

Synthesis and solid state conformation of phenylalanine mimetics constrained in a proline-like conformation

James Gardiner and Andrew D. Abell*

Department of Chemistry, University of Canterbury, Christchurch, New Zealand.

E-mail: andrew.abell@canterbury.ac.nz; Fax: +64-3-3642110; Tel: +64-3-3642818

Received 29th April 2004, Accepted 11th June 2004

First published as an Advance Article on the web 27th July 2004

We present the synthesis of five- and six-membered cyclic phenylalanine mimics (**1**, **9**, **16**, and **17**) that are constrained in a proline-like conformation. The five-membered mimetic **16** was prepared by Ring Closing Metathesis (RCM) of diene **15**, itself prepared by α -benzylation of the L-methionine derived oxazolidinone **10**, followed by oxidative elimination, ring hydrolysis and *N*-allylation. The six-membered mimetic **1** was prepared by allylating the L-phenylalanine-derived oxazolidinone **5**, followed by hydrolysis, *N*-allylation and RCM. Olefins **1** and **16** were catalytically hydrogenated to give **9** and **17**, respectively. The solid state structures of **9** and **16** were determined by X-ray crystallography and their conformations compared with that of **1**.

Introduction

The introduction of an unnatural amino acid(s) into a key position(s) in the primary sequence of a peptide or protein allows modification of its biological properties in a controllable way. The result of such a modification is to alter the spatial arrangement of key groups on the peptide backbone. This then defines, or modifies, a key binding domain that can interact with a biological receptor, or enzyme, to elicit a biological response. Conformationally constrained amino acid mimics have found widespread use in this context.¹

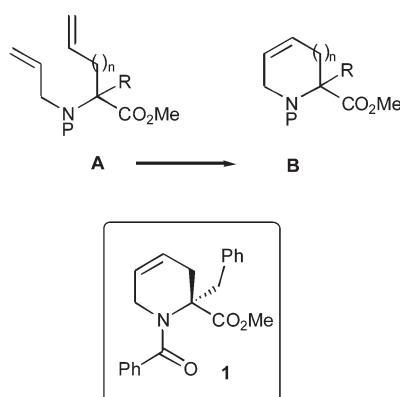
In a previous communication we reported the synthesis and X-ray crystal structure of a configurationally and conformationally well-defined 1,2,3,6-tetrahydropyridine-based phenylalanine mimetic **1**.² This derivative was the first rational example of a new and important class of mimetic of general structure **B** (Scheme 1) in which the constituent amino acid (phenylalanine in the case of **1**) is constrained in a proline-like conformation. A combination of an amino acid with a proline N-C α cyclisation provides a useful medicinal and biochemical tool since proline, and its derivatives, are known to play a key role in the stabilisation of secondary protein structure.¹ The extra substitution in **B**, relative to proline, expands the possibilities of generating secondary structure in oligomers derived from them, *e.g.* through π - π stacking and other noncovalent interactions. We initially chose to incorporate a benzyl group at the α -position as in **1** to mimic the side-chain of phenylalanine for this exact reason, and because it is commonly found at the P₁ subsite of many proteases that we have an interest in inhibiting.³ [Note the use of Schechter-Berger nomenclature⁴ – the residues on the N-terminal side of the peptide bond that is cleaved are denoted (in order) P₁–P_{*n*}, and those on the C-terminus are denoted P₁–P_{*n*}. In turn, the corresponding subsites on the enzyme are denoted S_{*n*}–S_{*n*}.].

We envisage that a range of mimetics **B** could be prepared by Ring Closing Metathesis (RCM) of dienes of type **A**, as depicted in Scheme 1. In this paper, we report full details for the synthesis of the six-membered mimetic **1** (Scheme 2) and further examples (Scheme 3) of this important class of amino acid mimetic, in particular the five-membered α -substituted dehydropyridine-based mimetic **16** and the saturated analogues **9** and **17**. A benzyl substituent was incorporated at the α -position of **16** to allow detailed comparison of its X-ray structure (as reported here, Fig. 3) with that of **1**, although as with the synthesis of **1**, the synthetic methodology lends itself well to the incorporation of a variety of substituents at this position. We also present an X-ray structure analysis of **9** and a comparison of its solid-state conformation with that of **1** and **16**.

Results and discussion

The synthesis of the dehydropyridine mimic **16** (Scheme 3) is based on our method reported in a preliminary communication for the preparation of **1** (Scheme 2).² Here, a diastereoselective allylation of the phenylalanine-derived oxazolidinone **5**⁵ gave **6**, which was hydrolysed to give **7**. Allylation on the amide nitrogen gave diene **8**, and this was finally cyclised on treatment with catalyst **2** (Fig. 1) to give **1**. The ee of the *N*-protected α -allyl phenylalanine **7**, an important intermediate here and in several other syntheses,⁶ was shown to be >95%.⁷ The synthesis of the dehydropyridine mimic **16** (Scheme 3) required a somewhat more difficult stereospecific incorporation of a vinyl group, rather than the allyl group of the six-membered series (refer step (i) Scheme 2), at the α -position of phenylalanine. To achieve this we chose to use the methylsulfanylethyl side-chain of L-methionine as a masked vinyl group and to then benzylate at the α -position in what is effectively the reverse of the sequence used in the preparation of **1**. A consequence of this approach is that the absolute configurations of **16** and **1** are opposite. Of course both stereochemistries are potentially available in each case by using either the D or L starting amino acid.

Hence, L-methionine was reacted with benzaldehyde and benzoyl chloride to give the diastereomerically pure *trans* oxazolidinone **10** in 63% overall yield after chromatography.⁵ Literature⁸ suggested



Scheme 1 RCM approach to α -substituted cyclic amino acid mimics.

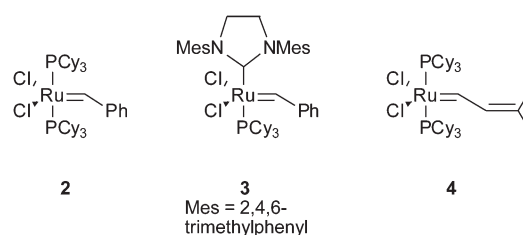
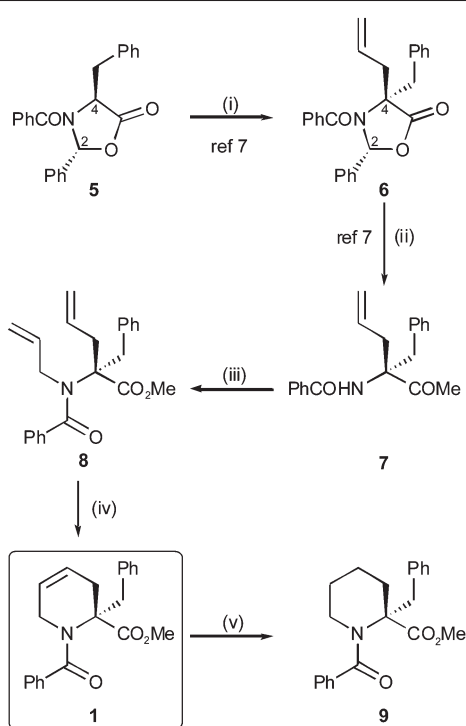


Fig. 1 RCM catalysts.



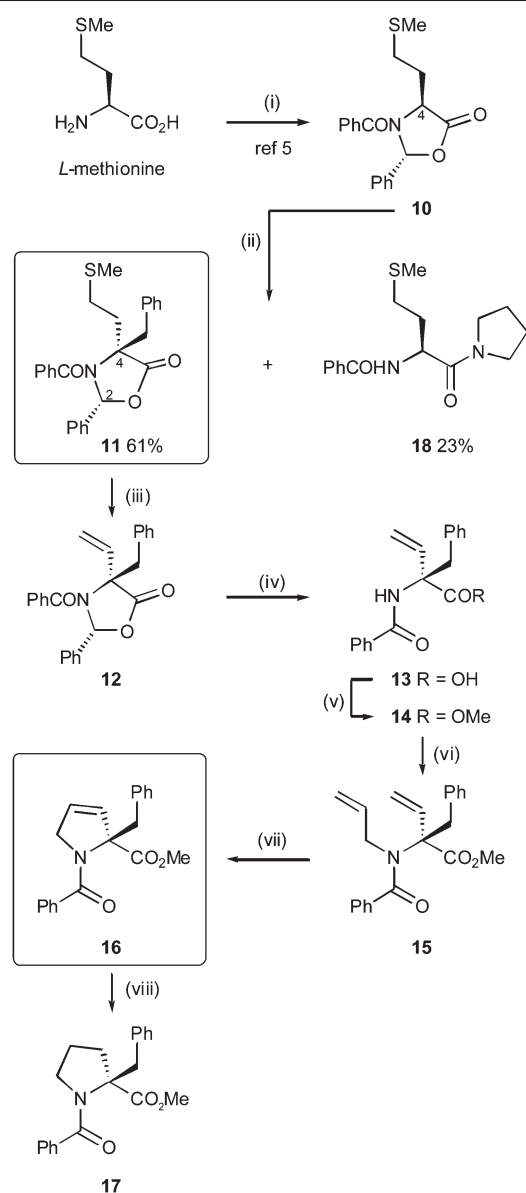
Scheme 2 Reagents and conditions: (i) LiHMDS, THF, -78°C then allyl bromide, 93%; (ii) NaOH, MeOH, reflux then CH_2N_2 , 0°C , 91%; (iii) NaH, allyl bromide, DMF, 0°C , 31%; (iv) **2**, benzene, reflux, 94%; (v) H_2 , palladium-on-carbon, MeOH, rt, 95%.

that the next step, *i.e.* deprotonation of the methionine-derived oxazolidinone **10** at C4, should be achievable using a sterically non-hindered base such as LDA or LDEA. However, these conditions proved problematic in our case. Treatment of **10** with *n*-butyl lithium and pyrrolidine at -50°C ,⁹ followed by benzylation of the resultant enolate from the face opposite the C2 phenyl group did, however, give **11** as a single diastereoisomer in 61% yield after chromatography. To our knowledge this is the first example of the use of a pyrrolidine-based base to generate lithium enolates of amino acid-based oxazolidinones. A by-product (**18**) was also isolated from this reaction in 23% yield.

With the key alkylated oxazolidinone **11** in hand we carried out an oxidation of its methionine side chain with hydrogen peroxide in acetic acid to give the sulfoxide, which was followed by a thermal elimination at 200°C in a sealed tube¹⁰ to give the vinyl oxazolidinone **12** in 86% yield over two steps. An X-ray crystal structure of **12** was determined (Fig. 2) to confirm the stereochemical outcome of the alkylation reaction depicted in Scheme 3 step (ii). The absolute configuration of **12** follows from the absolute configuration of **10**, which is defined by that of the starting amino acid, L-methionine.⁵ The vinyl oxazolidinone **12** was next hydrolysed with aqueous sodium hydroxide to give the acid **13**, and this was esterified to give methyl ester **14** in 99% yield over two steps. Deprotonation of **14** with sodium hydride in dimethylformamide at 0°C , followed by the addition of allyl bromide, gave diene **15** in 31% yield after purification. A further 51% of **14** was also recovered and recycled to obtain more diene. Finally, diene **15** was heated at reflux, in the presence of catalyst **4**, to give the dehydropoline mimic **16** as a white crystalline solid in 94% yield after chromatography.¹¹ Recrystallisation of **16** from ethyl acetate/petroleum ether gave crystals suitable for X-ray analysis. Hydrogenation of **16** in the presence of palladium-on-carbon under a hydrogen atmosphere, gave the saturated proline-based mimic **17** in 95% yield after purification. Attempts to obtain crystals of **17** suitable for X-ray analysis were unsuccessful.

X-ray structure analysis

With the solid-state structures of **1**, **9** and **16** in hand a conformational comparison could now be made (Fig. 3 and Table 1). The six-membered rings of **1**² and **9** impact significant confor-



Scheme 3 Reagents and conditions: (i) (a) NaOH, (b) PhCHO, CH_2Cl_2 , reflux, (c) PhCOCl , CH_2Cl_2 , 0°C to rt, 63% over 3 steps; (ii) pyrrolidine, *n*-BuLi, benzyl bromide, THF, -50°C , 61%; (iii) (a) H_2O_2 , acetic acid, 94%, (b) xylene, 200°C sealed tube, 93%; (iv) NaOH, MeOH, reflux, 99%; (v) CH_2N_2 , Et_2O , 0°C , 100%; (vi) NaH, allyl bromide, DMF, 0°C , 31%, 51% recovered starting material; (vii) **4**, benzene, reflux, 94%; (viii) H_2 , palladium-on-carbon, MeOH, rt, 95%.

mational restriction with the N-C α peptide backbone torsions ϕ (defined by C8-N-C3-C2, see Table 1) being $+38.7(2)^{\circ}/+40.2(2)^{\circ}$ and $-47.7(3)^{\circ}$, respectively. In both cases the benzoyl and benzyl groups are *anti*, despite differences in the conformation of the ring in each mimic. It is interesting to note that the sign and magnitude of

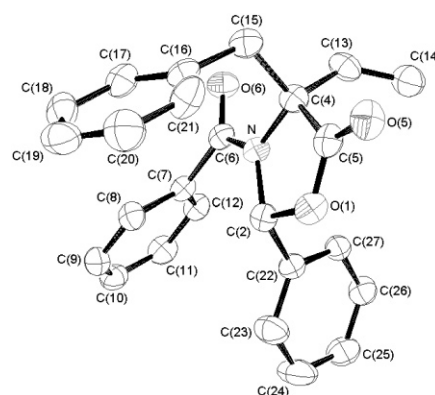
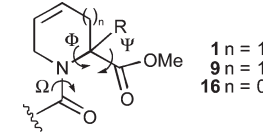


Fig. 2 X-ray crystal structure of 4-vinyl-oxazolidinone **12**.

Table 1 Key torsion angles for compounds **1**, **9** and **16**. See Fig. 3 for crystallographic numbering scheme


No.	C8–N–C3–C2 Φ	N–C3–C2–O2 Ψ	O8–C8–N–C3 Ω
1	+38.7/+40.2	−137.48	−5.99/−4.43
9	−47.7	+145.3	+0.3
16	+52.86	−138.36	−0.79

the peptide backbone torsion angles (Φ) of **1** [+38.7(2)°/+40.2(2)°] and its saturated analogue **9** [−47.7(3)°], reflect a ‘conformational flip’ of almost 90° clockwise rotation about the N–C α bond (Fig. 3). This is despite the fact that both **1** and **9** have the same absolute configuration. It is also worth noting that the ring atoms of **9**, denoted by N–C3–C4–C5–C6–C7, adopt a distinct boat conformation and the Ψ torsion angle for **9**, as defined by N–C3–C2–O2 (Table 1), is +145.3, with the adjacent torsion angles defined by N–C3–C2–O1 and C8–N–C3–C15 being −40.0(3)° and +71.4(3)° respectively. In addition, ‘twisting’ was not observed about the amide bond of **9** – the Ω torsion, defined by O8–C8–N–C3 (Table 1), is +0.3(4)° compared with −4.33 / −5.99° for **1** – and no significant pyramidalisation of the amide nitrogen of **9** was evident with the angles at N summing to 359.5°.

An analysis of the X-ray structure of the five-membered ring mimic **16** reveals that it adopts a similar geometry to that of **1** and **9**. The Φ torsion angle for **16** (see Table 1) is +52.86(13)°, a value significantly shorter than that for proline,^{13,14} but longer than that of the six-membered mimics **1** and **9** (+38.7(2)/+40.2(2)° and −47.7(3)° respectively). The Ψ torsion angle for **16** is −138.36(13)° (see Table 1), with the adjacent torsion angles defined by N–C3–C2–O1 and C8–N–C3–C15 having values of +44.99(14)° and −68.67(15)° respectively. The dehydropyrrolidine ring of **16**, defined by N–C3–C4–C5–C6, adopts an essentially planar conformation, with N deviating from the least squares plane defined by the other 4 atoms by

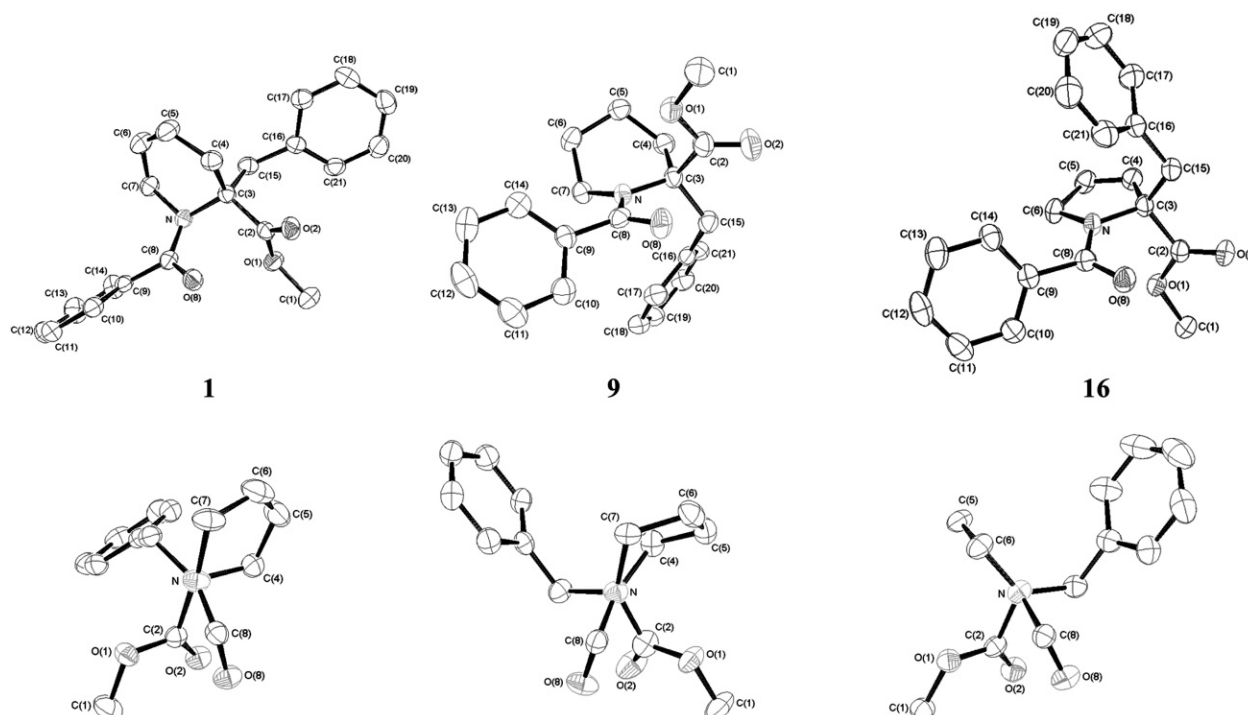
0.0365 Å. Slight pyramidalisation of nitrogen was observed, with the bond angles at N summing to 358.55°, and the benzoyl group deviating from the plane of the pyrrolidine ring. Minimal twisting of the amide bond was observed, with a Ω torsion angle of −0.79(19)°, compared with +0.3(4)° for **9** and −4.33/−5.99° for **1** (Table 1).

A comparison of the solid state structures of **16** and **1** reveals that, while the two mimics possess opposite stereochemistry at C3 (crystallographic numbering) both have a positive Φ torsion angle about the N–C α bond, and hence have the same ‘conformational sense’ (Fig. 3). It would be interesting to see if the ‘conformational sense’ of **17** is opposite to **16** as was the case for **1** and **9**, but unfortunately we were unable to grow suitable crystals of **17** for X-ray analysis.

Conclusion

In summary, we present for the first time a synthesis of the optically active five-membered cyclic phenylalanine mimic (**16**) that is constrained in a proline-like conformation. The synthetic sequence utilises a combination of Grubbs’ RCM chemistry to form the cycle, Seebach oxazolidinone chemistry to introduce an α -benzyl group with control of absolute configuration, and a methionine side chain to provide a masked vinyl group. The methodology is amenable to incorporation of a range of groups at the α -position¹⁵ and control of the absolute configuration by starting with either a D or L amino acid and the nature of the N-protecting group used in the oxazolidinone preparation.¹⁵ A comparison of the structures of the five-membered mimetic **16**, with the six-membered mimic **1**, reveals that, while the two mimics possess opposite configurations at C3, both have the same ‘conformational sense’ (Fig. 3).

Hydrogenation of **1** and **16** gave the saturated piperidine and proline analogues **9** and **17**, respectively. The solid-state conformation of **9** showed that the N–C α bond had undergone an inversion or ‘conformational flip’ relative to its precursor **1**, as revealed by the opposite sign of the respective Φ torsion angles as defined in Table 1. Thus, peptidomimetics incorporating either **1** or **9** could, conceivably, adopt significantly different conformations. This reinforces the idea that control of conformation is critical to the design and synthesis of peptidomimetics. It also highlights an ability to induce a significant conformational change by means of a small chemical manipulation that does not effect configuration *i.e.* the configuration of a compound does not necessarily define its conformation.

**Fig. 3** X-Ray crystal structures for **1**, **9** and **16** with perspective drawings (below) looking along the N–C α bond indicating the respective Φ torsion angles defined by C8–N–C3–C2 (the benzoyl phenyl rings have been omitted for clarity).

Experimental

Proton NMR spectra were recorded on a Varian 500 MHz NMR spectrometer. Carbon NMR spectra were recorded on a Varian 300 MHz NMR spectrometer operating at 75 MHz. 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. Optical rotations were measured on a Perkin Elmer polarimeter Model 341. All solvents were dried and freshly distilled prior to use. Dry degassed solvents were obtained by means of multiple freeze-pump-thaw cycles.

(2R)-1-Benzoyl-2-benzyl-1,2,3,6-tetrahydro-pyridine-2-carboxylic acid methyl ester (+)-1²

Catalyst **2** (114 mg, 0.14 mmol, 5 mol%) in dry degassed CH₂Cl₂ (3 mL), was added to a solution of diene (+)-**8** (1 g, 2.75 mmol, 1 eq.) in dry degassed CH₂Cl₂ (25 mL) under nitrogen, and the mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure to give a dark brown residue that was purified by radial chromatography (ethyl acetate/petroleum ether 1:3) to give (+)-**1** as a white solid (867 mg, 94%). An analytical sample and crystals suitable for X-ray crystallography were obtained by the diffusion of petroleum ether into a solution of (+)-**1** dissolved in ethyl acetate. Mp = 122–123 °C; $[\alpha]_D^{20} = +38.2^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 2947, 1742, 1634; ¹H NMR (CDCl₃) δ 2.43 (m, 1H, CCH₂CH=), 2.78 (m, 1H, CCH₂CH=), 3.18 (d $J = 13.2$ Hz, 1H, PhCH₂), 3.62 (d $J = 13.2$ Hz, 1H, PhCH₂), 3.68 (s, 3H, OMe), 3.80 (m, 1H, NCH₂CH=), 4.10 (m, 1H, NCH₂CH=), 5.67 (m, 1H, CCH₂CH=), 5.88 (m, 1H, NCH₂CH=), 7.15–7.52 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ 28.5, 38.9, 46.8, 51.9, 62.7, 124.6, 125.3, 127.0, 127.9, 128.1, 128.4, 130.5, 130.5, 135.7, 135.8, 172.4, 172.6; HRMS calcd for C₂₁H₂₁NO₃ (M) 335.1521, found 335.1520; C₂₁H₂₁NO₃ requires C, 75.19; H, 6.31; N, 4.18; found: C, 74.94; H, 6.23; N, 4.19%.

(2R)-2-(Allyl-benzoyl-amino)-2-benzyl-pent-4-enoic acid methyl ester (+)-8²

Sodium hydride (1.486 g of 60% in mineral oil, 37.2 mmol, 3 eq.) was slowly added to a 0 °C solution of methyl ester (–)-**7** (4 g, 12.4 mmol, 1 eq.) and allyl bromide (3.215 mL, 37.2 mmol, 3 eq.) in DMF (120 mL). The mixture was stirred at 0 °C for 1.5 h, then at room temperature for 30 min, whereupon the solution was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate (3 × 10 mL). The ethyl acetate extracts were combined and washed with water (2 × 10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. Purification by column chromatography (ethyl acetate/petroleum ether 1:3) gave an initial fraction of pure starting material (–)-**7** (920 mg, 23%). Further elution gave pure diene (+)-**8** as a white solid (1.343 g, 30%). Mp 92–93 °C; $[\alpha]_D^{20} = +64.3^\circ$ ($c = 1.0$ CHCl₃); ν_{\max} cm⁻¹ 3323, 2924, 1732, 1628; ¹H NMR (500 MHz, CDCl₃) δ 1.98 (m, 3H, 2 × NCH₂CH₂), 2.73 (m, 2H, NCH₂CH=), 3.09 (m, 1H, CCH₂CH=), 3.22 (d $J = 13.7$ Hz, 1H, PhCH₂), 3.63 (m, 1H, CCH₂CH=), 3.69 (d $J = 13.7$ Hz, 1H, PhCH₂), 3.75 (s, 3H, OMe), 5.08–5.34 (m, 4H, 2 × CH=CH₂), 5.54 (m, 1H, NCH₂CH=CH₂), 5.87 (m, 1H, CCH₂CH=CH₂), 7.21–7.43 (10H, PhH); ¹³C NMR (CDCl₃) δ 36.1, 36.6, 49.4, 52.0, 67.9, 116.6, 119.9, 126.2, 126.9, 128.2, 128.3, 129.4, 130.7, 132.2, 136.4, 136.5, 136.8, 172.7, 172.7; HRMS calcd for C₂₃H₂₄NO₃ (M – H) 362.1756, found 362.1758.

(2R)-1-Benzoyl-2-benzyl-piperidine-2-carboxylic acid methyl ester (+)-9

10% Palladium-on-carbon (4.5 mg, 20% w/w) was added to a solution of olefin (+)-**1** (23 mg, 0.07 mmol) in dry methanol (1.5 mL) and the mixture stirred vigorously under hydrogen for 12 h. The mixture was then filtered through a small bed of Celite™, washed with methanol, and the solvent removed under reduced pressure to

give (+)-**9** as a white solid (21 mg, 92%). An analytical sample and a crystal suitable for X-ray crystallography were obtained by the diffusion of petroleum ether into a solution of (+)-**9** dissolved in ethyl acetate. Mp 100–102 °C; $[\alpha]_D^{20} = +163.0^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 2949, 1736, 1630; ¹H NMR (CDCl₃) δ 1.35 (m, 1H, CH), 1.61 (m, 2H, CH₂), 1.75 (m, 2H, CCH₂ and CH), 2.15 (m, 1H, CCH₂), 2.34 (m, 1H, NCH₂), 3.05 (d $J = 13.7$ Hz, 1H, PhCH₂), 3.29 (m, 1H, NCH₂), 3.81 (s, 3H, OMe), 4.05 (d $J = 13.7$ Hz, 1H, PhCH₂), 7.24–7.40 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ 15.7, 21.3, 28.9, 39.0, 43.3, 52.2, 63.8, 126.6, 127.9, 128.3, 129.4, 131.1, 136.7, 136.8, 171.4, 173.5; HRMS calcd for C₂₁H₂₃NO₃ (M) 337.1678, found 337.1675.

(2R,4R)-3-Benzoyl-4-benzyl-4-(2-methylsulfanyl-ethyl)-2-phenyl-oxazolidin-5-one, (+)-11 and (3S)-N-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-benzamide 18

n-Butyl lithium (4.045 mL of a 2 M solution in THF, 8.07 mmol, 1.1 eq.) was added to a –50 °C solution of pyrrolidine (0.614 mL, 7.33 mmol, 1 eq.) in dry THF (5 mL) under argon, and the solution was stirred at –20 °C for 30 min. The mixture was recooled to –50 °C and a solution of oxazolidinone (+)-**10**⁵ (2.5 g, 7.33 mmol, 1 eq.) in dry THF (15 mL) added slowly. The mixture was stirred at –50 °C for 20 min whereupon benzyl bromide (1.311 mL, 11.02 mmol, 1.5 eq.) was added slowly and the reaction mixture stirred at –50 °C for 1 h, then warmed to rt overnight. The dark yellow solution was quenched with saturated aqueous NH₄Cl solution (10 mL) and the aqueous layer extracted with ether (3 × 20 mL). The ether extracts were combined and washed with water (20 mL), dried (MgSO₄), and the solvent removed under reduced pressure. Purification by radial chromatography (ethyl acetate/petroleum ether 1:9) gave a fraction containing (+)-**11** (1.925 g, 61%) as a white solid. Further elution (ethyl acetate/petroleum ether 1:1) gave a fraction containing **18** as a white solid (511 mg, 29%). Data for (+)-**11**: mp = 120–122 °C; $[\alpha]_D^{20} = +14.3^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 1788, 1654; ¹H NMR (CDCl₃) δ 2.22 (s, 3H, SMe), 2.69–2.75 (m, 1H, CH₂CH₂SMe), 2.84–2.98 (m, 3H, CH₂CH₂SMe), 3.37 and 3.88 (dd $J = 13.4$ Hz, 2H, CH₂Ph), 5.36 (s, 1H, C2H), 6.66 (d $J = 5.9$ Hz, 2H, PhH), 6.74 (d $J = 5.9$ Hz, 2H, PhH), 7.03 (m, 4H, PhH), 7.13 (m, 2H, PhH), 7.39 (m, 2H, PhH), 7.44 (m, 3H, PhH); ¹³C NMR (CDCl₃) δ 15.4, 29.2, 36.9, 40.1, 68.7, 90.4, 125.6, 127.2, 127.9, 128.1, 128.2, 129.0, 130.1, 135.0, 136.1, 169.3, 173.5; HMRS calcd for C₂₆H₂₆NO₃S (M + H) 432.1633, found 432.1637; C₂₆H₂₆NO₃S requires C, 72.36; H, 5.84; N, 3.25; S, 7.43; found: C, 72.39; H, 6.04; N, 3.47; S, 7.24%. Data for **18**: ¹H NMR (CDCl₃) δ 1.85 (m, 2H, 2 × NCH₂CH₂), 1.98 (m, 3H, 2 × NCH₂CH₂ and CH₂CH₂SMe), 2.08 (m, 4H, SMe and CH₂CH₂SMe), 2.56 (m, 2H, CH₂SMe), 3.41 (m, 1H, NCH₂), 3.48 (m, 1H, NCH₂), 3.53 (ddd $J = 6.1$, 10.1 and 16.9 Hz, 1H, NCH₂), 3.73 (ddd $J = 6.6$, 10.0 and 16.8 Hz, 1H, NCH₂), 5.07 (m, 3H, NH and PhH), 7.45 (m, 1H, PhH), 7.80 (t $J = 7.3$ Hz, 2H, PhH); ¹³C NMR (CDCl₃) δ 15.6, 24.0, 25.9, 30.2, 32.3, 46.0, 46.5, 50.3, 127.1, 128.3, 131.5, 133.7, 166.8, 169.8; HRMS calcd for C₁₆H₂₃N₂O₂S (M + H) 307.1480, found 307.1484.

(2R,4R)-3-Benzoyl-4-benzyl-2-phenyl-4-vinyl-oxazolidin-5-one (+)-12

Hydrogen peroxide (0.289 mL of a 50% w/w solution, 4.25 mmol, 1.4 eq.) was added to a solution of oxazolidinone (+)-**11** (1.312 g, 3.04 mmol, 1 eq.) in acetic acid (6 mL) and the mixture stirred at rt for 4 h. Dichloromethane (20 mL) was added and the solution was carefully neutralised with saturated aqueous Na₂CO₃. The organic phase was separated and washed with water (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure to give the intermediate sulfoxide as a tan solid (1.26 g, 94%) that was not purified further. ¹H NMR (CDCl₃) δ 2.70 (s, 3H, SMe), 2.84–3.32 (m, 4H, CH₂CH₂SMe), 3.41 (d $J = 13.6$ Hz, 1H, CH₂Ph), 3.91 (br d $J = 13.6$ Hz, 1H, CH₂Ph), 5.50 (m, 1H, H2), 6.63 (m, 2H, PhH), 6.73 (m, 2H, PhH), 7.05 (m, 4H, PhH), 7.16 (m, 2H, PhH), 7.36 (m, 2H, PhH), 7.44 (m, 3H, PhH). The sulfoxide was dissolved in degassed *m*-xylene (20 mL), sealed under vacuum in a glass tube, and heated

at 200 °C for 16 h. Removal of the solvent under reduced pressure and purification of the residue by radial chromatography (ethyl acetate/petroleum ether 1 : 3) gave the vinyl oxazolidinone (+)-**12** as a white solid (998 mg, 93%). An analytical sample and crystals suitable for X-ray crystallography were obtained by the diffusion of petroleum ether into a solution of (+)-**12** dissolved in ethyl acetate. Mp 148–149 °C; $[\alpha]_D^{20} = +139.0^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 3034, 2939, 1801, 1649; ¹H NMR (CDCl₃) δ 3.51 (d $J = 13.7$ Hz, 1H, CH_aPh), 4.06 (d $J = 13.7$ Hz, 1H, CH_bPh), 5.58 (d $J = 13.7$ Hz, =CH_a), 5.64 (m, 2H, =CH_b and CH=CH₂), 6.61 (d $J = 7.3$ Hz, 2H, PhH), 6.73 (m, 3H, PhH), 7.06 (m, 4H, PhH), 7.16 (t $J = 7.3$ Hz, 1H, PhH), 7.21 (t $J = 7.3$ Hz, 1H, PhH), 7.41 (m, 4H, PhH); ¹³C NMR (CDCl₃) δ 40.6, 69.1, 90.4, 117.9, 125.8, 127.0, 127.8, 128.3, 128.9, 129.6, 129.8, 130.1, 135.1, 135.8, 135.9, 168.8, 171.5; HRMS calcd for C₂₅H₂₁NO₃ (M) 383.1521, found 383.1521; C₂₅H₂₁NO₃ requires C, 78.2; H, 5.5; N, 3.7; found C, 77.8; H, 5.6; N, 3.7%.

(2R)-2-Benzoylamino-2-benzyl-but-3-enoic acid **13**

Sodium hydroxide (209 mg, 5.22 mmol, 2 eq. in 2 mL of water) was added to a solution of oxazolidinone (+)-**12** (998 mg, 2.61 mmol, 1 eq.) in MeOH (20 mL) and the mixture refluxed for 1 h. The solution was cooled and concentrated under reduced pressure. The residue was taken up in water, acidified to pH 1 with 10% HCl, and extracted with ether (3 × 10 mL). The combined ether extracts were washed with brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure to give acid **13** as a white solid (760 mg, 99%). ¹H NMR (CDCl₃) δ 3.54 (d $J = 13.7$ Hz, 1H, CH_aPh), 3.74 (d $J = 13.7$ Hz, 1H, CH_bPh), 5.38 (m, 2H, CH=CH₂), 6.18 (m, 1H, CH=CH₂), 6.87 (s, 1H, NH), 7.20–7.27 (m, 5H, PhH), 7.42 (t $J = 7.3$ Hz, 2H, PhH), 7.52 (t $J = 7.3$ Hz, 1H, PhH), 7.67 (m, 2H, PhH); HRMS calcd for C₁₈H₁₈NO₃ (M + H) 296.1287, found 296.1286.

(2R)-2-Benzoylamino-2-benzyl-but-3-enoic acid methyl ester (+)-**14**

Ethereal diazomethane was added to a 0 °C solution of acid **13** (760 mg, 2.58 mmol) in ether (20 mL) until the bright yellow colour persisted over an extended period. The mixture was stirred at rt for 2 h, whereupon the reaction was quenched with the addition of a few drops of acetic acid. The solvent was removed under reduced pressure to give methyl ester (+)-**14** as a colourless oil (797 mg, 100%). $[\alpha]_D^{20} = +54.1^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 3464, 1749, 1645, 1543; ¹H NMR (CDCl₃) δ 3.43 (d $J = 13.7$ Hz, 1H, CH_aPh), 3.83 (s, 1H, OMe), 3.92 (d $J = 13.7$ Hz, 1H, CH_bPh), 5.33 (m, 2H, CH=CH₂), 6.20 (m, 1H, CH=CH₂), 7.00 (br s, 1H, NH), 7.09 (m, 2H, PhH), 7.21 (m, 3H, PhH), 7.42 (t $J = 7.8$ Hz, 2H, PhH), 7.51 (t $J = 7.3$ Hz, 1H, PhH), 7.71 (dd $J = 7.3$ and 1.2 Hz, 2H, PhH); ¹³C NMR (CDCl₃) δ 40.0, 53.0, 65.8, 116.3, 126.9, 127.1, 128.3, 128.6, 129.9, 130.0, 131.6, 134.7, 135.6, 136.2, 166.4, 172.2; HRMS calcd for C₁₉H₁₉NO₃ (M) 309.1359, found 309.1365; C₁₉H₁₉NO₃ requires C, 73.7; H, 6.2; N, 4.5; found: C, 73.3; H, 6.2; N, 4.4%.

(2R)-2-(Allyl-benzoyl-amino)-2-benzyl-but-3-enoic acid methyl ester (-)-**15**

Sodium hydride (238 mg of 60% in oil, 5.94 mmol, 3 eq.) was slowly added to an ice-cooled solution of methyl ester (+)-**14** (612 mg, 1.98 mmol, 1 eq.) and allyl bromide (0.514 mL, 5.94 mmol, 3 eq.) in DMF (20 mL). The solution was stirred at 0 °C for 1.5 h and then at rt for 30 min. The mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate (3 × 10 mL). The ethyl acetate extracts were combined and washed with water (2 × 10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. Purification by radial chromatography (ethyl acetate/petroleum ether 15 : 85) gave a fraction containing 311 mg (51%) of starting material (+)-**14**. Further elution gave the diene (-)-**15** as a clear yellow oil (214 mg, 31%). $[\alpha]_D^{20} = -62.8^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 3395, 1736, 1624; ¹H NMR (CDCl₃) δ 3.33 (d $J = 13.4$ Hz, 1H, CH_aPh), 3.38 (m, 1H, NCH_a), 3.64 (m, 1H, NCH_b), 3.81 (s, 3H, OMe), 4.03 (d $J = 13.4$ Hz, 1H, CH_bPh), 4.99 (m, 2H,

NCH₂CH=CH₂), 5.34 (m, 1H, NCH₂CH=CH₂), 5.36 (d $J = 3.4$ Hz, 1H, CCH=CH_a), 5.39 (d $J = 3.4$ Hz, 1H, CCH=CH_b), 6.22 (m, 1H, CCH=CH₂), 7.24–7.42 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ 39.6, 50.7, 52.3, 70.1, 116.6, 117.3, 126.4, 126.9, 128.1, 128.1, 129.7, 131.0, 134.9, 135.8, 136.2, 136.5, 171.8, 173.0; HRMS calcd for C₂₂H₂₄NO₃ (M + H) 350.1756, found 350.1763; C₂₂H₂₄NO₃ requires C, 75.6; H, 6.6; N, 4.0; found: C, 75.6; H, 6.5; N, 4.0%.

(2R)-1-Benzoyl-2-benzyl-2,5-dihydro-1H-pyrrole-2-carboxylic acid methyl ester (-)-**16**

Catalyst **4** (18 mg, 0.02 mmol, 5 mol%) in dry degassed benzene (0.5 mL) was added to a solution of diene (-)-**15** (156 mg, 0.45 mmol) in dry degassed benzene (5 mL), under nitrogen, and the mixture stirred at reflux for 16 h. The solvent was removed under reduced pressure to give a dark brown residue that was purified by radial chromatography (ethyl acetate/petroleum ether 1 : 3) to give (-)-**16** as a white solid (133 mg, 94%). An analytical sample and a crystal suitable for X-ray crystallography were obtained by the diffusion of petroleum ether into a solution of (-)-**16** dissolved in ethyl acetate. $[\alpha]_D^{20} = -116.6^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 2951, 1738, 1645; ¹H NMR (CDCl₃) δ 3.29 (d $J = 13.7$ Hz, 1H, PhCH_a), 3.47 (d $J = 15.2$ Hz, 1H, NCH_a), 3.83 (s, 3H, OMe), 3.93 (d $J = 15.2$ Hz, 1H, NCH_b), 3.99 (d $J = 13.7$ Hz, 1H, PhCH_b), 5.71 (s, 2H, CH₂CH=CH and CH₂CH=CH), 7.19–7.40 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ 38.0, 52.7, 56.9, 76.6, 126.4, 126.5, 127.6, 128.3, 129.3, 129.8, 130.7, 136.4, 136.5, 169.1, 171.6; HRMS Calcd for C₂₀H₂₀NO₃ (M + H) 322.1443, found 322.1444.

Preparation of (2R)-1-Benzoyl-2-benzyl-pyrrolidine-2-carboxylic acid methyl ester (-)-**17**

10% palladium-on-carbon (3.6 mg, 20% w/w) was added to a solution of olefin (-)-**16** (18 mg, 0.06 mmol) in dry methanol (1.5 mL), and the mixture stirred vigorously under hydrogen for 12 h. The mixture was then filtered through a small bed of Celite™, washed with methanol, and the solvent removed under reduced pressure to give (-)-**17** as a white solid (17 mg, 95%). $[\alpha]_D^{20} = -106.5^\circ$, $c = 1.0$ CHCl₃; ν_{\max} cm⁻¹ 2930, 1736, 1634, 1408; ¹H NMR (CDCl₃) δ 1.32 (m, 1H, CH₂CH_aCH₂), 1.81 (m, 1H, CH₂CH_bCH₂), 2.07 (m, 1H, CCH_a), 2.22 (m, 1H, CCH_b), 2.82 (m, 1H, NCH_b), 3.13 (d $J = 13.7$ Hz, 1H, PhCH_a), 3.82 (s, 3H, OMe), 4.01 (d $J = 13.7$ Hz, 1H, PhCH_b), 7.24–7.46 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ 23.6, 34.5, 37.4, 51.7, 52.5, 68.7, 126.7, 127.1, 128.1, 128.2, 130.1, 131.2, 136.7, 136.8, 169.3, 174.3; HRMS calcd for C₂₀H₂₁NO₃ (M) 323.1521, found 323.1523.

X-Ray crystallography

Data were collected with a Siemens SMART CCD area detector, using graphite monochromatised MoK α radiation ($\lambda = 0.71073$ Å). The intensities were corrected for Lorentz and polarisation effects and for absorption.¹⁶ The structure was solved by direct methods using SHELXS¹⁷ and refined on F^2 , using all data, by full-matrix least-squares procedures using SHELXTL.¹⁸ CCDC reference numbers 234480–234482. See <http://www.rsc.org/suppdata/ob/b4/b406450j/> for crystallographic data in .cif or other electronic format.

Crystal data for 1. C₂₁H₂₁NO₃, $M = 335.39$, orthorhombic, $a = 11.000(4)$, $b = 13.360(4)$, $c = 24.060(4)$ Å, $U = 3535.9(18)$ Å³, $T = 293(2)$ K, space group P2₁2₁2₁, $Z = 8$, $\lambda(\text{Mo-K}\alpha) = 0.71073$ Å, 13962 reflections measured, 6730 unique ($R_{\text{int}} = 0.0398$ which were used in all calculation. The final $wR(F^2)$ was 0.0779 (all data).² (CCDC RefCode FIJQOE)

Crystal data for 9. C₂₁H₂₃NO₃, $M = 337.40$, orthorhombic, $a = 7.582(7)$, $b = 13.621(16)$, $c = 17.52(2)$ Å, $U = 1809(3)$ Å³, $T = 168(2)$ K, space group P2₁2₁2₁, $Z = 4$, $\lambda(\text{Mo-K}\alpha) = 0.71073$ Å, 7931 reflections measured, 3582 unique ($R_{\text{int}} = 0.0432$ which were used in all calculation. The final $wR(F^2)$ was 0.0867 (all data). (CCDC No 234480)

Crystal data for 12. C₂₅H₂₁NO₃, *M* = 383.43, orthorhombic, *a* = 8.612(4), *b* = 9.467(6), *c* = 24.782(15) Å, *U* = 2020(2) Å³, *T* = 293(2) K, space group P2₁2₁2₁, *Z* = 4, λ(Mo–K_α) = 0.71073 Å, 8002 reflections measured, 2030 unique (*R*_{int} = 0.0336 which were used in all calculation. The final *wR*(*F*²) was 0.0868 (all data). (CCDC No 234482)

Crystal data for 16. C₂₀H₁₉NO₃, *M* = 321.86, monoclinic, *a* = 19.516(4), *b* = 7.211(15), *c* = 24.682(15) Å, *U* = 3378(12) Å³, *T* = 168(2) K, space group C2/c, *Z* = 8, λ(Mo–K_α) = 0.71073 Å, 20377 reflections measured, 3414 unique (*R*_{int} = 0.0436 which were used in all calculation. The final *wR*(*F*²) was 0.1071 (all data). (CCDC No 234481)

Acknowledgements

We gratefully acknowledge financial support from a Royal Society of New Zealand Marsden grant. We also thank Professors Peter Steel and Ward Robinson (UC) for help with the X-ray crystallography.

Notes and references

- (a) *Advances in Amino Acid Mimetics and Peptidomimetics*, ed. A. D. Abell, JAI Press, Stamford, 1999, vol. 2; (b) *Advances in Amino Acid Mimetics and Peptidomimetics*, ed. A. D. Abell, JAI Press, Greenwich, London, 1997; vol. 1.
- A. D. Abell, J. Gardiner, A. J. Phillips and W. T. Robinson, *Tetrahedron Lett.*, 1998, **39**, 9563.
- D. C. Martyn, A. J. Vernall, B. M. Clark and A. D. Abell, *Org. Biomol. Chem.*, 2003, **1**, 2103–2110; A. D. Abell, *Lett. Pept. Sci.*, 2001, **8**, 267–272; B. C. H. May and A. D. Abell, *J. Chem. Soc., Perkin Trans. 1*, 2002, 172–178.
- I. Schechter and A. Berger, *Biochem. Biophys. Res. Commun.*, 1967, **27**, 157.
- A. Fadel and J. Salaun, *Tetrahedron Lett.*, 1987, **28**, 2243.
- (a) J. Duan and Z. Lu, PCT Int. Appl. (2003), 123 pp., WO 2003053940, A1 20030703, CAN 139:85367, AN 2003:511306; K. Dolbears, G. F. Pontoriero, S. K. Gupta, R. K. Mishra and R. L. Johnson, *J. Med. Chem.*, 2003, **46**, 727; (b) D. P. Boatman, C. O. Ogbu, M. Eguchi, H.-O. Kim, H. Nakanishi, B. Cao, J. P. Shea and M. Kahn, *J. Med. Chem.*, 1999, **42**, 1367; (c) E. M. Khalil, A. Pradhan, W. H. Ojala, W. B. Gleason, R. K. Mishra and R. L. Johnson, *J. Med. Chem.*, 1999, **42**, 2977; (d) J. E. Baldwin, V. Lee and C. J. Schofield, *Heterocycles*, 1992, **34**, 903; for related examples see; (e) B. M. Trost and K. Dogra, *J. Am. Chem. Soc.*, 2002, **124**, 7256; (f) A. B. Smith III, M. C. Guzman, P. A. Sprengeler, T. P. Keenan, R. C. Holcomb, J. L. Wood, P. J. Carroll and R. Hirschmann, *J. Am. Chem. Soc.*, 1994, **116**, 9947.
- J. Gardiner and A. D. Abell, *Tetrahedron Lett.*, 2003, **44**, 4227.
- D. Seebach and A. Fadel, *Helv. Chim. Acta*, 1985, **68**, 1243.
- (a) J.-P. Begue, D. Bonnet-Delpon, D. Bouvet and M. H. Rock, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1797; (b) R. K. Thaper, Y. K. Kumar, S. M. D. Kumar, S. Misra and J. M. Khanna, *Org. Process Res. Dev.*, 1999, **3**, 476.
- T. Weber, R. Aeschmann, T. Maetzke and D. Seebach, *Helv. Chim. Acta*, 1986, **69**, 1365.
- It is interesting to note that the sterically demanding diene **15** was successfully cyclised in excellent yield using catalyst **4**, whilst catalysts **2** and **3** were unreactive in this regard. This is consistent with the fact that catalysts with extended tethers, *i.e.* **4**, are known to effect RCM of sterically demanding substrates.¹²
- (a) P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100; (b) S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9858; (c) M. Ulman and R. H. Grubbs, *J. Org. Chem.*, 1999, **64**, 7202; (d) A. J. Phillips and A. D. Abell, *Aldrichim. Acta*, 1999, **32**, 75.
- C. Toniolo, *Int. J. Peptide Protein Res.*, 1990, **35**, 287.
- Proline torsion angles vary in the literature depending on the structure and environment of the molecule *i.e.* proline adopts a constrained but fluid system.
- D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem., Int. Ed.*, 1996, **35**, 2748.
- G. M. Sheldrick, *SADABS*, University of Göttingen, Germany, 1998.
- G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
- G. M. Sheldrick, *SHELXTL*, Bruker Analytical X-ray Systems, 1997.