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PAPER

A new general approach for the stereocontrolled synthesis of functionalised γ- and δ-lactams†

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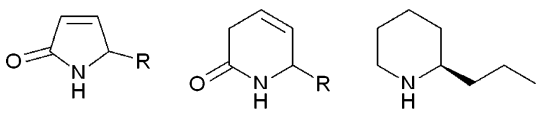
A new flexible approach for the stereoselective synthesis of substituted 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones has been developed. The general strategy employed the stereoselective reduction of a series of α,β-unsaturated ketones under chelation control to give the corresponding allylic alcohols. Overman rearrangement to install the key C–N bond followed by conversion to either prop-2-enoyl or but-3-enoyl derivatives and a ring closing metathesis reaction gave the target unsaturated γ- and δ-lactams. The synthetic utility of these compounds as building blocks was demonstrated by the preparation of the *N*-Boc derivative of (−)-coniine.

Introduction

Five and six-ring *N*-heterocycles are an important class of compounds that are widely used throughout academia and industry. A significant number of pharmaceuticals and agrochemicals as well as plastics, additives and modifiers contain a *N*-heterocyclic motif. Due to their importance, there have been substantial efforts in designing and developing highly efficient approaches for their synthesis.[1] In particular, much research has focused on the stereoselective synthesis of functionalised, unsaturated γ- and δ-lactams as key building blocks for the preparation of medicinally important compounds and natural products.[2,3] For example, 1*H*-pyrrol-2(5*H*)-ones **1** have been used in a range of reactions[2] such as conjugate additions, oxidations and pericyclic processes for the stereoselective synthesis of natural products including (−)-domoic acid,[2a] the cytochalasans,[2b] (+)-pramanicin[2e] and the oroidin alkaloids[2f] as well as for the preparation of pharmacologically active agents (*S*)-vigabatrin[2j] and analogues of baclofen.[2l] In a similar fashion, 3,6-dihydro-1*H*-pyridin-2-ones such as **2** have been further functionalised for the preparation of quinolizinones[3d] and used to prepare the piperidine alkaloids (+)-α-conhydrine[3e] and (+)-pumiliotoxin C.[3g]

A number of elegant approaches have been reported for the stereoselective preparation of 1*H*-pyrrol-2(5*H*)-ones **1**.[2] For example, Gallagher and co-workers used the reaction of chiral cyclic sulfamidates with sulfur-stabilised enolates,[2i] while the research group of Helmchen used an asymmetric iridium-catalysed allylic substitution with the pronucleophile *N*-Boc-*N*-(but-2-enoyl)amine followed by ring closing metathesis (RCM).[2l] Several efficient methods[3] have also been described for the stereoselective synthesis of 3,6-dihydro-1*H*-pyridin-2-ones **2** such as the palladium-catalysed decarboxylative carbonylation of 3-tosyl-5-vinyloxazolidin-2-ones described by Knight and co-workers.[3b] While many methods have been described for the preparation of either class of heterocycle, only one approach reported by Spino and co-workers involving the 3,3-sigmatropic rearrangement of azides or cyanates derived from menthyl substituted allylic alcohols followed by RCM allows the general stereoselective synthesis of both 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones.[2g,2k,3g] As part of a programme to identify new biologically active lactams,[3e,4] we were interested in developing a new approach for the stereoselective synthesis of substituted 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones. In this paper, we now report a general stereoselective synthesis of allylic secondary alcohols that can be transformed using an Overman rearrangement and a RCM reaction as the key steps to either 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones. We also describe the application of this approach for the synthesis of the Boc-derivative of (−)-coniine **3**.



1 **2** **3**

Results and discussion

Our synthesis of 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones is outlined in Scheme 1. It was proposed that the key substrates, chiral allylic secondary alcohols **6** could be prepared from commercially available methyl (2*S*)-2-hydroxy-3-phenylpropionate (**7**)[5] by conversion to the corresponding α,β-unsaturated ketone followed by a stereoselective reduction

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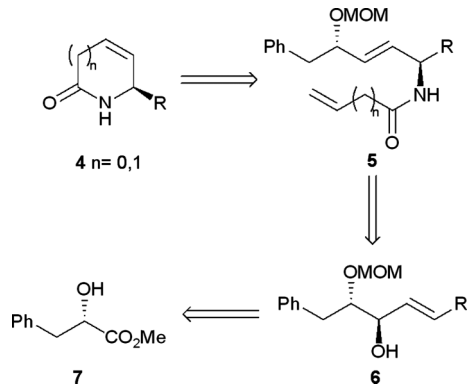
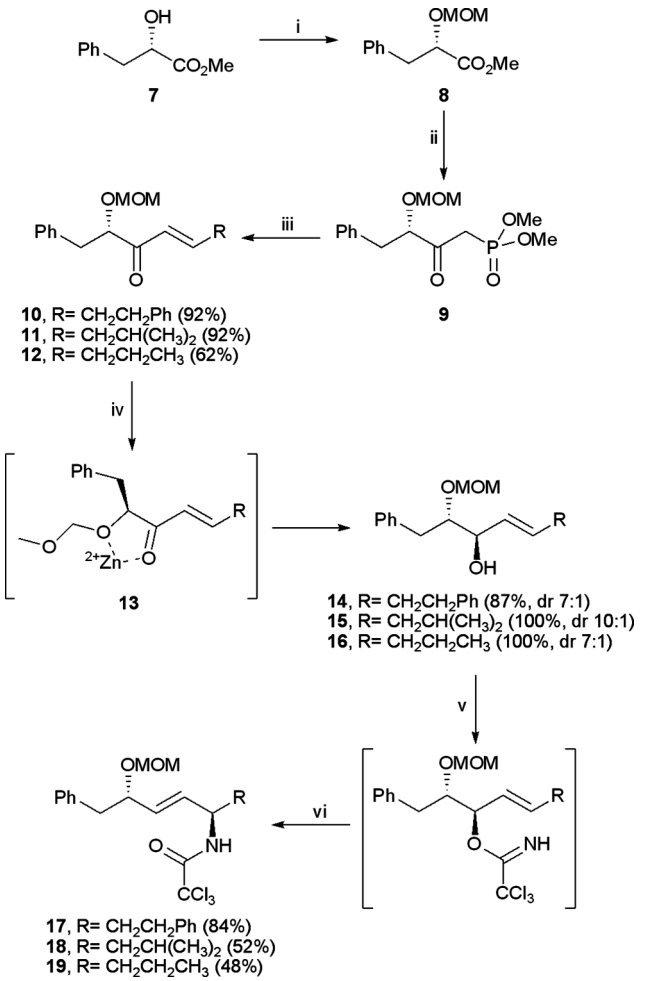
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c1ob05833a



Scheme 1 Proposed route to 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones.

(Scheme 1). Overman rearrangement and conversion to the prop-2-enoyl or but-3-enoyl derivatives **5** would then allow the use of a RCM reaction to form either 1*H*-pyrrol-2(5*H*)-ones or 3,6-dihydro-1*H*-pyridin-2-ones. The synthetic route was designed for the flexible preparation of different analogues and ring sizes. Thus, various R groups could be incorporated into the allylic alcohols **6** and by using enoyls of different length, the late stage synthesis of different ring sizes could be accomplished.

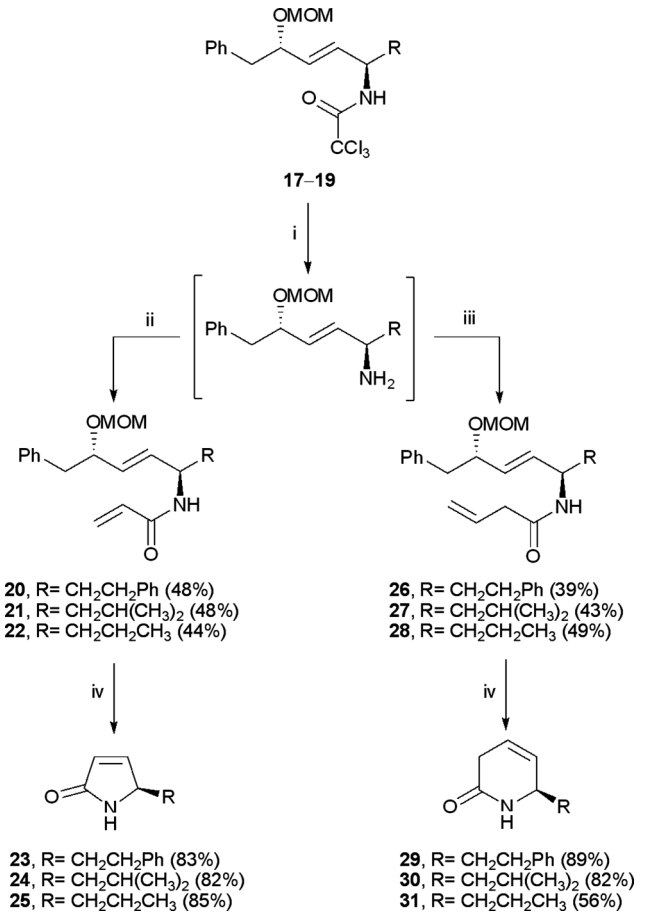
The first stage of this programme focused on the development of a general synthesis of allylic secondary alcohols **6**. Methyl (2*S*)-2-hydroxy-3-phenylpropionate (**7**) was protected as the MOM-ether in 89% yield using bromomethyl methyl ether and Hünig's base (Scheme 2). Reaction of **8** with the anion of dimethyl methylphosphonate gave phosphonate ester **9** in 90% yield. Using standard conditions,[6] the Horner–Wadsworth–Emmons reaction of **9** with a series of aldehydes gave the corresponding *E*-α,β-unsaturated ketones **10–12** in 62–92% yield. Stereoselective reduction of α,β-unsaturated ketones **10–12** was achieved using zinc borohydride prepared by modification of Gensler's procedure.[7,8] This gave *anti*-allylic alcohols **14–16** *via* the 5-membered zinc-chelate **13**[9,10] in excellent yields and with high diastereoselectivity. The diastereomers could be separated by column chromatography, however, it was found easier to do this using the enoyl derivatives at a later stage of the synthetic route. It should be noted that initial studies on developing a route to these types of allylic alcohols was attempted using ethyl (*S*)-lactate as the starting material. Reduction of the resulting α,β-unsaturated ketones with zinc borohydride gave the corresponding allylic alcohols with low *anti* : *syn* selectivity (3 : 1) and thus, the benzyl side chain of ketones **10–12** derived from **7** is necessary for a highly stereoselective reduction. With allylic alcohols **14–16** in hand, these were converted to allylic trichloroacetamides **17–19** using the Overman rearrangement.[11] Reaction of **14–16** with DBU and trichloroacetonitrile followed by a thermal rearrangement of the resulting allylic trichloroacetimidates in the presence of potassium carbonate[12] gave compounds **17–19** in 48–84% yields over the two steps. As expected, the 3,3-sigmatropic rearrangement proceeded with complete retention of stereochemistry giving the allyic trichloroacetamides with the same ratio of diastereomers as observed for allylic alcohols **14–16**.[13]



Scheme 2 *Reagents and conditions*: i. MOMBr, EtN(ⁱPr)$_2$, CH_2Cl_2, 40 °C, 89%; ii. $(MeO)_2P(O)Me$, ⁿBuLi, THF, –78 °C to rt, 90%; iii. RCHO, K_2CO_3, MeCN, 75 °C; iv. $ZnCl_2$, $NaBH_4$, THF, –78 °C; v. Cl_3CCN, DBU, CH_2Cl_2; vi. Δ, K_2CO_3, *p*-xylene.

Allylic trichloroacetamides **17–19** were then hydrolysed under standard conditions using sodium hydroxide (Scheme 3). The resulting amines were then either coupled with acryloyl chloride in the presence of triethylamine to give prop-2-enoyl derivatives **20–22** or with 3-butenoic acid and EDCI to give but-3-enoyl derivatives **26–28**. At this stage of the synthetic route, separation of the *anti*/*syn* mixture of diastereomers was readily achieved by column chromatography to give the enoyl derivatives as single stereoisomers in modest yields over the two steps.

Following literature precedent for the RCM reaction of sterically crowded alkenes,[2k] Grubbs 2nd generation catalyst was used for the final step. Treatment of prop-2-enoyls **20–22** with 4–5 mol% of Grubbs 2nd generation catalyst gave 1*H*-pyrrol-2(5*H*)-ones **23–25** in high yields (82–85%). In a similar manner, but-2-enoyls **26–28** were converted to the corresponding 3,6-dihydro-1*H*-pyridin-2-ones **29–31** in 56–89% yields.[14] To probe the enantiopurity of the target compounds, (5*R*)-5-phenethyl-1*H*-pyrrol-2(5*H*)-one (**23**) was used as an example and analysed using chiral HPLC. The enantiopurity was found to be 93% ee.[15] The commercially available methyl (2*S*)-2-hydroxy-3-phenylpropionate **7** used in



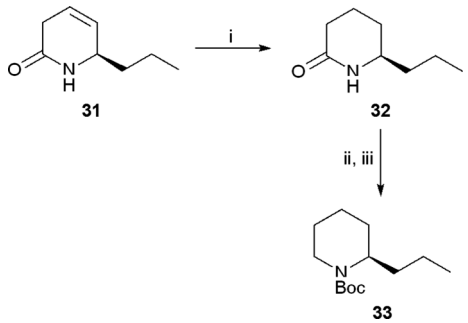
Scheme 3 *Reagents and conditions*: i. 1.0 M NaOH, MeOH, 70 °C; ii. $H_2C{=}CHCOCl$, Et_3N, Et_2O, −78 °C to rt; iii. $H_2C{=}CHCH_2CO_2H$, EDCI, DMAP, CH_2Cl_2, 0 °C to rt; iv. Grubbs' 2nd generation catalyst (4–5 mol%), CH_2Cl_2, 40 °C.

this study is known to have an enantiopurity of 98% and so this approach to optically active 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones generates products with excellent retention of stereochemical integrity.

As highlighted above, 1*H*-pyrrol-2(5*H*)-ones and 3,6-dihydro-1*H*-pyridin-2-ones are key synthetic intermediates for the preparation of a wide-range of medicinally important compounds and natural products.[2,3] To demonstrate the utility of this approach for the stereoselective synthesis of functionalised *N*-heterocyclic compounds, (6*R*)-6-propyl-3,6-dihydro-1*H*-pyridin-2-one (**31**) was used to prepared the *N*-Boc derivative of (−)-coniine (Scheme 4). Hydrogenation of **31** with 10% palladium on carbon gave the saturated piperidin-2-one **32** in quantitative yield. Reduction of **32** with lithium aluminium hydride gave (−)-coniine. As the free base of coniine is known to be toxic and volatile,[16] the product was isolated as the Boc-derivative **33**, by treatment with di-*tert*-butyl dicarbonate under standard conditions. This gave **33** in 48% yield over the two steps.

Conclusions

In summary, a general stereoselective approach for the flexible synthesis of either 1*H*-pyrrol-2(5*H*)-ones or 3,6-dihydro-1*H*-pyridin-2-ones has been developed. This involved the use of a (*S*)-phenyllactate derivative as a chiral auxiliary that was used in a chelation controlled stereoselective reduction. The resulting allylic secondary alcohols were subjected to the key steps of an Overman rearrangement and a RCM reaction to give the target unsaturated γ- and δ-lactams. In this study, we focused on a limited number of side-chain motifs and the synthesis of specifically 5- and 6-membered rings. However, we believe this approach can be easily expanded for the stereoselective preparation of functionalised unsaturated lactams with a wide range of side-chains and with various ring sizes. Access to the opposite enantiomers should also be possible using methyl (2*R*)-2-hydroxy-3-phenylpropionate as the starting material, easily prepared in two steps from D-phenylalanine.[5] Work to expand this scope of this process is currently under way.



Scheme 4 *Reagents and conditions*: i. H_2, 10% Pd/C, EtOAc, 100%; ii. $LiAlH_4$, Et_2O, 30 °C; iii. Boc_2O, Et_3N, DMAP, Et_2O, 48% over two steps.

Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey–Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with potassium permanganate. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Assignment of ^1H and ^{13}C NMR signals are based on two-dimensional COSY and DEPT experiments, respectively. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line ($\lambda = 589$ nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. The chiral HPLC methods were calibrated with their corresponding racemic mixtures.

Methyl (2*S*)-2-methoxymethoxy-3-phenylpropionate (8)[17]

To a solution of methyl (2*S*)-2-hydroxy-3-phenylpropionate (**7**) (4.69 g, 26.0 mmol) stirring at 0 °C in dichloromethane (250 mL)

was added diisopropylethylamine (9.07 mL, 52 mmol) followed by bromomethyl methyl ether (4.24 mL, 52.0 mmol). The reaction was heated to 40 °C for 18 h then cooled to room temperature. The mixture was washed with 1 M hydrochloric acid (100 mL) and water (100 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 6 : 4) afforded methyl (2*S*)-2-methoxymethoxy-3-phenylpropionate (**8**) (5.19 g, 89%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2952 (CH), 1751 (CO), 1438, 1210, 1022, 700; $[\alpha]_D^{23}$ −56.9 (*c* 0.9, $CHCl_3$), lit.[17] −56.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.98 (1H, dd, *J* 13.8, 9.0 Hz, 3-*H*H), 3.07 (3H, s, OCH_3), 3.11 (1H, dd, *J* 13.8, 4.0 Hz, 3-H*H*), 3.73 (3H, s, OCH_3), 4.34 (1H, dd, *J* 9.0, 4.0 Hz, 2-H), 4.51 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.21–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 38.8 (CH_2), 51.6 (CH_3), 55.3 (CH_3), 75.9 (CH), 95.6 (CH_2), 126.3 (CH), 127.9 (2 × CH), 129.0 (2 × CH), 136.6 (C), 172.2 (C); *m*/*z* (CI) 225.1124 (MH^+. $C_{12}H_{17}O_4$ requires 225.1127), 193 (100%), 162 (12), 133 (39) and 85 (22).

(3*S*)-1-(Dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (9)

To a solution of dimethyl methylphosphonate (6.39 mL, 60.0 mmol) in tetrahydrofuran (100 mL) stirring at −78 °C was added 1.6 M n-butyllithium in hexane (45 mL, 72.4 mmol) dropwise and the reaction stirred for 1 h. The mixture was added dropwise to a solution of methyl (2*S*)-2-methoxymethoxy-3-phenylpropionate (**8**) (6.01 g, 26.8 mmol) in tetrahydrofuran (200 mL) stirring at −78 °C. The mixture was allowed to warm to room temperature over 18 h, quenched with 2 M ammonium chloride solution (50 mL), then concentrated under reduced pressure. The residue was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (100% ethyl acetate) afforded (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (**9**) (7.62 g, 90%) as a pale yellow oil. ν_{max}/cm^{-1} (neat) 2955 (CH), 1723 (CO), 1455, 1257, 1031, 810; $[\alpha]_D^{21}$ −29.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.92 (1H, dd, *J* 13.9, 8.6 Hz, 4-*H*H), 3.05 (1H, dd, *J* 13.9, 4.2 Hz, 4-H*H*), 3.10–3.28 (5H, m, 1-H_2 and OMe), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.37 (1H, dd, *J* 8.6, 4.2 Hz, 3-H), 4.49 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.59 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.21–7.43 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 37.1 (d, J_{C-P} 132 Hz, CH_2), 38.0 (CH_2), 53.0 (CH_3), 53.1 (CH_3), 55.9 (CH_2), 83.1 (CH), 96.5 (CH_2), 126.8 (CH), 128.5 (2 × CH), 129.5 (2 × CH), 136.7 (C), 202.8 (C); *m*/*z* (FAB) 317.1158 (MH^+. $C_{14}H_{22}O_6P$ requires 317.1154), 285 (93%), 267 (51), 255 (39), 152 (54), 110 (12) and 86 (6).

(3*E*,6*S*)-1,7-Diphenyl-6-methoxymethoxyhept-3-en-5-one (10)

To a solution of (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (**9**) (0.10 g, 0.32 mmol) in acetonitrile (10 mL) was added anhydrous potassium carbonate (0.05 g, 0.38 mmol) followed by hydrocinnamaldehyde (0.09 g, 0.63 mmol) and the reaction was heated to 75 °C for 24 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The resulting residue was partitioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated then washed with water (2 × 25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/diethyl ether 1 : 0 to 8 : 2) afforded (3*E*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-one (**10**) (0.10 g, 92%) as a pale yellow oil. ν_{max}/cm^{-1} (neat) 3028, 2929 (CH), 1693 (CO), 1496, 1454, 1148, 1051; $[\alpha]_D^{23}$ −36.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.55 (2H, q, *J* 7.4 Hz, 2-H_2), 2.78 (2H, t, *J* 7.4 Hz, 1-H_2), 2.85 (1H, dd, *J* 13.8, 9.1 Hz, 7-*H*H), 2.95 (1H, dd, *J* 13.8, 4.2 Hz, 7-H*H*), 3.03 (3H, s, OCH_3), 4.35 (1H, dd, *J* 9.1, 4.2 Hz, 6-H), 4.44 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.49 (1H, d, *J* 6.9 Hz, OCH*H*O), 6.49 (1H, d, *J* 15.8 Hz, 4-H), 7.01 (1H, dt, *J* 15.8, 7.4 Hz, 3-H), 7.14–7.32 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 34.3 (CH_2), 34.4 (CH_2), 38.9 (CH_2), 55.7 (CH_3), 81.9 (CH), 96.0 (CH_2), 126.2 (CH), 126.3 (CH), 126.7 (CH), 128.4 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.5 (2 × CH), 137.2 (C), 140.7 (C), 148.1 (CH), 199.3 (CO); *m*/*z* (CI) 325.1806 (MH^+. $C_{21}H_{25}O_3$ requires 325.1804), 294 (100%), 266 (13), 220 (5), 159 (4), 137 (5), 85(9).

(4*E*,7*S*)-2-Methyl-7-methoxymethoxy-8-phenyloct-4-en-6-one (11)

The reaction was carried out as described above using (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (**9**) (4.52 g, 14.3 mmol) and 3-methylbutanal (3.08 mL, 28.6 mmol). Flash column chromatography (petroleum ether/diethyl ether 95 : 5 to 15 : 85) afforded (4*E*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-one (**11**) (3.63 g, 92%) as a pale yellow oil. ν_{max}/cm^{-1} (neat) 2955 (CH), 1693 (CO), 1625 (C═C), 1496, 1455, 1316, 1149, 920; $[\alpha]_D^{21}$ −37.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (6H, d, *J* 6.8 Hz, 1-H_3 and 2-CH_3), 1.77 (1H, nonet, *J* 6.8 Hz, 2-H), 2.11 (2H, td, *J* 6.8, 1.3 Hz, 3-H_2), 2.89 (1H, dd, *J* 14.0, 9.0 Hz, 8-*H*H), 3.01 (1H, dd, *J* 14.0, 4.2 Hz, 8-H*H*), 3.06 (3H, s, OCH_3), 4.40 (1H, dd, *J* 9.0, 4.2 Hz, 7-H), 4.49 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.54 (1H, d, *J* 6.9 Hz, OCH*H*O), 6.40 (1H, dt, *J* 15.6, 1.3 Hz, 5-H), 7.00 (1H, dt, *J* 15.6, 6.8 Hz, 4-H), 7.20–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.4 (2 × CH_3), 27.9 (CH), 39.0 (CH_2), 42.0 (CH_2), 55.7 (CH_3), 81.8 (CH), 96.0 (CH_2), 126.6 (CH), 126.7 (CH), 128.4 (2 × CH), 129.5 (2 × CH), 137.2 (C), 148.5 (CH), 199.3 (C); *m*/*z* (CI) 277.1802 (MH^+. $C_{17}H_{25}O_3$ requires 277.1804), 245 (100%), 217 (13), 215 (10), 157 (4), 111 (6), 85 (7).

(4*E*,7*S*)-7-Methoxymethoxy-8-phenyloct-4-en-6-one (12)

The reaction was carried out as described above using (3*S*)-1-(dimethoxyphosphoryl)-2-oxo-3-methoxymethoxy-4-phenylbutane (**9**) (5.28 g, 16.7 mmol) and butanal (3.01 mL, 33.4 mmol). Flash column chromatography (petroleum ether/diethyl ether 9 : 1 to 8 : 2) afforded (4*E*,7*S*)-7-methoxymethoxy-8-phenyloct-4-en-6-one (**12**) (2.71 g, 62%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2959 (CH), 1693 (CO), 1625 (C═C), 1455, 1149, 1053, 700; $[\alpha]_D^{28}$ −51.7 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.4 Hz, 1-H_3), 1.49 (2H, sextet, *J* 7.4 Hz, 2-H_2), 2.20 (2H, qd, *J* 7.4, 1.6 Hz, 3-H_2), 2.89 (1H, dd, *J* 14.0, 9.2 Hz, 8-*H*H), 3.00 (1H, dd, *J* 14.0, 4.4 Hz, 8-H*H*), 3.06 (3H, s, OCH_3), 4.40 (1H, dd, *J* 9.2, 4.4 Hz, 7-H), 4.48 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.40 (1H, d, *J* 15.7 Hz, 5-H), 7.01 (1H, dt, *J* 15.7, 7.4 Hz, 4-H), 7.20–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 21.3 (CH_2), 34.7 (CH_2), 39.0 (CH_2), 55.7 (CH_3), 81.9 (CH),

96.0 (CH_2), 125.8 (CH), 126.6 (CH), 128.4 (2 × CH), 129.5 (2 × CH), 137.2 (C), 149.4 (CH), 199.4 (C); *m/z* (CI) 263.1651 (MH^+. $C_{16}H_{23}O_3$ requires 263.1647), 231 (100%), 201 (8), 143 (5), 121 (9), 85 (9).

(3*E*,5*R*,6*S*)- and (3*E*,5*S*,6*S*)-1,7-Diphenyl-6-methoxymethoxyhept-3-en-5-ol (14)

To a solution of anhydrous zinc chloride (1.48 g, 10.8 mmol) in tetrahydrofuran (200 mL) stirring at 0 °C was added sodium borohydride (0.82 g, 21.5 mmol) and the reaction mixture was stirred while warming to room temperature over 18 h. Stirring of the reaction was stopped, the solids allowed to settle, and the solution was cooled to −78 °C. The supernatant solution was added dropwise *via* cannula to a solution of (3*E*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-one (**10**) (0.87 g, 2.69 mmol) in tetrahydrofuran (50 mL) at −78 °C. The reaction was stirred while warming to room temperature over 18 h, then cooled to 0 °C and quenched dropwise with water (20 mL). The mixture was partitioned between water (150 mL) and diethyl ether (150 mL). The organic phase was separated, washed with water (150 mL) then brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9 : 1 to 7 : 3) afforded (3*E*,5*R*,6*S*)- and (3*E*,5*S*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-ol (**14**) (0.76 g, 87%) in a 7 : 1 ratio, respectively as a colourless oil. ν_{max}/cm^{-1} (neat) 3435 (OH), 2927 (CH), 1638 (C=C), 1496, 1454, 1036, 699; NMR spectroscopic data for major diastereomer (3*E*,5*R*,6*S*): δ_H (400 MHz, $CDCl_3$) 2.44 (2H, q, *J* 7.0 Hz, 2-H_2), 2.59 (1H, dd, *J* 14.1, 5.1 Hz, 7-*H*H), 2.64–2.75 (3H, m, 1-H_2 and 7-H*H*), 2.99 (1H, d, *J* 6.8 Hz, OH), 3.23 (3H, s, OCH_3), 3.73 (1H, ddd, *J* 8.1, 5.1, 2.4 Hz, 6-H), 4.07 (1H, td, *J* 6.8, 2.4 Hz, 5-H), 4.38 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.60 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.61 (1H, ddt, *J* 15.5, 6.8, 1.3 Hz, 4-H), 5.78 (1H, dt, *J* 15.5, 7.0 Hz, 3-H), 7.15–7.30 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 34.2 (CH_2), 35.5 (CH_2), 37.5 (CH_2), 55.7 (CH_3), 73.9 (CH), 84.7 (CH), 97.2 (CH_2), 125.9 (2 × CH), 126.3 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.4 (2 × CH), 133.5 (CH), 138.6 (C), 141.7 (C); *m/z* (CI) 309.1853 (MH^+–H_2O. $C_{21}H_{25}O_2$ requires 309.1855), 277 (100%), 265 (24), 247 (18), 175 (6), 131 (16).

(4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-2-Methyl-7-methoxymethoxy-8-phenyloct-4-en-6-ol (15)

The reaction was carried out as described above using zinc chloride (6.50 g, 47.7 mmol), sodium borohydride (3.61 g, 95.5 mmol) and (4*E*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-one (**11**) (3.30 g, 11.9 mmol). Flash column chromatography (petroleum ether/ethyl acetate 95 : 5 to 3 : 1) afforded (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-ol (**15**) (3.32 g, 100%) in a 10 : 1 ratio, respectively as a colourless oil. ν_{max}/cm^{-1} (neat) 3451 (OH), 2955 (CH), 1667 (C=C), 1604, 1496, 1454, 1367, 1038, 918; NMR spectroscopic data for major diastereomer (4*E*,6*R*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.8 Hz, 1-H_3), 0.93 (3H, d, *J* 6.8 Hz, 2-CH_3), 1.68 (1H, nonet, *J* 6.8 Hz, 2-H), 1.96–2.03 (2H, m, 3-H_2), 2.75 (1H, dd, *J* 14.0, 5.2 Hz, 8-*H*H), 2.81 (1H, dd, *J* 14.0, 8.2 Hz, 8-H*H*), 2.99 (1H, d, *J* 6.4 Hz, OH), 3.24 (3H, s, OCH_3), 3.84 (1H, ddd, *J* 8.2, 5.2, 2.4 Hz, 7-H), 4.09 (1H, td, *J* 6.4, 2.4 Hz, 6-H), 4.40 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.62 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.58 (1H, ddt, *J* 15.2, 6.4, 1.2 Hz, 5-H), 5.74 (1H, dt, *J* 15.2, 7.6 Hz, 4-H), 7.18–7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 22.4 (CH_3), 28.3 (CH), 37.5 (CH_2), 41.9 (CH_2), 55.7 (CH_3), 74.0 (CH), 84.6 (CH), 97.2 (CH_2), 126.2 (CH), 128.3 (2 × CH), 128.9 (CH), 129.4 (2 × CH), 133.3 (CH), 138.7 (C); *m/z* (CI) 261.1854 (MH^+–H_2O. $C_{17}H_{25}O_2$ requires 261.1855), 262 (23%), 229 (16), 217 (17), 113 (42).

(4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-7-Methoxymethoxy-8-phenyloct-4-en-6-ol (16)

The reaction was carried out as described above using zinc chloride (4.63 g, 34.0 mmol), sodium borohydride (2.57 g, 68.0 mmol) and (4*E*,7*S*)-7-methoxymethoxy-8-phenyloct-4-en-6-one (**12**) (2.23 g, 8.50 mmol). Flash column chromatography (petroleum ether/ethyl acetate 85 : 15 to 4 : 1) afforded (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-7-methoxymethoxy-8-phenyloct-4-en-6-ol (**16**) (2.25 g, 100%) in a 7 : 1 ratio, respectively as a colourless oil. ν_{max}(film)/cm^{-1} 3441 (OH), 2924 (CH), 1450, 1149, 1096, 1034, 702; NMR spectroscopic data for major diastereomer (4*E*,6*R*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4 Hz, 1-H_3), 1.46 (2H, sextet, *J* 7.4 Hz, 2-H_2), 2.09 (2H, q, *J* 7.4 Hz, 3-H_2), 2.75 (1H, dd, *J* 14.4, 5.2 Hz, 8-*H*H), 2.81 (1H, dd, *J* 14.4, 8.0 Hz, 8-H*H*), 2.91 (1H, d, *J* 6.8 Hz, OH), 3.24 (3H, s, OCH_3), 3.84 (1H, ddd, *J* 8.0, 5.2, 2.6 Hz, 7-H), 4.09 (1H, td, *J* 6.8, 2.6 Hz, 6-H), 4.56 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.61 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.58 (1H, dd, *J* 15.6, 6.8 Hz, 5-H), 5.75 (1H, dt, *J* 15.6, 7.4 Hz, 4-H), 7.18–7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 22.4 (CH_2), 34.6 (CH_2), 37.5 (CH_2), 55.7 (CH_3), 74.0 (CH), 84.6 (CH), 97.2 (CH_2), 126.2 (CH), 128.0 (CH), 128.3 (2 × CH), 129.4 (2 × CH), 134.4 (CH), 138.7 (C); *m/z* (CI) 247.1699 (MH^+–H_2O. $C_{16}H_{23}O_2$ requires 247.1698), 215 (100%), 203 (55), 185 (36), 171 (21), 113 (14), 99 (42).

(3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-Diphenyl-3-(2′,2′,2′-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene (17)

To a solution of (3*E*,5*R*,6*S*)- and (3*E*,5*S*,6*S*)-1,7-diphenyl-6-methoxymethoxyhept-3-en-5-ol (**14**) (1.54 g, 4.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.71 mL, 4.7 mmol) in dichloromethane (150 mL) was added trichloroacetonitrile (0.95 mL, 9.4 mmol) and the reaction stirred for 48 h at room temperature. The mixture was filtered under reduced pressure through silica gel and washed with diethyl ether (50 mL). Concentration under reduced pressure gave a yellow oil. The oil was dissolved in *p*-xylene (250 mL), and potassium carbonate (0.10 g, 0.7 mmol) was added to the mixture. The mixture was heated to 140 °C for 18 h, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 95 : 5 to 7 : 3) gave (3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-diphenyl-3-(2′,2′,2′-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene (**17**) (1.85 g, 84% over two steps) in a 7 : 1 ratio, respectively as a yellow oil. ν_{max}/cm^{-1} (neat) 3328 (NH), 2928 (CH), 1697 (CO), 1516, 1040, 822; NMR spectroscopic data for major diastereomer (3*R*,4*E*,6*S*): δ_H (400 MHz, $CDCl_3$) 1.91 (2H, q, *J* 7.5 Hz, 2-H_2), 2.60 (2H, t, *J* 7.5 Hz, 1-H_2), 2.80 (1H, dd, *J* 13.6, 6.4 Hz, 7-*H*H), 2.92 (1H, dd, *J* 13.6, 6.4 Hz, 7-H*H*), 3.12 (3H, s, OCH_3), 4.27 (1H, q, *J* 6.4 Hz, 6-H), 4.39–4.46 (1H, m, 3-H), 4.47 (1H, d, *J* 6.9 Hz,

OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.54 (1H, dd, *J* 15.8, 5.2 Hz, 4-H), 5.61 (1H, dd, *J* 15.8, 6.4 Hz, 5-H), 6.42 (1H, d, *J* 8.2 Hz, NH), 7.10–7.32 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 31.9 (CH_2), 36.2 (CH_2), 42.2 (CH_2), 52.4 (CH), 55.3 (CH_3), 76.8 (CH), 92.7 (CCl_3), 93.9 (CH_2), 126.3 (CH), 126.4 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.7 (2 × CH), 129.7 (2 × CH), 131.0 (CH), 132.3 (CH), 137.8 (C), 140.7 (C), 161.0 (CO); *m*/*z* (CI) 470.1049 (MH^+. $C_{23}H_{27}{}^{35}Cl_3NO_3$ requires 470.1057), 408 (38%), 374 (100), 340 (43).

(4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-Methyl-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (18)

The reaction was carried out as described above using (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-2-methyl-7-methoxymethoxy-8-phenyloct-4-en-6-ol (**15**) (2.17 g, 7.79 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.17 mL, 7.79 mmol) and trichloroacetonitrile (1.56 mL, 15.6 mmol). Flash column chromatography (petroleum ether/diethyl ether 1 : 0 to 8 : 2) gave (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-methyl-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**18**) (1.54 g, 52% over two steps) in a 10 : 1 ratio, respectively as colourless oil. ν_{max}/cm^{-1} (neat) 3347 (NH), 2956 (CH), 2929, 1693 (CO), 1684 (C═C), 1519, 1037, 820; NMR spectroscopic data for major diastereomer (4*R*,5*E*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 7.6 Hz, 1-H_3) 0.95 (3H, d, *J* 7.6 Hz, 2-CH_3), 1.37–1.53 (2H, m, 3-H_2), 1.60 (1H, nonet, *J* 7.6 Hz, 2-H), 2.82 (1H, dd, *J* 13.6, 6.4 Hz, 8-*H*H), 2.92 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 3.13 (3H, s, OCH_3), 4.24–4.30 (1H, m, 7-H), 4.43–4.49 (2H, m, 4-H and OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.51 (1H, dd, *J* 16.0, 6.4 Hz, 5-H), 5.57–5.66 (1H, m, 6-H), 6.42 (1H, d, *J* 8.5 Hz, NH), 7.19–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 22.5 (CH_3), 24.8 (CH), 42.2 (CH_2), 43.8 (CH_2), 51.1 (CH_3), 55.2 (CH), 76.8 (CH), 92.8 (C), 93.7 (CH_2), 126.3 (CH), 128.2 (2 × CH), 129.7 (2 × CH), 131.6 (CH), 131.7 (CH), 137.8 (C), 160.9 (C); *m*/*z* (FAB) 444.0886 (MNa^+. $C_{19}H_{26}{}^{35}Cl_3NNaO_3$ requires 444.0876), 360 (100%), 325 (14), 199 (36), 143 (44).

(4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2′,2′,2′-Trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (19)

The reaction was carried out as described above using (4*E*,6*R*,7*S*)- and (4*E*,6*S*,7*S*)-7-methoxymethoxy-8-phenyloct-4-en-6-ol (**16**) (2.52 g, 9.53 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.43 mL, 9.53 mmol) and trichloroacetonitrile (1.91 mL, 19.06 mmol). Flash column chromatography (petroleum ether/diethyl ether 1 : 0 to 7 : 3) gave (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**19**) (1.94 g, 48% over two steps) in a 7 : 1 ratio, respectively as colourless oil. ν_{max}/cm^{-1} (neat) 3325 (NH), 2932 (CH), 1697 (CO), 1512, 1033, 817; NMR spectroscopic data for major diastereomer (4*R*,5*E*,7*S*): δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.4 Hz, 1-H_3), 1.26 (2H, sextet, *J* 7.4 Hz, 2-H_2), 1.47 (2H, q, *J* 7.4 Hz, 3-H_2), 2.72 (1H, dd, *J* 13.6, 7.0 Hz, 8-*H*H), 2.84 (1H, dd, *J* 13.6, 7.0 Hz, 8-H*H*), 3.05 (3H, s, OCH_3), 4.18 (1H, q, *J* 7.0 Hz, 7-H), 4.29–4.34 (1H, m, 4-H), 4.39 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.45 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.44 (1H, dd, *J* 15.6, 6.0 Hz, 5-H), 5.48–5.55 (1H, m, 6-H), 6.33 (1H, br d, *J* 8.2 Hz, NH), 7.10–7.21 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 18.8 (CH_2), 36.8 (CH_2), 42.2 (CH_2), 52.5 (CH), 55.2 (CH_3), 76.9 (CH), 92.8 (C), 93.8 (CH_2), 126.3 (CH), 128.2 (2 × CH), 129.7 (2 × CH), 131.5 (CH), 131.8 (CH), 137.8 (C), 161.0 (C); *m*/*z* (FAB) 430.0717 (MNa^+. $C_{18}H_{24}{}^{35}Cl_3NNaO_3$ requires 430.0719), 348 (52%), 346 (50), 297 (14), 185 (59), 117 (18).

(3*R*,4*E*,6*S*)-1,7-Diphenyl-3-(prop-2′-enoylamino)-6-methoxymethoxyhept-4-ene (20)

To a solution of (3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-diphenyl-3-(2′,2′,2′-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene (**17**) (0.67 g, 1.42 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 25 mL) and ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue (0.46 g, 1.42 mmol) was dissolved in diethyl ether (15 mL), cooled to −78 °C, and triethylamine (0.26 mL, 1.82 mmol) was added. A solution of acryloyl chloride (0.12 mL, 1.38 mmol) in diethyl ether (15 mL) was added dropwise and the reaction mixture was stirred while returning to room temperature over 18 h. The reaction mixture was partitioned between water (30 mL) and diethyl ether (15 mL) and the organic layer was separated, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 1 : 0 to 8 : 2) gave (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(prop-2′-enoylamino)-6-methoxymethoxyhept-4-ene (**20**) (0.26 g, 48%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3273 (NH), 2941 (CH), 1655 (CO), 1542, 1039, 699; $[\alpha]_D^{27}$ −20.7 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.83 (2H, q, *J* 6.9 Hz, 2-H_2), 2.57–2.61 (2H, m, 1-H_2), 2.79 (1H, dd, *J* 13.6, 6.1 Hz, 7-*H*H), 2.90 (1H, dd, *J* 13.6, 7.5 Hz, 7-H*H*), 3.09 (3H, s, OCH_3), 4.21–4.26 (1H, m, 6-H), 4.45 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.57–4.64 (1H, m, 3-H), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.34 (1H, d, *J* 8.6 Hz, NH), 5.53–5.54 (2H, m, 4-H and 5-H), 5.65 (1H, dd, *J* 10.2, 1.4 Hz, 3′-*H*H), 6.02 (1H, dd, *J* 17.0, 10.2 Hz, 2′-H), 6.26 (1H, dd, *J* 17.0, 1.4 Hz, 3′-H*H*), 7.00–7.47 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 32.1 (CH_2), 36.6 (CH_2), 42.3 (CH_2), 50.3 (CH), 55.2 (CH_3), 77.1 (CH), 93.7 (CH_2), 126.1 (CH), 126.3 (CH), 126.7 (CH_2), 128.2 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.7 (2 × CH), 130.8 (CH), 131.1 (CH), 132.9 (CH) 138.1 (C), 141.4 (C), 164.6 (CO); *m*/*z* (CI) 380.2227 (MH^+. $C_{24}H_{28}NO_3$ requires 380.2226), 318 (100%), 288 (9), 249 (6), 97 (18).

(4*R*,5*E*,7*S*)-2-Methyl-4-(prop-2′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (21)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-methyl-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**18**) (1.40 g, 3.31 mmol). Flash column chromatography (petroleum ether/ethyl acetate 8 : 2 to 7 : 3) afforded (4*R*,5*E*,7*S*)-2-methyl-4-(prop-2′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**21**) (0.53 g, 48%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3270 (NH), 2954 (CH), 1654 (CO), 1625 (C═C), 1542, 1148, 1040; $[\alpha]_D^{25}$ +12.7 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8 Hz, 1-H_3), 0.91 (3H, d, *J* 6.8 Hz, 2-CH_3), 1.28–1.41 (2H, m, 3-H_2), 1.56 (1H, nonet, *J* 6.8 Hz, 2-H), 2.78 (1H, dd, *J* 13.6, 6.4 Hz, 8-*H*H), 2.88

(1H, dd, *J* 13.6, 8.0 Hz, 8-H*H*), 3.07 (3H, s, OCH_3), 4.18–4.23 (1H, m, 7-H), 4.43 (1H, d, *J* 8.0 Hz, OC*H*HO), 4.57–4.64 (2H, m, OCH*H*O and 4-H), 5.31 (1H, br d, *J* 8.6 Hz, NH), 5.44 (1H, dd, *J* 15.6, 6.0 Hz, 5-H), 5.54 (1H, dd, *J* 15.6, 7.2 Hz, 6-H), 5.66 (1H, dd, *J* 10.2, 1.4 Hz, 3′-*H*H), 6.06 (1H, dd, *J* 16.9, 10.2 Hz, 2′-H), 6.29 (1H, dd, *J* 16.9, 1.4 Hz, 3′-H*H*), 7.19–7.27 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.5 (CH_3), 22.6 (CH_3), 24.8 (CH), 42.3 (CH_2), 44.6 (CH_2), 48.7 (CH_3), 55.2 (CH), 77.1 (CH), 93.6 (CH_2), 126.2 (CH), 126.6 (CH_2), 128.1 (2 × CH), 129.8 (2 × CH), 130.5 (CH), 130.9 (CH), 133.6 (CH), 138.1 (C), 164.5 (C); *m*/*z* (CI) 332.2222 (MH^+. $C_{20}H_{30}NO_3$ requires 332.2226), 333 (8%), 307 (12), 271 (100), 240 (7).

(4*R*,5*E*,7*S*)-4-(Prop-2′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (22)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**19**) (0.09 g, 0.23 mmol). Flash column chromatography (petroleum ether/ethyl acetate 8 : 2 to 6 : 4) gave (4*R*,5*E*,7*S*)-4-(prop-2′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**22**) (0.03 g, 44%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3278 (NH), 2931 (CH), 1656 (CO), 1626 (C═C), 1544, 1041, 700; $[\alpha]_D^{25}$ +3.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.3 Hz, 1-H_3), 1.24–1.36 (2H, m, 2-H_2), 1.45–1.52 (2H, m, 3-H_2), 2.80 (1H, dd, *J* 13.6, 6.0 Hz, 8-*H*H), 2.91 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 3.10 (3H, s, OCH_3), 4.21–4.26 (1H, m, 7-H), 4.46 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.52–4.60 (1H, m, 4-H), 4.65 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.31 (1H, d, *J* 8.9 Hz, NH), 5.46–5.58 (2H, m, 5-H and 6-H), 5.68 (1H, dd, *J* 10.2, 1.4 Hz, 3′-*H*H), 6.08 (1H, dd, *J* 16.9, 10.2 Hz, 2′-H), 6.31 (1H, dd, *J* 16.9, 1.4 Hz, 3′-H*H*), 7.18–7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 18.9 (CH_2), 37.2 (CH_2), 42.3 (CH_2), 50.2 (CH), 55.2 (CH_3), 77.1 (CH), 93.7 (CH_2), 126.2 (CH), 126.5 (CH_2), 128.1 (2 × CH), 129.7 (2 × CH), 130.6 (CH), 131.0 (CH), 133.3 (CH), 138.1 (C), 168.5 (C); *m*/*z* (CI) 318.2067 (MH^+. $C_{19}H_{28}NO_3$ requires 318.2069), 292 (45%), 256 (100), 226 (11), 85 (9).

(3*R*,4*E*,6*S*)-1,7-Diphenyl-3-(but-3′-enoylamino)-6-methoxymethoxyhept-4-ene (26)

To a solution of (3*R*,4*E*,6*S*)- and (3*S*,4*E*,6*S*)-1,7-diphenyl-3-(2′,2′,2′-trichlomethylcarbonylamino)-6-methoxymethoxyhept-4-ene (**17**) (1.37 g, 2.91 mmol) in methanol (100 mL) was added 1 M aqueous sodium hydroxide (50 mL, 50 mmol) and the solution heated to 70 °C for 18 h. The reaction mixture was cooled, concentrated under reduced pressure and extracted with dichloromethane (2 × 100 mL) and ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue (0.94 g, 2.91 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C, to which was added 3-butenoic acid (0.30 mL, 3.48 mmol), 4-dimethylaminopyridine (0.04 g, 0.30 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.67 g, 3.48 mmol). The reaction mixture was stirred while returning to room temperature over 18 h, then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 9 : 1 to 6 : 4) gave (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(but-3′-enoylamino)-6-methoxymethoxyhept-4-ene (**26**) (0.45 g, 39%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3287 (NH), 2942 (CH), 1648 (CO), 1546 (C═C), 1147, 1040; $[\alpha]_D^{28}$ −60.8 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.72–1.85 (2H, m, 2-H_2) 2.56 (2H, t, *J* 7.8 Hz, 1-H_2), 2.79 (1H, dd, *J* 13.6, 6.0 Hz, 7-*H*H), 2.90 (1H, dd, *J* 13.6, 7.6 Hz, 7-H*H*), 2.95 (2H, dt, *J* 7.2, 1.1 Hz, 2′-H_2), 3.10 (3H, s, OCH_3), 4.21–4.27 (1H, m, 6-H), 4.45 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.48–4.55 (1H, m, 3-H), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.17–5.25 (2H, m, 4′-H_2), 5.35 (1H, d, *J* 8.7 Hz, NH), 5.45–5.54 (2H, m, 4-H and 5-H), 5.86 (1H, ddt, *J* 17.2, 10.0, 7.2 Hz, 3′-H), 7.12–7.29 (10H, m, 2 × Ph); δ_C (100 MHz, $CDCl_3$) 32.1 (CH_2), 36.6 (CH_2), 41.8 (CH_2), 42.3 (CH_2), 50.2 (CH), 55.2 (CH_3), 77.0 (CH) 93.7 (CH_2), 120.1 (CH_2), 126.1 (CH), 126.3 (CH), 128.2 (2 × CH), 128.3 (2 × CH), 128.5 (2 × CH), 129.7 (2 × CH), 130.7 (CH), 131.3 (CH), 133.1 (CH), 138.0 (C), 141.4 (C), 169.6 (C); *m*/*z* (CI) 394.2376 (MH^+. $C_{25}H_{32}NO_3$ requires 394.2382), 374 (35%), 333 (100), 302 (82), 264 (5), 185 (4), 91 (7).

(4*R*,5*E*,7*S*)-2-Methyl-4-(but-3′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (27)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-2-methyl-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**18**) (1.37 g, 2.91 mmol). Flash column chromatography (petroleum ether/ethyl acetate 9 : 1 to 7 : 3) gave (4*R*,5*E*,7*S*)-2-methyl-4-(but-3′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**27**) (0.48 g, 43%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3277 (NH), 2954 (CH), 1646 (CO), 1635 (C═C) 1544, 1040, 916; $[\alpha]_D^{23}$ −15.5 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.81 (6H, d, *J* 6.8 Hz, 1-H_3 and 2-CH_3), 1.18–1.25 (2H, m, 3-H_2), 1.46 (1H, nonet, *J* 6.8 Hz, 2-H), 2.71 (1H, dd, *J* 13.6, 6.0 Hz, 8-*H*H), 2.81 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 2.91 (2H, dt, *J* 7.2, 1.2 Hz, 2′-H_2), 3.00 (3H, s, OCH_3), 4.11–4.16 (1H, m, 7-H), 4.35 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.40–4.47 (1H, m, 4-H), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.11–5.18 (2H, m, 4′-H_2), 5.31 (1H, d, *J* 8.6 Hz, NH), 5.34–5.44 (2H, m, 5-H and 6-H), 5.82 (1H, ddt, *J* 17.6, 14.3, 7.2 Hz, 3′-H), 7.09–7.21 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.0 (CH), 22.5 (CH_3), 22.6 (CH_3), 41.8 (CH_2), 42.3 (CH_2), 44.3 (CH_2), 48.6 (CH), 55.1 (CH_3), 77.0 (CH), 93.6 (CH_2), 119.9 (CH_2), 126.2 (CH), 127.9 (CH), 128.1 (CH), 129.7 (2 × CH), 130.0 (CH), 131.5 (CH), 133.8 (CH), 138.1 (C), 169.4 (C); *m*/*z* (CI) 346.2378 (MH^+. $C_{21}H_{32}NO_3$ requires 346.2382), 284 (100%), 254 (5), 107 (9), 81 (24).

(4*R*,5*E*,7*S*)-4-(But-3′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (28)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)- and (4*S*,5*E*,7*S*)-4-(2′,2′,2′-trichlomethylcarbonylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**19**) (1.45 g, 3.55 mmol). Flash column chromatography (petroleum ether/ethyl acetate 9 : 1 to 7 : 3) gave (4*R*,5*E*,7*S*)-4-(but-3′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**28**) (0.58 g, 49%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3284 (NH), 2931 (CH), 1646 (CO), 1635 (C═C), 1544, 1039, 916; $[\alpha]_D^{25}$ −34.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3 Hz, 1-H_3), 1.20–1.30

(2H, m, 2-H_2), 1.39–1.45 (2H, m, 3-H_2), 2.78 (1H, dd, *J* 13.6, 6.0 Hz, 8-*H*H), 2.89 (1H, dd, *J* 13.6, 7.6 Hz, 8-H*H*), 2.99 (2H, dt, *J* 7.2, 1.1 Hz, 2′-H_2), 3.09 (3H, s, OCH_3), 4.19–4.24 (1H, m, 7-H), 4.43–4.48 (2H, m, OC*H*HO and 4-H), 4.62 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.19–5.27 (2H, m, 4′-H_2), 5.34 (1H, d, *J* 8.5 Hz, NH), 5.44–5.47 (2H, m, 5-H and 6-H), 5.91 (1H, ddt, *J* 17.2, 14.4, 7.2 Hz, 3′-H), 7.17–7.28 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 18.9 (CH_2), 37.2 (CH_2), 41.8 (CH_2), 42.3 (CH_2), 50.0 (CH), 55.2 (CH_3), 77.0 (CH), 93.6 (CH_2), 119.9 (CH_2), 126.2 (CH), 128.1 (2 × CH), 129.7 (2 × CH), 130.2 (CH), 131.5 (CH), 133.6 (CH), 138.1 (C), 169.5 (C); *m*/*z* (FAB) 332.2224 (MH^+. $C_{20}H_{30}NO_3$ requires 332.2226), 270 (100%), 241 (68), 204 (96), 187 (16), 175 (15), 121 (14), 96 (22), 77 (24), 51 (98).

(5*R*)-5-Phenethyl-1*H*-pyrrol-2(5*H*)-one (23)

A solution of (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(prop-2′-enoylamino)-6-methoxymethoxyhept-4-ene (**20**) (0.19 g, 0.49 mmol) stirring in dichloromethane (250 mL) was heated to 40 °C for 0.25 h. Grubbs 2nd generation catalyst (0.02 g, 0.02 mmol) was added, and the mixture stirred at 40 °C for 18 h. The reaction was cooled and the mixture concentrated under vacuum. Flash column chromatography (dichloromethane/methanol 99 : 1) afforded (5*R*)-5-phenethyl-1*H*-pyrrol-2(5*H*)-one (**23**) (0.08 g, 83%) as a white solid. 93% ee determined by HPLC analysis using Chiralcel IB column (5% *i*PrOH/hexane at 1.00 mL min^{-1}), retention time: t_S = 10.9 min, and t_R = 13.7 min; Mp 124–126 °C (decomposition); ν_{max}/cm^{-1} (neat) 3176 (CH), 1676 (CO), 1647 (C=C) 1647, 1456, 820; $[\alpha]_D^{23}$ –93.5 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.81–1.92 (1H, m, 1′-*H*H), 1.94–2.04 (1H, m, 1′-H*H*), 2.68 (2H, t, *J* 8.0 Hz, 2′-H_2), 4.18–4.26 (1H, m, 5-H), 6.11 (1H, dt, *J* 5.8, 1.6 Hz, 3-H), 7.05 (1H, dt, *J* 5.8, 1.6 Hz, 4-H), 7.11–7.24 (5H, m, Ph), 7.75 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 32.4 (CH_2), 34.8 (CH_2), 59.4 (CH), 126.4 (CH), 127.2 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 140.7 (C), 150.2 (CH), 174.3 (C); *m*/*z* (EI) 187.0999 (M^+. $C_{12}H_{13}NO$ requires 187.0997), 118 (40%), 87 (100), 85 (100), 47 (100).

(5*R*)-5-Isobutyl-1*H*-pyrrol-2(5*H*)-one (24)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)-2-methyl-4-(prop-2′-enoylamino)-7-methoxymethoxy-8-phenyl-oct-5-ene (**21**) (0.15 g, 0.437 mmol) and Grubbs 2nd generation catalyst (0.02 g, 0.022 mmol). Flash column chromatography (100% ethyl acetate) gave (5*R*)-5-isobutyl-1*H*-pyrrol-2(5*H*)-one (**24**) (0.05 g, 82%) as a white solid. Mp 76–81 °C; ν_{max}/cm^{-1} 3184 (NH), 2925 (CH), 1681 (CO), 1370, 1220, 810; $[\alpha]_D^{24}$ –203.0 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.6 Hz, 2′-CH_3), 0.99 (3H, d, *J* 6.6 Hz, 3′-H_3), 1.37–1.50 (2H, m, 1′-H_2), 1.76 (1H, nonet, *J* 6.6 Hz, 2′-H), 4.25–4.29 (1H, m, 5-H), 6.09 (1H, dt, *J* 5.8, 1.6 Hz, 3-H), 7.08 (1H, dt, *J* 5.8, 1.6 Hz, 4-H), 7.46 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 23.2 (CH_3), 26.1 (CH), 42.3 (CH_2), 58.5 (CH), 126.7 (CH), 150.9 (CH), 174.4 (C); *m*/*z* (CI) 140.1072 (MH^+. $C_8H_{14}NO$ requires 140.1075), 133 (12%), 113 (16), 97 (20), 81 (66).

(5*R*)-5-Propyl-1*H*-pyrrol-2(5*H*)-one (25)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)-4-(prop-2′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**22**) (0.30 g, 0.09 mmol) and Grubbs 2nd generation catalyst (4.0 mg, 4.25 μmol). Flash column chromatography (100% ethyl acetate) gave (5*R*)-propyl-1*H*-pyrrol-2(5*H*)-one (**25**) (0.01 g, 85%) as a white solid. Mp 98–101 °C; ν_{max}/cm^{-1} (neat) 3150 (NH), 1681 (CO), 1654 (C=C), 1379, 1218, 826; $[\alpha]_D^{26}$ –134.2 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, and $CDCl_3$) 0.90 (3H, t, *J* 7.3 Hz, 3′-H_3), 1.33–1.60 (4H, m, 1′-H_2 and 2′-H_2), 4.13–4.16 (1H, m, 5-H), 6.02 (1H, dt, *J* 5.8, 1.6 Hz, 4-H), 7.00 (1H, dt, *J* 5.8, 1.6 Hz, 3-H), 7.06 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 19.5 (CH_2), 35.3 (CH_2), 59.9 (CH), 126.9 (CH), 150.4 (CH), 174.2 (C); *m*/*z* (EI) 125.0837 (M^+. $C_7H_{11}NO$ requires 125.0841), 110 (32%), 82 (100), 69 (39), 55 (29).

(6*R*)-6-Isobutyl-3,6-dihydro-1*H*-pyridin-2-one (30)

The reaction was carried out as described above using (4*R*,5*E*,7*S*)-2-methyl-4-(but-3′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**27**) (0.16 g, 0.46 mmol) and Grubbs 2nd generation catalyst (0.02 g, 0.02 mmol). Flash column chromatography (100% ethyl acetate) gave (6*R*)-6-isobutyl-3,6-dihydro-1*H*-pyridin-2-one (**30**) (0.06 g, 82%) as a white solid. Mp 69–71 °C; ν_{max}/cm^{-1} (neat) 3206 (NH), 2957 (CH), 1676 (C=C), 1655 (CO), 1406, 827; $[\alpha]_D^{22}$ –26.8 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (6H, t, *J* 6.8 Hz, 2′-CH_3 and 3′-H_3), 1.37–1.47 (2H, m, 1′-H_2), 1.74 (1H, nonet, *J* 6.8 Hz, 2′-H), 2.91–2.94 (2H, m, 3-H_2), 4.04–4.15 (1H, m, 6-H), 5.68–5.77 (2H, m, 4-H and 5-H), 6.03 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.1 (CH_3), 24.3 (CH), 31.3 (CH_2), 46.6 (CH_2), 52.1 (CH), 121.3 (CH), 125.8 (CH), 169.5 (C); *m*/*z* (CI) 154.1231 (MH^+. $C_9H_{16}NO$ requires 154.1232), 142 (4%), 113 (2), 96 (4), 69 (3).

(6*R*)-6-Propyl-3,6-dihydro-1*H*-pyridin-2-one (31)[3h]

The reaction was carried out as described above using (4*R*,5*E*,7*S*)-4-(but-3′-enoylamino)-7-methoxymethoxy-8-phenyloct-5-ene (**28**) (0.30 g, 0.92 mmol) and Grubbs 2nd generation catalyst (0.04 g, 0.05 mmol). Flash column chromatography (100% ethyl acetate) gave (6*R*)-6-propyl-3,6-dihydro-1*H*-pyridin-2-one (**31**) (0.07 g, 56%) as a white solid. Mp 134–136 °C (decomposition); ν_{max}/cm^{-1} (neat) 3185 (NH), 2959 (CH), 1679 (C=C), 1656 (CO), 1341, 1153, 827; $[\alpha]_D^{26}$ –122.8 (*c* 1.0, $CHCl_3$); lit.[3h] for opposite enantiomer, $[\alpha]_D^{23}$ +110.5 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.3 Hz, 3′-H_3), 1.34–1.44 (2H, m, 2′-H_2), 1.51–1.61 (2H, m, 1′-H_2), 2.90–2.94 (2H, m, 3-H_2), 4.06–4.10 (1H, m, 6-H), 5.66–5.72 (1H, m, 5-H), 5.76 (1H, dtd, *J* 10.0, 3.2, 1.6 Hz, 4-H), 6.58 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 17.8 (CH_2), 31.2 (CH_2), 39.3 (CH_2), 53.8 (CH), 121.6 (CH), 125.5 (CH), 169.8 (C); *m*/*z* (CI) 140.1078 (MH^+. $C_8H_{14}NO$ requires 140.1075), 113 (4%), 97 (8), 85 (12), 71 (17).

(6*S*)-6-Phenethylpiperidin-2-one

A solution of (3*R*,4*E*,6*S*)-1,7-diphenyl-3-(but-3′-enoylamino)-6-methoxymethoxyhept-4-ene (**26**) (0.24 g, 0.60 mmol) in dichloromethane (250 mL) was heated to 45 °C for 0.25 h. Grubbs 2nd generation catalyst (0.02 g, 0.03 mmol) was added, and the reaction mixture stirred for 42 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (dichloromethane/methanol 99 : 1) afforded (6*R*)-6-phenethyl-3,6-dihydro-1*H*-pyridin-2-one (**29**) (0.11 g, 89%) as a white solid. Dihydropyridin-2-one **29** was

found to be unstable and so was used without purification. δ_H (400 MHz, $CDCl_3$) 1.83–1.97 (2H, m, 1′-H_2), 2.68 (2H, td, *J* 8.0, 1.6 Hz, 2′-H_2), 2.91–2.95 (2H, m, 3-H_2), 4.07–4.14 (1H, m, 6-H), 5.69–5.74 (1H, m, 5-H), 5.80 (1H, dtd, *J* 10.4, 3.2, 1.6 Hz, 4-H), 6.72 (1H, br s, NH), 7.16–7.33 (5H, m, Ph). To a solution of (6*R*)-6-phenethyl-3,6-dihydro-1*H*-pyridin-2-one (**29**) (0.11 g, 0.55 mmol) in ethyl acetate (35 mL) was added 10% palladium on carbon (0.04 g, 0.04 mmol wrt Pd). The solution was purged with hydrogen gas for 0.25 h then stirred under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through Celite® and washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure to yield a white solid. Flash column chromatography (dichloromethane/methanol 1 : 0 to 96 : 4) gave (6*S*)-6-phenethylpiperidin-2-one (0.11 g, 100%) as a white solid. Mp 84–86 °C; ν_{max}/cm^{-1} (neat) 3214 (NH), 2942 (CH), 1651 (CO), 1603 (C=C), 1402, 1343, 1090; $[\alpha]_D^{22}$ +5.0 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37–1.47 (1H, m, 5-*H*H), 1.63–1.75 (1H, m, 5-H*H*), 1.78–1.84 (2H, m, 1′-H_2), 1.86–1.98 (2H, m, 4-H_2), 2.30 (1H, ddd, *J* 16.4, 10.4, 6.0 Hz, 3-*H*H), 2.35–2.44 (1H, m, 3-H*H*), 2.67 (2H, td, *J* 7.6, 2.8 Hz, 2′-H_2), 3.36–3.42 (1H, m, 6-H), 6.03 (1H, br s, NH), 7.16–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 28.4 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 38.6 (CH_2), 52.6 (CH_2), 126.2 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 140.9 (C), 172.4 (C); *m*/*z* (EI) 203.1313 (M^+. $C_{13}H_{17}NO$ requires 203.1310), 186 (5%), 125 (27), 112 (66), 98 (100).

(6*R*)-6-Propylpiperidin-2-one (32)[3h]

The hydrogenation reaction was carried out as described above using (6*R*)-6-propyl-3,6-dihydro-1*H*-pyridin-2-one (**31**) (0.07 g, 0.52 mmol). This gave (6*R*)-6-propylpiperidin-2-one (**32**) (0.07 g, 100%) as a white solid. Spectroscopic data consistent with literature.[3h] Mp 73–76 °C; ν_{max}/cm^{-1} (neat) 2960 (CH), 2360, 1653 (CO), 1410, 1215, 747; $[\alpha]_D^{25}$ −18.1 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2 Hz, 3′-H_3), 1.21–1.41 (5H, m, 1′-*H*H, 2′-H_2 and 4-H_2), 1.56–1.66 (1H, m, 5-*H*H), 1.79–1.87 (2H, m, 1′-H*H* and 5-H*H*), 2.21 (1H, ddd, *J* 13.6, 8.8, 4.8 Hz, 3-*H*H), 2.29–2.36 (1H, m, 3-H*H*), 3.26–3.32 (1H, m, 6-H), 5.76 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 18.5 (CH_2), 19.8 (CH_2), 28.5 (CH_2), 31.4 (CH_2), 39.1 (CH_2), 53.0 (CH), 172.3 (C); *m*/*z* (CI) 142.1236 (MH^+. $C_8H_{16}NO$ requires 142.1232), 113 (26%), 97 (42), 85 (78), 71 (100).

(6*R*)-*N*-(*tert*-Butoxycarbonyl)-6-propylpiperidine (33)[18]

To a solution of (6*R*)-6-propylpiperidin-2-one (**32**) (0.04 g, 0.31 mmol) in diethyl ether (50 mL) was added lithium aluminium hydride (1.87 mL, 1.87 mmol, 1 M in diethyl ether). The reaction was heated to 30 °C for 18 h. The reaction was quenched with 2 M potassium hydroxide solution (10 mL) then partitioned between diethyl ether (20 mL) and water (20 mL). The organic layer was separated, washed with water (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated at atmospheric pressure and 40 °C. The resulting residue was dissolved in diethyl ether (20 mL) and di-*tert*-butyl dicarbonate (0.27 g, 1.25 mmol), 4-dimethylaminopyridine (0.02 g, 0.13 mmol) and triethylamine (0.18 mL, 1.31 mmol) were added. The reaction was stirred at room temperature for 18 h, then washed with 1 M hydrochloric acid (10 mL), saturated sodium hydrogencarbonate solution (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 85 : 15) afforded (6*R*)-*N*-(*tert*-butoxycarbonyl)-6-propylpiperidine (**33**) (0.034 g, 48%) as a colourless oil. $[\alpha]_D^{24}$ −25.6 (*c* 0.6, $CHCl_3$), lit.[18] $[\alpha]_D^{23}$ −31.6 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.2 Hz, 3′-H_3), 1.14–1.32 (4H, m, 1′-H_2 and 2′-H_2), 1.38 (9H, s, O^{t}Bu), 1.41–1.63 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 2.67 (1H, td, *J* 13.6, 2.6 Hz, 6-*H*H), 3.89 (1H, br d, *J* 2.6 Hz, 6-H*H*), 4.14 (1H, br s, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 19.1 (2 × CH_2), 19.5 (2 × CH_2), 25.7 (CH_2), 28.5 (3 × CH_3), 31.9 (CH_2), 50.1 (CH), 17.9 (C), 155.2 (C); *m*/*z* (EI) 227 (M^+, 4%), 184 (18), 149 (17), 128 (100).

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