9**, R = Me, paves the way for this methodology to be applied to the kainoid alkaloids. Prior to extending this study to more substituted systems, we investigated the possibility of cyclization onto the *Z*-allylic ether **14** (Scheme 4).

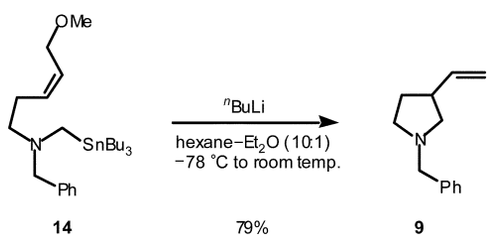
The corresponding *Z*-isomeric series was accessed from the same aldehyde **3** using the Still modification of the Horner–Wadsworth–Emmons reaction with the anion of bis(2,2,2-trifluoroethyl) (ethoxycarbonylmethyl)phosphonate (Scheme 4).[10] This reaction gave a low yield (unoptimized) of the product **10**, but as essentially a single *Z*-stereoisomer (ratio *Z* : *E* 20 : 1, separable by chromatography). Analogous transformations to those described in Scheme 2 above provided the *Z*-allylic ether **14**.

DOI: 10.1039/b303670g



Scheme 4 *Reagents and conditions:* i, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, THF, 18-crown-6, 22%; ii, DIBAL-H, PhMe, −78 °C, 70%; iii, NaH, THF then MeI, 85%; iv, TFA, CH_2Cl_2, 98%; v, $MsOCH_2SnBu_3$, MeCN, K_2CO_3, 70%.

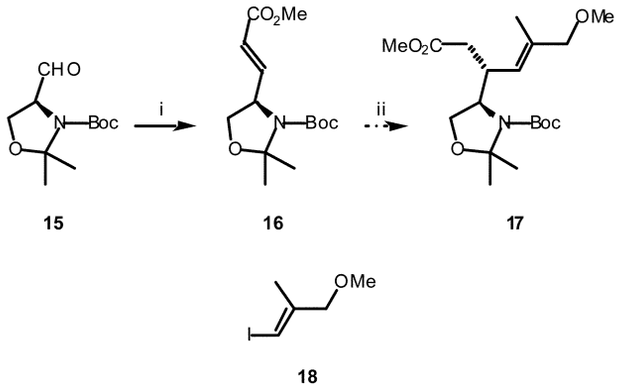
Treatment of the *Z*-allylic ether **14** with *n*-BuLi in hexane–Et_2O (10 : 1) at −78 °C, followed by warming to room temperature gave the pyrrolidine product **9** (R = H) (Scheme 5). The yield was essentially identical to that from the *E*-isomer **8**, R = H, indicating that the geometry of the alkene does not influence the extent of cyclization.



Scheme 5 Cyclization onto a *Z*-allylic ether.

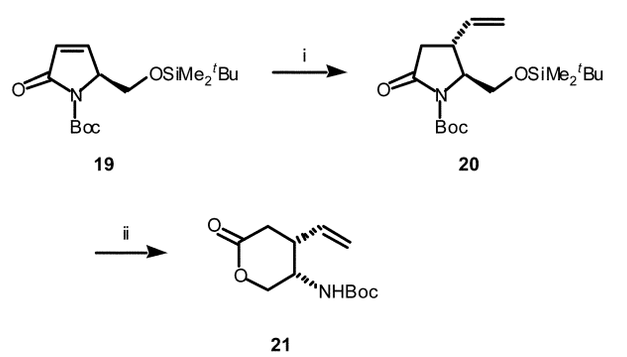
For a route to the kainoid alkaloids, we required a substituted allylic ether such as compound **2** (Scheme 1). On cyclization, a new chiral centre is generated and the stereochemistry is dependent upon the existing chiral centres in the substrate.[1] Based on literature precedent, it is likely that compound **2** would cyclize to give the incorrect stereoisomer (corresponding to allokainic acid), although the presence of heteroatom groups in the substituents, the choice of solvent or the use of a cyclic substrate which is later cleaved could invert this preference.[11] We were therefore interested in determining the stereoselectivity on cyclization of a substituted allylic ether substrate.

The first route to the kainoid ring system that we studied commenced with the Garner aldehyde **15** (Scheme 6).[12] Wittig olefination gave the unsaturated ester **16** in high yield. There is some precedent for conjugate addition in the presence of Me_3SiCl of organocuprates generated from Grignard reagents or organolithium species to unsaturated esters such as **16**.[13] For the preparation of the desired allylic ether **17**, we required the conjugate addition of a vinylmetal species to unsaturated ester **16**. The vinyliodide **18** was prepared from the known corresponding alcohol,[14] by *O*-methylation (NaH, THF, MeI, 81%). We were unable to prepare the Grignard reagent from this iodide using conventional procedures with activated magnesium, however, iodine–lithium exchange with *tert*-butyllithium occurred smoothly. Subsequent formation of a variety of different higher order organocuprates was investigated, but the resulting organometallic species failed to undergo conjugate addition to the unsaturated ester **16** under a variety of conditions (different additives and temperatures).



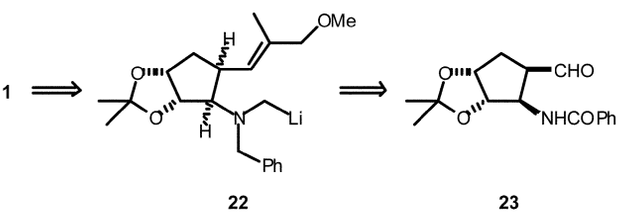
Scheme 6 *Reagents and conditions:* i, $Ph_3P{=}CHCO_2Me$, THF, 40 °C, 72%; ii, $MeOCH_2C(Me){=}CHCu(R)CNLi_2$ (R = Me, hexyl or 2-thienyl), TMSCl or $BF_3{\cdot}OEt_2$ or HMPA, various temperatures, 0%.

An alternative approach was investigated using the unsaturated lactam **19**, prepared from γ-methyl glutamic acid according to a reported procedure.[15] Formation of different organocuprate species from the iodide **18** was performed but these failed to add to the unsaturated lactam **19**. A small amount (22% yield) of the conjugate addition product was obtained when the *N*-protecting group was *N*-COPh rather than *N*-Boc (using 10 equivalents of the vinyllithium derived from **18** and 5 equivalents of CuI in Et_2O and TMSCl). More success was obtained using vinylmagnesium bromide and $CuBr_2{\cdot}SMe_2$ to give the conjugate addition product **20** (Scheme 7).[16] Treatment of the product **20** with fluoride ion resulted in ring-opening of the lactam and formation of the lactone **21**. Unfortunately, all attempts to protect the lactone or to functionalise or deprotect the *N*-Boc group failed to give identifiable products or resulted in recovered lactone **21**.



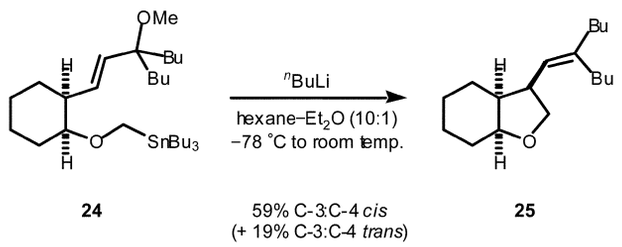
Scheme 7 *Reagents and conditions:* i, $CH_2{=}CHMgBr$, $CuBr{\cdot}SMe_2$, THF, −40 °C, 72%; ii, TBAF, THF, 100%.

With the failure to provide a suitable substrate starting from the unsaturated carbonyl compounds **16** and **19**, a different approach was needed. We had shown in our model studies (Schemes 2,3) that the required allylic ether group could be introduced by Wittig olefination and reduction. We therefore required a substituted β-aminoaldehyde such as **23** which would be converted to the allylic ether **22** (Scheme 8). The choice of a cyclopentane ring to tether the latent carboxylic acid groups (which should be accessible by diol cleavage) was made on the



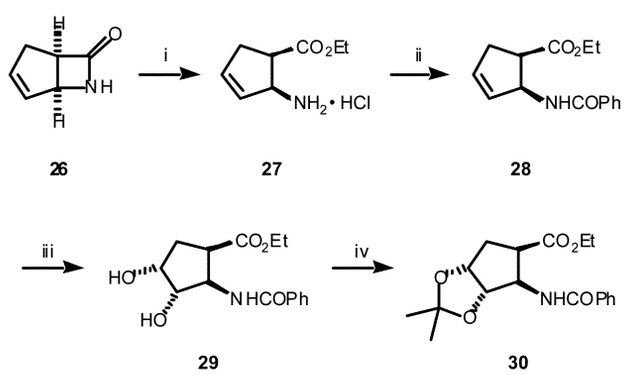
Scheme 8 Alternative retrosynthesis of α-kainic acid.

basis of the expected stereochemical outcome in the anionic cyclization reaction. Broka and co-workers have shown that treatment of the stannane **24** with *n*-butyllithium gave predominantly the product **25**, with a *cis*-arrangement of the substituents at C-3 and C-4 of the tetrahydrofuran ring (Scheme 9).[5a] We therefore anticipated that the substrate **22** would cyclize to give the desired relative stereochemistry at C-3 and C-4, although a direct comparison is not completely appropriate as **22** is a cyclopentane whereas **24** is a cyclohexane. If successful, the product would later require epimerisation at C-2 (a known process).[17]



Scheme 9 Cyclization to an oxabicyclo[4.3.0]nonane ring system.

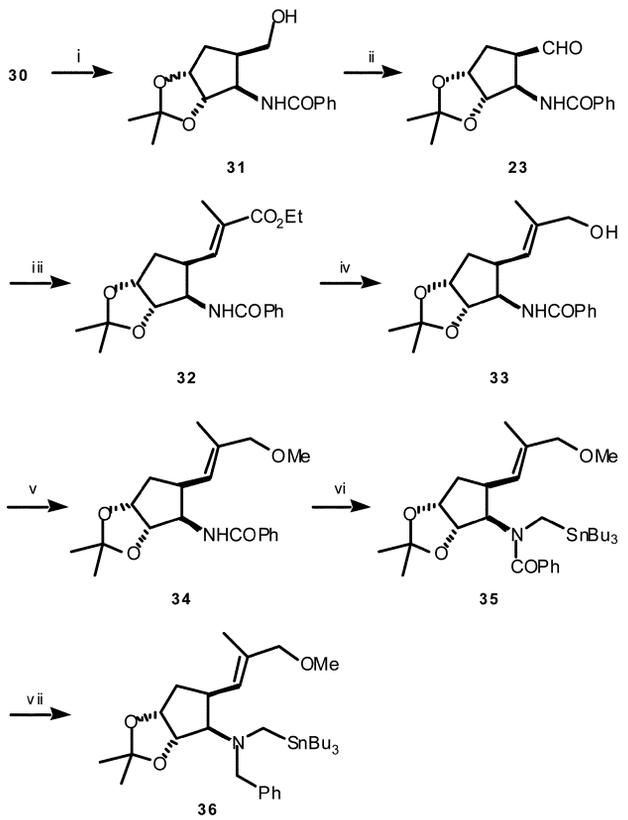
The β-lactam **26** (Scheme 10) was prepared according to the modified procedure reported by Evans and Biller, using cyclopentadiene and chlorosulfonyl isocyanate in Et_2O at −20 °C.[18] Ring-opening of the β-lactam with ethanol–HCl gave the amine·hydrochloride salt **27**, which was protected as the *N*-benzoyl derivative **28**. Dihydroxylation using catalytic osmium tetroxide and *N*-methyl morpholine *N*-oxide (NMO) gave a single diol product **29**, which was protected as its acetonide **30** using dimethoxypropane in acetone. The relative stereochemistry of the acetonide was confirmed by NOESY studies.



Scheme 10 *Reagents and conditions:* i, EtOH, HCl, 96%; ii, PhCOCl, Et_3N, Et_2O, 0 °C, 85%; iii, 1 mol% OsO_4, NMO, H_2O, acetone, ^{t}BuOH, room temp., 85%; iv, $Me_2C(OMe)_2$, acetone, CSA, 87%.

Reduction of the ester **30** with DIBAL-H (1.1 equiv., PhMe, −78 °C) gave a mixture of the aldehyde and alcohol products (and recovered ester **30**), so the ester **30** was reduced with $LiAlH_4$ to give the alcohol **31** and oxidised to the aldehyde **23** with iodoxybenzoic acid (IBX) in DMSO (Scheme 11). Use of the Swern oxidising system was also successful but gave variable amounts of the epimeric aldehyde, presumably formed by enolisation and re-protonation under the mildly basic (Et_3N) conditions.

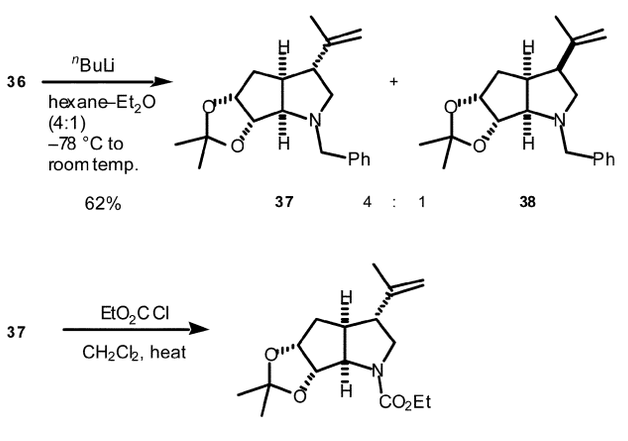
Wittig olefination of the aldehyde **23** with carboethoxyethylidene triphenylphosphorane gave the unsaturated ester **32**, which was reduced to the allylic alcohol **33** with calcium borohydride. Attempts to use DIBAL-H or $LiAlH_4$ to effect this transformation gave only low yields of the desired alcohol **33**. Treatment of the alcohol **33** with sodium hydride and iodomethane (DMF, 0 °C) resulted in the formation of a mixture of products, so the *O*-methylation to give the desired allylic ether



Scheme 11 *Reagents and conditions:* i, $LiAlH_4$, THF, 0 °C, 95%; ii, IBX, DMSO, room temp., 86%; iii, $Ph_3P{=}C(Me)CO_2Et$, THF, 40 °C, 89%; iv, $NaBH_4$, $CaCl_2$, EtOH, room temp., 92%; v, $NaOH_{(aq)}$, Bu_4NI, CH_2Cl_2, Me_2SO_4, room temp., 93%; vi, NaH, THF, ICH_2SnBu_3, room temp., 46%; vii, $LiAlH_4$, $AlCl_3$, Et_2O, 0 °C, 98%.

34 was carried out under phase-transfer conditions with dimethylsulfate and tetrabutylammonium iodide in a mixture of CH_2Cl_2 and 50% NaOH.[19] Finally, *N*-alkylation with sodium hydride and iodomethyl tributylstannane in THF gave the amide **35**, which was reduced to the amino-stannane **36** with alane.

The crucial tin–lithium exchange and cyclization was carried out with *n*-butyllithium in hexane–Et_2O (4 : 1) at −78 °C, followed by warming to room temperature. We were pleased to find that the desired pyrrolidine products **37** and **38** were formed in reasonable yield (Scheme 12). To our surprise, NOESY experiments indicated that the major product was in fact the stereoisomer **37**, contrary to expectations (based on the formation of the tetrahydrofuran **25**, Scheme 9). For example, irradiation of the signal corresponding to the methyl group of the 6-isopropenyl group caused an enhancement (3.0%) of the



Scheme 12 Cyclization to the azabicyclo[3.3.0]octane ring system.

signal for the ring junction proton (at C-6a); other enhancements supported this assignment (irradiation of the vinylic protons enhanced the signal for the proton at C-6a and for one of the protons on the NCH_2 group; irradiation of the NCH ring junction proton at C-4a enhanced the same proton on the NCH_2 group and enhanced the proton at C-6a, indicating that all these protons are on the same face of the molecule). The major product from this cyclization reaction has *trans*-stereochemistry across C-3 and C-4, corresponding to allokainic acid, rather than kainic acid. Attempts to alter the stereoselectivity, for example by changing the solvent were unsuccessful (addition of THF or TMEDA gave no isolated products). If the intramolecular carbolithiation reaction takes place through a six-membered chair-shaped transition state,[1] then different conformations must be preferred for the two different cyclizations leading to products **37** and **25**. We conclude that this substrate does not lead to the expected stereoisomer and we therefore did not take this chemistry further, other than to show that the *N*-benzyl group could be cleaved with ethyl chloroformate, to give the product **39**. The chemistry therefore allows access to the bicyclic amine **39**, related to the kainoid alkaloids, and this methodology could find application for the stereoselective synthesis of a variety of substituted 3-alkenylpyrrolidines.

Conclusions

Organolithium species α- to an amino substituent can be generated by tin–lithium exchange and cyclize onto allylic ethers to give 3-alkenylpyrrolidine products. The methodology can be used for the stereoselective synthesis of complex cyclic amines, including those related to the kainoid natural products.

Experimental

IR spectra were recorded as liquid films on NaCl plates unless otherwise stated, using a Nicolet FT-IR Magna 550 or a Perkin–Elmer 881 spectrometer. Optical rotations were recorded on an AA-1000 polarimeter using a cell of either 0.5 or 0.1 dm path length and are recorded in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were recorded on a Carlo Erba EA1110 elemental analyser. ^{1}H NMR spectra were recorded on a Bruker AM 300 MHz or a Bruker DRX 400 MHz spectrometer using the residual solvent peak as an internal reference. Chemical shifts are given in parts per million. Coupling constants, *J*, are given in Hz. ^{13}C NMR spectra are recorded on the above spectrometers operating at 75 or 100 MHz respectively and are proton decoupled. Additional analysis by DEPT, COSY, NOESY or HMQC experiments were performed where necessary. Mass spectra were recorded on a Kratos Profile HV3 or a Micromass Quattro II spectrometer or a ThermoQuest AS2000 GCMS machine, using electron impact, chemical ionisation or electrospray techniques. Accurate mass measurements were performed on the Kratos Profile spectrometer, a Finnigan MAT 900 XLT spectrometer or a Micromass Autospec spectrometer.

Petrol refers to light petroleum (bp 40–60 °C). Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium–benzophenone. Flash column chromatography was performed on silica gel (Merck 60H, 230–400 mesh) or basic aluminium oxide (Sigma type WB-2, activity grade 1). Thin layer chromatography was performed on Kieselgel 60F_{254} 0.25 mm plates, and visualised by UV irradiation at 254 nm or alkaline potassium permanganate.

E-Ethyl *N*-benzyl-*N*-*tert*-butoxycarbonyl-5-amino-2-pentenoate 4, R = H

To the freshly prepared crude aldehyde **3**[8] (722 mg, 2.7 mmol) in dry THF (7 mL) under nitrogen at room temperature was added carbethoxymethylene triphenylphosphorane (1.05 g, 3.0 mmol). After stirring for 48 h, MeOH (2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–Et_2O (2 : 1), to give the ester **4**, R = H (616 mg, 68%) as an oil; R_f 0.34 [petrol–Et_2O (2 : 1)]; ν_{max}(film)/cm^{-1} 1715 (C=O), 1690 (C=O), 1660 (C=C); δ_H(400 MHz, $CDCl_3$) 7.35–7.15 (5H, m, Ph), 6.85 (1H, dt, *J* 16 and 7, C*H*=CHCO$_2$Et), 5.75 (1H, br d, *J* 16, CH=C*H*CO$_2$Et), 4.44 (2H, br s, CH_2Ph), 4.15 (2H, q, *J* 7, OCH$_2$), 3.30 (2H, br s, NCH$_2$CH_2), 2.35 (2H, br s, NCH_2CH$_2$), 1.45 [9H, br s, C(CH$_3$)$_3$], 1.25 (3H, t, *J* 7, OCH$_2$CH_3); δ_C(100 MHz, $CDCl_3$) 167.2, 158.8, 145.4, 138.5, 128.4, 127.6, 127.1, 122.8, 79.8, 60.3, 50.8, 49.9, 31.2, 28.2, 14.1; Found: M$^+$, 333.1940. $C_{19}H_{27}NO_4$ requires *M*, 333.1946; *m*/*z* 333 (8%, M$^+$), 276 [100, M − C(CH$_3$)$_3$].

E-Ethyl *N*-benzyl-*N*-*tert*-butoxycarbonyl-5-amino-2-methyl-2-pentenoate 4, R = Me

In the same way as the ester **4**, R = H, the (crude) aldehyde **3** (2.74 g, 10.0 mmol) and carbethoxyethylidene triphenylphosphorane (4.00 g, 11.0 mmol) gave, after 24 h at 40 °C, the ester **4**, R = Me (4.04 g, 72%) as an oil; R_f 0.34 [petrol–Et_2O (2 : 1)]; ν_{max}(film)/cm^{-1} 1715 (C=O), 1690 (C=O), 1670 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.35–7.20 (5H, m, Ph), 6.67 (1H, t, *J* 7, C*H*=C), 4.44 (2H, br s, NCH_2Ph), 4.15 (2H, q, *J* 7, OCH$_2$), 3.25 (2H, br s, NCH$_2$CH_2), 2.35 (2H, br s, NCH_2CH$_2$), 1.92 (3H, s, C=CCH$_3$), 1.47 [9H, br s, C(CH$_3$)$_3$], 1.25 (3H, t, *J* 7, OCH$_2$CH_3); δ_C(75 MHz, $CDCl_3$) 167.8, 155.4, 138.1, 129.6, 128.5, 127.7, 127.2, 127.2, 76.8, 60.4, 54.7, 43.4, 28.4, 14.2, 14.1, 12.3; Found: M$^+$, 347.2096. $C_{20}H_{29}NO_4$ requires *M*, 347.2086; *m*/*z* 347 (0.5%, M$^+$), 57 [100, C(CH$_3$)$_3$].

E-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-aminopent-2-en-1-ol 5, R = H

Diisobutylaluminium hydride (12 mL, 1 M in toluene, 12.0 mmol) was added dropwise to the ester **4**, R = H (1.0 g, 3.0 mmol) in dry toluene (10 mL) at −78 °C under nitrogen. After 2.5 h MeOH (4 mL) was added and the mixture was allowed to warm to room temperature. The mixture was filtered over Celite and washed with EtOAc (100 mL). The filtrate was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1 : 1), to give the alcohol **5**, R = H (550 mg, 63%) as an oil; R_f 0.44 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3610 (OH), 1690 (C=O), 1660 (C=C), 1600 (Ph); δ_H(400 MHz, $CDCl_3$) 7.33–7.21 (5H, m, Ph), 5.60 (2H, br s, CH=CH), 4.42 (2H, br s, NCH_2Ph), 4.05 (2H, br s, CH$_2$O), 3.20 (2H, br s, NCH$_2$CH_2), 2.24 (2H, br s, NCH_2CH$_2$), 1.47 [9H, br s, C(CH$_3$)$_3$]; δ_C(100 MHz, $CDCl_3$) 155.8, 138.5, 131.1, 129.1, 128.6, 128.0, 127.1, 79.7, 63.5, 50.7, 50.2, 31.4, 28.4; Found: M$^+$, 291.1834. $C_{17}H_{25}NO_3$ requires *M*, 291.1828; *m*/*z* 291 (1%, M$^+$), 57 [100, C(CH$_3$)$_3$].

E-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-amino-2-methylpent-2-en-1-ol 5, R = Me

In the same way as the alcohol **5**, R = H, diisobutylaluminium hydride (23.5 mL, 1 M in toluene, 23.5 mmol) and the ester 4, R = Me (2.0 g, 5.76 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (1 : 1), the alcohol **5**, R = Me (1.49 g, 85%) as an oil; R_f 0.44 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3610 (OH), 1690 (C=O), 1670 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.35–7.15 (5H, m, Ph), 5.32 (1H, br s, CH=C), 4.45 (2H, br s, NCH_2Ph), 3.55 (2H, br s, CH$_2$O), 3.25 (2H, br d, *J* 7, NCH$_2$CH_2), 2.25 (2H, br s, NCH_2CH$_2$), 1.65 (3H, s, C=CCH$_3$), 1.45 [9H, br s, C(CH$_3$)$_3$]; δ_C(75 MHz, $CDCl_3$) 155.8, 138.5, 131.1, 129.6, 129.1, 128.9, 121.9, 79.7, 68.5, 58.4, 53.5, 30.2, 28.4, 14.2; Found: M$^+$, 305.1990. $C_{18}H_{27}NO_3$ requires *M*, 305.2001; *m*/*z* 305 (1%, M$^+$), 304 (28, M − CO$_2$^{t}Bu), 57 [100, C(CH$_3$)$_3$].

E-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-amino-1-methoxypent-2-ene 6, R = H

Sodium hydride (83 mg, 2.1 mmol, 60% dispersion in mineral oil) was added to the alcohol **5**, R = H (530 mg, 1.8 mmol) in dry THF (5 mL) under nitrogen. After 1.5 h, iodomethane (0.19 mL, 3.04 mmol) was added and after a further 30 min, water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), to give the ether **6**, R = H (556 mg, 96%) as an oil; R_f 0.21 [petrol–EtOAc (10 : 1)]; ν_{max}(film)/cm^{-1} 1690 (C=O), 1660 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.35–7.15 (5H, m, Ph), 5.60–5.52 (2H, m, CH=CH), 4.43 (2H, br s, NCH_2Ph), 3.85 (2H, br s, CH_2O), 3.28–3.21 (5H, m, NCH_2CH_2 and OCH_3), 2.25 (2H, br s, NCH_2CH_2), 1.48 [9H, br s, $C(CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 155.7, 138.5, 130.8, 129.3, 128.3, 127.7, 127.5, 79.7, 73.0, 70.2, 58.5, 50.1, 46.3, 28.4; Found: M$^+$ 305.1990. $C_{18}H_{27}NO_3$ requires *M*, 305.2001; *m*/*z* 305 (1%, M$^+$), 205 (32, M − $CO_2{}^tBu$), 57 [100, $C(CH_3)_3$].

E-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-amino-2-methyl-1-methoxypent-2-ene 6, R = Me

In the same way as the ether **6**, R = H, sodium hydride (354 mg, 8.85 mmol), the alcohol **5**, R = Me (1.79 g, 5.9 mmol) and iodomethane (0.72 mL, 12.0 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), the ether **6**, R = Me (1.33 g, 71%) as an oil; R_f 0.25 [petrol–EtOAc (10 : 1)]; ν_{max}(film)/cm^{-1} 1690 (C=O), 1660 (C=C), 1605 (C=C); δ_H(300 MHz, $CDCl_3$) 7.35–7.15 (5H, m, Ph), 5.32 (1H, br s, CH=C), 4.45 (2H, br s, NCH_2Ph), 3.55 (2H, br s, CH_2O), 3.25–3.19 (5H, m, NCH_2CH_2 and OCH_3), 2.25 (2H, br s, NCH_2CH_2), 1.63 (3H, s, $C=CCH_3$), 1.49 [9H, br s, $C(CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 155.8, 138.5, 131.1, 129.7, 128.6, 127.1, 121.3, 79.7, 68.5, 58.4, 53.5, 50.5, 30.2, 28.4, 14.2; Found: M$^+$, 319.2105. $C_{19}H_{29}NO_3$ requires *M*, 319.2114; *m*/*z* 319 (1%, M$^+$), 318 (46, M − $CO_2{}^tBu$), 57 [100, $C(CH_3)_3$].

E-*N*-Benzyl-5-amino-1-methoxypent-2-ene 7, R = H

Trifluoroacetic acid (0.25 mL, 3.6 mmol) was added to the ether **6**, R = H (358 mg, 1.2 mmol) in dry CH_2Cl_2 (4 mL) under nitrogen at 0 °C and the mixture was allowed to warm to room temperature. After 16 h $NaHCO_3$ (10 mL) was added, the organic phase was dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with CH_2Cl_2–EtOH (15 : 1), to give the amine **7**, R = H (236 mg, 95%) as needles after recrystallisation from Et_2O; mp 145–146 °C; R_f 0.24 [CH_2Cl_2–EtOH (15 : 1)]; ν_{max}(film)/cm^{-1} 3490 (NH), 1660 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.39–7.30 (5H, m, Ph), 5.61–5.53 (2H, m, CH=CH), 3.98 (2H, d, *J* 6, CH_2O), 3.63 (2H, br s, NCH_2Ph), 3.28 (3H, s, OCH_3), 2.86 (2H, br s, NCH_2CH_2), 2.32–2.27 (2H, m, $CH_2CH_2C=C$); δ_C(75 MHz, $CDCl_3$) 140.4, 131.9, 129.3, 128.1, 127.6, 126.9, 73.0, 57.7, 53.9, 48.5, 32.8; Found: M$^+$ 205.1467. $C_{13}H_{19}NO$ requires *M*, 205.1466; *m*/*z* 205 (1%, M$^+$), 91 (100, M − CH_2Ph); Found: C, 75.8; H, 9.2; N, 6.8. $C_{13}H_{19}NO$ requires C, 76.0; H, 9.3; N, 6.8%.

E-*N*-Benzyl-5-amino-2-methyl-1-methoxypent-2-ene 7, R = Me

In the same way as the amine **7**, R = H, trifluoroacetic acid (0.96 mL, 12.5 mmol) and the ether **6**, R = Me (1.0 g, 3.13 mmol) gave, after purification by column chromatography on silica gel, eluting with CH_2Cl_2–EtOH (15 : 1), the amine **7**, R = Me (652 mg, 95%) as needles; mp 130–131 °C; R_f 0.31 [CH_2Cl_2–EtOH (15 : 1)]; ν_{max}(KBr)/cm^{-1} 3540 (NH), 1670 (C=C), 1605 (Ph); δ_H(300 MHz, $CDCl_3$) 7.35–7.15 (6H, m, Ph and NH), 5.32 (1H, br s, CH=C), 4.45 (2H, br s, NCH_2Ph), 3.55 (2H, br s, CH_2O), 3.24 (3H, s, OCH_3), 2.76 (2H, br s, NCH_2CH_2), 2.59–2.53 (2H, m, NCH_2CH_2), 1.63 (3H, s, $C=CCH_3$); δ_C(75 MHz, $CDCl_3$) 138.5, 131.1, 128.6, 127.1, 126.8, 121.9, 79.7, 68.5, 58.4, 50.5, 30.2, 14.2; Found: M$^+$, 219.1615. $C_{14}H_{21}NO$ requires *M*, 219.1623; *m*/*z* 219 (12%, M$^+$), 91 (100, $PhCH_2$); Found: C, 76.9; H, 9.65; N, 6.4. $C_{14}H_{21}NO$ requires C, 76.7; H, 9.55; N, 6.4%.

E-*N*-Benzyl-*N*-tributylstannylmethyl-5-amino-1-methoxypent-2-ene 8, R = H

Potassium carbonate (315 mg, 2.28 mmol) was added to the amine **7**, R = H (236 mg, 1.14 mmol) in dry acetonitrile (5 mL) under nitrogen at room temperature. After 5 min, tributylstannylmethyl methanesulfonate[9] (545 mg, 1.40 mmol) was added. After 24 h water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (10 : 1), to give the stannane **8**, R = H (403 mg, 70%) as an oil; R_f 0.24 [petrol–EtOAc (10 : 1)]; ν_{max}(film)/cm^{-1} 1675 (C=C), 1605 (Ph); δ_H(300 MHz, $CDCl_3$) 7.36–7.21 (5H, m, Ph), 5.72–5.50 (2H, m, CH=CH), 3.88 (2H, d, *J* 8, NCH_2Ph), 3.51 (2H, s, CH_2O), 3.33 (3H, s, OCH_3), 2.64 (2H, s, NCH_2-Sn), 2.46–2.19 (4H, m, NCH_2CH_2), 1.68–0.80 {27H, m, Sn[$(CH_2)_3CH_3]_3$}; δ_C(75 MHz, $CDCl_3$) 139.9, 132.5, 128.7, 128.1, 127.2, 126.7, 73.2, 62.8, 57.6, 54.8, 42.9, 32.2, 29.2, 27.8, 13.6, 10.2; Found: M$^+$ 509.2669. $C_{26}H_{47}NO^{120}Sn$ requires *M*, 509.2679; *m*/*z* 509 (0.5%, M$^+$), 218 [24, M − $Sn(C_4H_9)_3$], 31 (100, OCH_3).

E-*N*-Benzyl-*N*-tributylstannylmethyl-5-amino-2-methyl-1-methoxypent-2-ene 8, R = Me

In the same way as the stannane **8**, R = H, potassium carbonate (126 mg, 2.28 mmol), the amine **7**, R = Me (250 mg, 1.14 mmol) and tributylstannylmethyl methanesulfonate (470 mg, 1.21 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (10 : 1), the stannane **8**, R = Me (298 mg, 50%) as an oil; R_f 0.23 [petrol–EtOAc (10 : 1)]; ν_{max}(film)/cm^{-1} 1675 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.42–7.20 (5H, m, Ph), 5.46 (1H, t, *J* 7, CH=C), 3.79 (2H, s, NCH_2Ph), 3.47 (2H, s, CH_2O), 3.35 (3H, s, OCH_3), 2.61 (2H, s, NCH_2Sn), 2.42–2.31 (2H, m, NCH_2CH_2), 2.28–2.20 (2H, m, NCH_2CH_2), 1.62 (3H, s, $C=CCH_3$), 1.50–0.80 {27H, m, Sn[$(CH_2)_3CH_3]_3$}; δ_C(75 MHz, $CDCl_3$) 139.1, 132.8, 128.7, 128.1, 126.1, 121.9, 78.6, 62.6, 57.5, 54.2, 42.8, 29.3, 27.5, 26.0, 13.8, 10.2, 8.5; Found: M$^+$, 523.2841. $C_{27}H_{49}NO^{120}Sn$ requires *M*, 523.2836; *m*/*z* 523 (1%, M$^+$), 291 [42, $Sn(C_4H_9)_3$], 31 (100, OCH_3).

N-Benzyl-3-vinylpyrrolidine 9, R = H

n-Butyllithium (0.59 mL, 1.47 mmol, 2.5 M in hexanes) was added to the stannane **8**, R = H (375 mg, 0.74 mmol) in hexane–Et_2O (7.5 mL, 10 : 1) at −78 °C. The mixture was warmed slowly to room temperature and then was cooled to −78 °C and MeOH (0.2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), to give the pyrrolidine **9**, R = H (112 mg, 81%) as an oil; R_f 0.13 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1660 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.33–7.21 (5H, m, Ph), 5.85–5.78 (1H, ddd, *J* 17, 10 and 7.5, CH=CH_2), 4.98 (1H, dd, *J* 17 and 1.5, CH=CH^AH^B), 4.91 (1H, dd, *J* 10 and 1.5, CH=CH^AH^B), 3.63 (2H, ABq, *J* 16, NCH_2Ph), 2.89–2.69 (3H, m, CH_2NCH), 2.56–2.46 (1H, m, CH), 2.29–2.18 (1H, m, CH), 2.14–2.00 (1H, m, CH), 1.65–1.56 (1H, m, CH); δ_C(75 MHz, $CDCl_3$) 155.7, 141.7, 128.9, 128.7, 127.0, 113.5, 60.5, 59.9, 53.9, 41.8, 28.4; Found: M$^+$ 187.1362. $C_{13}H_{17}N$ requires *M*, 187.1361); *m*/*z* 187 (4%, M$^+$), 77 (100, Ph).

N-Benzyl-3-isopropenylpyrrolidine 9, R = Me

In the same way as the pyrrolidine **9**, R = H, *n*-butyllithium (0.3 mL, 0.76 mmol) and the stannane **8**, R = Me (200 mg, 0.38

mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), the pyrrolidine **9**, R = Me (49 mg, 64%) as an oil; R_f 0.16 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1660 (C=C); δ_H(300 MHz, $CDCl_3$) 7.41–7.20 (5H, m, Ph), 4.74 (1H, s, C=CH), 4.69 (1H, s, C=CH), 3.63 (2H, ABq, *J* 13, NCH_2Ph), 2.91–2.71 (3H, m, 3 × CH), 2.55–2.46 (1H, m, CH), 2.37–2.28 (1H, m, CH), 2.10–1.94 (1H, m, CH), 1.80–1.69 (1H, m, CH), 1.74 (3H, s, CH_3); δ_C(75 MHz, $CDCl_3$) 147.4, 139.4, 128.7, 128.1, 126.8, 109.1, 60.7, 58.6, 54.2, 44.7, 29.3, 20.7; Found: M$^+$, 201.1517. $C_{14}H_{19}N$ requires *M*, 201.1518; *m*/*z* 201 (11%, M$^+$), 77 (100, Ph).

Z-Methyl *N*-benzyl-*N*-*tert*-butoxycarbonyl-5-amino-2-pentenoate 10

To a suspension of potassium hydride (1.18 g, 35% dispersion in mineral oil, 10.4 mmol) in dry THF (10 mL) was added hexamethyldisilazane (2.18 mL, 10.4 mmol) at 0 °C under argon. The mixture was cooled to −78 °C and a solution of 18-crown-6 (12.9 g, 50.0 mmol) and bis(2,2,2-trifluoroethyl)(ethoxycarbonylmethyl)phosphonate[10] (2.8 g, 10.0 mmol) in dry THF (20 mL) was added. After 10 min, the aldehyde **3** (2.48 g, 9.50 mmol) in dry THF (5 mL) was added. After 30 min, NH_4Cl (20 mL) was added and the mixture was allowed to warm to room temperature and was extracted with Et_2O (3 × 40 mL). The combined extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), to give the ester **10** (670 mg, 22%) as an oil; R_f 0.21 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1720 (C=O), 1695 (C=O), 1650 (C=C), 1605 (Ph); δ_C(75 MHz, $CDCl_3$) 7.31–7.10 (5H, m, Ph), 6.24 (1H, d, *J* 11.5, C=CH), 5.79 (1H, dt, *J* 11.5 and 1.5, CH=C), 4.47 (2H, s, NCH_2Ph), 3.65 (3H, s, OCH_3), 3.29 (2H, br s, NCH_2CH$_2$), 2.95–2.80 (2H, m, NCH$_2$CH_2), 1.48 [9H, br s, C(CH$_3$)$_3$]; δ_C(75 MHz, $CDCl_3$) 166.7, 156.7, 146.8, 138.7, 129.3, 128.4, 127.1, 120.9, 70.9, 55.0, 50.3, 45.2, 28.4, 15.4; Found: M$^+$, 319.1784. $C_{18}H_{25}NO_4$ requires *M*, 319.1783; *m*/*z* 319 (8%, M$^+$), 219 (33, M − CO$_2$^{t}Bu), 57 [100, C(CH$_3$)$_3$].

Z-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-aminopent-2-en-1-ol 11

In the same way as the alcohol **5**, R = H, diisobutylaluminium hydride (2.7 mL, 1.5 M in toluene, 4.05 mmol) and the ester 10 (420 mg, 1.32 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (2 : 1), the alcohol **11** (268 mg, 70%) as an oil; R_f 0.35 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3215 (OH), 1720 (C=O), 1670 (C=C), 1600 (Ph); δ_H(300 MHz, $CDCl_3$) 7.36–7.10 (5H, m, Ph), 5.72–5.55 (1H, m, CH=C), 5.45–5.39 (1H, m, C=CH), 4.41 (2H, s, NCH_2Ph), 4.13 (2H, d, *J* 6.5, CH_2O), 3.23–3.18 (2H, m, NCH_2CH$_2$), 2.28–2.24 (2H, m, NCH$_2$CH_2), 1.49 [9H, br s, (CH$_3$)$_3$]; δ_C(75 MHz, $CDCl_3$) 160.7, 138.4, 131.0, 129.7, 129.1, 128.5, 127.2, 79.9, 68.9, 58.2, 46.1, 28.4, 26.2; Found: MH$^+$ 292.1903. $C_{17}H_{25}NO_3$ requires *M*, 292.1912; *m*/*z* 292 (8%, MH$^+$), 191 (62, M − CO$_2$^{t}Bu), 57 [100, C(CH$_3$)$_3$].

Z-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-5-amino-1-methoxypent-2-ene 12

In the same way as the ether **6**, R = H, sodium hydride (43 mg, 1.08 mmol), the alcohol **11** (260 mg, 0.89 mmol) and iodomethane (253 mg, 1.78 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), the ether **12** (230 mg, 85%) as an oil; R_f 0.48 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1690 (C=O), 1665 (C=C), 1605 (Ph); δ_H(300 MHz, $CDCl_3$) 7.34–7.16 (5H, m, Ph), 5.61–5.49 (2H, m, CH=CH), 4.48 (2H, s, NCH_2Ph), 3.91 (2H, d, *J* 5.5, CH_2O), 3.30 (3H, s, OCH_3), 3.27–3.21 (2H, m, NCH_2CH$_2$), 2.27–2.23 (2H, m, NCH$_2$CH_2), 1.49 [9H, s, (CH$_3$)$_3$]; δ_C(75 MHz, $CDCl_3$) 160.7, 138.5, 129.7, 129.7, 128.5, 127.6, 127.2, 79.7, 67.9, 57.9, 51.2, 46.4, 28.4, 26.4; Found: M$^+$ 305.2001. $C_{18}H_{27}NO_3$ requires *M*, 305.1990; *m*/*z* 305 (4%, M$^+$), 57 [100, C(CH$_3$)$_3$].

Z-*N*-Benzyl-5-amino-1-methoxypent-2-ene 13

In the same way as the amine **7**, R = H, trifluoroacetic acid (0.116 mL, 1.5 mmol) and the ether **12** (230 mg, 0.75 mmol) gave, after purification by column chromatography on silica gel, eluting with CH_2Cl_2–EtOH (15 : 1), the amine **13** (154 mg, 99%) as an oil; R_f 0.24 [CH_2Cl_2–EtOH (15 : 1)]; ν_{max}(film)/cm^{-1} 3255 (NH), 1670 (C=C); δ_H(300 MHz, $CDCl_3$) 7.39–7.32 (5H, m, Ph), 5.90–5.80 (1H, m, C=CH), 5.65–5.50 (1H, m, CH=C), 4.18 (2H, s, NCH_2Ph), 3.95 (2H, d, *J* 6, CH_2O), 3.28 (3H, s, OCH_3), 3.12 (2H, q, *J* 6, NCH_2CH$_2$), 2.52 (2H, t, *J* 7, NCH$_2$CH_2); δ_C(75 MHz, $CDCl_3$) 130.1, 129.6, 129.5, 129.4, 129.0, 127.9, 68.2, 57.9, 52.3, 46.2, 22.7; Found: M$^+$ 205.2851. $C_{13}H_{18}NO$ requires *M*, 205.2868; *m*/*z* 205 (7%, M$^+$), 77 (100, Ph).

Z-*N*-Benzyl-*N*-tributylstannylmethyl-5-amino-1-methoxypent-2-ene 14

In the same way as the stannane **8**, R = H, the amine **13** (236 mg, 1.15 mmol) and tributylstannylmethyl methanesulfonate[9] (545 mg, 1.40 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (10 : 1), the stannane **14** (403 mg, 69%) as an oil; R_f 0.24 [petrol–EtOAc (10 : 1)]; ν_{max}(film)/cm^{-1} 1675 (C=C), 1605 (Ph); δ_H(300 MHz, $CDCl_3$) 7.21–7.36 (5H, m, Ph), 5.50–5.72 (2H, m, CH=CH), 4.41–4.28 (2H, m, PhCH_2N), 4.06 (2H, d, *J* 7, CH_2O), 3.85 (2H, br s, NCH_2CH$_2$), 3.49 (2H, t, *J* 7, NCH$_2$CH_2), 3.40 (3H, s, OCH_3), 2.61 (2H, s, $SnCH_2N$), 1.68–0.80 {27H, m, Sn[(CH$_2$)$_3$CH$_3$]$_3$}; δ_C(75 MHz, $CDCl_3$) 139.8, 131.3, 128.7, 128.1, 126.9, 126.8, 68.2, 62.8, 57.8, 57.5, 42.9, 29.2, 27.4, 26.7, 13.6, 12.1; Found: M$^+$ 509.2669. $C_{26}H_{47}NO^{120}Sn$ requires *M*, 509.2679); *m*/*z* 509 (0.5%, M$^+$), 291 [20, Sn(C_4H_9)$_3$], 31 (100, OCH_3).

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldimethylsiloxymethyl-4-vinyl-1,5-dihydro-2*H*-pyrrol-2-one 20

Vinylmagnesium bromide (13.1 mL, 13 mmol, 1.0 M in THF) was added to a suspension of CuBr·SMe_2 (1.34 g, 6.55 mmol) in dry THF (20 mL) at −40 °C under argon. The black suspension was stirred at −40 °C for 30 min and then was cooled to −78 °C. The lactam **19** (320 mg, 0.97 mmol) in dry THF (5 mL) and chlorotrimethylsilane (0.40 mL, 2.93 mmol) were added. The mixture was stirred at −78 °C for 1 h, diluted with Et_2O (50 mL) and quenched with NH_4Cl (20 mL). This mixture was allowed to warm to room temperature and was extracted with NH_4Cl (3 × 20 mL). The organic phase was dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), to give the lactam **20** (240 mg, 61%) as an oil; R_f 0.6 [petrol–EtOAc (4 : 1)]; $[\alpha]_D^{25}$ −14.2 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1725 (C=O), 1695 (C=O), 1660 (C=C); δ_H(300 MHz, $CDCl_3$) 5.91–5.81 (1H, m, C*H*=CH$_2$), 5.12–5.05 (2H, m, CH=CH_2), 3.94 (1H, dd, *J* 16 and 7, CH^AH^{B}O), 3.91–3.88 (1H, m, NCH), 3.75 (1H, dd, *J* 16 and 7, CH^AH^BO), 2.95–2.89 (2H, m, O=CCH^AH^B and C*H*CH=C), 2.31–2.26 (1H, m, O=CCH^AH^B), 1.53 [9H, s, C(CH$_3$)$_3$], 1.42 [9H, s, C(CH$_3$)$_3$], 0.04 [6H, s, Si(CH$_3$)$_2$]; δ_C(75 MHz, $CDCl_3$) 173.7, 150.5, 139.3, 115.0, 82.8, 64.4, 63.3, 38.0, 37.1, 28.1, 25.9, 18.1, −5.5; Found: M$^+$, 355.2184. $C_{18}H_{33}NO_4Si$ requires M, 355.2179; *m*/*z* 355 (10%, M$^+$), 254 (35, M − CO$_2$^{t}Bu), 57 [100, C(CH$_3$)$_3$].

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-amino-4-vinyl-2-pyrone 21

Tetrabutylammonium fluoride (1.8 mL, 1.8 mmol, 1.0 M in THF) was added to the lactam **20** (160 mg, 0.45 mmol) in dry THF (2 mL) at 0 °C under nitrogen and the mixture was stirred at room temperature for 4 days. The solvent was evaporated, CH_2Cl_2 (10 mL) was added and the organic phase was washed

with NH_4Cl (3 × 10 mL). The organic phase was dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with Et_2O, to give the lactone **21** (108 mg, 100%) as needles; mp 55–56 °C; R_f 0.31 (Et_2O); $[\alpha]_D^{25}$ −32.0 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3675 (NH), 1735 (C=O), 1695 (C=O), 1625 (C=C); δ_H(300 MHz, $CDCl_3$) 5.92 (1H, br s, NH), 5.76 (1H, dt, *J* 8 and 2, C*H*=CH_2), 5.14–5.06 (2H, m, CH=CH_2), 4.28 (1H, dd, *J* 8 and 3.3, OCH^AH^B), 3.89 (1H, dd, *J* 8 and 4.2 OCH$^AH^B$), 3.63 (1H, dt, *J* 7.5 and 3.3, CHN), 2.76 (1H, quintet, *J* 8.5, C*H*CH=C), 2.55 (1H, dd, *J* 8 and 8.5, O=CCH^AH^B), 2.27 (1H, dd, *J* 8 and 8.5, O=CCH$^AH^B$), 1.48 [9H, s, C$(CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 176.0, 153.2, 137.0, 117.3, 82.9, 67.9, 58.2, 41.5, 36.1, 27.7; Found: MH^+, 242.1314. $C_{12}H_{20}NO_4$ requires MH, 242.1315; *m*/*z* 242 (9%, MH^+), 57 [100, C$(CH_3)_3$]; Found: C, 59.8; H, 7.9; N, 5.8. $C_{12}H_{19}NO_4$ requires C, 59.75; H, 7.95; N, 5.8%.

(1*SR*,2*RS*)-Ethyl 2-aminocyclopent-3-enecarboxylate hydrochloride 27

Hydrogen chloride (prepared from addition of concentrated sulfuric acid to anhydrous ammonium chloride) was bubbled through a solution of the lactam **26**[18] (9.75 g, 89 mmol) in EtOH (100 mL) at −20 °C for 30 min. After 2 h at room temperature, the solvent was evaporated and the residue was recrystallised from EtOH to give the hydrochloride salt of the ester **27** (16.42 g, 96%) as needles; mp 175–176 °C; R_f 0.30 [CH_2Cl_2 − MeOH (9 : 1)]; ν_{max}(film)/cm^{-1} 3100 (NH), 1725 (C=O), 1640 (C=C); δ_H(400 MHz, MeOD) 1.30 (3H, t, *J* 7, OCH_2CH_3), 2.78–2.82 (2H, m, CH=CHCH_2), 3.50 (1H, q, *J* 8, C*H*CO_2Et), 4.17–4.31 (2H, m, OCH_2CH_3), 4.39–4.41 (1H, m, CHN), 5.84–5.86 (1H, m, CH=C), 6.27–6.29 (1H, m, C=CH); δ_C(100 MHz, MeOD) 13.0, 34.3, 43.4, 55.8, 61.1, 126.3, 138.1, 171.7; Found: MH^+ − HCl, 156.1024. $C_8H_{14}NO_2$ requires *M*, 156.1024; *m*/*z* 156 (100%, MH^+ − HCl), 82 [100, M − (HCl + CO_2Et)]; Found: C, 50.05; H, 7.45; N, 7.15. $C_8H_{14}NO_2Cl$ requires C, 50.25; H, 7.4; N, 7.30%.

(1*SR*,2*RS*)-Ethyl 2-(benzoylamino)cyclopent-3-enecarboxylate 28

Benzoyl chloride (13.2 g, 94 mmol) was added to Et_3N (17.4 g, 172 mmol) and the hydrochloride salt **27** (15 g, 78 mmol) in Et_2O (500 mL) at 0 °C. After 18 h, water (250 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined Et_2O extracts were washed with saturated $NaHCO_3$ (2 × 100 mL), water (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and filtered. The solvent was evaporated and the solid residue was recrystallised from Et_2O to give the ester **28** (17.25 g, 85%) as needles; mp 83–85 °C; R_f 0.53 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3275 (NH), 1730 (C=O), 1640 (C=C), 1540 (C=O); δ_H(400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7, OCH_2CH_3), 2.55–2.65 (1H, m, CH^AH^BCH=C), 2.85–2.91 (1H, m, CH^A-H^BCH=C), 3.45 (1H, td, *J* 9 and 6, CHCO), 4.02–4.12 (2H, m, OCH_2CH_3), 5.55–5.62 (1H, m, CHN), 5.70–5.72 (1H, m, CH=C), 5.97–5.99 (1H, m, C=CH), 6.50 (1H, br d, NH), 7.39–7.74 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 14.1, 35.1, 45.7, 56.1, 60.9, 126.9, 128.5, 129.9, 131.5, 133.5, 134.4, 166.5, 173.7; Found: M^+, 259.1211. $C_{15}H_{17}NO_3$ requires *M*, 259.1208); *m*/*z* 259 (3%, M^+), 154 (61, M − PhCO), 105 (100, PhCO); Found: C, 69.45; H, 6.6; N, 5.35. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%.

(1*SR*,2*SR*,3*RS*,4*SR*)-Ethyl 2-(benzoylamino)-3,4-dihydroxycyclopentanecarboxylate 29

The ester **28** (2.0 g, 7.7 mmol) was added to *N*-methylmorpholine-*N*-oxide (0.96 g, 8.2 mmol) and osmium tetroxide (20 mg, 0.077 mmol) in H_2O : acetone : ^{t}BuOH (16 mL, 5 : 2 : 1) at room temperature. After 18 h sodium hydrosulfite (270 mg, 1.5 mmol), magnesium silicate (2.9 g, 7.7 mmol) and water (20 mL) were added, the mixture was filtered and the solvent was evaporated. The residue was extracted with CH_2Cl_2 (3 × 25 mL), the organic extracts were dried ($MgSO_4$) and evaporated to give the crude solid, which was recrystallised from CH_2Cl_2 to give the diol **29** (1.92 g, 85%) as needles; mp 129–130 °C; R_f 0.47 [CH_2Cl_2–MeOH (9 : 1)]; ν_{max}(film)/cm^{-1} 3300 (OH) and (NH), 1730 (C=O), 1535 (C=O); δ_H(400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7, OCH_2CH_3), 2.16–2.30 (2H, m, CH_2CHCO), 3.19 (1H, s, OH), 3.47 (1H, q, *J* 9, CHCO), 4.09–4.12 (1H, m, C*H*OH), 4.16–4.22 (3H, m, OCH_2CH_3 and C*H*OH), 4.55–4.63 (1H, m, CHN), 5.01 (1H, s, OH), 7.42–7.80 (5H, m, Ph), 8.05 (1H, br d, *J* 8, NH); δ_C(100 MHz, $CDCl_3$) 14.1, 34.6, 41.0, 56.7, 61.4, 70.4, 80.1, 127.0, 128.7, 131.9, 133.4, 169.1, 175.2; Found: M^+, 293.1252. $C_{15}H_{19}NO_5$ requires *M*, 293.1263; *m*/*z* 293 (1%, M^+), 105 (100, PhCO); Found: C, 61.3; H, 6.45; N, 4.65. $C_{15}H_{19}NO_5$ requires C, 61.4; H, 6.55; N, 4.8%.

(3a*R*,4*SR*,5*SR*,6a*S*)-Ethyl 4-(benzoylamino)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxole-5-carboxylate 30

The diol **29** (13.34 g, 45 mmol) was added to (1*R*)-(−)-10-camphorsulfonic acid (211 mg, 0.91 mmol) and 2,2-dimethoxypropane (42.6 g, 409 mmol) in anhydrous acetone (500 mL) at room temperature. After 1 h $NaHCO_3$ (3 g, 36 mmol) was added and the mixture was filtered through silica gel, eluting with petrol–EtOAc (1 : 1). The solvent was evaporated and the residue was recrystallised from Et_2O to give the ester **30** (13.28 g, 87%) as needles; mp 175–177 °C; R_f 0.53 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3300 (NH), 1730 (C=O), 1550 (C=O); δ_H(400 MHz, $CDCl_3$) 1.24–1.28 [6H, m, C(CH_3^A)CH_3^B and OCH_2CH_3], 1.48 [3H, s, C(CH_3^A)CH_3^B], 2.17–2.24 (2H, m, CH_2CHCO, 3.32–3.39 (1H, m, CHCO), 4.14–4.21 (2H, m, OCH_2CH_3), 4.46 (1H, t, *J* 6, CHN), 4.72–4.75 (2H, m, HOC*H*-C*H*OH), 7.05 (1H, br d, *J* 6, NH), 7.39–7.77 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 14.1, 23.8, 26.2, 35.3, 42.8, 58.0, 61.4, 78.7, 84.7, 110.3, 126.9, 128.6, 131.7, 134.0, 167.3, 173.7; Found: M^+, 333.1579. $C_{18}H_{23}NO_5$ requires *M*, 333.1576; *m*/*z* 333 (1%, M^+), 105 (100, PhCO); Found: C, 64.8; H, 7.1; N, 4.1. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.2%.

(3a*R*,4*SR*,5*SR*,6a*S*)-*N*-[5-(Hydroxymethyl)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-yl]benzamide 31

The ester **30** (1.29 g, 3.9 mmol) in THF (20 mL) was added to lithium aluminium hydride (290 mg, 7.7 mmol) in THF (20 mL) at 0 °C. After 15 min at room temperature, the mixture was cooled to 0 °C and water was added until the precipitated inorganic salts became granular. The mixture was filtered through Celite and washed with THF. The filtrate was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1 : 1) to give the alcohol **31** (1.07 g, 95%) as platelets; mp 145–146 °C; R_f 0.31 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3300 (OH and NH), 1540 (C=O); δ_H(400 MHz, MeOD) 1.30 [3H, s, C(CH_3^A)CH_3^B], 1.45 [3H, s, C(CH_3^A)CH_3^B], 1.75–1.89 (2H, m, CH_2CHOH), 2.57–2.64 (1H, m, C*H*CH_2OH), 3.63 (2H, d, *J* 6, CH_2OH), 4.33 (1H, d, *J* 6, CHN), 4.58 (1H, d, *J* 6, C*H*OH), 4.76–4.79 (1H, m, C*H*OH), 7.44–7.81 (5H, m, Ph); δ_C(100 MHz, MeOD) 22.7, 25.1, 32.8, 41.7, 57.8, 60.4, 79.4, 85.3, 109.7, 127.0, 128.2, 131.4, 134.0, 169.6; Found: M^+, 291.1469. $C_{16}H_{21}NO_4$ requires *M*, 291.1470; *m*/*z* 291 (0.1%, M^+), 105 (100, PhCO); Found: C, 65.8; H, 7.3; N, 4.65. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.25; N, 4.8%.

[(3a*R*,4*SR*,5*SR*,6a*S*)-*N*-[5-Formyl-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-yl]benzamide 23

o-Iodoxybenzoic acid (1.92 g, 6.9 mmol) was added to dimethyl sulfoxide (10 mL) at room temperature. After 20 min the alcohol **31** (1.0 g, 3.4 mmol) was added and the mixture was stirred at room temperature for 2 h. Water (20 mL) was added, the mixture was filtered and extracted with CH_2Cl_2 (3 × 20 mL).

The combined organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9 : 1) to give the aldehyde **23** (852 mg, 86%) as a foam; R_f 0.50 [CH_2Cl_2–MeOH (9 : 1)]; ν_{max}(film)/cm^{-1} 3300 (NH), 1720 (C=O), 1540 (C=O); δ_H(400 MHz, $CDCl_3$) 1.29 [3H, s, C(CH_3^A)CH_3^B], 1.49 [3H, s, C(CH_3^A)CH_3^B], 2.03–2.10 (1H, m, CH^AH^{B}CHCO), 2.19–2.26 (1H, m, CH^AH^BCHCO), 3.56–3.62 (1H, m, CHC=O), 4.63–4.65 (1H, m, C*H*OH), 4.70–4.77 (2H, m, CHN and C*H*OH), 6.48 (1H, br d, NH), 7.37–7.69 (5H, m, Ph), 9.93 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 23.9, 26.3, 31.7, 51.8, 56.7, 78.5, 85.1, 110.7, 126.9, 128.6, 131.8, 133.8, 167.5, 201.9; Found: M$^+$, 289.1318. $C_{16}H_{19}NO_4$ requires *M*, 289.1314; *m*/*z* 289 (0.5%, M$^+$), 105 (100, PhCO); Found: C, 66.3; H, 6.6; N, 4.65. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.85%.

(3a*R*,4*SR*,5*RS*,6a*S*)-*E*-Ethyl [4-(benzoylamino)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl]-2-methylpropenoate 32

1-Carboethoxyethylidene triphenylphosphorane (4.37 g, 12 mmol) was added to the aldehyde **23** (3.17 g, 11 mmol) in THF (100 mL) at room temperature and the mixture was warmed to 40 °C. After 5 h the solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1 : 1), to give the ester **32** (3.63 g, 89%) as needles; mp 136–138 °C; R_f 0.50 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3300 (NH), 1710 (C=O), 1640 (C=C), 1540 (C=O); δ_H(400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7, OCH$_2$C*H*$_3$), 1.30 [3H, s, C(CH_3^A)CH_3^B], 1.51 [3H, s, C(CH_3^A)CH_3^B], 1.86–1.94 (4H, m, C=CCH_3 and CH^AH^{B}CHC=C), 2.08–2.15 (1H, m, CH^AH^B-CHC=C), 3.41–3.47 (1H, m, CH$_2$C*H*C=C), 4.11–4.19 (2H, m, OCH_2CH$_3$), 4.44 (1H, t, *J* 7, CHN), 4.66 (1H, d, *J* 6, OCH), 4.78 (1H, t, *J* 6, OCH), 6.12 (1H, br d, *J* 7, NH), 6.70 (1H, d, *J* 9, CH=C), 7.38–7.70 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 13.1, 14.1, 23.9, 26.3, 37.4, 38.1, 59.1, 60.7, 79.2, 85.5, 110.5, 126.9, 128.6, 131.2, 131.6, 134.4, 137.6, 167.6, 167.8; Found: M$^+$, 373.1896. $C_{21}H_{27}NO_5$ requires *M*, 373.1889; *m*/*z* 373 (10%, M$^+$), 105 (100, PhCO); Found: C, 67.3; H, 7.4; N, 3.55. $C_{21}H_{27}NO_5$ requires C, 67.5; H, 7.3; N, 3.75%.

(3a*R*,4*SR*,5*RS*,6a*S*)-*E*-*N*-[5-(3-Hydroxy-2-methylprop-1-enyl)-2,2-dimethyl tetrahydrocyclopenta[1,3]dioxol-4-yl]benzamide 33

Calcium chloride (9.54 g, 86 mmol) was added to the ester **32** (5.35 g, 14 mmol) in EtOH (150 mL) at 0 °C. Sodium borohydride (6.5 g, 172 mmol) was added and the mixture was stirred at room temperature for 3 h. Aqueous K_2CO_3 (50 mL, 2 M) was added, the solvent was evaporated and the residue partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), the organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (1 : 1), to give the alcohol **33** (4.37 g, 92%) as a foam; R_f 0.18 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3300 (OH and NH), 1640 (C=C), 1540 (C=O); δ_H(400 MHz, $CDCl_3$) 1.28 [3H, s, C(CH_3^A)CH_3^B], 1.50 [3H, s, C(CH_3^A)CH_3^B], 1.69 (3H, s, C=CCH_3), 1.73–1.82 (1H, m, CH^AH^{B}CHC=C), 2.00–2.05 (1H, m, CH^AH^BCHC=C), 3.34–3.45 (1H, m, CH$_2$C*H*C=C), 3.95 (2H, s, CH$_2$O), 4.35 (1H, t, *J* 7, CHN), 4.59 (1H, d, *J* 6, OCH), 4.71 (1H, t, *J* 6, OCH), 5.36 (1H, d, *J* 9, CH=C), 6.28 (1H, br d, *J* 7, NH), 7.35–7.70 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 14.4, 23.9, 26.3, 37.2, 37.6, 59.1, 67.9, 79.1, 85.3, 110.3, 120.8, 126.9, 128.6, 131.6, 134.4, 139.1, 168.0; Found: MH$^+$, 332.1861. $C_{19}H_{26}NO_4$ requires *M*, 332.1862; *m*/*z* 332 (84%, MH$^+$), 139 (100), 105 (36, PhCO).

(3a*R*,4*SR*,5*RS*,6a*S*)-*E*-*N*-[5-(3-Methoxy-2-methylprop-1-enyl)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-yl]benzamide 34

Tetrabutylammonium iodide (7 mg, 18 μmol) was added to the alcohol **33** (600 mg, 1.8 mmol) in 50% aqueous NaOH (25 mmol) and CH_2Cl_2 (4 mL) at room temperature. After 30 min, dimethyl sulfate (340 mg, 2.7 mmol) was added. After 18 h, concentrated ammonia (1 mL) and water (10 mL) were added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (1 : 1), to give the ether **34** (581 mg, 93%) as a foam; R_f 0.48 [petrol–EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3300 (NH), 1640 (C=C), 1540 (C=O); δ_H(400 MHz, $CDCl_3$) 1.30 [3H, s, C(CH_3^A)CH_3^B], 1.51 [3H, s, C(CH_3^A)CH_3^B], 1.70 (3H, s, C=CCH_3), 1.73–1.83 (1H, m, CH^AH^{B}CHC=C), 2.06–2.12 (1H, m, CH^AH^BCHC=C), 3.26 (3H, s, OCH$_3$), 3.38–3.43 (1H, m, CH$_2$C*H*C=C), 3.78 (2H, s, CH$_2$O), 4.36 (1H, t, *J* 7, CHN), 4.65 (1H, d, *J* 6, OCH), 4.74 (1H, t, *J* 6, OCH), 5.36 (1H, d, *J* 9, CH=C), 6.02 (1H, br d, *J* 7, NH), 7.39–7.71 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 14.6, 23.9, 26.3, 37.1, 37.8, 57.7, 59.2, 77.8, 79.1, 85.3, 110.3, 122.7, 126.8, 128.6, 131.5, 134.6, 136.9, 167.6; Found: MH$^+$, 346.2016. $C_{20}H_{28}NO_4$ requires *M*, 346.2018; *m*/*z* 346 (100%, MH$^+$), 139 (100); Found: C, 69.25; H, 8.0; N, 3.9. $C_{20}H_{27}NO_4$ requires C, 69.5; H, 7.9; N, 4.0%.

(3a*R*,4*SR*,5*RS*,6a*S*)-*E*-*N*-[5-(3-Methoxy-2-methylprop-1-enyl)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-*N*-tributylstannylmethylbenzamide 35

Sodium hydride (46 mg, 1.1 mmol, 60% dispersion in mineral oil) was added to the amide **34** (133 mg, 0.4 mmol) in THF (2 mL) under nitrogen at room temperature. After 2 h iodomethyltributyltin (249 mg, 0.6 mmol) was added. After 70 h the solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9 : 1), to give the stannane **35** (115 mg, 46%) as an oil; R_f 0.47 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1650 (C=O), 1640 (C=C); δ_H(400 MHz, $CDCl_3$) 0.85–0.95 [15H, m, (CH_3CH$_2$CH$_2$CH_2)$_3$Sn], 1.30 [3H, s, C(CH_3^A)CH_3^B], 1.31–1.36 [6H, m, (CH$_3$CH_2CH$_2$CH$_2$)$_3$-Sn], 1.38 [3H, s, C(CH_3^A)CH_3^B], 1.47–1.57 [9H, m, (CH$_3$CH$_2$-CH_2CH$_2$)$_3$Sn and C=CCH_3], 2.06–2.10 (2H, m, CH_2CHC=C), 2.30 (1H, d, *J* 12, NCH^AH^{B}Sn), 2.76 (1H, d, *J* 12, NCH^AH^BSn), 3.19–3.24 (1H, m, CH$_2$C*H*C=C), 3.30 (3H, s, OCH$_3$), 3.79–3.86 (2H, m, CH$_2$O), 4.36 (1H, d, *J* 8, CCHN), 4.72 (1H, d, *J* 6, OCH), 4.82–4.87 [1H, m, OCH), 5.30–5.35 (1H, m, CH=C), 7.26–7.38 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 11.1, 13.7, 14.3, 23.5, 26.3, 27.5, 29.2, 31.9, 38.8, 40.5, 57.8, 69.3, 78.2, 80.5, 85.4, 109.9, 124.8, 127.3, 128.3, 129.0, 135.9, 136.2, 171.7; Found: MH$^+$, 650.3224. $C_{33}H_{56}NO_4{}^{120}Sn$ requires *M*, 650.3231; *m*/*z* 650 (6%, MH$^+$), 105 (82, PhCO).

(3a*R*,4*SR*,5*RS*,6a*S*)-*E*-*N*-[5-(3-Methoxy-2-methylprop-1-enyl)-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-*N*-tributylstannylmethylbenzylamine 36

Et_2O (1.5 mL) was added to lithium aluminium hydride (12 mg, 0.3 mmol) and aluminium chloride (14 mg, 0.1 mmol) under nitrogen at −78 °C. The mixture was allowed to warm to 0 °C for 1 h and the amide **35** (100 mg, 0.15 mmol) in Et_2O (1.5 mL) was added. After 1 h water (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on alumina, eluting with petrol–EtOAc (49 : 1), to give the stannane **36** (96 mg, 98%) as an oil; R_f 0.60 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1640 (C=C); δ_H(400 MHz, $CDCl_3$) 0.85–0.89 [15H, m, (CH_3CH$_2$CH$_2$CH_2)$_3$Sn], 1.26–1.31 [9H, m, (CH$_3$CH_2CH$_2$CH$_2$)$_3$Sn and C(CH_3^A)CH_3^B], 1.42–1.50 [9H, m, (CH$_3$CH$_2$CH_2CH$_2$)$_3$Sn and C(CH_3^A)CH_3^B], 1.58 (3H, s, C=CCH_3), 1.98–2.01 (2H, m, CH_2CHC=C), 2.62–2.67 (2H, m, NCH$_2$Sn), 2.82 (1H, dd, *J* 6 and 5, CHN), 3.24–3.29 (4H, m, CH$_2$C*H*C=C and OCH$_3$), 3.41 (1H, d, *J* 14, CH^AH^{B}Ph), 3.66 (1H, d, *J* 14, CH^AH^BPh), 3.82–3.83 (2H, m, CH$_2$O), 4.67–4.71 (1H, m, OCH), 4.71–4.77 (1H, m, OCH), 5.67 (1H, d, *J* 9, CH=C), 7.19–7.32 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 10.8, 13.6, 13.7, 24.6, 27.1, 27.5, 29.3, 38.5, 41.7, 41.7, 57.3, 60.1, 74.0,

78.5, 79.3, 83.9, 112.3, 126.6, 127.9, 128.1, 128.3, 132.7, 140.1; Found: MH^+, 636.3438. $C_{33}H_{58}NO_3{}^{120}Sn$ requires *M*, 636.3438; *m*/*z* 636 (100%, MH^+), 345 (100, MH − $^{120}SnBu_3$).

(3a*R*,3b*S*,6*S*,6a*R*,7a*S*) and (3a*R*,3b*S*,6*R*,6a*R*,7a*S*)-4-Benzyl-6-isopropenyl-2,2-dimethyloctahydro[1,3]dioxolo[4,5]cyclopenta-[1,2]pyrrole 37 and 38

n-Butyllithium (0.22 mL, 0.53 mmol, 2.5 M in hexanes) was added to the stannane **36** (85 mg, 0.13 mmol) in hexane–Et_2O (2 mL, 4 : 1) at −78 °C under argon. After 1 h the mixture was warmed to room temperature. After 16 h the mixture was cooled to −78 °C and MeOH (1 mL) was added. The mixture was evaporated and purified by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), to give the amine **37** (21 mg, 50%) as an oil; R_f 0.54 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1645 (C=C); δ_H(400 MHz, $CDCl_3$) 1.31 [3H, s, C(CH_3^A)-CH_3^B], 1.47 [3H, s, C(CH_3^A)CH_3^B], 1.70 (3H, s, C=CCH_3), 1.83–1.88 (1H, m, CH^AH^{B}CHO), 2.14 (1H, t, *J* 9, NCH^A-H^{B}CH), 2.22–2.28 (1H, m, CH^AH^BCHO), 2.40–2.45 (1H, m, NCH$_2$CH), 2.72–2.76 (1H, m, NCHCHCH$_2$), 2.96 (1H, d, *J* 8, NCH), 3.08 (1H, dd, *J* 9 and 7, NCH^AH^BCH), 3.25 (1H, d, *J* 13, NCH^AH^{B}Ph), 4.09 (1H, d, *J* 13, NCH^AH^BPh), 4.46 (1H, d, *J* 5, OCH), 4.68 (2H, s, C=CH$_2$), 4.82 (1H, dd, *J* 5 and 4, OCH), 7.23–7.33 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 21.1, 24.7, 27.0, 39.8, 46.2, 50.9, 58.4, 59.5, 76.5, 83.1, 84.5, 109.5, 109.8, 126.9, 128.2, 128.7, 139.0, 146.3; Found: MH^+, 314.2117. $C_{20}H_{28}NO_2$ requires *M*, 314.2120); *m*/*z* 314 (100%, MH^+), 223 (15, MH–PhCH$_2$) and the amine **38** (5 mg, 12%) as an oil; R_f 0.62 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1650 (C=C); δ_H(400 MHz, $CDCl_3$) 1.30 [3H, s, C(CH_3^A)CH_3^B], 1.46 [3H, s, C(CH_3^A)-CH_3^B], 1.72 (3H, s, C=CCH_3), 1.76–1.78 (2H, m, CH_2CHO), 2.51 (1H, t, *J* 9, NCH^AH^{B}CH), 2.86–2.92 (1H, m, NCH$_2$CH), 2.93–3.00 (1H, m, NCHCHCH$_2$), 3.10 (1H, t, *J* 9, NCH^AH^B-CH), 3.18 (1H, d, *J* 5, NCH), 3.46 (1H, d, *J* 14, NCH^AH^{B}Ph), 4.05 (1H, d, *J* 14, NCH^AH^BPh), 4.44 (1H, d, *J* 5, OCH), 4.62 (1H, s, C=CH), 4.78 (1H, s, C=CH), 4.82 (1H, br s, OCH), 7.24–7.32 (5H, m, Ph); δ_C(100 MHz, $CDCl_3$) 23.3, 24.0, 26.5, 32.7, 44.3, 44.7, 54.5, 58.3, 78.0, 82.5, 83.7, 109.0, 109.7, 126.7, 128.2, 128.3, 139.0, 144.2; Found: MH^+, 314.2122. $C_{20}H_{28}NO_2$ requires *M*, 314.2120; *m*/*z* 314 (100%, MH^+), 223 (14, MH − PhCH$_2$).

(3a*R*,3b*S*,6*S*,6a*R*,7a*S*)-Ethyl 6-isopropenyl-2,2-dimethyloctahydro[1,3]dioxolo[4,5]cyclopenta[1,2]pyrrole-4-carboxylate 39

Ethyl chloroformate (66 mg, 0.6 mmol) was added to the pyrrolidine **37** (32 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) and the mixture was heated under reflux for 18 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (4 : 1), to give the carbamate **39** (20 mg, 66%) as an oil; R_f 0.32 [petrol–EtOAc (4 : 1)]; ν_{max}(film)/cm^{-1} 1700 (C=O), 1650 (C=C); δ_H(400 MHz, $CDCl_3$) 1.25–1.35 [6H, br m, C(CH_3^A)CH_3^B and OCH$_2$CH_3], 1.45 [3H, s, C(CH_3^A)CH_3^B], 1.58–1.65 (1H, m, CH^AH^{B}CHO), 1.72 (3H, s, C=CCH_3), 2.12–2.18 (1H, m, CH^AH^BCHO), 2.40–2.45 (1H, m, NCH$_2$CH), 2.85–2.95 (1H, m, NCHCHCH$_2$), 3.44–3.65 (2H, m, NCH_2CH), 3.97–4.25 (3H, m, NCH and OCH_2CH$_3$), 4.56–4.84 (4H, m, OCHCHO and C=CH$_2$); δ_C(100 MHz, $CDCl_3$) 14.8, 21.4, 24.4, 26.8, 36.5, 45.9, 47.0, 50.1, 61.3, 68.2, 81.1, 86.1, 110.1, 110.3, 145.7, 155.3; Found: MH^+, 296.1868. $C_{16}H_{26}NO_4$ requires *M*, 296.1862; *m*/*z* 296 (72%, MH^+).

Acknowledgements

We thank the EPSRC for funding, the EPSRC mass spectrometry service at the University of Wales, Swansea and the EPSRC Chemical Database Service at Daresbury.

References

1 (*a*) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel and K. B. Wiberg, *J. Am. Chem. Soc.*, 1991, **113**, 5720; (*b*) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, 2002.
2 M. J. Mealy and W. F. Bailey, *J. Organomet. Chem.*, 2002, **646**, 59.
3 (*a*) I. Coldham, R. Hufton and D. J. Snowden, *J. Am. Chem. Soc.*, 1996, **118**, 5322; (*b*) I. Coldham and R. Hufton, *Tetrahedron*, 1996, **52**, 12541; (*c*) N. J. Ashweek, I. Coldham, D. J. Snowden and G. P. Vennall, *Chem. Eur. J.*, 2002, **8**, 195.
4 (*a*) M. P. Cooke, *J. Org. Chem.*, 1992, **57**, 1495; (*b*) W. F. Bailey and K. V. Gavaskar, *Tetrahedron*, 1994, **50**, 5957; (*c*) A. Krief, B. Kenda and B. Remacle, *Tetrahedron*, 1996, **52**, 7435; (*d*) M. J. Woltering, R. Fröhlich and D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1764; (*e*) R. W. Hoffmann, R. Koberstein and K. Harms, *J. Chem. Soc., Perkin Trans. 2*, 1999, 183; (*f*) A. Krief, B. Remacle and W. Dumont, *Synlett*, 1999, 1142; (*g*) X. Wei and R. J. K. Taylor, *Angew. Chem., Int. Ed.*, 2000, **39**, 409; (*h*) J. Barluenga, F. J. Fañanás, R. Sanz and C. Marcos, *Org. Lett.*, 2002, **4**, 2225; (*i*) see ref. 3c.
5 (*a*) C. A. Broka, W. J. Lee and T. Shen, *J. Org. Chem.*, 1988, **53**, 1338; (*b*) C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, 1989, **111**, 2981; (*c*) M. Lautens and S. Kumanovic, *J. Am. Chem. Soc.*, 1995, **117**, 1954; (*d*) W. F. Bailey and P. H. Aspris, *J. Org. Chem.*, 1995, **60**, 754; (*e*) A. Krief, B. Remacle and J. Mercier, *Synlett*, 2000, 1443; (*f*) A. Deiters, B. Wibbeling and D. Hoppe, *Adv. Synth. Catal.*, 2001, **343**, 181; (*g*) G. Christoph and D. Hoppe, *Org. Lett.*, 2002, **4**, 2189.
6 For a review, see: A. F. Parsons, *Tetrahedron*, 1996, **52**, 4149; for recent syntheses of α-kainic acid, see: (*a*) H. Nakagawa, T. Sugahara and K. Ogasawara, *Org. Lett.*, 2000, **2**, 3181; (*b*) A. D. Campbell, T. M. Raynham and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3194; (*c*) Q. Xia and B. Ganem, *Org. Lett.*, 2001, **3**, 485; (*d*) H. Hirasawa, T. Taniguch and K. Ogasawara, *Tetrahedron Lett.*, 2001, **42**, 7587; (*e*) J. Clayden, C. J. Menet and K. Tchabanenko, *Tetrahedron*, 2002, **58**, 4727.
7 I. Coldham, M. M. S. Lang-Anderson, R. E. Rathmell and D. J. Snowden, *Tetrahedron Lett.*, 1997, **38**, 7621.
8 A. Barco, S. Benetti, C. De Risi, G. P. Pollini, R. Romagnoli, G. Spalluto and V. Zanirato, *Tetrahedron*, 1994, **50**, 2583.
9 D. E. Seitz, J. J. Carroll, C. P. Cartaya, S.-H. Lee and A. Zapata, *Synth. Commun.*, 1983, **13**, 129.
10 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405.
11 The stereoselectivity on cyclization of a methoxy-substituted organolithium species has been found to be dependent on the solvent system used, see : W. F. Bailey and X.-L. Jiang, *J. Org. Chem.*, 1994, **59**, 6528; for a cyclic substrate that gives predominantly the desired 3,4-*cis* substitution pattern after anionic cyclization, see Scheme 9, ref. 5a.
12 P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361.
13 (*a*) I. Jako, P. Uiber, A. Mann and C.-G. Wermuth, *J. Org. Chem.*, 1991, **56**, 5729; (*b*) S. Hanessian, W. Wang and Y. Gai, *Tetrahedron Lett.*, 1996, **37**, 7477; (*c*) C. Flamant-Robin, Q. Wang, A. Chiaroni and N. A. Sasaki, *Tetrahedron*, 2002, **58**, 10475.
14 R. Baker and J. L. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1990, 47.
15 K. Shimamoto, M. Ishida, H. Shinozaki and Y. Ohfune, *J. Org. Chem.*, 1991, **56**, 4167.
16 For a related conjugate addition see: C. Herdeis and H. P. Hubmann, *Tetrahedron: Asymmetry*, 1992, **3**, 1213.
17 (*a*) H. Maeda and G. A. Kraus, *J. Org. Chem.*, 1997, **62**, 2314; (*b*) P. Klotz and A. Mann, *Tetrahedron Lett.*, 2003, **44**, 1927.
18 (*a*) D. A. Evans and S. A. Biller, *Tetrahedron Lett.*, 1985, **26**, 1907; (*b*) J. R. Malpass and N. J. Tweddle, *J. Chem. Soc., Perkin Trans. 1*, 1977, 874.
19 A. Merz, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 846.