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Ring closing metathesis of α- and β-amino acid derived dienes

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Abstract

Three new classes of conformationally constrained peptidomimetics, derived from modified α- and β-amino acids, have been prepared by ring closing metathesis (RCM). The first involves C_α–N′ cyclisation of the peptidic diene (**23**, **24**, **26**), the second $C_{\beta 2}$–N′ cyclisation (**27**, **28**, **29**), and the third N–$C_{\beta 2}$ cyclisation (**30**). The key C-centred olefin of the dienes was introduced by stereoselective α-allylation of either an α- or β-amino acid. The normal favourable influence of a tertiary amide linker in the diene towards RCM is negated by significant steric congestion, and the combination of a secondary amide linker and α,α-disubstitution promotes ring contraction on RCM.

Keywords: Cyclic peptidomimetics; β-Amino acids; Ring closing metathesis; Conformation; β-Turn

1. Introduction

The introduction of conformational restriction (e.g. a ring) into a peptide can lead to increased binding, and hence potency, towards its corresponding bio-receptor. This is not a random process since the geometry and electrostatics of the modified peptide must complement that of the binding site in the receptor. Each system has its own requirements and as such versatile and reliable synthetic methods are needed that introduce rings into linear peptides in a variety of ways, as shown in Fig. 1 for α- and β-peptides. One method that has recently shown much promise in this area is ring closing metathesis (RCM) [1–11].

The advantage of RCM is that it allows the introduction of rings of varying size, and hence conformation, into a modified peptide. However, one must first construct a suitable diene substrate by introducing olefinic groups into a precursor acyclic peptide. This is now possible in a number of ways as evidenced in this paper and discussed elsewhere [2,3,9,12,13]. The commercial availability of well-defined metathesis catalysts with high activity, thermal stability, functional group tolerance and resistance to oxygen and moisture has also greatly facilitated progress in this area [14,15].

β-Strands and β-turns are ideal targets for work in this area since these geometries are central to a number of important biological interactions and hence effects. For example, proteases are known to bind their substrates in an extended β-strand geometry, a fact that has been put to good effect in inhibitor design [16]. RCM has been used to prepare potent inhibitors (**1**) of the Hepatitis C Virus NS3 protease by linking the side chains of the first and third residues of an acyclic precursor (C_α–C_α, Fig. 1) to give a β-strand constraint [17]. A good example of the use of turn motifs can be found in the area of peptide-activated G protein-coupled receptors. Here agonists and antagonists are designed to adopt turn motifs that mimic the intramolecular hydrogen bond between the carbonyl of residue *i* and the NH of either the third, fourth or fifth residue of the natural peptide backbone [18]. The antagonist **2**, prepared by RCM, functions as a turn mimetic in binding to the Grb2 SH2 domain protein [19] (see Fig. 2).

We have had an interest for some time in developing general RCM-based methods for the preparation of a variety of constrained peptides, e.g. cyclic β-amino acids ($C_{\beta 3}$–$C_{\beta 2}$) [2,20], proline peptidomimetics (N–C_α) [3,21] and

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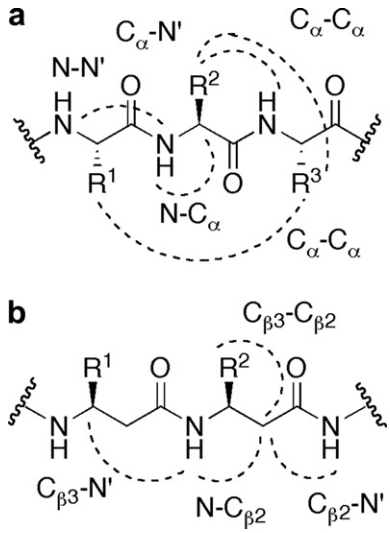


Fig. 1. Possible sites for the inclusion of ring constraints into (a) α-peptides, and (b) β-peptides.

cyclic dipeptides (C_α–C_α) [22]. We now extend this work to prepare new conformationally constrained peptidomimetics **23**, **24**, and **26** (C_α–N′ cyclisation), **27**, **28**, **29**, ($C_{\beta2}$–N′ cyclisation) and **30** (N–$C_{\beta2}$ cyclisation), that literature [9,23], and some preliminary modeling, suggested would adopt turn geometries. Our work also provides some insights into the factors that influence RCM in peptide-like structures. In addition, we demonstrate some approaches for introducing olefins into amino acids and peptides to give the diene substrates for RCM. With these factors in mind the dienes **4**, **9**, **13**, **17**, **20**, **21**, and **22** were prepared, and subjected to RCM to give previously unknown 6- and 7-membered peptidomimetics (Table 1). Some work is also presented on determining the ability of the cyclic peptidomimetics to form turns: the lactams **26**, **27**, **28** and **30** were modeled *in-silico* to determine their ability to stabilize β-turn conformations in penta-residue peptides, and the azepine unit of **30** was incorporated into a calpain inhibitor.

2. Results and discussion

It has been reported that dienes in which a secondary amide links the component double bonds do not readily undergo RCM [24]. By contrast a tertiary amide linker facilitates RCM by increasing the population of the amide rotamer in which the alkenes are *cis* [25,26]. In fact, the introduction of a further and removable substituent onto nitrogen of an amide, has been used to promote RCM [24]. Increased substitution of a diene, as provided by a tertiary amide, would also be expected to enhance the rate of cyclisation via the Gem-Dimethyl effect [27,28]. Examples of the use of secondary amides in RCM are known and these generally give rise to larger-ring lactams, such as 9- [29], 10- [24,30], and 18-membered systems [31]. However, little is known about the effect on the RCM of introducing substituents into the α- and particularly β-amino acids

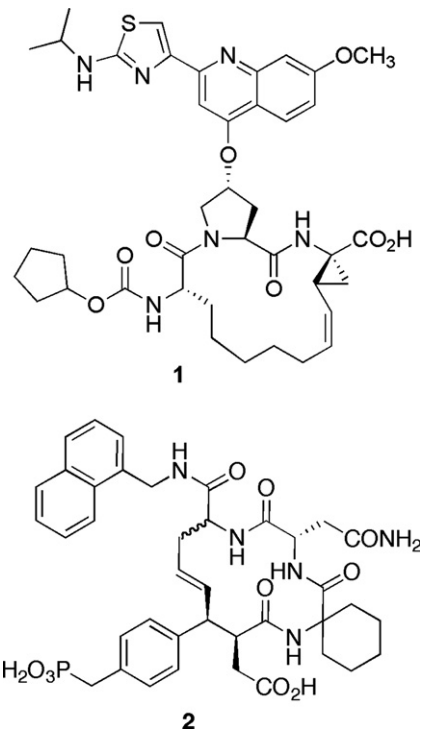
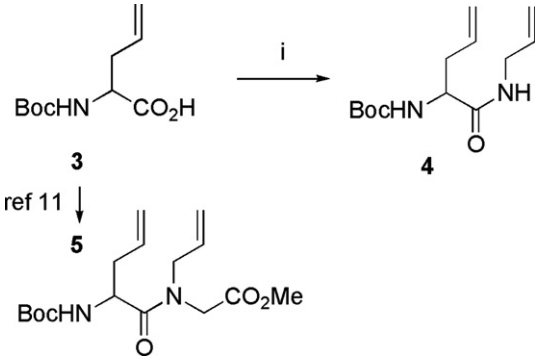


Fig. 2. Conformationally constrained peptidomimetics.

components of dienes, particularly those giving rise to small and medium sized rings. With these points in mind dienes with secondary amides (**4**, **9**, **17** and **20**) and tertiary amides (**13** and **21**) where prepared to gain some insight into the effect of ring size and substitution on the outcome of RCM. Phenylalanine-containing systems were targeted due to ease of synthesis, but the methods presented are amenable to introducing a variety of amino acids into structures of this type.

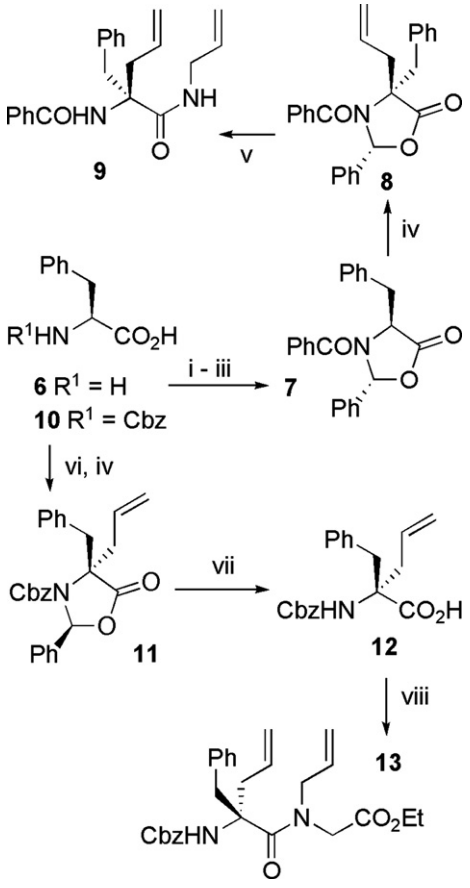
The requisite diene **4** (92%) was prepared by coupling (±)-*N*-Boc-allyl glycine with allylamine under standard *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) conditions, see Scheme 1. Dienes **9** and **13** required the introduction an allyl substituent at the α-carbon of (*S*)-phenylalanine with control of stereochemistry and this was



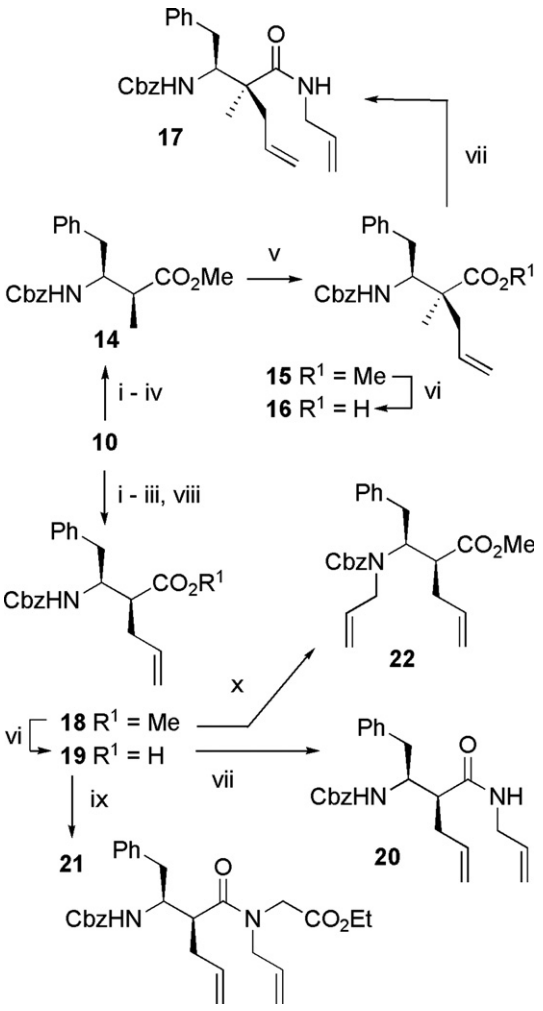
Scheme 1. Allylamine, EDCI, HOBt, DIPEA, DCM, rt.

achieved using Seebach oxazolidinone chemistry (Scheme 2). In particular, the *anti*-oxazolidinone **7** [32], obtained from the sodium salt of **6** on treatment with benzaldahyde followed by benzoyl chloride, was allylated to give α,α-disubstituted **8** as the single stereoisomer shown [33]. Treatment of this with the lithium salt of allylamine in THF gave the desired diene **9** in 91% after purification by chromatography. The diene **13** was similarly prepared (Scheme 2), but using *N*-carbobenzyloxy (Cbz) protection to provide products after RCM that were suitably protected for incorporation into peptide synthesis. It is interesting to note that this change in protecting group gives rise to compounds with the opposite absolute configuration in the allylation step, but this was not considered of significance. Preparation of the tertiary amide **13** required hydrolysis of the oxazolinone **11** [34] followed by coupling with *N*-allyl-glycine ethyl ester in the presence of the peptide coupling agent, (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphoniumm hexafluorophosphate (PyAOP). This gave a modest 18% yield of **13**.

The β-amino acid based dienes **17**, **20**, **21** and **22** were prepared as shown in Scheme 3. Arndt-Eistert homologation [35,36] of *N*-Cbz-(*S*)-phenylalanine **10**, followed by



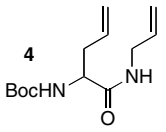
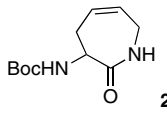
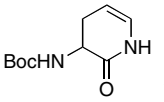
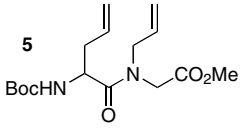
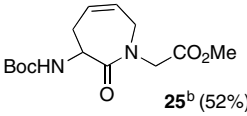
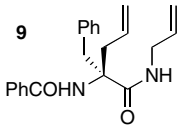
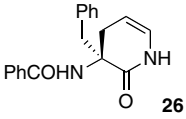
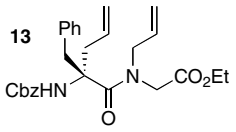
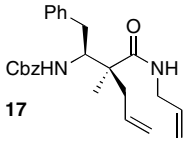
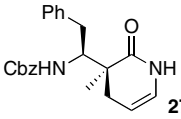
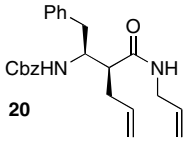
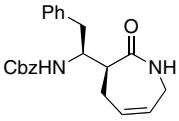
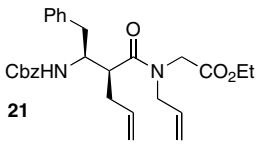
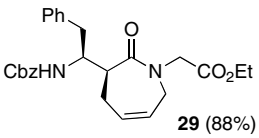
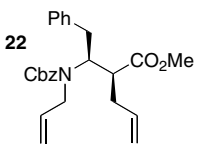
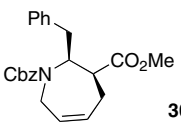
Scheme 2. (i) NaOH(aq); (ii) PhCHO, DCM, reflux; (iii) PhCOCl, DCM, 0 °C; (iv) LiHMDS, allyl bromide, THF, −78 °C; (v) *n*-BuLi, allylamine, THF, −78 °C to rt; (vi) benzaldehyde dimethylacetyl, $BF_3 \cdot OEt_2$, 4 Å sieves, ether; (vii) NaOH, THF, H_2O, MeOH; (viii) *N*-allylglycine ethyl ester, PyAOP, DIPEA, DMF.



Scheme 3. (i) Et_3N, $ClCO_2Et$, THF, −20 °C; (ii) CH_2N_2; (iii) $PhCO_2Ag$, Et_3N, MeOH −20 °C to rt; (iv) MeI, LDA, LiCl, THF −78 °C; (v) allyl bromide, LDA, LiCl, THF −78 °C; (vi) NaOH, MeOH, reflux; (vii) allyl amine, EDCI, HOBt, DIPEA, DCM; (viii) allyl bromide, LDA, LICl, THF −78 °C; (ix) PyAOP, *N*-allylglycine ethyl ester, DIPEA, DMF; (x) allyl bromide, P4-phosphazene, THF.

stereocontrolled allylation or methylation, gave **18** and **14**, respectively [37,38]. The disubstituted β-amino acid **14** was then allylated to give α,α-disubstituted **15**. The methyl esters of **18** and **15** were hydrolyzed, on treatment with NaOH, and the resulting free acids **19** and **16** (respectively) were coupled with allylamine, in the presence of EDCI and HOBt, to give **20** (74%) and **17** (71%). Here again the more active peptide coupling agent PyAOP was required to couple *N*-allyl-glycine ethyl ester with **19**, to give **21**, in 29% after purification by chromatography. Diene **22** required an alternative allylation on nitrogen and this was achieved on treatment of **18** with allyl bromide and 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2^5,4^5-catenadi(phosphazene) (P4-phosphazene) (Scheme 3). From our experience this is the preferred base for the allylation of an amide [11] or carbamate nitrogen, and reaction does not proceed with more conventional bases such as sodium hydride.

Table 1
RCM of amino acid based dienes

Diene	Conditions[a]	Product (yield)
	**A** 4 h	 **23** (46%)  **24** (45%)
	**C** 4 h	 **25**[b] (52%)
	**A** 2 h	 **26** (32%)
	**A** 4 h	**13**
	**A** 4 h	 **27** (71%)
	**B** 2 h	 **28** (89%)
	**B** 2 h	 **29** (88%)
	**B** 2 h	 **30** (82%)

[a] Grubbs 2nd generation catalyst [$Cl_2(PCy_3)$(IMes)Ru(:CHPh)] under a nitrogen atmosphere. **A**, reflux in benzene; **B**, reflux in DCM; **C**, $CHCl_3$, 50 °C.

[b] Reaction details from [11].

Each of the dienes was then subjected to Grubbs second-generation ruthenium catalyst [$Cl_2(PCy_3)$(IMes)-Ru(:CHPh)] under conditions **A** (refluxing benzene), or **B** (refluxing dichloromethane) and the results obtained are presented in Table 1. Treatment of diene **4**, under conditions **B**, gave returned starting material only. However, reaction in refluxing benzene (conditions **A**) for 4 h, gave a 1:1 mixture of the expected 7-membered lactam **23** and the ring contracted 6-membered lactam **24.** Purification of this sample by silica chromatography gave **23** and **24** in 45% and 46%, respectively. Ring contraction presumably results from isomerization of the *N*-allyl group prior to RCM, rather than from any subsequent reaction of **23** [31,39,40]. This is supported by the fact that (i) a sample of **23** was shown to be stable to conditions **A** and that (ii) alkenes are known to isomerize in the presence of ruthenium catalysts due to the action of ruthenium hydride complexes formed under the reaction reactions [41]. It has also been suggested that coordination of the ruthenium catalyst to the least sterically crowded olefin (*N*-allyl group in this case), followed by deprotonation at the allylic position gives a π-allyl complex that leads to double bond isomerism [40]. By contrast the analogue **5**, which contains a tertiary amide linker known to favour RCM, is reported to cyclise efficiently in refluxing chloroform to give only a 7-membered lactam (**25**) [11]. It is interesting to note that we observed the formation of **23** and ring contracted **24** on refluxing **4** in chloroform with Grubbs second generation catalyst.

The α,α-disubstituted diene **9** was similarly difficult to cyclise, and treatment for 2 h in refluxing benzene (conditions **A**) gave consumption of starting material with formation of the 6-membered lactam **26** as the sole product, which was isolated in 32% after chromatography. The 7-membered lactam was not isolated, nor was it evident in the crude product by NMR. The absence of 7-membered product in this case is likely due to increased steric congestion in **9** (relative to **4**) retarding RCM to allow competing isomerization, and hence ring contraction, under the extended reaction conditions [39,42]. In support of this we found that diene **13**, which contains still further steric congestion, did not undergo RCM, or double bond isomerization, under conditions **C** (2 h) or **A** (4 h). Here, both the direct formation of the 7-membered product and also isomerism to allow formation of the 6-membered lactam are disfavoured. Thus only starting material was recovered from these reactions. As discussed earlier, a tertiary amide (as in **13**) normally favours RCM but this effect would appear to be negated by significant steric congestion in this case. It is interesting that reaction of the α,α-disubstituted β-amino acid based diene **17**, in refluxing benzene, also gave rise to ring contracted amide as the sole product, with **27** being isolated in 71%. Dienes **9** and **17** are similar in that they both contain a secondary amide linker and α,α-disubstitution. A secondary amide of this type has been reported to favour isomerism of an allyl group on nitrogen [31] and thus facilitate ring contraction. The secondary amide in **4**

also appears to promote ring contraction, but to a lesser extent.

The less congested β-amino acid derived dienes **20** and **21** gave the 7-membered lactams **28** (89%) and **29** (88%), without evidence of ring contraction under the relatively mild conditions **C**. These results compare favourably to those obtained for **5** [11], and to a lesser extent **4**, which both possess monosubstitution at the α-carbon. The secondary amide linker in **4** does, however, necessitate the use of harsher reaction conditions to allow some competing isomerism and ring contraction. Ring contraction was also apparent on the introduction of a further substituent at the α-carbon as in **9** (α-amino acid) and **17** (β-amino acid). In the final example, RCM of diene **22** under conditions **C** gave the β-phenylalanine derived azepine **30** in 82% yield after purification by chromatography.

In general, it appears that a secondary amide linker (as in **4**, **9**, and **17**) and α,α-disubstitution both necessitate the use of harsher RCM conditions. As a result competing isomerism of the allyl group on nitrogen is favoured, with subsequent RCM giving ring-contracted product. In fact ring contraction is the sole pathway when both factors are present (see **9** and **17**). On the other hand, a tertiary amide linker is well documented to favour RCM (e.g. see **5**) by encouraging the formation of the requisite rotamer for cyclisation. However, the favourable influence of this group can be negated with the introduction of significant and further steric congestion as in **13**.

Next, the representative lactams **26**, **27**, **28**, and **30** were modeled *in-silico* as components of a penta-peptide (Ac-Ala-Ala-Xaa-Gly-Ala-NHMe) using MacroModel [43] to gain some insight into their ability to stabilize β-turn conformations. In each case a Monte Carlo investigation was carried out and the ensembles of generated structures, within a 12 kJ/mol window of the global minima, were further analyzed on the basis of hydrogen bonding between $C{=}O_i$ and HN_{i+3}, the $C_{\alpha i}$–$C_{\alpha i+3}$ distance, and the pseudo-dihedral angle defined by $C_{\alpha i}$–$C_{\beta 2}$–$C_{\alpha i+2}$–$C_{\alpha i+3}$. The result of this analysis indicates that the model peptides containing **26** and **28** do not adopt turn like structures. This was apparent by the lack of a hydrogen bond between $C{=}O_i$ and HN_{i+3} and a wide distribution of values for the $C_{\alpha i}$–$C_{\alpha i+3}$ distance and pseudo-dihedral angle across the ensembles of generated structures. By contrast **30** gave a global minimum structure (E −523.3 kJ/mol) with an 11-membered ring hydrogen bond between $C{=}O_i$ and HN_{i+3} which is characteristic of a β-turn (Fig. 3). This hydrogen bond existed in 62% of the structures found within the range up to 12 kJ/mol above the global minimum energy. The average $C_{\alpha i}$–$C_{\alpha i+3}$ distance in these structures was 5.8 Å, which is slightly longer than the optimal for an α-amino acid β-turn [44] The observed average pseudo-dihedral angle of −31° is also consistent with a β-turn like geometry, where the ideal value lies between 50° and −50° [44]. The model penta-peptide containing **27** gave a global minimum structure (E −554.4 kJ/mol) with a 12-membered hydrogen-bonded ring between HN_{i+1} and $C{=}O_{i+3}$ and an

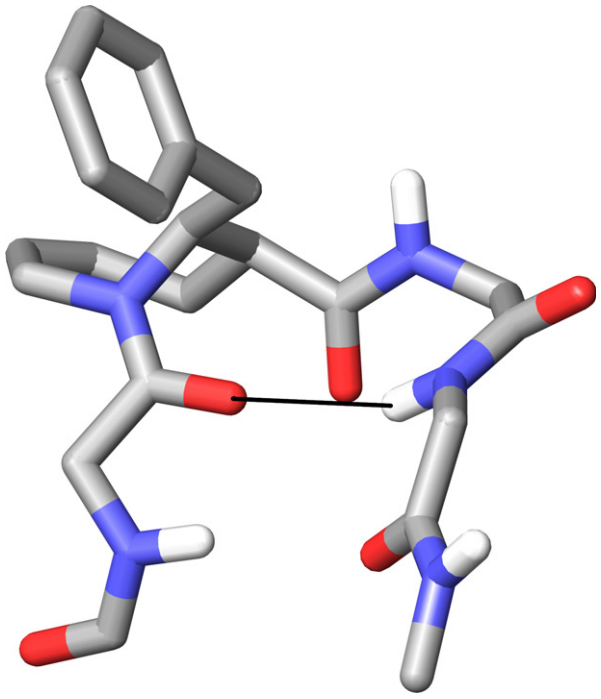
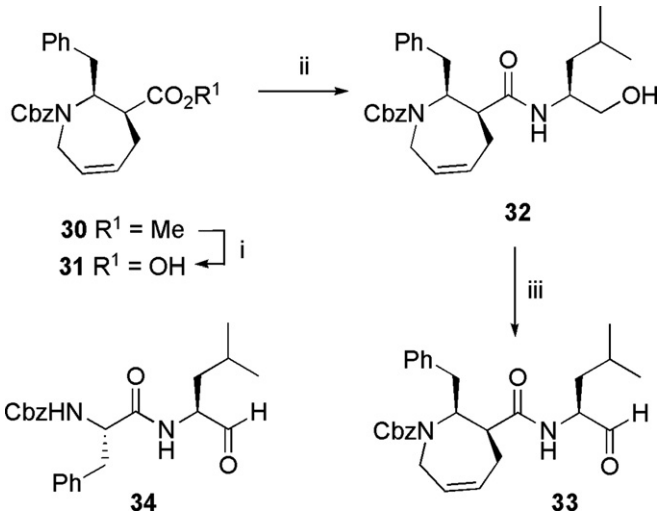


Fig. 3. Global minima β-turn adopted by the model peptide containing **30** (a truncated carbon peptide backbone is shown for clarity).

8-membered hydrogen-bonded ring between $C{=}O_{i+1}$ and HN_{i+3}. This hydrogen bonding pattern existed in 87% of the structures found within a range up to 12 kJ/mol above the global minimum energy. The absence of hydrogen bonding between $C{=}O_i$ and HN_{i+3} indicates a non-classical β-turn. However, the high proportion of structures in the ensemble with the two before mentioned hydrogen bonds, coupled with an average $C_{\alpha i}$–$C_{\alpha i+3}$ distance value of 5.9 Å and an average pseudo-dihedral angle of −54°, is consistent with a turn like structure.

Finally, the β-turn mimic **30** was elaborated into a peptidic aldehyde **33** (Scheme 4) and this was assayed against a



Scheme 4. (i) NaOH, THF, H_2O, MeOH; (ii) (*S*)-leucinol, EDC, HOAT, DIPEA, DMF; (iii) $SO_3 \cdot$ Pyr, DIPEA, DMSO, DCM.

protease (calpain 1) [45] to give an IC_{50} of 4.23 μM. This compares to a value of 0.23 μM [46] for the acyclic dipeptide aldehyde *N*-Cbz-Phe-LeuH **34**, which is able to adopt a β-strand geometry known to favour binding. The 20-fold decrease in potency of **33** reflects the inability of **30** to adopt the requisite β-strand binding geometry as predicted by the modeling.

3. Conclusions

Three new classes of conformationally constrained peptidomimetics, derived from modified α- and β-amino acids, have been prepared by RCM. The first involves C_{α}–N′ cyclisation (see Fig. 1 and **23**, **24**, **26**), the second $C_{\beta 2}$–N′ cyclisation (see Fig. 1 and **27**, **28**, **29**) and the third N–$C_{\beta 2}$ cyclisation (see Fig. 1 and **30**). The olefins of the precursor dienes were introduced by either (i) α-allylation of α- and β-amino acids with control of absolute configuration or (ii) *N*-allylation using P4-phosphazene as the base (see Schemes 2 and 3). It appears that a secondary amide linker (as in **4**, **9**, and **17**), and α,α-disubstitution, both necessitate the use of harsher conditions for RCM. This then favours isomerism of an allyl group on nitrogen and hence RCM to give the ring-contracted product. Ring contraction would appear to be the sole pathway when both α,α-disubstitution and a secondary amide linker are present (see **9** and **17**). The normal favourable influence of a tertiary amide linker on RCM is negated with the introduction of significant steric congestion as in **13**. Peptidomimetics **22** and **26** have been shown to promote turn like structures in model peptides.

4. Experimental

4.1. General methods

All synthetic manipulations were carried out under a nitrogen atmosphere and CH_2Cl_2, benzene and THF were dried by distillation over the appropriate drying agents prior to use. Dry degassed solvents were obtained by means of multiple freeze–pump–thaw cycles. Allylamine, (*S*)-phenylalanine, *N*-Cbz-(*S*)-phenylalanine, *n*-butyl lithium, Grubbs' 2nd generation catalyst were all used as received. Proton NMR spectra were recorded on a Varian 500 MHz NMR spectrometer, unless otherwise stated. Carbon NMR spectra were recorded on a Varian 300 MHz NMR spectrometer operating at 75 MHz, unless otherwise stated. Spectra were recorded in deuterochloroform using TMS as the internal reference, unless stated otherwise. Melting points were measured on a Gallenkamp electrothermal melting point apparatus. Infrared spectra were obtained using a Shimadzu 8201PC series FTIR interfaced with an Intel 486 PC operating Shimadzu's HyperIR software. Mass spectrometry data were detected on Kratos MS80 RFA and Micromass LCT TOF mass spectrometers. Radial chromatography was carried out using a Chromatotron (Harrison Research Inc.) using glass plates coated with Merck type 60 PF254 silica gel.

The following compounds were prepared as described: *N*-allylglycine ethyl ester [47], **7** [32], **8** [33], **11** [34], **12** [34], **14** [37], **15** [37], **18** [38]. Compounds **31**–**34** were prepared by standard methods.

4.2. Synthesis of dienes

4.2.1. Preparation of (1-allycarbamoylbut-3-enyl)carbamic acid tert-butyl ester (±)-4

A mixture of EDCI (459 mg, 2.24 mmol), HOBt (378 mg, 2.58 mmol), allylamine (145 mL, 2.58 mmol) and *N*-Boc (±)-allylglycine (370 mg, 1.72 mmol) were dissolved in CH_2Cl_2 (15 mL). Diisopropylethylamine (205 mL, 0.95 mmol) was added and the mixture was stirred at rt for 16 h. The reaction mixture was then diluted with EtOAc and partitioned with 1 M $HCl_{(aq)}$. The organic phase was washed with saturated $NaHCO_{3(aq)}$, brine and dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by radial chromatography (EA/PE 1:3) gave **4** (404 mg, 92%) as a colourless solid. ^{1}H NMR δ_H 6.53 (H, br s, N*H*CH_2), 5.68–5.85 (2H, m, 2 × C*H*=CH_2) 5.05–5.20 (5H, m, 2 × CH=CH_2 and N*H*CH), 4.18 (H, br s, NHC*H*C=O), 3.80–3.93 (2H, m, NHCH_2CH=CH_2), 2.40–2.55 (2H, m, CHCH_2CH=CH_2), 1.42 (9H, s, CCH_3). ^{13}C NMR δ_C 171.3, 155.6, 133.8, 133.1, 118.8, 116.2, 80.1, 53.8, 41.7, 36.9, 28.2. FTIR (KBr) 3261, 2980, 1697, 1661, 1547 cm^{-1}. HRMS (ES+) found (MNa) *m*/*z* 277.1517, calculated for $C_{13}H_{22}N_2NaO_3$ requires *m*/*z* 277.1528.

4.2.2. Preparation of (1R)-N-(1-allylcarbamoyl-1-benzylbut-3-enyl)benzamide 9

Allylamine (11.5 μL, 0.15 mmol) was dissolved in dry THF (2 mL) and cooled to −78 °C. *n*-Butyl lithium (95 μL, 0.15 mmol) was added and the mixture stirred at −78 °C for 5 min. A solution of **8** [33] (20 mg, 0.05 mmol) in dry THF (1 mL) was added and allowed to warm to rt overnight. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and successively washed with saturated $NaHCO_{3(aq)}$ (5 mL), $NaCl_{(aq)}$ (5 mL) and dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by radial chromatography (EA/PE 1:3) gave **9** (16 mg, 91%) as a colourless solid. ^{1}H NMR δ_H 7.64–7.70 (2H, m, Ar*H*), 7.49 (H, m, Ar*H*), 7.38–7.43 (2H, m, Ar*H*), 7.20–7.25 (3H, m, Ar*H*), 7.10–7.16 (3H, m, Ar*H* and PhCON*H*), 6.51 (H, br t, $J = 4.5$ Hz, N*H*), 5.80–5.90 (H, m, NHCH_2C*H*=CH_2), 5.68–5.78 (H, m, CCH_2C*H*=CH_2), 5.12–5.26 (4H, m, 2 × CH=CH_2), 3.88–4.02 (2H, m, NHCH_2), 3.67 (H, d, $J = 13.9$ Hz, PhCH*H*), 3.37 (H, d, $J = 13.9$ Hz, PhC*H*H), 3.25 (H, dd, $J = 14.3$ and 8.1 Hz, CCH*H*CH=), 2.77 (H, dd, $J = 14.3$ and 6.4 Hz, CC*H*HCH=). ^{13}C NMR δ_C 171.91, 167.29, 135.68, 135.03, 133.62, 132.33, 131.61, 130.10, 128.61, 128.31, 127.08, 126.83, 119.82, 117.14, 64.43, 42.48, 40.87, 40.00. HRMS (EI+) found (M^+) *m*/*z* 348.1829, calculated for $C_{22}H_{24}N_2O_2$ requires *m*/*z* 348.1838.

*4.2.3. Synthesis of [N-allyl((S)-2-benzoylamino-2-benzylpent-4-enoyl)amino]acetic acid ethyl ester **13***

Carboxylic acid **12** [34] (302 mg, 0.89 mmol), *N*-allylglycine ethyl ester (191 mg, 1.34 mmol) and PyAOP (600 mg, 1.16 mmol) were dissolved in anhydrous DMF (20 mL). DIPEA (360 μL, 2.05 mmol) was added and the reaction mixture stirred at rt for 18 h. This was partitioned between EtOAc and 1 M $HCl_{(aq)}$. The organic phase was then washed sequentially with 1 M $HCl_{(aq)}$, brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica using a gradient of EtOAc and petroleum ether (50/70) to give a mixture of rotamers **13** (146 mg, 35%) as a colourless oil. Data for the mixture: ^{1}H NMR δ_H 7.15–7.40 (11H, m, Ar*H* and N*H*), 5.54–5.65 (H, m, $NCH_2CH{=}CH_2$), 5.51 (H, br d, N*H*), 5.01–5.18 (6H, m, $2\times CH{=}CH_2$ and OCH_2Ph), 4.87–4.93 and 4.64–4.70 (H, m, $CCH_2CH{=}CH_2$), 3.68–4.22 (7H, m), 2.92–3.14 (2H, m), 1.27 and 1.24 (3H, t, $J = 7.2$ Hz, $CO_2CH_2CH_3$). ^{13}C NMR δ_C 172.0, 171.9, 168.9, 168.7, 155.6, 155.5, 136.2, 135.9, 132.0, 129.5, 129.3, 128.3, 127.9, 127.8, 127.7, 126.9, 126.8, 118.5, 118.3, 66.7, 61.6, 61.1, 52.2, 51.8, 51.1, 49.5, 48.1, 47.1, 39.4, 14.0, 13.9. HRMS (ES+) found (MNa) *m*/*z* 487.2201, calculated for $C_{27}H_{32}N_2NaO_5$ requires *m*/*z* 487.2209.

*4.2.4. Preparation of (1S,2S)-(2-allylcarbamoyl-1-benzyl-2-methylpent-4-enyl)carbamic acid benzyl ester **17***

Sodium hydroxide (1 M aq 2.36 mL, 2.36 mmol) was added to a solution of **15** [37] (450 mg, 1.18 mmol) dissolved in MeOH (20 mL), and refluxed for 4 h. The MeOH was removed in vacuo and 20 mL of water was added. The solution was acidified to pH 2 with 10% $HCl_{(aq)}$ and extracted with EtOAc (3×10 mL). The combined EtOAc extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to give **16** (420 mg, 97%) as a yellow oil. This was used without further purification. ^{1}H NMR δ_H 7.17–7.39 (10H, m, Ar*H*), 5.78 (H, m, $CH{=}CH_2$), 5.12 (2H, m, $CH{=}CH_2$), 4.87 (2H, dd, $J = 74.9$ and 12.2 Hz, $PhCH_2O$), 4.11 (H, td, $J = 11.1$ and 3.4 Hz, NHC*H*), 3.07 (H, dd, $J = 13.9$ and 3.4 Hz, CHC*H*HPh), 2.62 (H, dd, $J = 13.7$ and 7.3 Hz, C*H*HCH=CH_2), 2.51 (H, dd, $J = 13.9$ and 11.5 Hz, CHCH*H*Ph), 2.36 (H, dd, $J = 13.7$ and 7.8 Hz, CH*H*CH=CH_2), 1.44 (3H, s, CCH_3). HRMS (ES+) found (MH^+) *m*/*z* 368.1864, calculated for $C_{22}H_{26}NO_4$ requires *m*/*z* 368.1862.

A mixture of EDC (118 mg, 0.57 mmol), HOBt (97 mg, 0.66 mmol), allylamine (37 mL, 0.66 mmol) and **16** (160 mg, 0.44 mmol) were dissolved in CH_2Cl_2 (5 mL). Diisopropylethylamine (0.104 mL, 0.48 mmol) was added and the mixture was stirred at rt for 16 h. The residue was partitioned between EtOAc and 1 M $HCl_{(aq)}$. The organic phase was washed sequentially with 1 M $HCl_{(aq)}$ and brine before being dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by radial chromatography (EA/PE 1:3) gave **17** (128 mg, 71%) as colourless crystals. mp 99–101 °C. ^{1}H NMR δ_H 7.16–7.37 (10H, m, Ar*H*), 6.09 (H, d, $J = 10.3$ Hz, N*H*CH), 5.79–5.87 (2H, m, N*H*CH_2 and $NHCH_2CH{=}CH_2$), 5.68–5.74 (H, m, $CCH_2CH{=}CH_2$), 5.06–5.22 (4H, m, $2\times CH{=}CH_2$), 4.94 (H, d, $J = 12.7$ Hz, PhC*H*HO), 4.86 (H, d, $J = 12.7$ Hz, PhCH*H*O), 3.85–3.90 (3H, m, NHC*H* and $NHCH_2$), 2.98 (H, dd, $J = 13.6$ and 3.4 Hz, PhC*H*HCH), 2.58 (H, dd, $J = 13.5$ and 6.5 Hz, C*H*HCH=CH_2), 2.48 (H, dd, $J = 13.6$ and 10.7 Hz, PhCH*H*CH), 2.27 (H, dd, $J = 13.5$ and 7.8 Hz, CH*H*CH=CH_2), 1.28 (3H, s, CCH_3). ^{13}C NMR δ_C 175.4, 156.2, 138.2, 136.9, 133.3, 129.3, 128.3, 128.2, 127.7, 127.6, 126.3, 119.1, 116.8, 66.1, 59.0, 48.8, 42.0, 41.9, 37.8, 19.9. FTIR (KBr) 3279, 1709, 1634, 1547 cm^{-1}. HRMS (ES+) found (MH^+) *m*/*z* 407.2334, calculated for $C_{25}H_{31}N_2O_3$ requires *m*/*z* 407.2335. Microanalysis calculated for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.56; H, 7.54; N, 6.98%.

*4.2.5. Preparation of (1S,2S)-(2-allylcarbamoyl-1-benzylpent-4-enyl)carbamic acid benzyl ester **20***

Aqueous sodium hydroxide (1 M 1.74 mL, 1.74 mmol) was added to a solution of **18** [38] (320 mg, 0.87 mmol) dissolved in MeOH (15 mL), and the solution was refluxed for 4 h. The MeOH was removed in vacuo and 20 mL of water was added. The solution was acidified to pH 2 with 10% $HCl_{(aq)}$ and extracted with EtOAc (3×10 mL). The combined EtOAc extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to give **19** (305 mg, 99%) as a yellow oil. This was used without further purification. ^{1}H NMR δ_H 7.14–7.37 (10H, m, Ar*H*), 5.71 (H, d, $J = 9.8$ Hz, PhCON*H*), 5.68 (H, m, CH=C*H*H), 5.00–5.15 (4H, m, $PhCH_2$ and CH=CH*H*), 4.24 (H, m, NHC*H*), 2.95 (H, dd, $J = 13.9$ and 6.6 Hz, C*H*HPh), 2.77 (H, dd, $J = 13.7$ and 8.8 Hz, CH*H*Ph), 2.64 (H, m, $CHCO_2H$), 2.46 (H, m, C*H*HCH=CH_2), 2.34 (H, m, C*H*HCH=CH_2).

A mixture of EDC (232 mg, 1.12 mmol), HOBt (190 mg, 1.3 mmol), allylamine (73 μL, 1.3 mmol) and **19** (305 mg, 0.86 mmol) were dissolved in CH_2Cl_2 (10 mL). Diisopropylethylamine (0.205 mL, 0.95 mmol) was added and the mixture was stirred at rt for 16 h. The reaction mixture was then diluted with EtOAc and partitioned with 1 M $HCl_{(aq)}$. The organic phase was washed with saturated $NaHCO_{3(aq)}$, brine and dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by radial chromatography (EA/PE 1:4) gave **20** (261 mg, 74%) as colourless crystals. mp 168–169 °C. ^{1}H NMR δ_H 7.16–7.36 (10H, m, Ar*H*), 6.50 (H, d, $J = 8.8$ Hz, N*H*CH), 5.80–5.90 (H, m, $NHCH_2CH{=}CH_2$), 5.58–5.68 (H, m, $CHCH_2CH{=}CH_2$), 5.47 (H, br s, N*H*CH_2), 5.15–5.26 (2H, m, $CH{=}CH_2$), 5.09 (H, d, $J = 12.7$ Hz, PhC*H*HO), 5.07 (H, d, $J = 12.7$ Hz, PhCH*H*O), 4.94–5.04 (2H, m, $CH{=}CH_2$), 4.00–4.10 (H, m, NHC*H*), 3.82–3.94 (2H, m, $NHCH_2CH{=}CH_2$), 3.05 (H, dd, $J = 13.8$ and 6.1 Hz, CHC*H*HPh), 2.62 (H, dd, $J = 13.8$ and 9.2 Hz, CHCH*H*Ph), 2.38–2.47 (2H, m, CHC*H*HCH=CH_2), 2.22–2.30 (H, m, CHCH*H*CH=CH_2), 2.10–2.16 (H, m, $CHCH_2CH{=}CH_2$).^{13}C NMR δ_C 173.6, 156.2, 138.1, 136.8, 134.7, 133.7, 129.0, 128.6, 128.4, 127.9, 127.8,

126.6, 117.7, 117.1, 66.3, 53.8, 47.2, 41.8, 40.4, 34.9. FTIR (KBr) 3433, 1693, 1643, 1551, 1265 cm^{-1}. HRMS (EI+) found (MH^+) m/z 393.2176, calculated for $C_{24}H_{29}N_2O_3$ requires m/z 393.2178.

4.2.6. Preparation of (1S,2S)-{N-allyl-[2-(1-benzyloxycarbonylamino-2-phenylethyl)pent-4-enoyl]amino}acetic acid ethyl ester **21**

Carboxylic acid **19** (64 mg, 0.18 mmol), *N*-allylglycine ethyl ester (44 mg, 0.31 mmol) and PyAOP (123 mg, 0.24 mmol) were dissolved in anhydrous DMF. DIPEA (85 μL, 0.49 mmol) was added and the reaction mixture stirred at room temperature for 18 h. This was partitioned between EtOAc and 1 M $HCl_{(aq)}$. The organic phase was then washed sequentially with 1 M $HCl_{(aq)}$, brine and dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by radial chromatography (EA/PE 1:4) gave **21** (25 mg, 29%) as a colourless oil. ^{1}H NMR δ_H 7.12–7.38 (10H, m, Ar*H*), 6.67 (H, d, $J = 9.5$ Hz, N*H*CH), 5.60–5.80 (2H, m, $2 \times CH_2CH$=CH_2), 5.08–5.22 (2H, m, CH=CH_2), 4.98–5.08 (4H, m, CH=CH_2 and PhCH_2O), 4.22 (2H, q, $J = 7.1$ Hz, OCH_2CH$_3$), 4.14–4.19 (H, m, NHC*H*CH), 4.13 (H, d, $J = 17.6$ Hz, C*H*HCO$_2$CH$_2$CH$_3$), 3.90 (H, d, $J = 17.1$ Hz, C*H*HCO$_2$CH$_2$CH$_3$), 3.79 (2H, br d, $J = 5.6$ Hz, NHCH_2CH=CH$_2$), 2.97 (H, dd, $J = 13.6$ and 6.74 Hz, PhC*H*H), 2.76–2.82 (H, m, CHC*H*CO), 2.71 (H, dd, $J = 13.6$ and 9.1 Hz, PhCH*H*), 2.28–2.42 (2H, m, CHCH_2CH=CH$_2$), 1.29 (3H, t, $J = 7.1$ Hz, OCH$_2$CH_3). ^{13}C NMR δ_C 175.3, 169.0, 156.2, 138.2, 136.8, 134.5, 132.4, 129.1, 128.4, 128.3, 127.8, 127.7, 126.4, 118.5, 117.7, 66.2, 61.2, 53.3, 51.9, 47.0, 41.36, 40.0, 34.4, 14.1. FTIR (KBr) 3402, 2945, 1747, 1717, 1635 cm^{-1}. HRMS (ES+) found (MH^+) m/z 479.2542, calculated for $C_{28}H_{35}N_2O_5$ requires m/z 479.2546.

4.2.7. Synthesis of (1S,2S)-2-[1-(allylbenzyloxycarbonylamino)-2-phenylethyl]pent-4-enoic acid methyl ester **22**

A solution of **18** [38] (960 mg, 2.61 mmol) was dissolved in anhydrous THF (25 mL). This was cooled to −78 °C and P4-phosphazene (5.22 mL, 5.22 mmol) was added, and stirred at −78 °C for 1 h and then allyl bromide (454 mL, 5.22 mmol) was added. This was stirred at −78 °C for a further 2 h and then at rt for 18 h before being concentrated in vacuo. The residue was partitioned between EtOAc and 1 M $HCl_{(aq)}$. The organic phase was washed sequentially with 1 M $HCl_{(aq)}$ and brine before being dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica using a gradient of EtOAc and petroleum ether (50/70) to give as a mixture of rotamers **22** (0.926 g, 87%) as a colourless oil. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz, 80 °C) δ_H 7.20–7.49 (10H, m, Ar*H*), 5.77–5.92 (H, m, CH$_2$C*H*=CH$_2$), 5.25–5.50 (H, m, CH$_2$C*H*=CH$_2$), 4.85–5.24 (6H, m, OCH_2Ph and CH$_2$CH=CH_2), 4.05–4.25 (H, m), 3.50–3.70 (5H, m), 3.00–3.30 (3H, m), 2.35–2.65 (2H, m). ^{13}C NMR δ_C 174.1, 173.6, 156.0, 155.2, 138.3, 137.9, 136.9, 136.4, 134.4, 134.2, 134.1, 129.4, 129.3, 128.4, 128.3, 128.2, 127.8, 127.7, 126.4, 126.3, 117.3, 117.2, 116.8, 116.4, 67.3, 66.5, 53.3, 51.5, 51.3, 49.2, 48.2, 36.5, 35.3, 34.5, 34.4. LRMS (ES+) found (MH^+) m/z 408.2, calculated for $C_{25}H_{30}NO_4$ requires m/z 408.2.

4.3. RCM reactions

4.3.1. General procedure A

The diene was dissolved in the appropriate amount of distilled benzene and to this Grubbs 2nd generation catalyst was added. This was heated at reflux for 4 h, cooled and concentrated in vacuo. Purification of the residue was carried out by radial silica chromatography.

4.3.2. General procedure B

The diene was dissolved in the appropriate amount of distilled dichloromethane and to this Grubbs 2nd generation catalyst was added. This was heated at reflux for 2 h, cooled and concentrated in vacuo. Purification of the residue was carried out by silica chromatography.

4.3.3. Preparation of (2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl)carbamic acid tert-butyl ester (±)-**23** and (2-oxo-1,2,3,4-tetrahydropyridin-3-yl)carbamic acid tert-butyl ester (±)-**24**

The diene **4** (60 mg, 0.24 mmol) and Grubbs 2nd generation catalyst (9 mg, 0.01 mmol) in *dry degassed* benzene (10 mL) were reacted according to general procedure A giving **23** (23 mg, 46%) as a colourless solid and **24** (24 mg, 45%) as a colourless solid.

Data for (±)-**23**: ^{1}H NMR δ_H 6.34 (H, br s, N*H*CH$_2$), 5.65–5.80 (2H, m, C*H*=CHCH$_2$ and N*H*CH$_2$), 4.78–4.87 (H, m, CH=C*H*CH$_2$), 4.15 (H, br d,$J = 7.1$ Hz, NHC*H*CH$_2$), 3.40–3.50 (H, m, NHC*H*H), 2.60–2.70 (H, m, NHCH*H*), 2.20–2.34 (2H, m, CHCH_2CH=CH), 1.44 (9H, s, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$)δ_C 174.7, 155.1, 142.5, 129.0, 124.6, 79.6, 49.8, 39.5, 32.6, 28.3. HRMS (ES+) found (MNa) m/z 249.1220, calculated for $C_{11}H_{18}N_2NaO_3$ requires m/z 249.1215.

Data for (±)-**24**: ^{1}H NMR δ_H 7.67 (H, br s, CH=CHN*H*), 6.02–6.10 (H, m, C*H*=CHNH), 5.49 (H, br s, N*H*CHCH$_2$), 5.16 (H, t, $J = 7.1$ Hz, CH=C*H*NH), 4.23–4.32 (H, m, NHC*H*CH$_2$), 2.78–2.88 (H, m, C*H*HCH=), 2.15–2.25 (H, m, CH*H*CH=CH), 1.44 (9H, s, C(CH_3)$_3$). ^{13}C NMR δ_C 170.1, 155.6, 124.7, 105.5, 79.8, 50.0, 28.3, 27.2. HRMS (ES+) found (MNa) m/z 235.1051 (M^++Na), calculated for $C_{10}H_{16}N_2O_3Na$ requires m/z 235.1059.

4.3.4. Preparation of (R)-N-(3-benzyl-2-oxo-1,2,3,4-tetrahydropyridin-3-yl)benzamide **26**

The diene **9** (48 mg, 0.14 mmol) and Grubbs 2nd generation catalyst (117 mg, 0.014 mmol) in benzene (10 mL) were reacted according to general procedure A giving **26** (14 mg, 32%) as a colourless oil. ^{1}H NMR δ_H 7.68–7.74 (2H, m, Ar-*H*), 7.38–7.52 (3H, m, Ar-*H*), 7.32 (H, br s,

N*H*), 7.18–7.22 (3H, m, Ar-*H*), 7.04–7.10 (2H, m, Ar-*H*), 6.93 (H, br s, N*H*), 6.14–6.18 (H, m, CH=C*H*NH), 5.28–5.34 (H, m, CH_2CH=CH), 3.67 (H, dd, $J = 17.7$ and 6.7 Hz, NHCH=CHC*H*H), 3.66 (H, d, $J = 13.8$ Hz, C*H*HPh), 3.42–3.50 (H, m, NHCH=CHCH*H*), 3.26 (H, d, $J = 13.8$ Hz, C*H*HPh), 2.70–2.80 (H, m, CH*H*Ph). LRMS (ES+) found (MH^+) *m*/*z* 307.1, calculated for $C_{19}H_{19}N_2O_2$ *m*/*z* requires 307.1.

4.3.5. Preparation of (1S,3S)-[1-(3-methyl-2-oxo-1,2,3,4-tetrahydropyridin-3-yl)-2-phenylethyl]carbamic acid benzyl ester 27

The diene **17** (75 mg, 0.19 mmol) and Grubbs 2nd generation catalyst (8 mg, 0.009 mmol) in benzene (3.5 mL) were reacted according to general procedure A giving **27** (59 mg, 88%) as a colourless solid. ^{1}H NMR δ_H 7.11–7.32 (10H, m, Ar*H*), 6.96–7.02 (H, m, N*H*), 5.95–6.00 (H, m, NHC*H*=CH), 5.00–5.10 (2H, m, CCH_2CH=CH and N*H*), 4.93 (H, d, $J = 12.7$ Hz, PhC*H*HO), 4.80 (H, d, $J = 12.7$ Hz, PhCH*H*O), 4.07–4.13 (H, m, NHC*H*), 3.14 (H, dd, $J = 13.7$ and 3.4 Hz, PhC*H*HCH), 2.97–3.04 (H, m, PhCH*H*CH), 2.62 (H, br d, $J = 17.1$ Hz, C*H*HCH=CH), 2.03 (H, dd, $J = 17.1$ and 5.6 Hz, CH*H*CH=CH), 1.31 (3H, s, CCH_3). ^{13}C NMR δ_C 174.7, 156.6, 138.9, 136.6, 129.2, 128.4, 128.2, 127.8, 127.7, 126.2, 123.7, 103.9, 66.3, 57.5, 45.1, 37.7, 31.1, 20.3. HRMS (ES+) found (MH^+) *m*/*z* 365.1866, calculated for $C_{22}H_{25}N_2O_3$ requires *m*/*z* 365.1865.

4.3.6. Preparation of (1S,3S)-[1-(2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl)-2-phenylethyl]carbamic acid benzyl ester 28

The diene **20** (70 mg, 0.18 mmol) and Grubbs 2nd generation catalyst (8 mg, 0.009) in benzene (3.5 mL) were reacted according to general procedure B giving **28** (58 mg, 89%) as a colourless solid.^{1}H NMR δ_H 7.20–7.37 (10H, m, Ar*H*), 6.58 (H, d, $J = 9.8$ Hz, N*H*CH), 6.16 (H, br s, $NHCH_2$), 5.65–5.70 (H, m, $CHCH_2CH$=CH_2), 5.56–5.61 (H, m, $NHCH_2CH$=CH_2), 5.10 (H, d, $J = 12.5$ Hz, PhC*H*HO), 5.06 (H, d, $J = 12.5$ Hz, PhCH*H*O), 3.96–4.02 (H, m, NHC*H*), 3.81 (H, br d, $J = 7.6$ Hz, NHC*H*HCH=CH), 3.25–3.32 (H, m, NHCH*H*CH=CH), 3.06 (H, dd, $J = 13.2$ and 6.3 Hz PhC*H*H), 2.91–2.99 (2H, m, $CHCH_2CH$=CH and PhCH*H*), 2.44–2.51 (H, m, CHC*H*HCH=CH), 2.15 (H, br d, $J = 9.0$ Hz, CHC*H*HCH=CH). ^{13}C NMR δ_C 177.5, 156.5, 138.6, 136.7, 130.5, 129.1, 128.6, 128.4, 127.9, 127.8, 126.4, 124.3, 66.4, 55.5, 40.6, 39.9, 39.2, 29.5. FTIR (KBr) 3275, 2924, 1699, 1651 cm^{-1}. HRMS (ES+) found (MH^+) *m*/*z* 365.1862, calculated for $C_{22}H_{25}N_2O_3$ requires *m*/*z* 365.1865.

4.3.7. Preparation of (1S,3S)-[3-(1-benzyloxycarbonyl-amino-2-phenylethyl)-2-oxo-2,3,4,7-tetrahydro-azepin-1-yl]acetic acid ethyl ester 29

The diene **21** (25 mg, 0.05 mmol) and Grubbs 2nd generation catalyst (4.4 mg, 0.005 mmol) in DCM (5 mL) were reacted according to general procedure B. Residual ruthenium was removed according to the literature [48] to give **29** (20.3 mg, 88%) as a colourless oil. ^{1}H NMR δ_H 7.16–7.38 (10H, m, Ar*H*), 6.62 (H, d, $J = 9.9$ Hz, N*H*CH), 5.68–5.74 (H, m, CH_2CH=CH), 5.58–5.64 (H, m, NCH_2CH=CH), 5.10 (H, d, $J = 12.3$ Hz, PhC*H*HO), 5.07 (H, d, $J = 12.3$ Hz, PhCH*H*O), 4.52 (H, d, $J = 17.1$ Hz, C*H*HCO_2Me), 4.24 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 4.18–4.28 (H, m, NCH*H*CH=CH), 3.95 (H, dddd, 10.1, 8.7, 5.9, 2.8 Hz, NHC*H*CH), 3.86 (H, d, $J = 17.1$ Hz, CH*H*CO_2Me), 3.23 (H, dd, $J = 17.4$ and 5.9 Hz, NCH*H*CH=CH), 3.09 (H, dt, $J = 13.1$ and 2.8 Hz, CHC*H*CO), 3.03 (H, dd, $J = 13.1$ and 5.5 Hz, PhC*H*H), 2.92 (H, dd, $J = 13.1$ and 9.9 Hz, PhCH*H*), 2.42–2.52 (H, m, CHC*H*HCH=CH), 2.10–2.20 (H, m, CHCH*H*CH=CH), 1.30 (3H, t, $J = 7.1$ Hz, OCH_2CH_3). ^{13}C NMR δ_C 175.4, 169.1, 156.6, 138.7, 136.8, 131.2, 129.3, 128.6, 128.4, 127.8, 127.7, 126.4, 123.3, 66.4, 61.3, 55.9, 49.8, 47.3, 40.6, 39.9, 30.0, 14.2. FTIR (KBr) 3410, 2981, 1744, 1717, 1647 cm^{-1}. HRMS (ES+) found (MH^+) *m*/*z* 451.2252, calculated for $C_{26}H_{31}N_2O_5$ requires *m*/*z* 451.2233.

4.3.8. Synthesis of (2S,3S)-2-benzyl-2,3,4,7-tetrahydroazepine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester 30

The diene **22** (930 mg, 2.28 mmol) and Grubbs 2nd generation catalyst (193 mg, 0.228 mmol) in DCM (200 mL) were reacted according to general procedure B giving as a mixture of rotamers **30** (710 mg, 82%) as a brown solid. Data for the mixture: ^{1}H NMR δ_H 7.13–7.33 (10H, m, Ar*H*), 5.71–5.80 (2H, m, NCH_2CH=CH and CH=C*H*CH_2), 5.25–5.33 and 5.15–5.20 (H, m, C*H*CH_2Ph), 5.05–5.13 (2H, m, OCH_2Ph), 4.45–4.51 and 4.25–4.32 (2H, m, NCH_2CH=CH), 3.71–3.77 (H, m, C*H*CO_2CH_3), 3.64 (3H, s, CO_2CH_3), 3.01–3.04 (H, m, CHC*H*HPh), 2.89–2.95 (H, m, CHCH*H*Ph), 2.50–2.70 (2H, m, $CHCH_2CH$=CH). LRMS (ES+) found (MH^+) *m*/*z* 380.1, calculated for $C_{23}H_{26}NO_4$ requires *m*/*z* 380.2.

4.4. Computational methods

Molecular mechanics calculations were carried out on a SGI IRIX 6.5 workstation, with use of MacroModel (v6.5) molecular modelling software, OPLS_01 force field and the implicit H_2O/chloroform GB/SA solvation system. Monte Carlo conformational searches were carried out without imposition of any constraint and with inclusion of amide bonds in the rotatable bonds. Ring-closure was defined for the 6- and 7-membered rings of our peptidomimetics. 5000 structures were generated and minimized until the gradient was less than 0.05 kJ/Å mol by the TNCG gradient implemented in MacroModel. All conformers with energy 12 kcal/mol above the global minimum conformer were discarded.

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