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Synthesis of 2-(4-carboxybutenyl)- and 2-(4-carboxybutynyl)-cyclopentene-1-carboxamides

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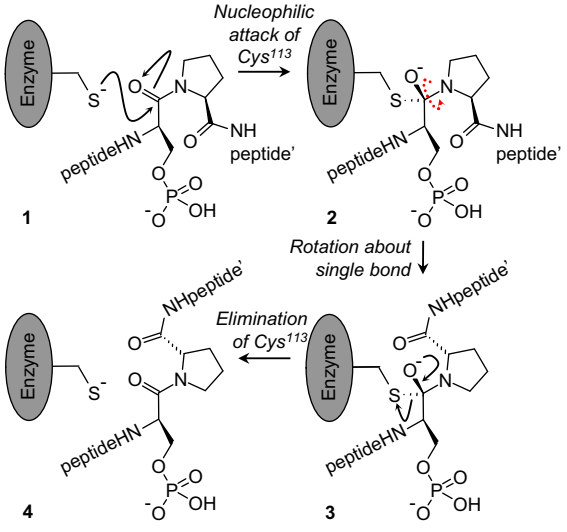
ABSTRACT

Syntheses of 2-(4-carboxybut-1-enyl/4-carboxypent-1-ynyl)cyclopentene-1-carboxamides, compounds designed to mimic the phosphoSer–Pro dipeptide motif (the recognition sequence for the prolyl *cis–trans* isomerase Pin1), have been developed. Stille, Sonogashira and Suzuki couplings were envisaged to join the pentynoic and pentenoic acid side chains to the 2-position of cyclopentene-1-carboxylate esters. The ring- and side-chain carboxylic acids required orthogonal protection for later attachment of a Ph-NH(4-nitrophenyl) unit to the cyclopentene-1-carbonyl. The cyclopentenecarboxylates were unmasked and standard PyBOP peptide coupling afforded the target compounds. Comparisons of two routes using Bu^t and Me esters are reported.

1. Introduction

Most peptide bonds in proteins are secondary amides and exist almost exclusively in the *trans*-amide conformation. However, peptide bonds to proline are tertiary amides and can exist in both *cis*-amide and *trans*-amide conformations, with similar energy,[1] which interconvert only slowly at 37 °C. Since interchange of conformation is important in the folding of all proteins and in activating some, there exist peptidyl-prolyl *cis–trans* isomerases (PPIases), which catalyse this interconversion.[2] There are several families of PPIases, which recognise different amino-acid sequences surrounding the Pro in the substrate proteins. The endogenous substrate proteins for the prolyl *cis–trans* isomerase Pin1 all contain phosphoserine–proline or phosphothreonine–proline units. Phosphorylation of proteins on SerPro or ThrPro sequences is an important signalling mechanism controlling many cellular processes, including cell cycle regulation, transcription and proliferation. Deregulation of this process can result in cell transformation and oncogenesis.[3] Ser/Thr–Pro motifs are the major phosphorylation sites for a large superfamily of kinases, including cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs) and glycogen synthase kinase 3β (GSK-3β),[3] many of which (and the corresponding phosphatases) are Pro-conformation-specific. For example, the MAPKs ERK2 and p42 phosphorylate only the *trans* conformer of their substrate proteins.[4]

The PPIases differ in their catalytic molecular mechanisms. To lower the energy barrier to rotation of the amide C–N bond, either the nitrogen or the carbon must be converted temporarily to an sp^3-like state to disturb the π-bond-like nature of the amide. Pin1 employs a mechanism in which the carbonyl of **1** undergoes reversible nucleophilic attack by the Cys^{113} thiol/thiolate, located in the active site (Scheme 1).[5] This produces an intermediate **2** in which the carbon is tetrahedral and the C–N bond is free to rotate to give **3**. After bond rotation, the thiol leaves, restoring the tertiary amide but in the new conformation **4**.



Scheme 1. Mechanism of *cis*↔*trans* interconversion of phosphoSer–Pro peptides catalysed by Pin1.

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As part of our studies on Pin1, we required molecules that could mimic the phosphoserine–proline unit, such as **5** and **6** (Fig. 1). In these compounds, the cyclopentene represents the pyrrolidine ring of the Pro of **4**, with the endocyclic C=C ensuring that the atom corresponding to the N is sp^2 and planar; the pendant carboxylate mimics the anionic phosphate and the PheNP module represents the continuing C-terminal peptide. The nitroanilide was required to provide a suitable chromophore in the enzymic studies.

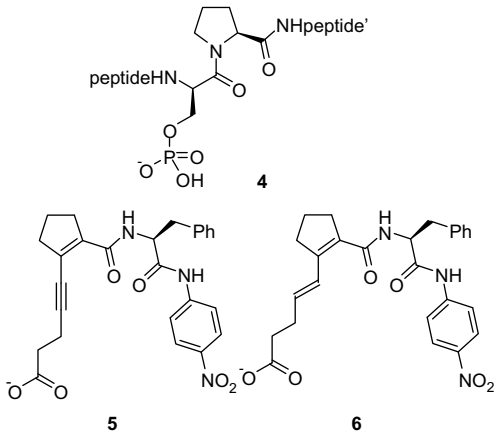


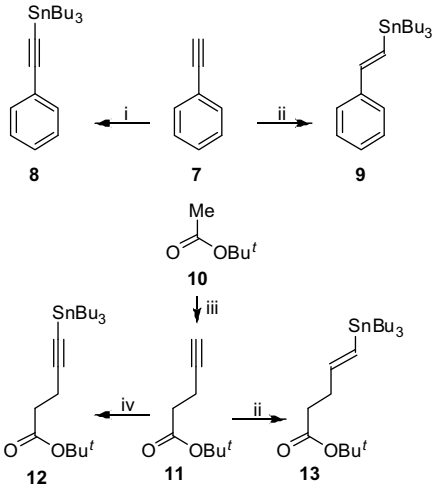
Figure 1. Structures of target 2-(4-carboxybutynyl)cyclopentene-1-carboxamide **5** and 2-(4-carboxybutenyl)cyclopentene-1-carboxamide **6** in their carboxylate anionic forms and comparison with sequence **4** recognised by Pin1.

2. Results and discussion

Retrosynthetic analysis of the structure of **5** and **6** and related structures indicated that the important disconnection would be between the five-carbon pentynoic acid and pentenoic acid moieties and the cyclopentene-1-carboxamide. This important bond could then be formed by a Pd-catalysed coupling of a cyclopentenyl triflate with an appropriate five-carbon coupling partner. Simple methyl and ethyl esters of 2-triflyloxycyclopentene-1-carboxylic acid have been reported to couple in this way with varying degrees of success. These couplings include conventional Heck couplings of alkenes,[6] Negishi-type couplings with organo-zinc,[7–9] organo-bismuth[10] and organo-aluminium reagents,[11] Suzuki reactions with arylboronic acids,[12,13] alkylboronic acids,[14] pinacol-borates[15,16] and trifluoroborate anions,[17] Sonogashira couplings with terminal alkynes[18,19] and Buchwald couplings.[20]

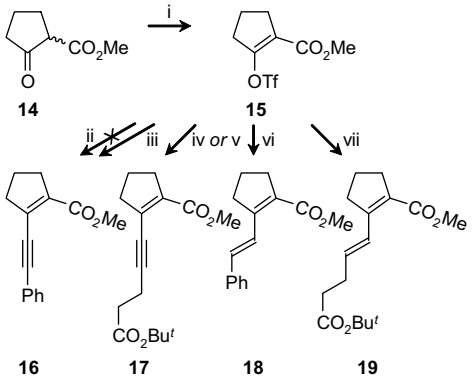
The synthetic strategy thus involved preparation of cyclopentene-1-carboxylic acid carrying a pentynoic acid or pentenoic acid moiety at the 2-position. For later attachment of the PheNP unit at the correct cyclopentenyl-1-carbonyl, the two carboxylic acids required orthogonal ester protection, either as the 2-methyl ester 5′-*t*-butyl esters **17** and **19** (Schemes 3 and 6) or the 2-*t*-butyl ester 5′-methyl esters **42** and **45** (Scheme 8). Initially, the 2-methyl ester strategy was investigated, as the starting methyl 2-oxocyclopentane-1-carboxylate is commercially available.

A study was therefore initiated to develop suitable Pd-catalysed couplings in this series, conducting model reactions as appropriate. Sonogashira and Stille couplings were envisaged, so appropriate coupling partners were prepared, as shown in Scheme 2. Firstly, to supply compounds for model experiments, phenylethyne **7** was deprotonated with lithium hexamethyldisilazide and the acetylenic carbanion was quenched with chlorotributylstannane to afford the phenylethynylstannane **8** in excellent yield. However, this approach could not be used for synthesis of the *t*-butyl 5-tributylstannylpent-4-ynoate **12**. Firstly, the commercially available pent-4-ynoic acid **34** could not be readily converted to its *t*-butyl ester **11**. The procedure of Trost[21] was adapted; the anion formed by deprotonation of *t*-butyl acetate **10** was alkylated with propargyl bromide to give **11** in high yield. Secondly, attempts to remove the alkyne proton from **11** and quench with chlorotributylstannane failed but simple heating of the alkyne with methoxytributylstannane provided the required potential Stille coupling partner **12**. Radical addition of tributyltin hydride across the terminal alkynes of phenylethyne **7** and *t*-butyl prop-4-ynoate **11** furnished the vinylstannanes **9** and **13**, respectively, as almost exclusively the required *E* stereoisomers. These vinylstannanes were found to be unstable to extensive purification and were used immediately for the Stille coupling reactions.

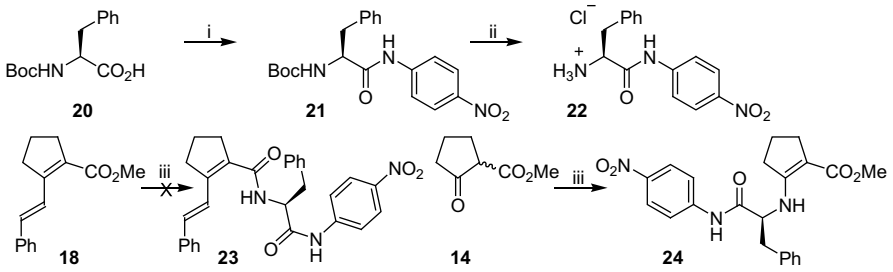


Scheme 2. Synthesis of Sonogashira and organo-tin Stille coupling partners. *Reagents and conditions*: i, $LiN(SiMe_3)_2$, Bu_3SnCl, THF −78 °C, 99%; ii, Bu_3SnH, AIBN, PhMe, 85 °C, 50% (**9**), 60% (**13**), 40% (**18**); iii, $LiNPr^i_2$, $BrCH_2C{\equiv}CH$, THF, HMPA, −78 °C, 88%; iv, Bu_3SnOMe, 110 °C, 88%.

Scheme 3 shows the development of Stille and Sonogashira coupling reactions with the cyclopentene triflate methyl ester **15**. Firstly, commercially available methyl 2-oxocyclopentanecarboxylate **14** was converted to **15** with triflic anhydride, by the method of Norman et al.[9] Stille coupling of the phenylethynylstannane **8** with **15**, catalysed by palladium(II) acetate, proceeded in almost quantitative yield to give the 2-phenylethynyl product **16**, indicating the facile transfer of sp-hybridised carbon in the transmetallation step. Interestingly, the corresponding Sonogashira reaction of **7** with **15** failed to give any identifiable coupling products, despite a report of efficient Sonogashira coupling of **7** with the corresponding ethyl ester.[23] The situation was reversed for the couplings of the



Scheme 3. Stille and Sonogashira with Me 2-TfO-cyclopentene-1-carboxylate **15**. *Reagents and conditions*: i, Pr^i_2NEt, Tf_2O, CH_2Cl_2, 95%; ii, $PhC{\equiv}CH$, various Pd catalysts; iii, **8**, $Pd(OAc)_2$, Ph_3P, THF, 55 °C, 99%; iv, **11**, $PdCl_2$, Ph_3P, CuI, Et_3N, THF, 98%; v, **12**, $Pd(OAc)_2$, Ph_3P, 22%; vi, **9**, $Pd(OAc)_2$, Ph_3P, THF, 55 °C, 95%; vii, **13**, $Pd(OAc)_2$, PPh_3, THF, 57%.

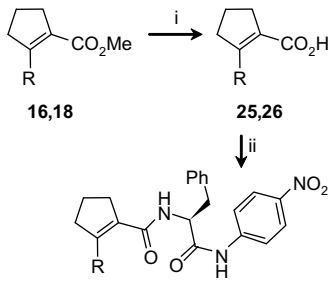


Scheme 4. Synthesis of Phe *N*-(4-nitrophenyl)amide **22** and preliminary studies on its reactions with **19** and **23**. *Reagents and conditions*: i, $POCl_3$, 4-nitroaniline, pyridine, −10 °C, 84%; ii, HCl, CH_2Cl_2, 73%; iii, **22** (free base), DMAP, PhMe, reflux, 14%.

pentynoate esters, i.e., for ω-alkylalkynes. Stille coupling of the alkynylstannane **12** with **15** gave the required diester **17** in poor yield but the analogous Sonogashira reaction of **11** with **15** was highly efficient. Moving to the couplings of the vinylstannanes, the reaction of the model phenylethenylstannane **9** with **15** gave an excellent yield of the coupled product **18**, as expected, with complete retention of the *E* configuration, as demonstrated by the large ^3J=16 Hz for the vinyl protons in the ^{1}H NMR spectrum. Correspondingly, the coupling of the ester-bearing vinylstannane **13** with **15** provided the required orthogonally protected diester **19** in a lower yield of 57%.

Assembly of the target phosphoSer–Pro peptide mimics **5** and **6** also required the preparation of L-phenylalanine 4-nitroanilide **22** (Scheme 4). Conventional peptide couplings of Boc-L-PheOH **20** with the very weak nucleophile 4-nitroaniline failed but activation of the carboxylic acid of **20** by treatment with phosphorus oxychloride at low temperature, followed by reaction with the aniline, gave **21** in good yield. Acid-catalysed deprotection gave the salt **22**. In the model series, direct treatment of the α,β,γ,δ-unsaturated ester **18** with **22** under forcing conditions failed to produce the amide **23**. Rationalising that the conjugated unsaturated system may hinder the reaction, it was repeated with the β-keto ester **14**; again, the ester failed to react but the enamine **24** was formed by reaction at the electrophilic ketone. Thus it would be necessary to hydrolyse the methyl cyclopentenecarboxylate ester to the corresponding carboxylic acid to allow generation of a suitably reactive electrophile for formation of the amide bond.

In model reactions (Scheme 5), the 2-(2-phenylethynyl)-cyclopentenecarboxylate **16** was hydrolysed to the acid **25**. The corresponding phenylethenylcyclopentenecarboxylate **18** was cleaved to the corresponding acid **26** with aqueous sodium hydroxide. In both cases, the yield was modest, again indicating possible involvement



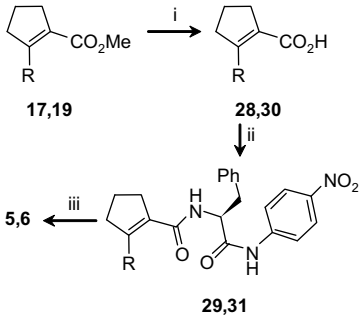
	R	Yield (%)
25	C≡CPh	57
26	C=CPh	33
27	C≡CPh	76

Scheme 5. Model reactions for hydrolysis of Me esters and peptide coupling to PheNP. *Reagents and conditions*: i, aq NaOH, EtOH; ii, **22**, PyBOP, Et_3N, CH_2Cl_2.

of the conjugate electrophilic system. Carboxylic acid **25** was then used as a model for the peptide coupling reaction, in that reaction with **22** and PyBOP gave amide **27** in good yield.

However, selective base hydrolysis of the methyl ester of the orthogonal diester **17** could only be achieved in a maximum 5% yield, using lithium hydroxide (Scheme 6). Reaction of the incoming nucleophile with the conjugated yne-ene-carbonyl unit is likely to have resulted in the myriad of unidentifiable by-products. The monoester **28** thus formed was coupled efficiently with **22** by the PyBOP method to give **29**, from which the side-chain Bu^t ester was removed by acidolysis to provide the target carboxylic acid **5**.

In the pentenoic acid series, the selective cleavage of the methyl ester of **19** was also problematic, affording the monoester **30** in a modest 24% yield, after optimisation. Again, the conjugated electrophilic system led to the formation of unidentifiable by-products. Coupling with **22** by the PyBOP method gave the amide **31**, which was readily deprotected to afford **6** (Scheme 6).

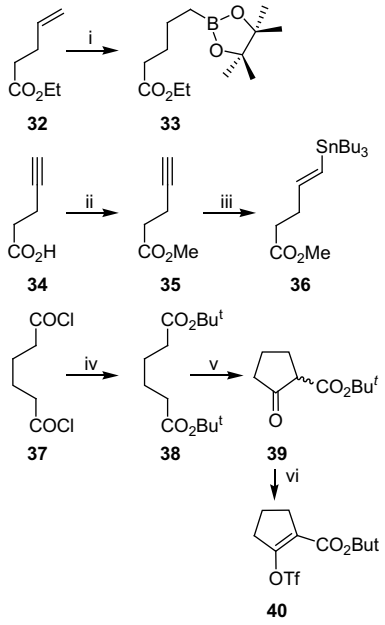


	R	Yield (%)
28	C≡C(CH$_2$)$_2$CO$_2$Bu^t	5
30	C=C(CH$_2$)$_2$CO$_2$Bu^t	24
29	C≡C(CH$_2$)$_2$CO$_2$Bu^t	88
31	C=C(CH$_2$)$_2$CO$_2$Bu^t	42
5	C≡C(CH$_2$)$_2$CO$_2$H	51
6	C=C(CH$_2$)$_2$CO$_2$H	60

Scheme 6. Approaches to target phosphoSer–Pro mimics. *Reagents and conditions*: i, LiOH, THF, MeOH, H_2O; ii, **22**, PyBOP, Et_3N, CH_2Cl_2; iii, CF_3CO_2H, CH_2Cl_2.

The overall yields of the target compounds **5** and **6** by this route, using couplings to the methyl ester **15**, were 2.1% and 3.3%, respectively, from **14**. Thus the alternative orthogonal ester protecting group strategy shown in Schemes 7 and 8 was investigated.

For use in this 2-*t*-butyl ester 5′-(m)ethyl ester sequence, addition of pinacol-borane across the alkene double bond of ethyl pent-4-enoate **32**[22] proceeded regiospecifically to give the terminal borate ester **33** in good yield; this is a potential Suzuki coupling partner. Esterification of pent-4-ynoic acid **34** readily gave the

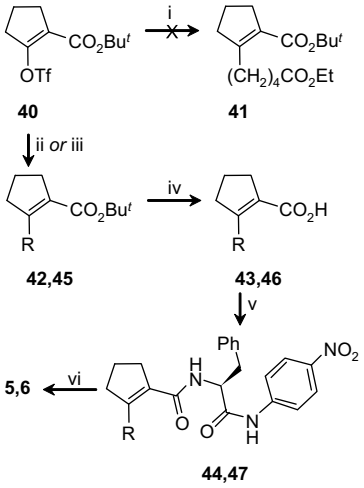


Scheme 7. Preparation of coupling partners for alternative synthetic sequence. *Reagents and conditions*: i, $Rh(PPh_3)_3Cl$, pinacol-borane, CH_2Cl_2, 79%; ii, MeOH, $TsOH \cdot H_2O$, CH_2Cl_2, 66%; iii, Bu_3SnH, AIBN, PhMe, 85 °C, 40%; iv, Bu^tOH, $PhNMe_2$, Et_2O, 89%; v, NaH, Bu^tOH, PhMe, 60 °C, 55%; vi, Et_3N, Tf_2O, −78 °C, 63%.

methyl ester **35**, which was converted to the vinylstannane **36** by radical addition of tributyltin hydride, as for **9** and **13**.

In this sequence, the vinyl triflate **40** has not been reported previously and the corresponding β-keto ester **39** is not commercially available. A Dieckmann condensation would form the β-keto ester, although it may be subject to steric hindrance as the electrophilic carbonyl is a *t*-butyl ester. The bis-acyl chloride **37** was transformed to the bis-*t*-butyl **38** ester by reaction with *t*-butanol in the presence of the weak base *N*,*N*-dimethylaniline (Scheme 7). The Dieckmann cyclisation then proceeded smoothly, catalysed by sodium hydride in hot toluene, to form the 2-oxocyclopentanecarboxylate ester **39** in good yield. The enol of this compound was triflylated readily to afford the coupling partner **40**.

As shown in Scheme 8, the *t*-butyl ester vinyl triflate **40** reacted with methyl pent-4-ynoate **35** in a Sonogashira coupling to give **42**, which is a regioisomer of **17**. Now, cleavage of the ester to expose the cyclopentene carboxylic acid could be effected under acidic conditions, which would not affect the conjugated electrophilic system adversely; treatment with trifluoroacetic acid gave the monoester **43** in excellent yield. Coupling with **22** using PyBOP gave **44**, from which the terminal methyl ester could be hydrolysed readily with mild base to provide the target **5**. That the yield in this hydrolysis is much higher than the 5% achieved in the hydrolysis of the methyl ester of **17** attests to the lower electrophilicity of the yne-ene-amide in **44**, compared to that of the yne-ene-ester in **17**, leading to fewer side reactions. Unfortunately, all attempts to couple **40** with alkylboronic acids failed. In particular, no coupling of the pinacol-borate **33**, carrying the pentanoate moiety, could be achieved, preventing access to the analogous targets where the remote carboxylate is linked to the cyclopentene ring through a fully flexible $(CH_2)_4$ chain. The improved yields of this route were reflected in the corresponding reactions to make the pentenoic acid **6**. Stille coupling of **40** with the vinylstannane **36** proceeded in excellent yield to give **45**, which is the regioisomer of **23**. Selective acidolysis of the *t*-butyl ester furnished **46**, which was coupled by the PyBOP method to provide amide **47**. Simple base-catalysed hydrolysis then led to the target **6** in overall yields of 5.3% from acyl chloride **37** and 11% from β-keto ester **39** (a more rigorous comparison with the earlier synthetic sequence).



	R	Yield (%)
42	$C{\equiv}C(CH_2)_2CO_2Me$	23
45	$C{=}C(CH_2)_2CO_2Me$	84
43	$C{\equiv}C(CH_2)_2CO_2Me$	33
46	$C{=}C(CH_2)_2CO_2Me$	72
44	$C{\equiv}C(CH_2)_2CO_2Me$	23
47	$C{=}C(CH_2)_2CO_2Me$	42
5	$C{\equiv}C(CH_2)_2CO_2H$	22
6	$C{=}C(CH_2)_2CO_2H$	68

Scheme 8. Synthesis of **5** and **6** through couplings with Bu^t 2-TfO-cyclopentene-1-carboxylate **40**. *Reagents and conditions*: i, **33**, various Pd catalysts, various conditions; ii, **35**, $PdCl_2$, Ph_3P, CuI, Et_3N, THF, reflux; iii, **36**, Ph_3P, $Pd(OAc)_2$, THF; iv, CF_3CO_2H, CH_2Cl_2; v, **22**, PyBOP, Et_3N, CH_2Cl_2; vi, LiOH, THF, MeOH, H_2O.

3. Conclusion

Effective synthetic routes to **5** and **6** have been developed. Two routes were compared, both relying on Pd-catalysed couplings to 2-triflyloxycyclopentene-1-carboxylate esters to assemble the core carbon framework. Stille, Sonogashira and Suzuki couplings met with widely varying degrees of success, depending on the conditions used, the nature of the catalyst and the sp^2- or sp^3-character of the coupling partner. Individual steps or routes were optimised or studied using informative model reactions. The synthetic route to **6** through Stille coupling of the vinylstannane **36** with *t*-butyl 2-TfO-cyclopentene-1-carboxylate **40**, deprotection, peptide coupling with **22** and final cleavage of the side-chain methyl ester was particularly effective. This work provides useful approaches to potential conformationally controlled mimics of the phosphoserylproline dipeptide motif. The results of the biochemical studies will be published later elsewhere.

4. Experimental

4.1. General

NMR spectra were recorded on JEOL/Varian GX270 and EX400 spectrometers of samples in $CDCl_3$, unless otherwise stated. Mass spectra were obtained using a Brüker ESI-TOF spectrometer. IR spectra were measured as thin films or as KBr discs on a Perkin–Elmer RXI FT-IR spectrometer. The stationary phase for chromatography was silica gel. Solvents were evaporated under reduced pressure. Solutions in organic solvents were dried with $MgSO_4$. Melting points were determined by using a Reichert-Jung Thermo Galen instrument and are uncorrected.

4.2. *N*-(2-(5-Hydroxy-1-oxopent-1-ynyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (5). Method A

Ester **35** (40 mg, 75 μmol) was stirred with CF_3CO_2H (2.0 mL) and CH_2Cl_2 (2.0 mL) for 2 h. The evaporation residue was dissolved in MeOH (5 mL) and CH_2Cl_2 (5 mL) and the solvents were evaporated. The residue, in CH_2Cl_2, was washed twice with water. Drying and evaporation gave **5** (18 mg, 51%) as a white powder: mp 90–92 °C; IR ν_{max} 3475, 3361, 1627, 1482 cm^{-1}; ^1H NMR δ 1.79–1.80 (2H, m, pentynyl 3-H_2 or 4-H_2), 1.84–1.85 (2H, m, cyclopentene 4-H_2), 2.60–2.69 (4H, m, cyclopentene 3,5-H_2), 3.12–3.14 (2H, m, pentynyl 4-H_2 or 3-H_2), 3.22 (1H, dd, *J*=14.0, 7.0 Hz, Phe β-H), 3.31 (1H, dd, *J*=14.0, 7.0 Hz, Phe β-H), 4.94–4.95 (1H, m, Phe α-H), 7.20–7.28 (5H, m, Ph-H_5), 7.61 (2H, d, *J*=8.6 Hz, Ar 2,6-H_2), 8.11 (2H, d, *J*=8.6 Hz, Ar 3,5-H_2), 9.37 (1H, br, NH); ^{13}C NMR (HMQC/HMBC) δ 21.47 (pentynyl 3-C or 4-C), 26.43 (cyclopentene 4-C), 33.52 (cyclopentene 3-C or 5-C), 36.93 (Phe β-C), 39.79 (cyclopentene 5-C or 3-C), 46.33 (pentynyl 4-C or 3-C), 56.25 (Phe α-C), 68.98 (pentynyl 1-C or 2-C), 101.53 (pentynyl 2-C or 1-C), 119.65 (Ar 2,6-C_2), 124.85 (Ar 3,5-C_2), 127.09 (Ph 4-C), 128.72 (Ph 3,5-C_2), 129.18 (cyclopentene 1-C), 129.22 (Ph 2,6-C_2), 136.39 (Ph 1-C), 140.36 (cyclopentene 2-C), 143.29 (Ar 1-C or 4-C), 143.69 (Ar 4-C or 1-C), 165.15 (C=O), 170.89 (C=O), 173.74 (C=O); MS (ES −ve ion) *m*/*z* 474.1674 (M−H) ($C_{26}H_{24}N_3O_6$ requires 474.1665).

4.3. *N*-(2-(5-Hydroxy-1-oxopent-1-ynyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (5). Method B

Compound **46** (10.0 mg, 20 μmol) was stirred with $LiOH\cdot H_2O$ (2.0 mg, 50 μmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) for 16 h. Water (5 mL) and EtOAc (3 mL) were added to the mixture, which was acidified by addition of aq HCl (0.5 M, 5.0 mL). The mixture was extracted rapidly with EtOAc (twice). The combined extracts were dried and the solvent was evaporated to give **5** (2.1 mg, 22%), with properties as above.

4.4. *N*-(2-(*E*-5-Hydroxy-1-oxopent-1-enyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (6). Method A

The *t*-butyl ester **31** (70 mg, 140 μmol) was stirred with CF_3CO_2H (2.0 mL) and CH_2Cl_2 (2.0 mL) for 2 h. The evaporation residue was dissolved in MeOH (5 mL) and CH_2Cl_2 (5 mL) and the solvents were evaporated. The residue, in CH_2Cl_2, was washed twice with water. Drying and evaporation gave **6** (40 mg, 60%) as a white powder: mp 98–100 °C; IR ν_{max} 3413, 1695, 1612, 1503 cm^{-1}; ^1H NMR δ 1.85 (2H, qn, *J*=7.4 Hz, cyclopentene 4-H_2), 2.35–2.49 (4H, m, pentenyl 3,4-H_4), 2.51–2.78 (4H, m, cyclopentene 3,5-H_4), 3.11 (1H, dd, *J*=14.0, 7.0 Hz, Phe β-H), 3.21 (1H, dd, *J*=14.0, 7.0 Hz, Phe β-H), 4.99 (1H, q, *J*=7.4 Hz, Phe α-H), 5.90 (1H, td, *J*=16.0, 5.8 Hz, pentenyl 2-H), 7.15 (1H, d, *J*=16.0 Hz, pentenyl 1-H), 7.19–7.30 (5H, m, Ph-H_5), 7.57 (2H, d, *J*=9.0 Hz, Ar 2,6-H_2), 8.06 (2H, d, *J*=9.0 Hz, Ar 3,5-H_2), 9.66 (1H, br, NH), 9.82 (1H, br, OH); ^{13}C NMR (HMQC/HMBC) δ 21.94 (cyclopentene 4-C), 27.87 (pentenyl 3-C or 4-C), 32.92 (pentenyl 4-C or 3-C), 34.02 (cyclopentene 3-C or 5-C), 34.19 (cyclopentene 5-C or 3-C), 37.73 (Phe β-C), 55.39 (Phe α-C), 119.42 (Ar 2,6-C_2), 124.76 (Ar 3,5-C_2), 125.99 (pentenyl 2-C), 127.20 (Ph 4-C), 128.74 (cyclopentene 1-C), 129.14 (Phe), 129.21 (Phe), 135.94 (pentenyl 1-C), 136.06 (Ph 1-C), 143.57 (Ar 1-C or 4-C), 143.60 (Ar 4-C or 1-C), 150.44 (cyclopentene 2-C), 171.20 (cyclopentene 1-C=O), 176.45 (ArCONH), 176.99 (ester C=O); MS (ES −ve ion) *m*/*z* 476.1826 (M−H) ($C_{26}H_{26}N_3O_6$ requires 476.1826).

4.5. *N*-(2-(*E*-5-Hydroxy-1-oxopent-1-enyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (6). Method B

Compound **47** (200 mg, 0.4 mmol) was stirred with $LiOH\cdot H_2O$ (43 mg, 1.0 mmol) in THF (1.0 mL), MeOH (0.5 mL) and water (0.5 mL) for 16 h. Water (5 mL) and EtOAc (3 mL) were added to the mixture, which was acidified by addition of aq H_2SO_4 (5%, 5.0 mL). The mixture was extracted rapidly with EtOAc (twice). The combined extracts were washed (brine) and dried and the solvent was evaporated to give **6** (130 mg, 68%), with properties as above.

4.6. Phenylethynyltributylstannane (8)

$LiN(SiMe_3)_2$ (1.0 M in THF, 3.3 mL, 3.3 mmol) was added slowly to ethynylbenzene **7** (280 mg, 2.7 mmol) in dry THF (5.0 mL) at −78 °C. The solution was stirred at −78 °C for 1 h, then Bu_3SnCl (1.0 g, 3.3 mmol) was added dropwise and the mixture was allowed to warm to 20 °C. After 100 min, saturated aq NH_4Cl (3.0 mL) was added and the aq phase was extracted with Et_2O (thrice). This extract was washed with brine (twice) and dried and the solvent was evaporated to give **8** (1.33 g, 99%) as a pale yellow liquid (lit.[24] oil): IR ν_{max} 2138, 1486 cm^{-1}; ^1H NMR δ 0.87 (9H, t, *J*=7.4 Hz, 3×Me), 1.05–1.06 (6H, m, 3×$SnCH_2$), 1.32 (6H, sextet, *J*=7.4 Hz, 3×CH_2Me), 1.55–1.57 (6H, m, 3×$SnCH_2CH_2$), 7.20–7.23 (3H, m, Ph 3,4,5-H_3), 7.38–7.39 (2H, m, Ph 2,6-H_2); ^{13}C NMR (HMQC, HMBC) δ 11.15 (3×butyl 1-C), 13.68 (3×Me), 26.97 (3×butyl 3-C), 28.89 (3×butyl 2-C), 93.20 (*C*≡C), 110.02 (C≡*C*), 124.02 (Ph 1-C), 127.79 (Ph 4-C), 128.09 (Ph 3,5-C_2), 131.91 (Ph 2,6-C_2). This material was used for subsequent couplings without further purification or characterisation.

4.7. *E*-Phenylethenyltributylstannane (9)

Ethynylbenzene **7** (300 mg, 2.7 mmol) was heated with Bu_3SnH (950 mg, 3.3 mmol) and AIBN (45 mg, 0.27 mmol) in toluene (10 mL) at 85 °C for 1 h. Evaporation and chromatography (hexane) gave **9**[25] (520 mg, 50%) as a yellow oil: IR ν_{max} 2955, 2923 cm^{-1}; ^1H NMR δ 0.79–1.00 (15H, m, 3×CH_2CH_3), 1.33–1.34 (6H, m, 3×Bu 2-H_2), 1.52–1.54 (6H, m, 3×Bu 1-H_2), 6.86 (2H, 2×s, CH=CH), 7.21 (1H, t, *J*=7.6 Hz, Ph 4-H), 7.32 (2H, t, *J*=7.6 Hz, Ph 3,5-H_2), 7.41 (2H, dd, *J*=7.6, 1.2 Hz, Ph 2,6-H_2); ^{13}C NMR δ 9.6, 13.71, 27.30, 29.11, 125.97, 127.48, 128.45, 129.58, 138.82, 146.00. This material was used for subsequent couplings without further purification or characterisation.

4.8. 1,1-Dimethylethyl pent-4-ynoate (11)

BuLi (1.6 M in hexane, 13.5 mL, 21.6 mmol) was added to Pr^i_2NH (2.18 g, 21.6 mmol) in THF (200 mL) under N_2 at −78 °C. After 10 min, *t*-butyl acetate **10** (1.91 g, 18 mmol) was added and the mixture was stirred for 1 h at −78 °C. HMPA (9.4 mL, 54 mmol) was added and the mixture was stirred for 5 min before 3-bromopropyne (2.14 g, 18 mmol) was introduced. The mixture was stirred at 20 °C for 21 h. The reaction was quenched with satd aq NH_4Cl (2.0 mL) before the mixture was diluted with hexane (100 mL) and washed with aq HCl (1.0 M, twice) and with water (twice). Drying and evaporation gave **11**[21] (2.44 g, 88%) as a yellow oil: IR ν_{max} 2121, 1730 cm^{-1}; ^1H NMR δ 1.44 (9H, s, Bu^t), 1.95 (1H, t, *J*=1.2 Hz, 5-H), 2.42–2.45 (4H, m, 3,4-H_4); ^{13}C NMR (HMBC) δ 14.46 (CH_2), 28.06 (3×Me), 34.44 (CH_2), 68.75 (C≡CH), 80.83 (Me_3C), 82.75 (5-C), 171.08 (C=O).

4.9. 1,1-Dimethylethyl 5-(tributylstannyl)pent-4-ynoate (12)

Compound **11** (500 mg, 3.2 mmol) was heated with Bu_3Sn-nOMe (1.03 g, 3.2 mmol) at 110 °C for 4 h. Evaporation and chromatography (hexane) gave **12** (1.26 g, 88%) as a pale yellow oil: IR ν_{max} 2221, 1728 cm^{-1}; ^1H NMR δ 0.89 (9H, t, J=7.4 Hz, 3×Bu 4-H_3), 0.93 (6H, t, J=7.4 Hz, 3×Bu 1-H_2), 1.30 (6H, sextet, J=7.4 Hz, 3×Bu 2-H_2), 1.42 (9H, s, Bu^t), 1.48–1.50 (6H, m, 3×Bu 3-H_2), 2.44 (2H, t, J=7.4 Hz, 3-H_2), 2.48 (2H, t, J=7.4 Hz, 2-H_2); ^{13}C NMR (HMQC/HMBC) δ 10.92 (3×Bu 1-C), 13.64 (3×Bu 4-C), 16.22 (3-C), 26.96 (3×Bu 2-C), 28.08 ($C(CH_3)_3$), 28.82 (3×Bu 3-C), 35.35 (2-C), 80.48 ($C(CH_3)_3$), 82.37 (4-C), 109.58 (5-C), 171.36 (C=O). This compound was too unstable to provide a mass spectrum.

4.10. Methyl 2-trifluoromethanesulfonyloxycyclopentene-1-carboxylate (15)

Pr^i_2NEt (30 mL) was added to methyl 2-oxocyclopentanecarboxylate **14** (5.0 g, 35 mmol) in dry CH_2Cl_2 (70 mL) at −78 °C. After 10 min, trifluoromethanesulfonic anhydride (11.8 g, 42 mmol) was added dropwise, followed by slow warming to 20 °C during 16 h. The mixture was washed with water (50 mL) and aq citric acid (10%, twice). Drying, evaporation and chromatography (hexane/EtOAc 19:1) gave **15**[9] (9.13 g, 95%) as a pale yellow oil: IR ν_{max} 1725, 1668, 1426, 1354, 1208, 1141 cm^{-1}; ^1H NMR δ 2.01 (2H, qn, J=7.4 Hz, 4-H_2), 2.66–2.78 (4H, m, 3,5-H_4), 3.78 (3H, s, Me); ^{13}C NMR δ 18.78, 29.14, 32.74, 51.84, 118.31 (q, J=250 Hz CF_3), 122.97, 153.97, 162.68; ^{19}F NMR ($CDCl_3$) δ −74.50 (s); MS m/z 297.0032 (M+Na) ($C_8H_9F_3NaO_5S$ requires 297.0020).

4.11. Methyl 2-phenylethynylcyclopentene-1-carboxylate (16)

The triflate **15** (300 mg, 1.1 mmol) was stirred with **8** (510 mg, 1.3 mmol), Ph_3P (40 mg, 0.15 mmol) and $Pd(OAc)_2$ (17 mg, 77 μmol) in dry THF (3.0 mL) at 55 °C under N_2 for 1 h. Evaporation and chromatography (hexane/EtOAc 19:1) gave **16** (260 mg, 99%) as yellow crystals: mp 109–109°C; IR ν_{max} 2215, 1728 cm^{-1}; ^1H NMR δ 1.96 (2H, qn, J=7.6 Hz, 4-H_2), 2.72–2.75 (4H, m, 3,5-H_4), 3.80 (3H, s, Me), 7.30–7.34 (3H, m, Ph 3,4,5-H_3), 7.50 (2H, dd, J=6.8, 2.8 Hz, Ph 2,6-H_2); ^{13}C NMR (HMQC, HMBC) δ 22.27 (4-C), 33.32 (3-C or 5-C), 39.17 (5-C or 3-C), 51.44 (Me), 85.67 (C≡C), 99.73 (C≡C), 122.96 (Ph 1-C), 128.31 (Ph 3,5-C_2), 128.79 (Ph 4-C), 131.88 (Ph 2,6-C_2), 134.73 and 137.89 (1,2-C_2), 164.98 (C=O); MS m/z 227.1067 (M+H) ($C_{15}H_{15}O_2$ requires 227.1022).

4.12. Methyl 2-(5-(1,1-dimethylethoxy)-5-oxopent-1-ynyl)cyclopent-1-enecarboxylate (17). Method A

Compound **11** (54 mg, 0.4 mmol) was boiled under reflux under N_2 with **15** (110 mg, 0.4 mmol), $PdCl_2$ (3.0 mg, 20 μmol), Ph_3P (10 mg, 40 μmol), CuI (4.0 mg, 20 μmol) and Et_3N (60 mg, 0.6 mmol) in THF (3.0 mL) for 90 min. Evaporation and chromatography (hexane/EtOAc 9:1) gave **17** (110 mg, 98%) as a pale yellow oil: IR ν_{max} 2222, 1731, 1698 cm^{-1}; ^1H NMR δ 1.44 (9H, s, Bu^t), 1.88 (2H, qn, J=7.4 Hz, 4-H_2), 2.50 (2H, t, J=7.4 Hz, pentynyl 4-H_2), 2.58 (2H, tt, J=7.4, 2.3 Hz, 3-H_2 or 5-H_2), 2.66 (2H, H, tt, J=7.4, 2.3 Hz, 5-H_2 or 3-H_2), 2.69 (2H, t, J=7.0 Hz, pentenyl 3-H_2), 3.73 (3H, s, Me); ^{13}C NMR (HMQC/HMBC) δ 16.02 (pentynyl 3-C), 22.10 (4-C), 28.05 ($C(CH_3)_3$), 33.06 (5-C or 3-C), 34.57 (pentynyl 4-C), 39.46 (3-C or 5-C), 51.32 (OMe), 76.69 (pentynyl 1-C), 80.76 ($C(CH_3)_3$), 99.94 (pentynyl 2-C), 135.45 (3-C or 5-C), 136.76 (5-C or 3-C), 165.04 (cyclopentene 1-C=O), 171.05 (pentynyl 5-C); MS m/z 579.2867 (2 M+Na) ($C_{32}H_{44}NaO_8$ requires 579.2928), 301.1384 (M+Na) ($C_{16}H_{22}NaO_4$ requires 301.1410); 279.1568 (M+H) ($C_{16}H_{23}O_4$ requires 279.1590).

4.13. Methyl 2-(5-(1,1-dimethylethoxy)-5-oxopent-1-ynyl)cyclopent-1-enecarboxylate (17). Method B

The triflate **15** (77 mg, 0.28 mmol) was stirred at 55 °C with **12** (150 mg, 0.34 mmol), Ph_3P (10 mg, 39 μmol) and $Pd(OAc)_2$ (4.4 mg, 20 μmol) for 1 h. Evaporation and chromatography (hexane/EtOAc 3:2) gave **17** (17 mg, 22%), with properties as above.

4.14. Methyl *E*-2-(2-phenylethenyl)cyclopentene-1-carboxylate (18)

The triflate **15** (300 mg, 1.1 mmol) was stirred with **9** (500 mg, 1.3 mmol), Ph_3P (40 mg, 0.15 mmol) and $Pd(OAc)_2$ (17 mg, 77 μmol) in dry THF (2.0 mL) at 55 °C under N_2 for 1 h. Evaporation and chromatography (hexane/EtOAc 19:1) gave **18** (240 mg, 95%) as white crystals: mp 36–37 °C; IR ν_{max} 1698, 1588, 1433 cm^{-1}; ^1H NMR δ 1.92 (2H, qn, J=7.4 Hz, 4-H_2), 2.74 (2H, t, J=7.6 Hz, 3-H_2), 2.80 (2H, t, J=7.6 Hz, 5-H_2), 3.78 (3H, s, Me), 6.75 (1H, d, J=16 Hz, ethenyl 1-H), 7.25 (1H, t, J=7.2 Hz, Ph 4-H), 7.33 (2H, t, J=7.2 Hz, Ph 3,5-H_2), 7.51 (2H, d, J=7.2 Hz, Ph 2,6-H_2), 8.05 (1H, d, J=16 Hz, ethenyl 2-H); ^{13}C NMR δ 21.42, 34.06, 34.27, 51.19, 123.74, 127.15, 128.33, 128.65, 129.49, 135.31, 136.99, 152.38, 166.41; MS m/z 229.1208 (M+H) ($C_{15}H_{17}O_2$ requires 229.1223).

4.15. Methyl *E*-2-(5-(1,1-dimethylethoxy)-1-oxopent-1-enyl)cyclopentene-1-carboxylate (19)

Alkyne **11** (500 mg, 3.3 mmol) was heated with Bu_3SnH (1.12 g, 3.9 mmol) and AIBN (52 mg, 0.32 mmol) in toluene (10 mL) at 85 °C for 1 h. Evaporation and chromatography (hexane) gave crude **13** (0.88 g, 60%) as a yellow oil: IR ν_{max} 1732 cm^{-1}. The triflate **15** (150 mg, 0.56 mmol) was stirred with **13** (300 mg, 0.67 mmol), Ph_3P (20 mg, 78 μmol) and $Pd(OAc)_2$ (8.8 mg, 39 μmol) in dry THF (2.0 mL) at 55 °C under N_2 for 1 h. Evaporation and chromatography (hexane/CH_2Cl_2 3:2) gave **19** (90 mg, 57%) as a pale yellow oil: IR ν_{max} 1728 cm^{-1}; ^1H NMR 1.42 (9H, s, Bu^t), 1.84 (2H, qn, J=7.4 Hz, 4-H_2), 2.35 (2H, t, J=7.2 Hz, pentenyl 4-H_2), 2.44 (2H, t, J=7.2 Hz, pentenyl 3-H_2), 2.61 (2H, t, J=7.6 Hz, 3-H_2 or 5-H_2), 2.65 (2H, t, J=7.6 Hz, 5-H_2 or 3-H_2), 3.72 (3H, s, Me), 5.92 (1H, dt, J=6.6, 15.7 Hz, pentenyl 2-H), 7.27 (1H, d, J=15.7 Hz, pentenyl 1-H); ^{13}C NMR (HMQC, HMBC) δ 21.26 (4-C), 28.03 ($C(CH_3)_3$), 28.64 (pentenyl 3-C), 34.02 (3-C or 5-C), 34.16 (5-C or 3-C), 34.87 (pentenyl 4-C), 51.02 (Me), 80.30 ($C(CH_3)_3$), 126.21 (pentenyl 1-C), 127.60 (1-C), 136.51 (pentenyl 2-C), 152.13 (2-C), 166.31 (CO_2Me), 172.13 (CO_2Bu^t); MS m/z 303.1571 (M+Na) ($C_{16}H_{24}NaO_4$ requires 303.1572), 247.0943 (M+Na–Me_2C=CH_2) ($C_{12}H_{16}NaO_4$ requires 247.0947).

4.16. *N*-(1,1-Dimethylethoxycarbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (21)

$POCl_3$ (1.68 g, 11 mmol) was added dropwise to a vigorously stirred mixture of Boc-L-PheOH **20** (2.65 g, 10 mmol) and 4-nitroaniline (1.38 g, 10 mmol) in dry pyridine (30 mL) at −10 °C. After 15 min, the reaction was quenched by addition of ice-water (100 mL) and the mixture was extracted with EtOAc (thrice). The combined extracts were washed with satd aq $NaHCO_3$ (twice) and brine (twice). Drying and evaporation gave **21** (3.25 g, 84%) as a pale yellow powder: mp 158–160 °C (lit.[27] mp 150–151 °C); IR ν_{max} 3286, 1717, 1549, 1507 cm^{-1}; ^1H NMR δ 1.41 (9H, s, Bu^t), 3.11 (1H, dd, J=14.0, 7.7 Hz, β-H), 3.16 (1H, dd, J=14.0, 8.3 Hz, β-H), 4.48 (1H, br q, J=7.3 Hz, α-H), 5.10 (1H, br d, J=7.3 Hz, BocNH), 7.20–7.30 (5H, m, Ph-H_5), 7.54 (2H, d, J=9.0 Hz, Ar 2,6-H_2), 8.13 (2H, d, J=9.0 Hz, Ar 3,5-H_2), 8.60 (1H, br, ArNH); MS m/z 408.1518 (M+Na) ($C_{20}H_{23}NaN_3O_5$ requires 408.1535).

4.17. L-Phenylalanine *N*-(4-nitrophenyl)amide hydrochloride (22)

HCl was passed through **21** (3.25 g, 8.43 mmol) in CH_2Cl_2 (100 mL) for 1 h. The precipitate was collected and dried to give **22** (1.98 g, 73%) as a pale yellow powder: mp 140–141 °C; IR ν_{max} 3043, 2927, 1695, 1569, 1512 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.14 (1H, dd, J=13.8, 7.4 Hz, β-H), 3.24 (1H, dd, J=13.8, 6.1 Hz, β-H), 4.31–4.32 (1H, m, α-H), 7.22–7.34 (5H, m, Ph-H_5), 7.89 (2H, d, J=9.0 Hz, Ar 2,6-H_2), 8.25 (2H, d, J=9.0 Hz, Ar 3,5-H_2), 8.49 (3H, br, N^+H_3), 11.75 (1H, br, NH); ^{13}C NMR δ 37.26, 54.74, 119.86, 125.61, 127.90, 129.17, 130.07, 135.00, 143.46, 144.40, 168.20; MS m/z 308.1012 (M+Na) ($C_{15}H_{15}N_3NaO_3$ requires 308.1011), 286.1188 (M+H) ($C_{15}H_{16}N_3O_3$ requires 286.1188).

4.18. *N*-(2-Methoxycarbonylcyclopenten-1-yl)-L-phenylalanine *N*-(4-nitrophenyl)amide (24)

Compound **14** (355 mg, 2.5 mmol) was heated with DMAP (91 mg, 0.75 mmol) and **22** (free base, 1.6 g, 5.0 mmol) in PhMe (15 mL) at reflux for 19 h. Evaporation and chromatography (hexane/EtOAc 7:3) gave **24** (140 mg, 14%) as a pale yellow oil: IR ν_{max} 1684, 1591, 1508 cm^{-1}; ^1H NMR δ 1.75, (2H, qn, J=7.4 Hz, cyclopentene 4-H_2), 2.31–2.38 (2H, m, cyclopentene 3-H_2), 2.46 (2H, t, J=7.4 Hz, cyclopentene 5-H_2), 3.11 (1H, dd, J=14.0, 8.2 Hz, Phe β-H), 3.33 (1H, dd, J=14.0, 4.0 Hz, Phe β-H), 3.70 (3H, s, OMe), 4.22–4.23 (1H, m, Phe α-H), 7.23–7.33 (5H, m, Ph-H_5), 7.60 (1H, d, J=7.8 Hz, Phe NH), 7.69 (2H, d, J=9.0 Hz, Ar 2,6-H_2), 8.20 (2H, d, J=9.0 Hz, Ar 2,6-H_2), 8.40 (1H, s, ArNH); ^{13}C NMR (HMQC/HMBC) δ 20.60 (cyclopentene 4-C), 29.09 (cyclopentene 5-C), 32.27 (cyclopentene 3-C), 39.35 (Phe β-C), 50.54 (OMe), 61.27 (Phe α-C), 98.13 (cyclopentene 2-C), 119.44 (Ar 2,6-C_2), 124.96 (Ar 3,5-C_2), 127.38 (Ph 4-C), 128.78 (Ph 3,5-C_2), 129.37 (Ph 2,6-C_2), 135.82 (Ph 1-C), 142.80 (Ar 1-C), 143.86 (Ar 4-C), 162.17 (cyclopentene 1-C), 168.64 (amide C=O), 170.79 (ester C=O); MS m/z 432.1513 (M+Na) ($C_{22}H_{23}N_3NaO_5$ requires 432.1535), 410.1708 (M+H) ($C_{22}H_{24}N_3O_5$ requires 410.1715).

4.19. 2-Phenylethynylcyclopentene-1-carboxylic acid (25)

Ester **16** (150 mg, 0.66 mmol) was treated with aq NaOH in EtOH, as for the synthesis of **26**, to give **25**[23] (40 mg, 57%) as a pale yellow oil: IR ν_{max} 2351, 1636, 1510 cm^{-1}; ^1H NMR δ 1.98 (2H, qn, J=7.4 Hz, 4-H_2), 2.75–2.78 (4H, m, 3,5-H_4), 7.28–7.33 (3H, m, Ph 3,4,5-H_4), 7.49 (2H, d, J=6.6 Hz, Ph 2,6-H_2); MS 235.0737 (M+Na) ($C_{14}H_{12}NaO_2$ requires 235.0729), 213.0910 (M+H) ($C_{14}H_{13}O_2$ requires 213.0910).

4.20. *E*-2-(2-Phenylethenyl)cyclopentene-1-carboxylic acid (26)

Ester **18** (130 mg, 0.57 mmol) was stirred with aq NaOH (5 M, 0.13 mL, 0.63 mmol) in EtOH (30 mL) for 16 h. The evaporation residue, in water (10 mL), was acidified to pH 2 with aq HCl (0.5 M) and extracted with EtOAc (thrice). The extract was dried and the solvent was evaporated to give **26** (40 mg, 33%) as a colourless gum: IR ν_{max} 1731 cm^{-1}; ^1H NMR δ 1.90–1.96 (2H, qn, J=7.4 Hz, 4-H_2), 2.72–2.82 (4H, m, 3,5-H_4), 6.73 (1H, d, J=16.2 Hz, ethenyl 1-H), 7.30–7.33 (3H, m, Ph 3,4,5-H_3), 7.49 (2H, d, J=7.2 Hz), 8.06 (1H, d, J=16.2 Hz); ^{13}C NMR δ 14.50, 21.49, 34.20, 34.42, 60.03, 123.96, 127.19, 128.37, 128.74, 135.16, 137.16, 151.99; MS (ES −ve ion) 213.0941 (M−H) ($C_{14}H_{13}O_2$ requires 213.0921).

4.21. *N*-(2-Phenylethynylcyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (27)

2-Phenylethynylcyclopentene-1-carboxylic acid **25** (35 mg, 170 μmol) was stirred with **22** (53 mg, 170 μmol), PyBOP (100 mg, 200 μmol) and Et_3N (33 mg, 330 μmol) in CH_2Cl_2 (5.0 mL) for 24 h. Evaporation and chromatography (hexane/EtOAc 1:1) gave **27** (60 mg, 76%) as a yellow powder: mp 110–112 °C; IR ν_{max} 3403, 3268, 2121, 1627, 1508 cm^{-1}; ^1H NMR δ 1.94 (2H, qn, J=7.4 Hz, 4-H_2), 2.79–2.80 (2H, m, 3-H_2), 2.81–2.83 (2H, m, 5-H_2), 3.08 (1H, dd, J=13.7, 7.4 Hz, β-H), 3.22 (1H, dd, J=13.7, 6.6 Hz, β-H), 5.05 (1H, q, J=7.4 Hz, α-H), 7.08–7.15–7.20 (5H, m, Phe Ph-H_5) 7.34–7.39 (3H, m, Ph 3,4,5-H_3), 7.47 (2H, d, J=8.0 Hz, Ph 2,6-H_2), 7.59 (2H, d, J=9.1 Hz, Ar 2,6-H_2), 7.96 (1H, d, J=7.4 Hz), 8.27 (2H, d, J=9.1 Hz, Ar 3,5-H_2), 9.55 (1H, s, NH); ^{13}C NMR (HMQC, HMBC) δ 21.86 (4-C), 33.84 (3-C or 5-C), 38.18 (Phe β-C), 39.75 (5-C or 3-C), 55.93 (Phe α-C), 84.71 (*C*≡C), 101.89 (C≡*C*), 119.38 (Ar 2,6-C_2), 121.55 (C_q), 124.87 (Ar 3,5-C_2), 127.20 (Phe Ph 4-C), 128.73 (Phe Ph 3,5-C_2+Ph 3,5-C_2), 129.19 (C_q), 129.31 (Phe Ph 2,6-C_2), 129.74 (Ph 4-C), 131.88 (Ph 2,6-C_2), 136.09 (C_q), 140.87 (C_q), 143.44 (C_q), 143.84 (C_q), 165.00 (C=O), 170.05 (C=O); MS m/z 480.1919 (M+H) ($C_{29}H_{26}N_3O_4$ requires 480.1853).

4.22. 2-(5-(1,1-Dimethylethoxy)-1-oxopent-1-ynyl)-cyclopentene-1-carboxylic acid (28)

The diester **17** (830 mg, 2.8 mmol) was stirred with $LiOH\cdot H_2O$ (320 mg, 7.6 mmol) in THF (4.0 mL), MeOH (2.0 mL) and water (2.0 mL) for 16 h. Water (5 mL) was added to the evaporation residue. The solution was washed with Et_2O (2×5 mL) and acidified with aq H_2SO_4 (5%) before being extracted rapidly with Et_2O (3×10 mL). The combined extracts were washed with brine and dried. Evaporation gave **28** (40 mg, 5%) as a pale yellow oil: IR ν_{max} 2222, 1733 cm^{-1}; ^1H NMR δ 1.43 (9H, s, Bu^t), 1.88 (2H, qn, J=7.4 Hz, 4-H_2), 2.50 (2H, t, J=7.4 Hz, pentynyl 4-H_2), 2.62 (2H, dt, J=7.7, 1.9 Hz, pentynyl 3-H_2), 2.66–2.75 (4H, m, 3,5-H_4); ^{13}C NMR δ 14.27, 16.13, 20.09, 28.13 (C(*C*H_3)$_3$), 33.00, 34.38, 39.88, 81.04 (pentynyl 2-C), 102.12 (pentynyl 1-C), 136.80 (Cq), 137.35 (Cq), 168.35 (C=O), 171.11 (C=O); MS (ES −ve ion) m/z 263.1224 (M−H) ($C_{15}H_{19}O_4$ requires 263.1283).

4.23. *N*-(2-(5-(1,1-Dimethylethoxy)-1-oxopent-1-ynyl)-cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (29)

The carboxylic acid **28** (40 mg, 150 μmol) was treated with **22**, PyBOP and Et_3N, as for the synthesis of **27** except that the chromatographic eluant was hexane/EtOAc (7:3), to give **29** (70 mg, 88%) as a pale yellow oil: IR ν_{max} 3423, 2121, 1726, 1632, 1508 cm^{-1}; ^1H NMR δ 1.42 (9H, s, Bu^t), 1.85 (2H, qn, J=7.4 Hz, 4-H_2), 2.44 (2H, dd, J=1.4, 5.5 Hz, pentynyl 3-H_2), 2.55–2.70 (6H, m, pentenyl 4-H_2 and 3,5-H_4), 3.12 (1H, dd, J=14.0, 10.1 Hz, Phe β-H), 3.22 (1H, dd, J=14.0, 6.6 Hz, Phe β-H), 5.01 (1H, dd, J=10.1, 6.6 Hz, Phe α-H), 7.17–7.25 (5H, m, Ph-H_5), 7.64 (2H, d, J=7.2 Hz, Ar 2,6-H_2), 8.10 (2H, d, J=7.2 Hz, Ar 3,5-H_2), 9.59 (1H, br, NH); ^{13}C NMR δ 15.83, 21.65, 28.17, 33.53, 33.96, 38.20, 39.70, 41.00, 55.71, 81.09, 102.24, 119.35, 124.92, 127.11, 128.67, 129.20, 129.46, 136.34, 140.40, 143.39, 144.06, 164.79, 169.97, 170.97; MS m/z 1085.4608 (2 M+Na) ($C_{60}H_{66}N_6O_{12}Na$ requires 1085.4544); 554.2238 (M+Na) ($C_{30}H_{33}N_3O_6Na$ requires 554.2267).

4.24. *E*-2-(5-(1,1-Dimethylethoxy)-1-oxopent-1-enyl)-cyclopentene-1-carboxylic acid (30)

Diester **19** (90 mg, 0.32 mmol) was stirred with $LiOH\cdot H_2O$ (13.4 mg, 0.32 mmol) in THF (2.0 mL), MeOH (1.0 mL) and water (1.0 mL) for 6 h. The solvents were evaporated and water (5 mL) was added. The solution was washed with Et_2O (twice) and acidified with aq HCl (0.5 M) to pH 5. The mixture was immediately extracted with Et_2O (thrice). The combined extracts were washed with brine and dried. Evaporation gave **30** (20 mg, 24%) as

a colourless oil: IR ν_{max} 3424, 1710, 1633 cm^{-1}; ^1H NMR δ 1.42 (9H, s, Bu^t), 1.84–1.85 (2H, m, 4-H_2), 2.25–2.37 (2H, m, CH_2), 2.43–2.56 (2H, m, CH_2), 2.64–2.73 (4H, m, 3,5-H_4), 5.93–6.05 (1H, m, pentenyl 2-H), 7.29 (1H, d, J=15.4 Hz, pentenyl 1-H); MS m/z 289.1439 (M+Na) ($C_{15}H_{22}NaO_4$ requires 289.1410).

4.25. *N*-(2-(*E*-5-(1,1-Dimethylethoxy)-1-oxopent-1-enyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (31)

The carboxylic acid **30** (90 mg, 340 μmol) was treated with **22**, PyBOP and Et_3N, as for the synthesis of **27**, to give **31** (70 mg, 42%) as a white powder: mp 78–80 °C; IR ν_{max} 3288, 1720, 1622, 1565, 1508 cm^{-1}; ^1H NMR δ 1.42 (9H, s, Bu^t), 1.83–1.93 (2H, m, 4-H_2), 2.29 (2H, t, J=7.0 Hz, pentenyl 4-H_2), 2.39 (2H, q, J=7.0 Hz, pentenyl 3-H_2), 2.60–2.69 (4H, m, 3,5-H_4), 3.17–3.26 (2H, m, Phe β-H_2), 4.02 (1H, d, J=5.1 Hz, Phe α-NH), 4.90 (1H, ca. q, J=7 Hz, Phe α-H), 5.95–5.97 (1H, m, pentenyl 1-H), 7.23–7.32 (6H, m, pentenyl 2-H+Ph-H_5), 7.57–7.61 (2H, m, Ar 3,5-H_2), 8.13 (2H, d, J=9.0 Hz, Ar 3,5-H_2), 9.36–9.38 (1H, m, ArNH); ^{13}C NMR (HMQC/HMBC) δ 21.36 (cyclopentene 4-C), 28.08 (C(CH_3)$_3$), 28.66 (pentenyl 3-C), 33.90 (cyclopentene 3,5-C_2), 34.84 (pentenyl 2-C), 36.74 (Phe β-C), 55.37 (Phe α-H), 70.54, 71.24, 119.29 (Ar 2,6-C_2), 124.89 (Ar 3,5-C_2), 126.36, 127.33 (Ph 4-C), 128.86, 128.88, 128.96 (Ph 3,5-C_2), 129.21 (Ph 2,6-C_2), 134.33, 136.07, 136.14, 137.01, 150.96, 167.44 (cyclopentene 1-C=O), 169.86 (Phe C=O), 172.04 (ester C=O); MS m/z 1089.4926 (2 M+Na) ($C_{60}H_{70}N_6NaO_{12}$ requires 1089.4949), 556.2403 (M+Na) ($C_{30}H_{35}N_3NaO_6$ requires 556.2424), 534.2587 (M+H) ($C_{30}H_{36}N_3O_6$ requires 534.2598), 478.1972 (M+H−Me_2C=CH_2) ($C_{26}H_{28}N_3O_6$ requires 478.1978).

4.26. Ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)-pentanoate (33)

$Rh(PPh_3)_3Cl$ (72 mg, 78 μmol) was stirred in CH_2Cl_2 (10 mL) for 5 min. 4,4,5,5-Tetramethyl-1,3,2-dioxaborane (499 mg, 3.9 mmol) was added and the mixture was stirred for 5 min. Ethyl pent-4-enoate **32**[22] (500 mg, 3.9 mmol) was added and the mixture was stirred for 16 h. Washing (water), drying, evaporation and chromatography (CH_2Cl_2→CH_2Cl_2/EtOH 200:1) gave **33** (788 mg, 79%) as a colourless oil: ^1H NMR δ 0.77 (2H, t, J=7.8 Hz, 5-H_2), 1.22 (12H, s, dioxaborole-Me_4), 1.23 (3H, t, J=7.4 Hz, CH_2CH_3), 1.41–1.42 (2H, m, 4-H_2), 1.60–1.62 (2H, m, 3-H_2), 2.27 (2H, t, J=6.8 Hz, 2-H_2), 4.09 (2H, q, J=7.4 Hz, OCH_2); ^{13}C NMR (HMQC, HMBC) δ 14.22 (CH_2CH_3), 23.61 (CH_2), 24.66 (4×Me), 24.78 (4-C), 27.56 (3-C), 34.21 (2-C), 60.11 (OCH_2), 82.94 (2×CMe_2), 173.87 (C=O). This material was used without further purification or characterisation.

4.27. Methyl pent-4-ynoate (35)

Pent-4-ynoic acid **34** (500 mg, 5.0 mmol) was boiled under reflux with TsOH·H_2O (95 mg, 500 μmol) in MeOH (2.0 mL) and CH_2Cl_2 (4.0 mL) for 24 h. Satd aq NH_4Cl (2 mL) was added and the mixture was extracted with Et_2O (4×15 mL). Drying and careful evaporation gave **35** (370 mg, 66%) as a pale yellow liquid (lit.[26] bp 143–144 °C): IR ν_{max} 2121, 1735 cm^{-1}; ^1H NMR δ 1.96 (1H, t, J=2.2 Hz, 5-H), 2.47–2.54 (4H, m, 2,3-H_4), 3.68 (3H, s, Me); ^{13}C NMR δ 14.40, 33.20, 51.90, 69.08, 82.51, 172.31; MS m/z 111.0456 (M+H) ($C_6H_7O_2$ requires 111.0446).

4.28. Bis(1,1-dimethylethyl) hexanedicarboxylate (38)

Hexanedioyl dichloride **37** (11.39 g, 62 mmol) in Et_2O (50 mL) was added dropwise to Bu^tOH (14.2 g, 192 mmol) and $PhNMe_2$ (22.5 g, 186 mmol) and the mixture was stirred for 16 h before being diluted with water. The organic phase was washed with aq HCl (2 M, twice), satd aq $NaHCO_3$ (twice) and satd brine. Drying and evaporation gave **38** (14.2 g, 89%) as white crystals: mp 25–28 °C (lit.[28] mp 29–31 °C); ^1H NMR δ 1.40 (18H, s, 2×Bu^t), 1.54–1.58 (4H, m, 3,4-H_4), 2.18–2.19 (4H, m, 2,5-H_4).

4.29. 1,1-Dimethylethyl 2-oxocyclopentanecarboxylate (39)

NaH (3.52 g, 60% in oil, 88 mmol) was washed thrice with pentane and suspended in PhMe (40 mL). This suspension was heated to 60 °C. The diester **38** (300 mg, 1.7 mmol) in Bu^tOH (300 μL) was added and the mixture was stirred at 60 °C for 30 min. Further **38** (7.30 g, 27.6 mmol) in PhMe (10 mL) was added and the mixture was stirred at 100°C for 4 h. The mixture was cooled to 5 °C and MeOH (2.0 mL), water (2.0 mL) and satd aq NH_4Cl (10 mL) were added sequentially and carefully. The aq phase was extracted with PhMe (thrice). The combined organic phases were dried. Evaporation and chromatography (hexane/EtOAc 20:1→10:1) gave **39** (2.97 g, 55%) as a colourless oil (lit.[29] oil): ^1H NMR δ 1.41 (9H, s, Bu^t), 1.84–1.85 (1H, m, 4-H), 2.03–2.29 (5H, m, 3,4,5-H_5), 3.02 (1H, t, J=8.5 Hz, 1-H).

4.30. 1,1-Dimethylethyl 2-trifluoromethanesulfonyloxy-cyclopentene-1-carboxylate (40)

Et_3N (660 mg, 6.5 mmol) was added to **39** (1.00 g, 5.4 mmol) in CH_2Cl_2 (10 mL) at −78 °C, followed by $(F_3CSO_2)_2O$ (1.59 g, 5.9 mmol). The mixture was stirred for 5 h. Washing (water, aq HCl, aq $NaHCO_3$), drying, evaporation and chromatography (hexane/EtOAc 10:1) gave **40** (1.07 g, 63%) as a colourless oil: IR ν_{max} 2907, 1689, 1663, 1419 cm^{-1}; ^1H NMR δ 1.49 (9H, s, Bu^t), 1.95 (2H, qn, J=7.7 Hz, 4-H_2), 2.59–2.73 (4H, m, 3,5-H_4); ^{13}C NMR δ 19.0, 28.2, 29.8, 33.3, 82.5, 121.0 (q, J=251 Hz CF_3), 124.9, 156.2, 166.8; ^{19}F NMR ($CDCl_3$) δ −74.34 (s); MS m/z 317.0670 (M+H) ($C_{11}H_{16}F_3O_5S$ requires 317.0670), 339.0481 (M+Na) ($C_{11}H_{15}F_3NaO_5S$ requires 339.0489).

4.31. 1,1-Dimethylethoxycarbonyl 2-(5-methoxy-1-oxopent-1-ynyl)cyclopentene-1-carboxylate (42)

Alkyne **35** (200 mg, 1.9 mmol) was heated at reflux under N_2 with **40** (590 mg, 1.9 mmol), $PdCl_2$ (16 mg, 90 μmol), Ph_3P (49 mg, 190 μmol), CuI (18 mg, 90 μmol) and Et_3N (283 mg, 2.8 mmol) in THF (10 mL) for 2 h. Evaporation and chromatography (hexane/EtOAc 7:3) gave **42** (110 mg, 23%) as a pale yellow oil: IR ν_{max} 3423, 2121, 1731 cm^{-1}; ^1H NMR δ 1.48 (9H, s, Bu^t), 1.84 (2H, qn, J=7.4 Hz, 4-H_2), 2.55 (2H, d, J=6.8 Hz, pentenyl 3-H_2 or 4-H_2), 2.61 (4H, dd, J=6.9, 1.4 Hz, 3,5-H_4), 2.74 (2H, t, J=6.9 Hz, pentenyl 4-H_2 or 3-H_2), 3.69 (3H, s, OMe); ^{13}C NMR δ 15.95, 22.07, 28.29, 33.28, 33.38, 39.72, 51.92, 80.48, 127.69, 130.00, 133.47, 135.20, 172.34; MS m/z 301.1406 (M+Na) ($C_{16}H_{22}O_4Na$ requires 301.1415), 279.1568 (M+H) ($C_{16}H_{23}O_4$ requires 279.1596).

4.32. *N*-(2-(5-Methoxy-1-oxopent-1-ynyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (44)

The diester **42** (110 mg, 0.4 mmol) was treated with CF_3CO_2H and CH_2Cl_2, as for the synthesis of **6** (Method A), to give **43** (30 mg, 33%) as a pale yellow oil: ^1H NMR δ 1.90 (2H, t, J=7.7 Hz, 4-H_2), 2.60–2.62 (2H, m, pentynyl 3-H_2 or 4-H_2), 2.65–2.79 (6H, m, 3,5-H_4 and pentynyl 4-H_2 or 3-H_2), 3.60 (3H, s, OMe). Compound **43** (30 mg, 140 μmol) was treated with **22**, PyBOP and Et_3N, as for the synthesis of **29**, to give **44** (15.8 mg, 23%) as a colourless oil: IR ν_{max} 3423, 2121, 1726, 1632, 1560 cm^{-1}; ^1H NMR δ 1.87 (2H, qn, J=7.4 Hz, cyclopentene 4-H_2), 2.56 (2H, t, J=6.8 Hz, pentynyl 3-H_2 or 4-H_2), 2.62–2.70 (6H, m, cyclopentene 3,5-H_4 and pentynyl 4-H_2 or 3-H_2), 3.18–3.32 (2H, m, Phe β-H_2), 3.69 (3H, s, OMe), 4.96 (1H, q, J=6.8 Hz, Phe α-H), 7.22–7.27 (5H, m, Ph-H_5), 7.61 (2H, d, J=9.1 Hz, Ar 2,6-H_2),

8.14 (2H, d, J=9.1 Hz, Ar 3,5-H_2), 9.13 (1H, s, NH); ^{13}C NMR δ 15.71, 21.66, 32.57, 33.57, 37.50, 39.76, 52.12, 56.04, 100.00 (pentynyl 1-C or 2-C), 101.76 (pentynyl 2-C or 1-C), 119.36, 119.97, 124.47, 125.01, 127.19, 128.82, 129.17, 129.39, 140.60, 143.75, 161.34 (C=O), 169.84 (C=O), 171.82 (C=O); MS m/z 512.1749 (M+Na) ($C_{27}H_{27}N_3NaO_6$ requires 512.1797).

4.33. 1,1-Dimethylethyl *E*-2-(5-methoxy-1-oxopent-1-enyl)cyclopentene-1-carboxylate (45)

Methyl pent-4-ynoate **35** (280 mg, 2.5 mmol) was heated at 85 °C with Bu_3SnH (870 mg, 3.0 mmol) and AIBN (41 mg, 250 μmol) in PhMe (10 mL) for 1 h. Evaporation and chromatography (hexane/EtOAc 3:2) gave **36** (380 mg, 40%) as a pale yellow oil: IR ν_{max} 1743 cm^{-1}. The triflate **40** (540 mg, 1.7 mmol) and **36** (820 mg, 2.0 mmol) were stirred with Ph_3P (62 mg, 240 μmol) and $Pd(OAc)_2$ (27 mg, 120 μmol) in dry THF (10 mL) at 55 °C under N_2 for 1 h. Evaporation and chromatography (hexane/EtOAc 9:1) gave **45** (400 mg, 84%) as a colourless oil: IR ν_{max} 1737 cm^{-1}; ^{1}H NMR δ 1.49 (9H, s, Bu^t), 1.80 (2H, qn, J=7.4 Hz, 4-H_2), 2.45 (2H, t, J=5.8 Hz, pentenyl 4-H_2), 2.47 (2H, q, J=5.8 Hz, pentenyl 3-H_2), 2.60–2.62 (4H, m, 3,5-H_2), 3.66 (3H, s, Me), 5.88 (1H, td, J=6.0, 15.6 Hz, pentenyl 2-H), 7.26 (1H, d, J=16.4 Hz, pentenyl 1-H); ^{13}C NMR (HMQC/HMBC) δ 21.14 (4-C), 28.28 (C(CH_3)$_3$), 28.39 (pentenyl 3-C), 33.46 (pentenyl 4-C), 34.32 (3-C or 5-C), 34.43 (5-C or 3-C), 51.60 (OMe), 80.08 (C(CH$_3$)$_3$), 126.58 (pentenyl 1-C), 130.02 (C_q), 135.26 (pentenyl 2-C), 150.21 (Cq), 165.47 (C=O), 173.30 (C=O). This compound was used immediately without further characterisation.

4.34. *E*-2-(5-Methoxy-1-oxopent-1-enyl)cyclopentene-1-carboxylic acid (46)

The diester **45** (400 mg, 1.4 mmol) was treated with CF_3CO_2H and CH_2Cl_2, as for the synthesis of **6** (Method A), to give **46** (230 mg, 72%) as a pale yellow oil: IR ν_{max} 2946, 1728 cm^{-1}; ^{1}H NMR δ 1.85 (2H, qn, J=7.4 Hz, 4-H), 2.46 (2H, t, J=5.8 Hz, pentenyl 3-H_2), 2.51 (2H, q, J=5.8 Hz, pentenyl 4-H_2), 2.67–2.69 (4H, m, 3,5-H_2), 3.66 (3H, s, Me), 5.99 (1H, td, J=6.3, 16.0 Hz, pentenyl 2-H), 7.30 (1H, d, J=16.0 Hz, pentenyl 1-H); ^{13}C NMR δ 13.69, 18.87, 21.31, 27.11, 28.47, 33.47, 34.66, 51.79, 126.59, 137.23, 171.08, 173.38. This compound was used immediately without further characterisation.

4.35. *N*-(2-(5-*E*-Methoxy-1-oxopent-1-enyl)cyclopentene-1-carbonyl)-L-phenylalanine *N*-(4-nitrophenyl)amide (47)

Compound **46** (230 mg, 1.0 mmol) was treated with **22**, PyBOP and Et_3N, as for the synthesis of **29**, to give **47** (210 mg, 42%) as a pale yellow powder: mp 74–75 °C; IR ν_{max} 3434, 1737, 1619, 1563, 1511, 1342 cm^{-1}; ^{1}H NMR δ 1.83–1.90 (2H, m, cyclopentene 3-H_2), 2.36–2.46 (6H, m, pentene 3-H_2 and cyclopentene 3,5-H_4), 2.61 (2H, t, J=7.0 Hz, pentenyl 4-H_2), 3.16 (1H, dd, J=14.0, 7.8 Hz, Phe β-H), 3.25 (1H, dd, J=14.0, 6.6 Hz, Phe β-H), 3.65 (3H, s, Me), 4.93 (1H, q, J=7.0 Hz, Phe α-H), 5.89 (1H, td, J=6.6, 16.0 Hz, pentenyl 2-H), 6.09 (1H, d, J=7.4 Hz, Phe α-NH), 7.20 (1H, d, J=16.0 Hz, pentenyl 1-H), 7.23–7.31 (5H, m, Ph-H_5), 7.60 (2H, d, J=9.0 Hz, Ar 2,6-H_2), 8.12 (2H, d, J=9.0 Hz, Ar 3,5-H_2); ^{13}C NMR (HMQC/HMBC) δ 21.34 (pentenyl 4-C), 28.30 (cyclopentene 3-C or 4-C or 5-C), 33.26 (cyclopentene 3-C or 4-C or 5-C), 33.90 (cyclopentene 3-C or 4-C or 5-C), 34.15 (pentenyl 3-C), 37.00 (Phe β-C), 51.67 (Me), 55.32 (Phe α-C), 119.28 (Ar 2,6-C_2), 124.88 (Ar 3,5-C_2), 126.05 (pentenyl 1-|C), 127.25 (Ph 4-C), 128.26 (Cq), 128.90 (Ph-C), 129.18 (Ph), 136.06 (cyclopentene 2-C), 136.45 (pentenyl 2-C), 143.70 (Cq), 143.42 (Ar 3,5-C_2 or 2,6-C_2), 143.62 (Ar 2,6-C_2 or 3,5-C_2), 167.34 (C=O), 169.97 (C=O), 173.14 (C=O); MS m/z 492.2085 (M+H) ($C_{27}H_{30}N_3O_6$ requires 492.2134).

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