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Synthetic applications of aliphatic unsaturated α-H-α-amino acids†

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This article provides an overview of the literature concerning synthetic applications of unsaturated aliphatic amino acids in the period May 2000 to December 2004.

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1. Introduction

Naturally-occurring amino acids have found a broad spectrum of applications in all fields of chemistry. In particular, synthetic organic chemists have embraced them as cheap and readily available optically pure building blocks in asymmetric synthesis.[2] However, the use of these amino acids is limited by the narrow range of functionalities offered in their side chains. In the past decade or so, non-proteinogenic amino acids have appeared on

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Jasper Kaiser

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Hans Schoemaker was born in Haarlem, the Netherlands, in 1952. He studied chemistry at the University of Amsterdam and received his PhD at the same university with Professor W. Nico Speckamp in 1979. That year, he joined DSM Research (Geleen, the Netherlands), where he is now corporate scientist advanced synthesis and (bio)-catalysis. In 1990, he was awarded the Gold Medal of the Royal Netherlands Chemical Society (KNCV). In 1994, he was appointed part-time professor of Industrial Fine Chemistry at the J. H. van't Hoff Institute of Molecular Sciences, University of Amsterdam.

Richard Blaauw was born in Eindhoven, The Netherlands, in 1974. He received his MSc from the University of Amsterdam in 1997 and his PhD from the same university under the supervision of Professor Henk Hiemstra in 2001. Then he joined the group of Professor Floris Rutjes as a post-doctoral researcher, during which he founded the company Chiralix. Currently, he is managing director of this innovative, technology-driven contract research organization.

Floris Rutjes was born in Heiloo, the Netherlands, in 1966. He studied chemistry at the University of Amsterdam, where he also received his PhD with Professor Nico Speckamp in 1993. After a post-doctoral stay in the group of Professor K. C. Nicolaou (The Scripps Research Institute, La Jolla, USA), he was appointed at the University of Amsterdam in 1995. Four years later, he became full professor in synthetic organic chemistry at the University of Nijmegen. In 2002, he was awarded the Gold Medal of the Royal Netherlands Chemical Society (KNCV) and in 2003 the AstraZeneca award for research in organic chemistry. His research interests include the use of bio- and metal-catalysts in organic synthesis and the development of novel synthetic methodology.

Hans Schoemaker

Richard Blaauw

Floris Rutjes

stage to fill the gap left by their natural counterparts and have since then widened the applications of amino acids in chemistry, including, but not limited to, synthetic organic chemistry.

Unsaturated amino acids comprise a class of non-proteinogenic amino acids that has gained much interest in the field of synthetic chemistry.[3] They have proven useful in providing a handle for a range of transformations, especially transition metal-mediated functionalisations. Among those, the metathesis-type reactions deserve a special mentioning as they have manifested themselves as a standard tool in organic synthesis. While their use is still focussed on olefinic substrates, more and more examples of acetylene metathesis have emerged from the literature.[4] Also, with the advent of the 'click chemistry' concept,[5] an amplified interest in acetylenic amino acids can be expected. Furthermore, unsaturated α-amino acids nowadays play an important role in peptide chemistry due to their facile incorporation in (biologically relevant) protein structures. Their increasing importance as building blocks in synthetic routes is reflected by the large number of articles appearing on strategies for preparing these molecules.[6,7]

In this article, we will provide an overview of synthetic efforts involving unsaturated amino acids, covering the literature from May 2000 to December 2004. Thereby, we have limited ourselves to aliphatic, unsaturated α-H-α-amino acids as shown in Fig. 1.[8]

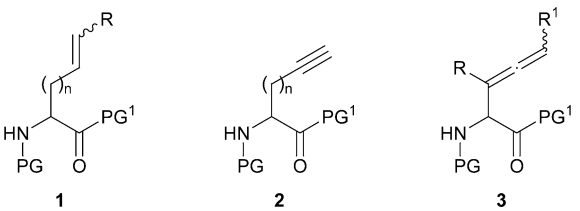
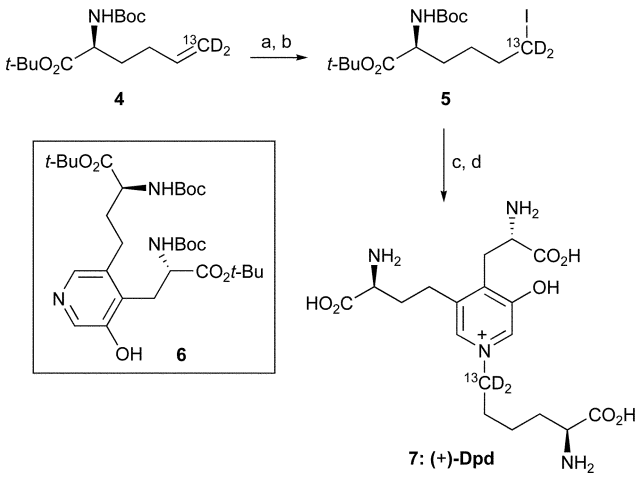


Fig. 1 Aliphatic, unsaturated α-H-α-amino acids.

The inventorised applications can be roughly divided into six categories, namely those which concern (i) modifications of the side chain, (ii) direct cyclisations of the amino acids, (iii) cyclisations of the side chain *via* a substituent on the nitrogen atom, (iv) cyclisations making use of the ester substituent and the side chain, (v) miscellaneous applications, and (vi) biosynthetic applications.

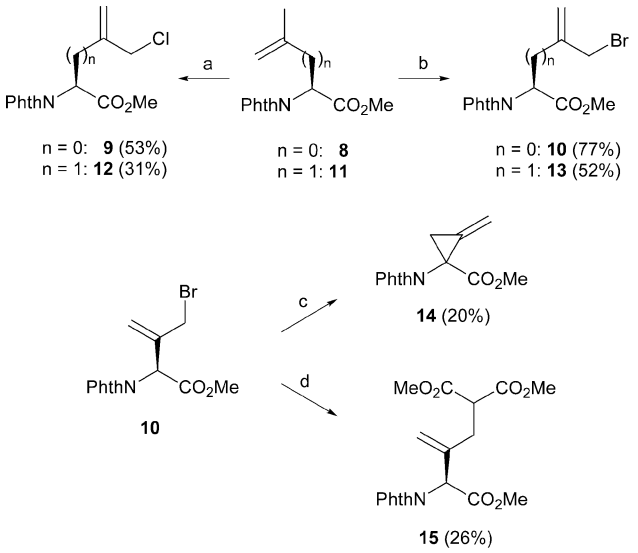
2. Side chain modifications

Based on their earlier work on the synthesis of (+)-deoxypyrrololine,[9] Adamczyk *et al.* reported the transformation of isotopically labelled homoallylglycine into (+)-deoxypyridinoline **7** (Scheme 1).[10]



Scheme 1 *Reagents and conditions*: (a) BH_3·THF, 0 °C to rt, 17 h (48%); (b) I_2, PPh_3, imidazole, THF, rt, 3 h (78%); (c) **6**, dioxane, reflux, 7 h (40%); (d) TFA, H_2O, rt, 1.5 h (84%).

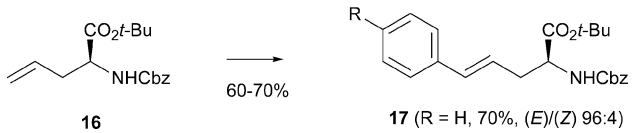
Hydroboration of isotopically labelled **4** [derived from (*S*)-glutamic acid] and subsequent conversion into the iodide led to the formation of iodide **5** in 37% overall yield. Coupling of this enantiomerically pure iodide with pyridine derivative **6** and hydrolysis in aqueous TFA completed the synthesis of labelled (+)-deoxypyridinoline **7**. Instead of using a substitution reaction, a direct method to obtain halogenated non-natural amino acids was studied by Easton *et al.* (Scheme 2).[11]



Scheme 2 *Reagents and conditions*: (a) Cl_2, CCl_4, rt; (b) NBS, CCl_4, reflux; (c) NaH, THF, rt, 48 h; (d) *n*-BuLi, dimethyl malonate, THF, 10 min, then **10**, 15 h.

Treatment of the unsaturated amino acids **8** and **11** with molecular chlorine at room temperature resulted in the formation of the allylic halides **9** and **12**, in 53% and 31% yield, respectively (only major products are given). The corresponding brominated products **10** and **13** were obtained in 77% and 52% yield by treatment with *N*-bromosuccinimide in refluxing CCl_4. Easton's group also used bromide **10** to synthesise the racemic cyclopropyl amino acid **14** *via* NaH-induced intramolecular C–C bond formation in 20% yield and malonate **15** through an intermolecular substitution of the bromide with dimethyl malonate anion.

Important and frequently used side chain modifications involve transition metal-mediated processes. An example of such a side chain modification is given by Gurjar and Talukdar, who utilised the Heck reaction for this purpose (Scheme 3).[12]

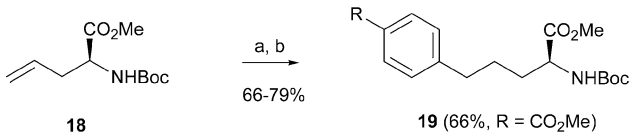


Scheme 3 *Reagents and conditions*: RC_6H_4I, $NaHCO_3$, Bu_4NBr, $Pd(OAc)_2$, MeCN, 70 °C, 6 h.

The palladium-catalysed Heck coupling of protected allylglycine **16** led to the formation of the phenylallylglycine derivatives **17** in 70% yield. Several aryl iodides with electron-withdrawing and electron-donating R groups were successfully coupled using this protocol. A similar type of Heck coupling was used by Collier *et al.* to synthesise bis-homophenylalanine derivatives such as **19** (Scheme 4).[13]

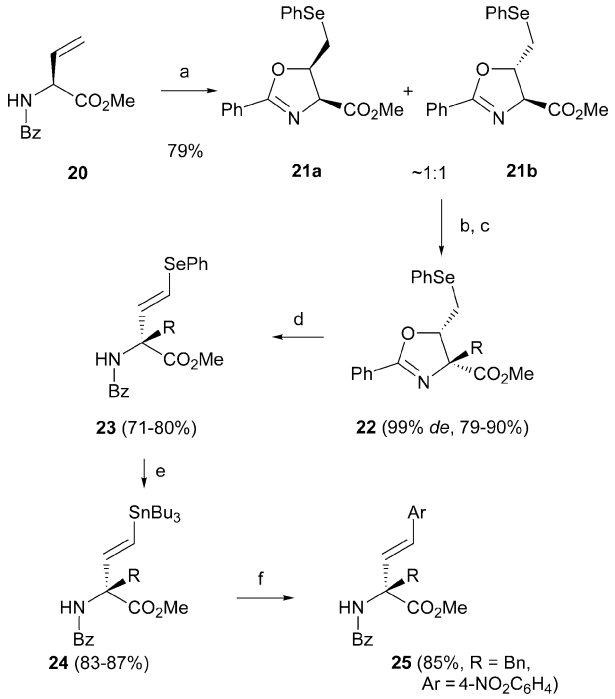
For example, the Heck coupling of allylglycine derivative **18** with 4-iodobenzoic acid methyl ester followed by double bond hydrogenation resulted in protected bis-homophenylalanine **19** (R = CO_2Me) in 66% yield over these two steps.

Alternatively, the Stille coupling was applied on different olefinic α-amino acids to achieve double bond substitution with



Scheme 4 *Reagents and conditions*: (a) RC_6H_4X (X = Br or I), K_2CO_3, $Pd(OAc)_2$, *n*-Bu_3P, DMF, 100 °C, 1 h; (b) Pd/C, H_2, EtOH.

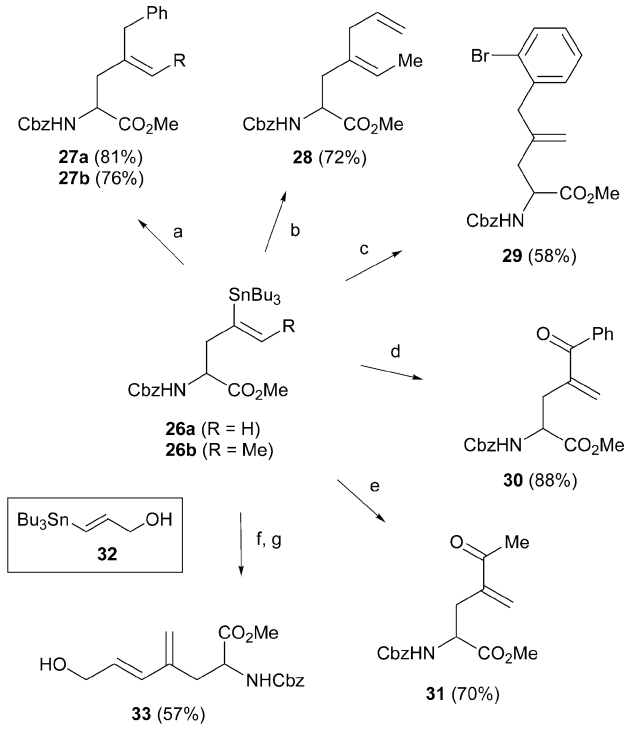
aryl groups. The group of Berkowitz reported a stereodivergent route for α-alkylated, stannylated vinylglycines that were useful in the Stille-type coupling.[14] The organoselenium oxazoline intermediate **21** was obtained in 79% yield by treatment of the vinylglycine derivative **20** with phenylselenium chloride in the presence of silver triflate at −100 °C in THF (Scheme 5). The diastereoisomers could be separated by silica gel chromatography. Diastereoselective alkylation of product **21b** proceeded in good yield (79–90%) and excellent de (>98%) for different alkyl halides. This resulted in the formation of α,α-disubstituted vinyl selenides **23** after the base-induced ring opening of the alkylation products **22**. A novel type of deselenative stannylation upon treatment of the vinyl selenides **23** with Bu_3SnH in the presence of AIBN resulted in the vinyl stannanes **24** in good yield (83–87%).



Scheme 5 *Reagents and conditions*: (a) PhSeCl, AgOTf, THF, −100 °C; (b) separation by chromatography; (c) KHMDS, RX, −78 °C; (d) KO*t*-Bu, DMF; (e) AIBN, Bu_3SnH, toluene, Δ; (f) Pd_2dba_3, *p*-$NO_2C_6H_4I$, THF.

These types of stannanes could be hydrolysed under acidic conditions to the free α-substituted vinylglycines for a variety of R groups. Alternatively, a Stille coupling with *p*-nitrophenyl iodide resulted in the formation of arylvinylglycine **25** in 85% yield for R = Bn. A full paper published by the same group covered additional examples of couplings performed with stannane **24** (R = Bn).[15] The Kazmaier group reported the use of the Stille coupling on the tributyltin-substituted allylglycines **26a** and **26b** which were obtained *via* the Claisen rearrangement of α-stannylated allylic esters (Scheme 6).[16]

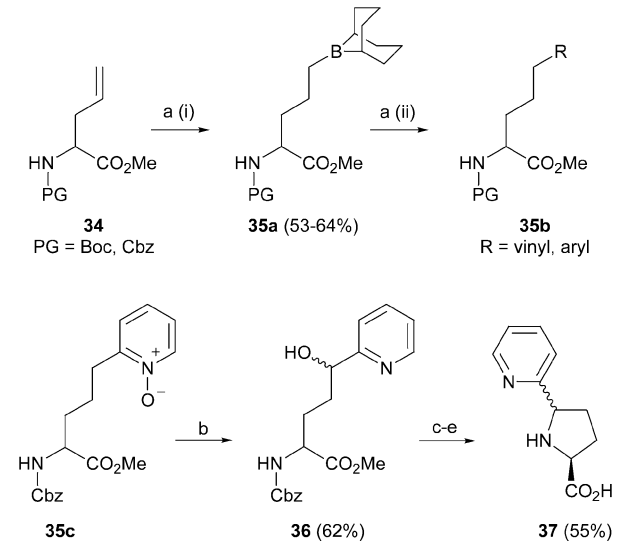
The palladium-catalysed coupling of these stannanes with benzyl bromide was performed with Pd_2dba_3 and with $AsPh_3$ as the ligand, providing the allylglycines **27a** and **27b** in 81 and 76% yield, respectively. Other examples comprise the introduction of an allyl (**28**, 72% yield), an *o*-bromobenzyl (**29**, 58% yield), a benzoyl (**30**, 88% yield) and an acetyl group (**31**, 70% yield).



Scheme 6 *Reagents and conditions*: (a) BnBr, $Pd_2dba_3{\cdot}CHCl_3$, $AsPh_3$, THF, 20 h; (b) allyl bromide, $Pd_2dba_3{\cdot}CHCl_3$, $AsPh_3$, toluene, 60 °C, 20 h; (c) *o*-$BrC_6H_4CH_2Br$, $Pd_2dba_3{\cdot}CHCl_3$, $AsPh_3$, THF, reflux, 5 h; (d) BzCl, π-C_3H_5PdCl, MeCN; (e) AcCl, π-C_3H_5PdCl, MeCN, 10 min; (f) I_2, $CHCl_3$, rt; (g) **32**, $(MeCN)_2PdCl_2$, DMF, 80 °C, 2 h.

These Stille couplings could also be performed on the crude starting materials with respectable yields. Stannane **26a** could also be converted to the iodide, followed by a palladium-catalysed cross-coupling with the (*E*)-vinyl stannane **32** to afford the allylic alcohol **33** in 57% overall yield.

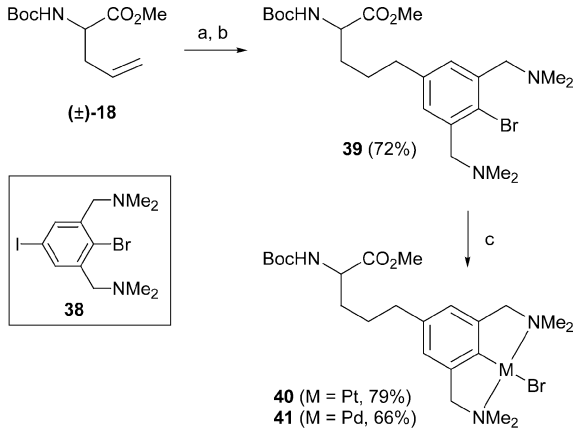
The hydroboration–Suzuki cross-coupling sequence with unsaturated amino acids also proved to be a viable strategy for the synthesis of enantiopure, non-proteinogenic α-amino acids.[17] In this way, Collier *et al.* showed that hydroboration of the protected allylglycine **34** afforded the borane intermediate **35a**, which was subjected to Suzuki coupling conditions with various aryl and vinyl halides (X = Br, I; Scheme 7).[18] This resulted in a range of coupling products of type **35b**, containing different R groups. The Cbz-protected product **35c** was successively treated with TFAA to give the Boekelheide reaction. After saponification of the intermediate trifluoroacetates, hydroxy compound **36** was obtained in 62% yield. Oxidation of the benzylic hydroxy group with MnO_2 afforded the ketone in 71% yield.



Scheme 7 *Reagents and conditions*: (a) (i) 9-BBN, THF, rt, 2 h, (ii) RX, $PdCl_2(dppf){\cdot}CH_2Cl_2$, 3 M aqueous K_3PO_4, THF–DMF, 16 h; (b) (i) TFAA, CH_2Cl_2, rt, 16 h, (ii) 2 M aqueous Na_2CO_3, 3 h; (c) MnO_2; (d) 0.5 M aqueous LiOH, THF; (e) H_2, Pd/C, EtOH.

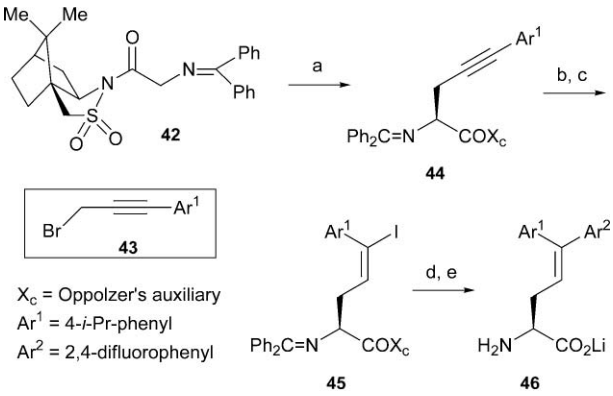
Saponification of the ester, followed by hydrogenolysis of the Cbz group led to cyclisation of the free amine onto the ketone. The resulting pyrroline was further hydrogenated in the same pot to afford the substituted proline derivative **37** as a mixture of diastereoisomers in 55% yield over the last three steps.

An organometallic pincer complex-oriented application of the hydroboration–Suzuki cross-coupling sequence with unsaturated amino acids was studied by the group of van Koten. Allylglycine **18** was reacted with 9-BBN to give the hydroborated intermediate, which was coupled with 1-bromo-4-iodo-2,6-bis[(dimethylamino)methyl]benzene (**38**) under Suzuki-type conditions (Scheme 8).[19] This afforded bromide **39** in 72% yield over two steps. Metallation of **39** was carried out with a platinum or palladium complex to afford complexes **40** and **41** in good yield. Removal of the Boc group and saponification was also possible, giving access to the free amino acids, suitable for incorporation in peptides.



Scheme 8 *Reagents and conditions*: (a) 9-BBN, THF, rt, 2 h; (b) **38**, $[PdCl_2(dppf)]$, K_3PO_4, DMF, Δ, 12 h; (c) $[Pt(\mu\text{-}SEt_2)(p\text{-tol})_2]_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$, benzene, 50 °C, 3 h.

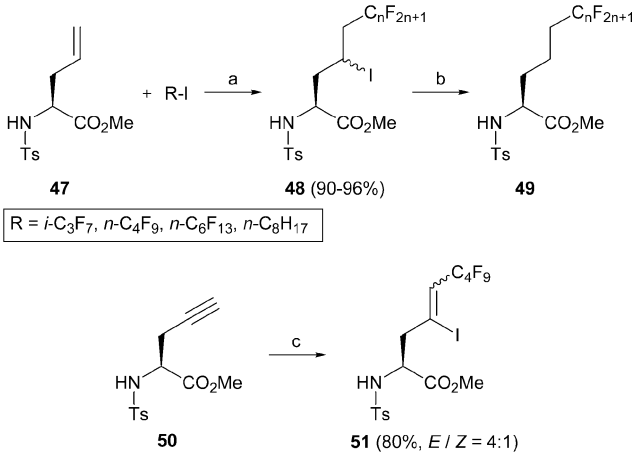
Researchers of NPS Allelix made use of the Suzuki reaction in the synthesis of pharmacologically valuable 5,5-diaryl-substituted allylglycines (Scheme 9).[20] Compound **46** was found to be a potent glycine transporter type-2 reuptake inhibitor. Its synthesis commenced with glycine diphenylketimine connected to the Oppolzer's auxiliary [(2*R*)-bornane-10,2-sultam, **42**] which was alkylated using 3-arylpropargyl bromide **43**. The resulting (*S*)-propargylglycine derivative **44** was subjected to hydrostannylation, yielding the vinyl stannane as its (*E*)-isomer



Scheme 9 *Reagents and conditions*: (a) LDA, THF, HMPA, −78 °C then **43**; (b) Bu_3SnH, $PdCl_2(PPh_3)_2$, THF; (c) I_2, CH_2Cl_2; (d) $Ar_2{-}B(OH)_2$, $Pd(PPh_3)_4$, DME/Na_2CO_3; (e) (i) TFA, H_2O, CH_2Cl_2, (ii) 2.5 N LiOH, H_2O–THF; yields not given.

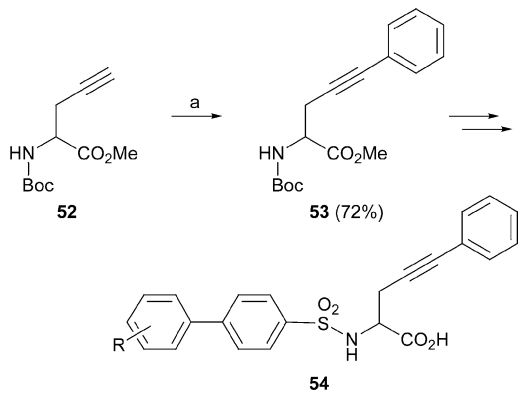
selectively that, in turn, could be transformed to the iodide **45** by treatment with iodine. A Suzuki-type coupling reaction with 2,4-difluorophenylboronic acid completed the carbon framework of the target compound. Deprotection and hydrolysis furnished the desired allylglycine derivative **46** as its lithium salt.

Blaauw *et al.* investigated the synthesis of optically active perfluoroalkyl-containing amino acids.[21] Starting from protected enantiopure allylglycine **47**, they introduced perfluorinated moieties by means of a palladium-catalysed addition of the appropriate fluoroalkyl iodide (Scheme 10). The resulting fluorinated products (**48**) were all obtained in >90% yield, except for trifluoromethyl iodide and perfluoro-*tert*-butyl iodide, which gave low (10%) or no yield, respectively. Hydrogenation of the fluorinated intermediates provided the targeted fluorinated amino acids **49**. The same researchers reported similar additions to propargylglycine. Thus, the protected (*R*)-propargylglycine methyl ester **50** was treated with perfluoro-*n*-butyl iodide in the presence of zinc and TFA to furnish the allylglycine derivative **51** in 80% yield as a 4 : 1 mixture of (*E*)/(*Z*)-isomers.



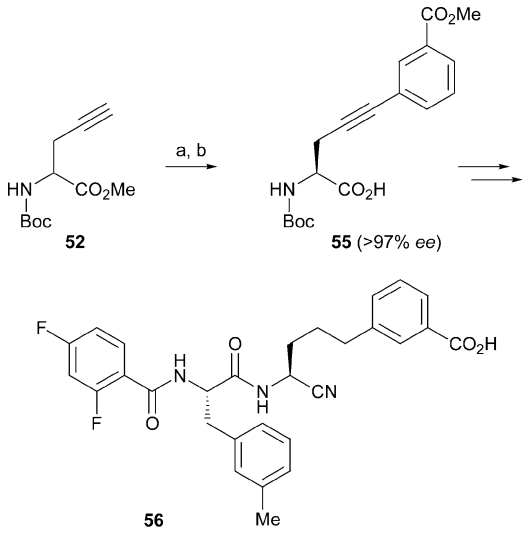
Scheme 10 *Reagents and conditions*: (a) $Pd(PPh_3)_4$, CuI, hexane, rt, 16 h; (b) Pd/C, H_2, Et_3N, EtOAc, rt, 4 h; (c) C_4F_9I, Zn, TFA, CH_2Cl_2, rt 16 h.

At Procter and Gamble Pharmaceuticals, the Sonogashira reaction was applied in the synthesis of the phenyl-substituted propargylglycine derivative **53**, which served as a scaffold for the development of new matrix metalloprotease inhibitors.[22] The Pd-catalysed coupling of **52** with phenyl iodide gave the substituted counterpart in 72% yield. Compound **53** was subsequently converted into the carboxylic acids **54**, of which the inhibitory activity was evaluated (Scheme 11).



Scheme 11 *Reagents and conditions*: (a) PhI, $Pd(PPh_3)_2$, CuI, Et_3N, DMF.

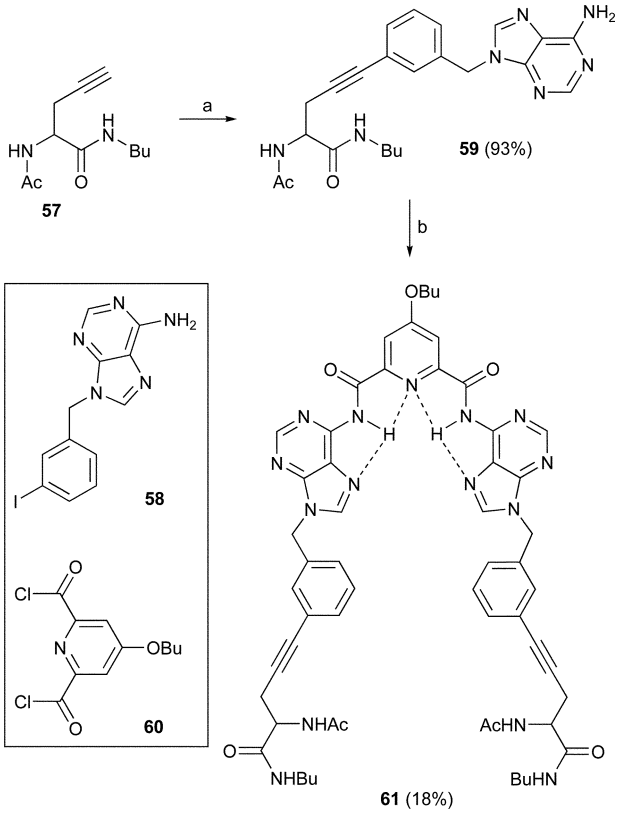
Researchers at Novartis Pharmaceuticals utilised the Sonogashira coupling in the synthesis of propargylglycine derivative **55** (Scheme 12).



Scheme 12 *Reagents and conditions*: (a) methyl 3-bromobenzoate, $PdCl_2(PPh_3)_2$, CuI, Et_3N; (b) alcalase, MeCN, 0.2 M aqueous $NaHCO_3$.

In this case, racemic propargylglycine **52** was first coupled with methyl 3-bromobenzoate after which an enzymatic hydrolysis afforded **55** in high enantioselectivity. This acetylenic amino acid was then converted in a multi-step sequence into the dipeptidyl nitrile **56**, which was tested as an inhibitor of the lysosomal cysteine protease cathepsin B.[23]

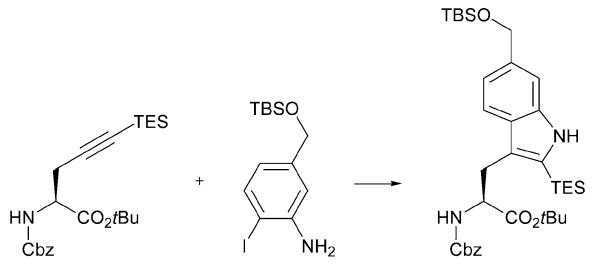
Crisp and Jiang reported the use of the Sonogashira reaction in the functionalisation of propargylglycine derivative **57** with the 9-substituted adenine **58**.[24] The coupling reaction proceeded smoothly to give the substituted propargylglycine derivative **59**, which was used as an amine coupling partner in the reaction with the diacid chloride **60** (Scheme 13).



Scheme 13 *Reagents and conditions*: (a) **58**, $Pd(PPh_3)_4$, PPh_3, CuI, piperidine; (b) **60**, pyridine.

The latter condensation led to the formation of compound **61** in 18% yield, which can be considered as a potential host for organic guests or as a ligand for metal cations. Proton NMR and FT-IR studies on **61** indicated that the hydrogen bonding gives rise to a planar *cis*-conformation of the molecule.

The versatility of the acetylenic side chain in Pd-mediated modifications was further demonstrated by Castle and Srikanth in the asymmetric synthesis of tryptophan derivative **64**, which represents the central tryptophan residue of the bicyclic octapeptide celogentin C.[25] The key transformation in the synthesis of **64** was the Pd-catalysed heteroannulation of triethylsilyl (TES)-substituted propargylglycine derivative **62** and iodoaniline **63** (Scheme 14).

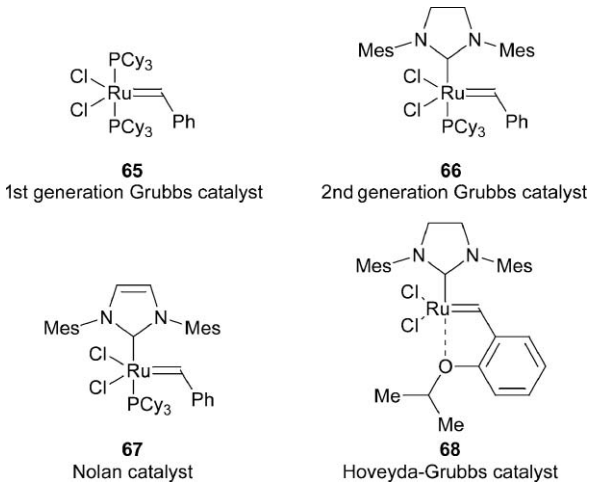


62 **63** **64** (58%)

Scheme 14 *Reagents and conditions*: $Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 90 °C.

Under the basic heteroannulation conditions, tryptophan **64** was formed in 58% yield without loss of enantiopurity according to chiral HPLC analysis.

A different, but important type of side chain modification of unsaturated amino acids can be achieved through olefin metathesis. With the advent of air-stable, ruthenium-based catalysts that tolerate a wide range of functional groups in the early 1990s,[26] metathesis reactions have found an ever increasing interest. The most commonly used catalysts are displayed in Fig. 2, the 1st and 2nd generation Grubbs catalysts (**65** and **66**, respectively), the Nolan catalyst (**67**), and the Hoveyda–Grubbs catalyst (**68**).



65 1st generation Grubbs catalyst

66 2nd generation Grubbs catalyst

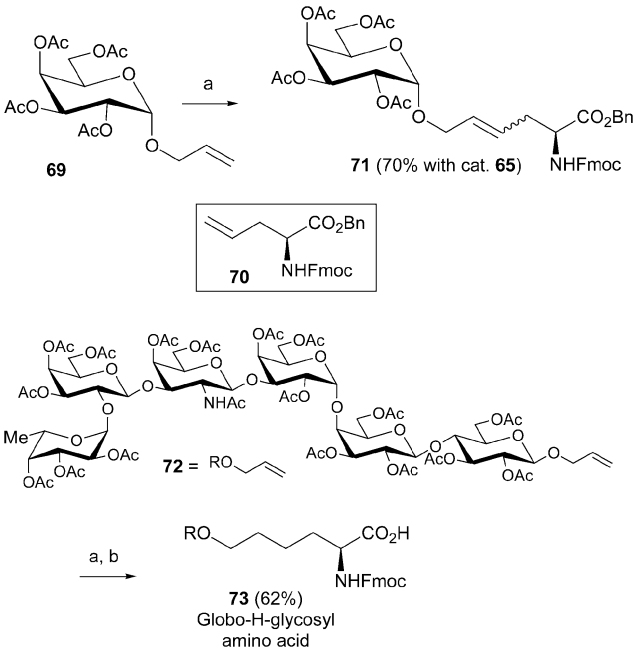
67 Nolan catalyst

68 Hoveyda-Grubbs catalyst

Fig. 2 Air-stable, ruthenium-based metathesis catalysts.

The cross-metathesis of allylglycines with *O*-allylglycosides was found to be a good route for the synthesis of glycosyl amino acids as exemplified by the Danishefsky group.[27] Cross-metathesis between allylglycine **70** and allylglycoside **69** was successful when using an excess of the amino acid (5 equiv.) and applying 20 mol% of catalyst **65** in refluxing dichloromethane (Scheme 15).

In this way, the metathesis product **71** was obtained in a yield of 70% as a mixture of double bond isomers. The reaction was



Scheme 15 *Reagents and conditions*: (a) **70** (5 equiv.), **65** (20 mol%), CH_2Cl_2, 40 °C, 12 h; (b) Pt/C, H_2, MeOH–H_2O, 12 h.

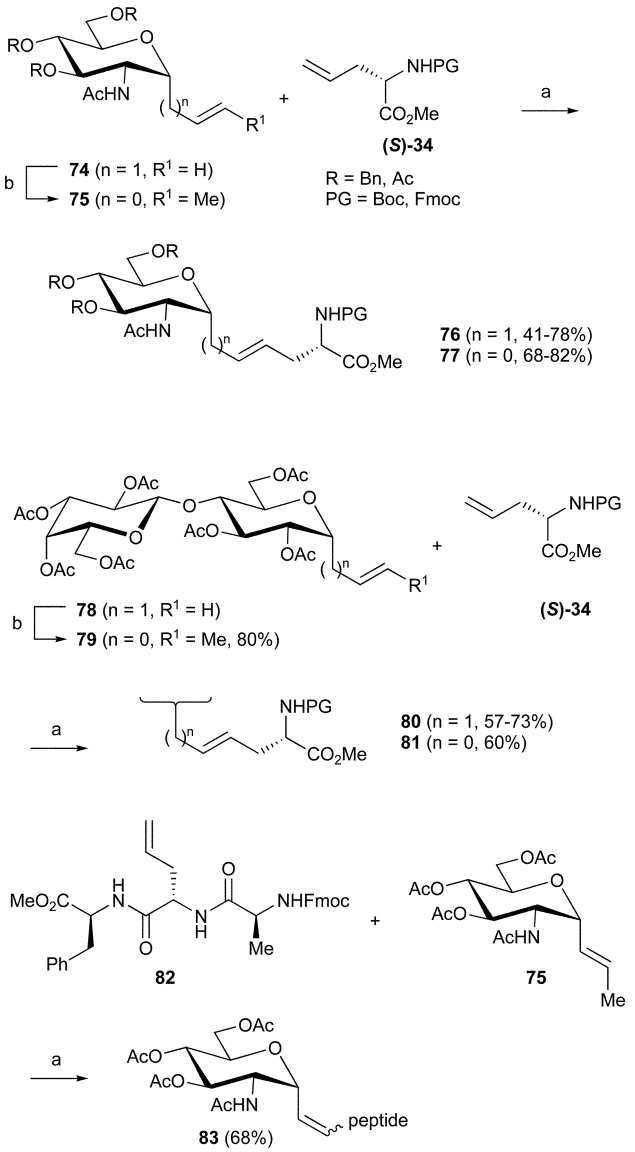
also used in the synthesis of Globo-H-glycosyl amino acid **73**, starting from hexasaccharide **72** and allylglycine **70**. Applying the optimised cross-metathesis conditions, followed by double bond hydrogenation led to the desired target in a yield of 62% over these two steps. The second generation Grubbs catalyst **66** was also tested, but appeared inferior compared with **65**.

A related, but different study towards the cross-metathesis of allylglycines with *C*-glycosides was disclosed by McCarvey *et al*.[28] They reported the successful metathesis between *C*-glycosides of type **74** or **75** (R = Bn, Ac) with allylglycines **34** (PG = Boc, Fmoc) to afford the *C*-neoglycopeptides **76** and **77** in generally good yields (Scheme 16). This time, the 2nd generation Grubbs catalyst **66** proved to be more satisfactory. The same strategy was applied onto the *C*-allyllactose **78** and the *C*-vinylglucoside **79** to give the metathesis products **80** and **81** in yields ranging from 57 to 73%. After having established this so-called co-translational approach for building up glycopeptides, a post-translational strategy was tested with tripeptide **82** containing the allylglycine moiety. Indeed, the post-translational metathesis product **83** was obtained in 68% yield upon reaction of **82** with *C*-glycoside **75**.

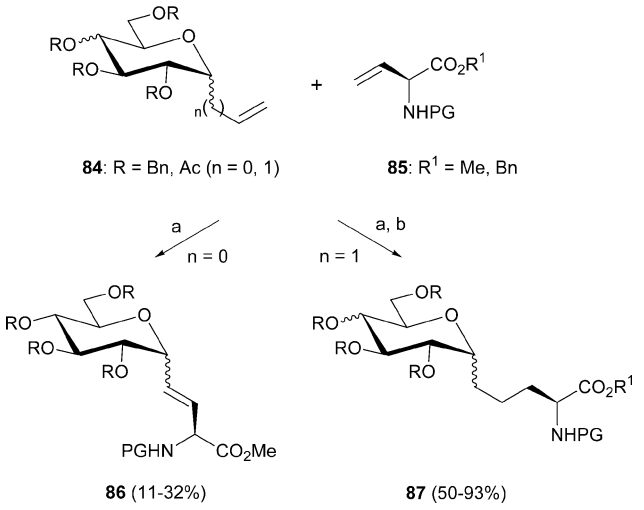
A survey on the cross-metathesis of α- and β-*C*-glycosides with protected vinylglycines and subsequent hydrogenation of the new double bond was published by Nolen *et al.* (Scheme 17).[29]

In this study, a range of olefinic α- and β-*C*-glycosides **84** was cross-coupled with diversely protected vinylglycines **85**. For the substrates with $n = 0$, the metathesis proved to be difficult and products of type **86** were formed in low yields. The use of the allyl homologues improved the yields significantly and afforded the desired metathesis products in good yields using the 2nd generation Grubbs catalyst **66**. Subsequent hydrogenation by different methods were all high yielding. Thus, the targeted synthesis of a range of *C*-glycosylasparagines of type **87** through cross-metathesis with vinylglycines was achieved.

The group of Abell[30] made use of α-amino acids in the synthesis of cyclic β-amino esters. Among several amino acids, allylglycine **88** and homoallylglycine **92** were utilised as starting materials (Scheme 18). An Arndt–Eistert homologation provided the corresponding β-amino acid esters that were alkylated at the α-position to give dienes **89** and **93** as optically pure compounds. The desired cyclic β-amino acid esters (**91** and **95**) were obtained in good yields after ring-closing metathesis

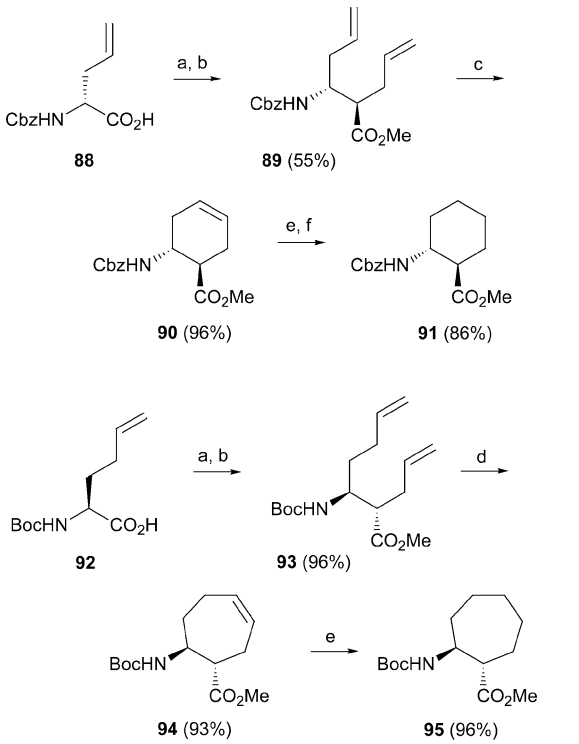


Scheme 16 *Reagents and conditions*: (a) catalyst **66** (10–20 mol%), CH_2Cl_2, reflux, 16–48 h; (b) $(Ph_2MeP)_2IrCOD{\cdot}PF_6$ (10 mol%), THF, rt.



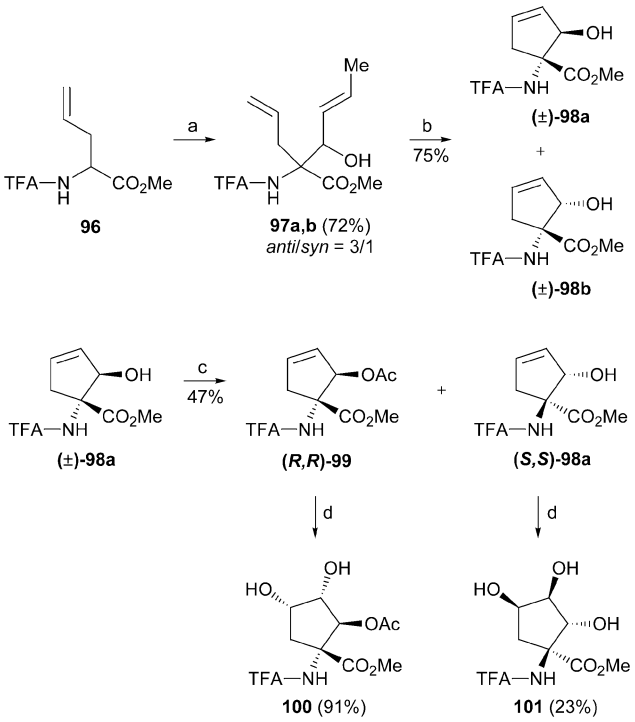
Scheme 17 *Reagents and conditions*: (a) catalyst **66** (20 mol%), CH_2Cl_2, reflux, 12 h; (b) hydrogenation.

(RCM) catalysed by either **65** or **66** followed by reduction of the resulting cycloalkenes (**90**, **94**) and – if necessary – reprotection of the amine.



Scheme 18 *Reagents and conditions*: (a) (i) Et_3N, $ClCO_2Et$, THF, −15 °C, 15 min, (ii) CH_2N_2, 0 °C, (iii) AgBz, Et_3N, MeOH, −25 °C; (b) LiCl, LDA, allyl bromide, THF, −78 °C; (c) catalyst **65**, benzene, reflux; (d) catalyst **66**, benzene, rt; (e) 10% Pd/C, H_2, MeOH, rt; (f) DIEA (*N*,*N*-diisopropylethylamine), CbzCl, DMAP, CH_2Cl_2, rt.

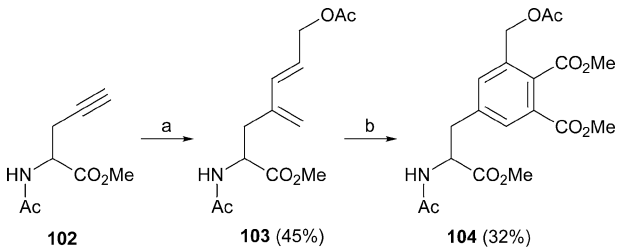
Kummeter and Kazmaier presented an efficient route to polyhydroxylated aminocyclopentanes based on racemic allylglycine.[31] Addition of crotonaldehyde to the chelated amino acid ester enolate of **96** yielded the 1,2-addition product **97** exclusively in a *syn*/*anti* ratio of 1 : 3 (Scheme 19). The diene was treated with Grubbs catalyst **66** to give the ring-closed products



Scheme 19 *Reagents and conditions*: (a) (i) LiHMDS, $ZnCl_2$, THF, −78 °C, (ii) crotonaldehyde, −78 °C, 1 h; (b) catalyst **66**, CH_2Cl_2, rt, 10 h; (c) Novozym® 435, vinyl acetate, rt, 14 d; (d) K_2OsO_4 (cat.), NMO, acetone/H_2O, rt, 48 h.

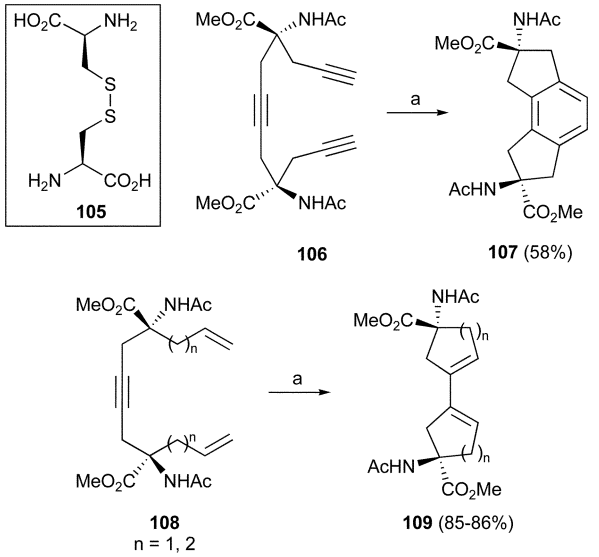
98, with **98a** as the major diastereomer. Treatment of this isomer with Novozym® 435 and vinyl acetate afforded the acetylated (*R*,*R*)-product **99** and left the (*S*,*S*)-alcohol unchanged, both showing enantiomeric purities of >99% ee after the reaction. A *syn* dihydroxylation of these cyclopentenes afforded the corresponding carbocycles **100** and **101**. As expected, the configuration of the newly introduced diol was *trans* relative to the directing alcohol/acetyl groups. In a final step, the protecting groups were removed (not shown).

Kotha *et al.* reported the use of propargylglycine in a metathesis-based approach towards highly functionalised phenylalanine derivatives.[32] In this method, propargylglycine derivative **102** served among others as a substrate in a cross-enyne metathesis reaction with allyl acetate using the 1st generation Grubbs catalyst (**65**) to give the 1,3-diene **103** in 45% yield (Scheme 20). This diene subsequently underwent a Diels–Alder reaction with the indicated dienophile (*e.g.* dimethyl acetylenedicarboxylate = DMAD), followed by DDQ oxidation to afford the targeted phenylalanine derivative **104**.



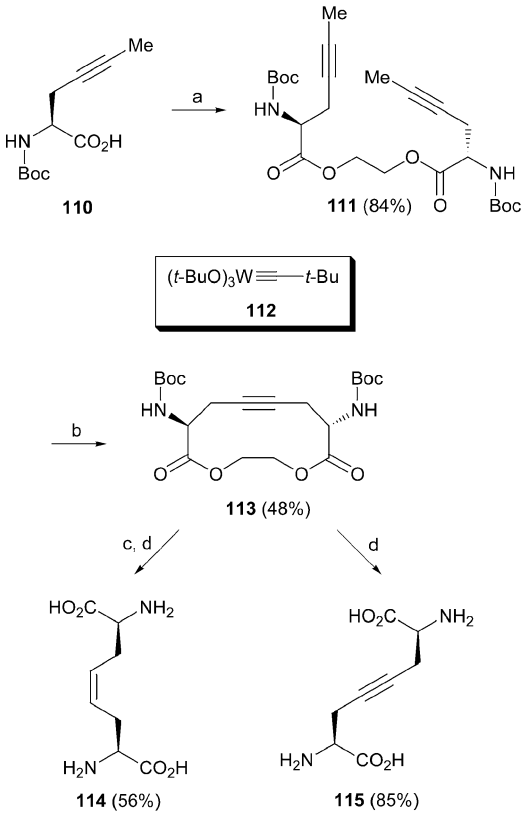
Scheme 20 *Reagents and conditions*: (a) allyl acetate, catalyst **65**, benzene, reflux; (b) (i) DMAD, toluene, 120 °C, (ii) DDQ, benzene, reflux.

Undheim and co-workers were involved in the development of conformationally constrained analogues of cystine (**105**). In the course of their studies, they became interested in the synthesis of the tricyclic bis-amino acid derivative **107** which can be considered as a very rigid cystine analogue (Scheme 21).[33] The key step in the synthetic sequence towards **107** concerned the construction of the tricyclic system. This was achieved by subjecting the acetylene-tethered bis-propargylglycine derivative **106** to Grubbs catalyst **65**, which led to a metathesis cascade reaction to give **107** in 58% yield. The same RCM cascade reaction could be applied for the construction of the bicyclic dienes **109**. These products were designed to be used in Diels–Alder reactions to furnish tricyclic cystine derivatives.



Scheme 21 *Reagents and conditions*: (a) catalyst **65**, toluene.

The groups of van Boom and Rutjes also aimed at the synthesis of conformationally restricted cystine isosteres.[34] The constrained cystine analogues **114** and **115** were selected as target compounds and prepared *via* a ring-closing alkyne metathesis strategy using the enantiomerically pure propargylglycine derivative **110** as the starting material. A representative example of this approach is shown in Scheme 22, where two propargylglycine residues were first coupled with ethylene glycol to give the tethered system **111** in 84% yield.

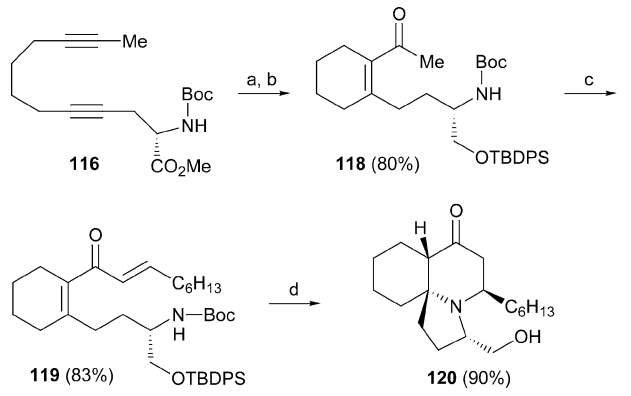


Scheme 22 *Reagents and conditions*: (a) (i) ethylene glycol, DCC, DMAP, CH_2Cl_2, rt, (ii) **110**, DCC, DMAP, CH_2Cl_2, reflux; (b) catalyst **112**, PhCl, 80 °C; (c) H_2, Lindlar catalyst, EtOAc, MeOH, rt; (d) (i) LiOH, MeOH, H_2O, rt, (ii) TFA, CH_2Cl_2, rt.

Subjection of precursor **111** to the Schrock alkyne metathesis catalyst **112** gave the cyclic acetylene **113** in an acceptable yield. At this point, the acetylenic mesocycle could be transformed into two different cystine isosteres containing either a (*Z*)-alkene or an alkyne functionality: stereoselective reduction of acetylene **113**, followed by hydrolysis of the ester linkages and cleavage of the Boc protecting groups led to isostere **114** in 56% yield. Alternatively, immediate saponification of **113** with LiOH, followed by deprotection of the Boc groups provided the acetylenic isostere **115** in 85% over two steps.

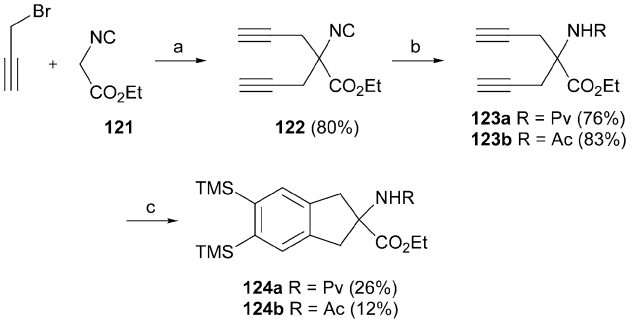
Trost and Rudd exploited a Ru-catalysed hydrative diyne cyclisation, previously developed in their laboratory, in the total synthesis of the tricyclic alkaloid (+)-cylindricine C (**120**, Scheme 23).[35]

Ester reduction of the required diyne **116** followed by protection of the resulting primary alcohol set the scene for the hydrative diyne cyclisation. Addition of 5% of $[CpRu(MeCN)_3]PF_6$ (**117**) led to the chemoselective formation of the desired ketone **118** in 90% yield. An LDA-mediated aldol reaction between **118** and heptanal was immediately followed by an elimination (MsCl, Et_3N) to provide divinyl ketone **119** in 83% yield. Subsequent cleavage of the Boc group with TFA and basic work-up liberated the amine, which was refluxed in the presence of base to construct the tricyclic core of the natural product. Finally, removal of the TBDPS group using TBAF afforded (+)-cylindricine C in 90% yield over three steps.



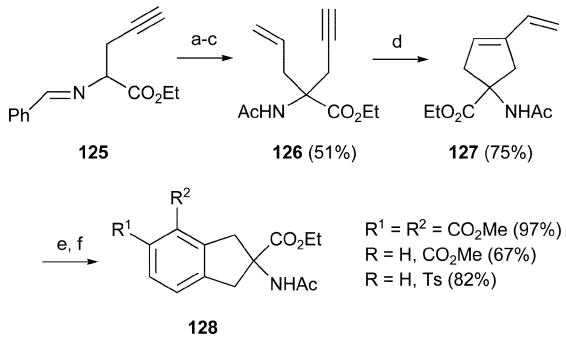
Scheme 23 *Reagents and conditions*: (a) (i) $LiBH_4$, THF, rt, (ii) TBDPSCl, imidazole, DMF, rt; (b) catalyst **117**, H_2O, acetone, 60 °C; (c) (i) LDA, heptanal, THF, −78 °C, (ii) MsCl, Et_3N, CH_2Cl_2, rt; (d) (i) TFA, CH_2Cl_2, rt, (ii) K_2CO_3, toluene, reflux, (iii) TBAF, THF, rt.

Silyl-bearing aromatic compounds readily undergo electrophilic *ipso* substitution reactions thereby providing access to a variety of aromatic derivatives. Kotha and Brahmachary presented a simple strategy for the synthesis of TMS-containing indan-based amino acids (Scheme 24).[36a] Starting from ethyl isocyanoacetate **121** they prepared the dialkynyl amino acids **123**. In a cobalt-catalysed [2 + 2 + 2] cycloaddition between **123** and bis(trimethylsilyl)acetylene (BTMSA), the silicon-substituted indanylglycine derivatives **124** were obtained albeit in low yields. *Ipso* substitution of the TMS groups allowed the preparation of several derivatives.



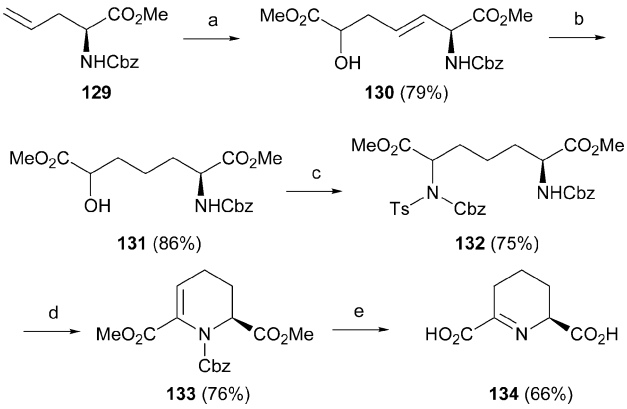
Scheme 24 *Reagents and conditions*: (a) K_2CO_3, *t*-Bu_4NHSO_4, MeCN, 80 °C; (b) (i) HCl, EtOH, rt, (ii) Ac_2O or pivaloyl chloride, CH_2Cl_2; (c) $CpCo(CO)_2$ (cat.), BTMSA, 140 °C.

Another entry to indanylglycine derivatives is shown in Scheme 25.[36b] Allylation of the imine-activated propargylglycine derivative **125** followed by hydrolysis and acetamide formation resulted in amino acid **126**. Enyne RCM using catalyst **65** yielded diene **127** which was subjected to a variety of dienophiles in [4 + 2] cycloaddition reactions. The resulting bicyclic structures could be oxidised by DDQ to give indanylglycines **128**.



Scheme 25 *Reagents and conditions*: (a) allyl bromide, KOH, *n*-Bu_4NBr, MeCN, 0 °C; (b) 3 M HCl, Et_2O, rt; (c) Ac_2O, DMAP, CH_2Cl_2; (d) catalyst **65**, CH_2Cl_2, rt; (e) dienophile; (f) DDQ.

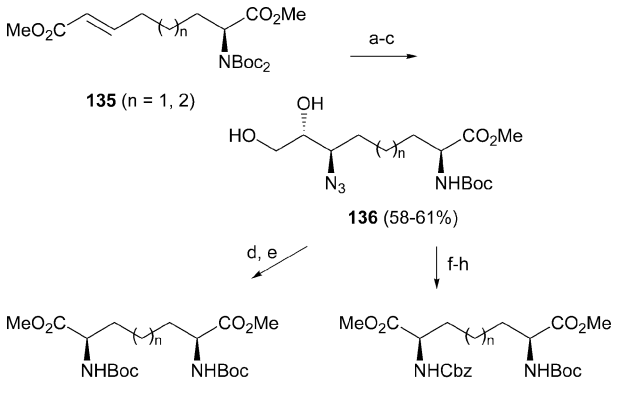
Diaminopimelic acid (DAP) and tetrahydrodipipecolinic acid are part of a class of biologically interesting compounds that have been the subject of independent studies by the groups of Vederas and Cox. Starting from protected allylglycine **129**, the Vederas group developed a synthetic route towards the latter compound (Scheme 26).[37]



Scheme 26 *Reagents and conditions*: (a) MeO_2CCHO, $SnCl_4$, CH_2Cl_2; (b) H_2, Rh/C, EtOAc; (c) TsNHCbz, DEAD, PPh_3, THF; (d) LiOH, MeCN, H_2O; (e) (i) LiOH, MeOH, H_2O, (ii) Li in NH_3(l).

The ene-type reaction of **129** with methyl glyoxylate afforded the ene-adduct **130** in 79% yield as a 1 : 1 mixture of diastereoisomers. Hydrogenation (86%), followed by Mitsunobu reaction with Cbz-protected tosylamide gave the DAP derivative **132** in 75% yield. Cyclisation was achieved by the action of LiOH in aqueous acetonitrile. This base led to α-deprotonation, followed by eliminiation of toluenesulfinic acid to give the imine. Cyclisation of the second NHCbz group onto the imine and subsequent enamide formation through the elimination of $CbzNH_2$ during acidic work up gave **133** in 76% yield. Subjection of this compound to LiOH in aqueous methanol, followed by reaction with lithium in liquid ammonia furnished the tetrahydrodipicolinic acid **134** in 66% yield, which is in equilibrium with the enamine and its open form. Cox *et al.* used this protocol for the synthesis of a water-soluble epoxide analogue of compound **131** for *in vitro* activity studies.[38]

Hernández and Martín aimed at a synthetic approach to DAP and 2,7-diaminosuberic acid (DAS) with control over the second stereocentre.[39] Their synthesis proceeded *via* the olefinic amino acids **135**, derived from (*S*)-aspartic ($n = 1$) and (*S*)-glutamic acid ($n = 2$, Scheme 27). The ester functionality

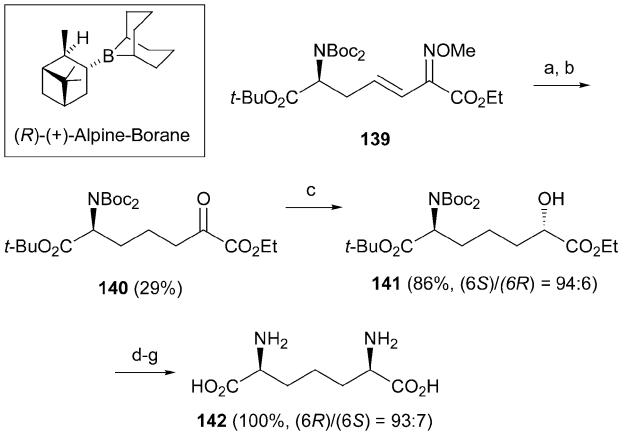


Scheme 27 *Reagents and conditions*: (a) DIBAL-H, −78 °C; (b) Ti(O*i*-Pr)$_4$, (*R*,*R*)-(+)-diethyl tartrate (DET), *tert*-butyl hydroperoxide (TBHP), CH_2Cl_2, −20 °C; (c) NaN_3, NH_4Cl, MeOH–H_2O, reflux; (d) (i) H_2, $Pd(OH)_2$, Boc_2O, MeOH, rt, (ii) $NaIO_4$, Na_2CO_3, $KMnO_4$, dioxane–H_2O, rt; (e) CH_2N_2, Et_2O, rt; (f) CH_2=C(OMe)Me, PPTS (cat.), CH_2Cl_2, rt; (g) (i) H_2, Pd/C, EtOAc, rt, (ii) $(Cbz)_2O$, CH_2Cl_2, rt, (iii) MeOH, *p*-toluensulfonic acid (PTSA) (cat.), rt, (iv) $NaIO_4$, Na_2CO_3, $KMnO_4$, dioxane–H_2O, rt; (h) CH_2N_2, Et_2O, 0 °C.

was carefully reduced with DIBAL-H to afford the allylic alcohols in 85–87% yield.

Subsequent Katsuki–Sharpless asymmetric epoxidation of the allylic alcohols followed by regioselective epoxide opening with NaN_3 afforded the azides **136** in 58–61% yield over these two steps. For the symmetrical bis-Boc-protected DAP/DAS compounds a sequence involving (i) hydrogenation of the azide, (ii) Boc protection and (iii) esterification afforded the compounds (*R*,*S*)-**137** in 71–76% yield over these steps. To achieve Cbz-protection, the vicinal diol had to be protected as the acetonide. Hydrogenation, Cbz-protection of the resulting nitrogen, and acetonide cleavage provided the corresponding diol. Further oxidative cleavage and esterification led to the desired chemically differentiated compounds **138** in 49–51% overall yield. Access to the other diastereoisomer was gained by formation of the optical antipode of the epoxide (step b).

Researchers of Hoffmann–La Roche published a diastereoselective route to *meso*-DAP *via* the substituted allylglycine **139** derived from aspartic acid (Scheme 28).[40] Hydrogenation of **139** in aqueous acetic acid, followed by oxidation led to the α-keto ester **140** in 29% yield.



Scheme 28 *Reagents and conditions*: (a) H_2, 10% Pd/C, H_2O–HOAc; (b) $CrO_3{\cdot}Py_2$, CH_2Cl_2; (c) (*R*)-(+)-Alpine-Borane, CH_2Cl_2; (d) MsCl, pyridine, DMAP, CH_2Cl_2; (e) NaN_3, DMF; (f) Pd/C, H_2; (g) 2.5 M aqueous HCl, Δ.

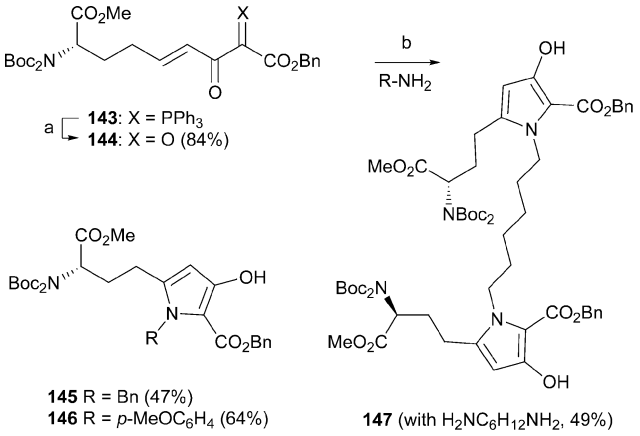
The key step consisted of the stereoselective reduction of **140** with (*R*)-(+)-Alpine-Borane to afford the desired (*S*)-hydroxy ester **141** in 86% yield. A sequence of four quantitative steps eventually led to *meso*-DAP (**142**) in good diastereomeric excess.

Some pyrrole-based products were targeted by Wasserman *et al.* following a route that also involved substituted allylglycine intermediates, either derived from aspartic or glutamic acids.[41]

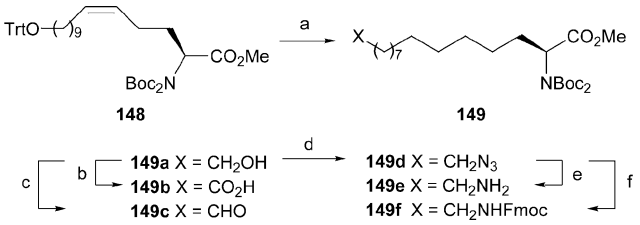
Oxidation of triphenylphosphonium ylide **143** with magnesium monoperphthalate (MMPP) led to diketoester **144** in 84% yield (Scheme 29). The *N*-heterocycles could be obtained by treatment of **144** with a primary amine leading to the pyrroles **145** and **146** in 47 and 64% yield, respectively. Reaction with 1,6-diaminohexane gave rise to the corresponding alkyl-bridged bipyrrole **147** in 49% yield.

Glutamic acid aldehyde served Markidis and Kokotos as a starting material for the preparation of homoallylglycine derivative **148** which in turn was used in the peparation of ω-functionalised α-amino acids (Scheme 30).[42] Double bond reduction of key intermediate **148** provided the enantiopure alcohol **149a** in 89% yield. Functional group transformations furnished a variety of ω-functionalised α-amino acids (**149b**–**f**).

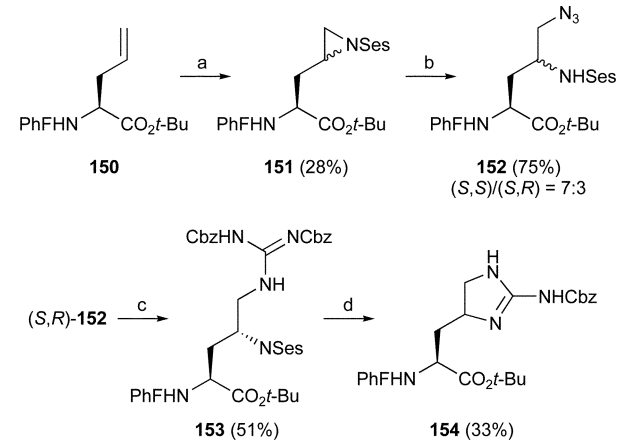
Dauban, Dodd and co-workers[43] reported the synthesis of the rigid arginine derivative enduracididine which is a component of the peptide antibiotic enduracidin.[44] A copper-catalysed aziridination of allylglycine was the pivotal step in their synthesis of enduracididine. The reaction of 9-phenylfluorenyl-protected allylglycine **150** with $Cu(MeCN)_4PF_6$, $SesNH_2$ [Ses = 2-(trimethylsilyl)ethanesulfonyl], and iodosylbenzene, provided aziridine **151** in 28% with a de of 40% (Scheme 31). After ring opening with sodium azide and separation of the diastereomers, the azide function was reduced under Staudinger conditions. A guanidyl functionality was introduced by means of (*S*)-methyl *N*,*N*′-bis(benzyloxycarbonyl)isothiourea. Finally, CsF treatment of **153** provided the protected enduracididine **154**.



Scheme 29 *Reagents and conditions*: (a) MMPP; (b) $BnNH_2$, *p*-anisidine or 1,6-diaminohexane.



Scheme 30 *Reagents and conditions*: (a) 10% Pd/C, H_2 (89%); (b) NaOCl, AcNH–TEMPO, Aliquat, KBr, $NaHCO_3$, CH_2Cl_2, H_2O (78%); (c) NaOCl, AcNH–TEMPO, NaBr, $NaHCO_3$, EtOAc, toluene, H_2O (76%); (d) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaN_3, DMF (73%); (e) H_2, 10% Pd/C, MeOH (65%); (f) H_2, Pd/C, FmocOSu (Su = succinimidyl), CH_2Cl_2.

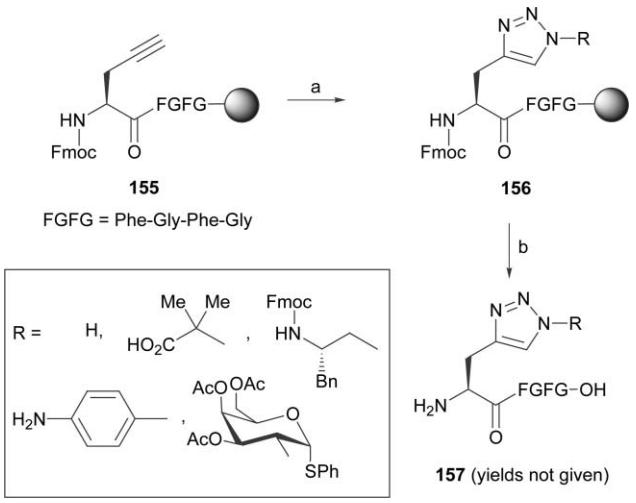


Scheme 31 *Reagents and conditions*: (a) $SesNH_2$, $Cu(MeCN)_4PF_6$ (25 mol%), iodosylbenzene, MeCN, rt, 18 h; (b) NaN_3, $BF_3{\cdot}Et_2O$, DMF, 65 °C, 80 h; (c) (i) PPh_3, THF, H_2O, reflux, 20 h, (ii) MeSC(=NCbz)NHCbz, $HgCl_2$, DMF, Et_3N, rt, 84 h; (d) CsF, DMF, 90 °C, 24 h.

The Huisgen 1,3-dipolar cycloaddition reaction between azides and terminal acetylenes has gained a lot of interest due to the facility with which the stable triazole linkage is established between the reactants and due to the remarkable tolerance of functionalities.

The group of Meldal was one of the first to report the copper(I)-catalysed version of this cycloaddition[4b] that yielded

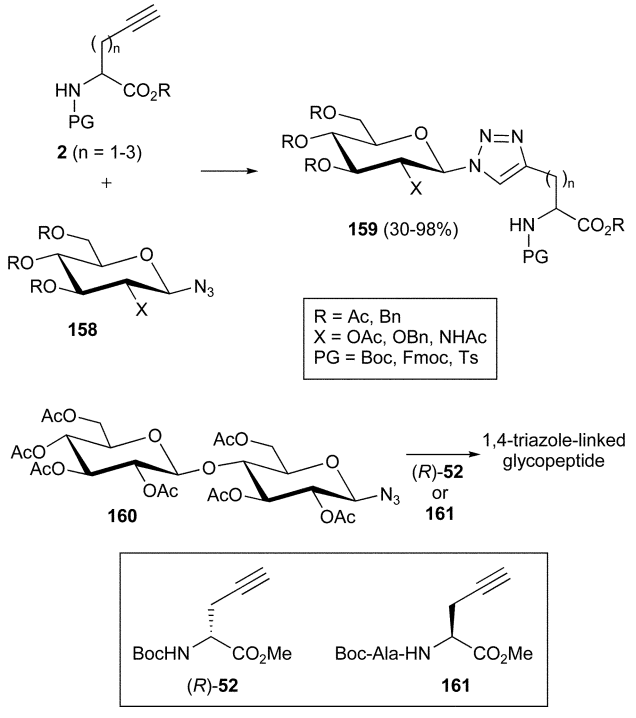
the 1,4-substituted products exclusively.[45] They employed the immobilized propargylglycine derivative **155** (connected to a $PEGA_{800}$ resin) as a substrate in the Huisgen reaction with (substituted) azides (Scheme 32).



Scheme 32 *Reagents and conditions*: (a) RN_3, diisopropylethylamine (DIPEA), CuI; (b) (i) 20% piperidine in DMF, (ii) 0.1 M aqueous NaOH.

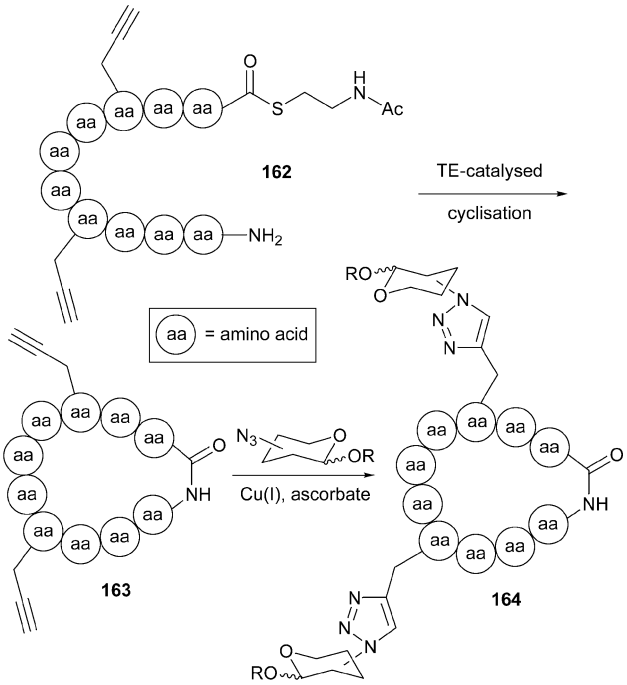
The regiospecific copper(I)-catalysed cycloaddition led to the formation of the 1,4-substituted triazoles **156**, which could be conveniently cleaved from the resin to afford the peptidotriazoles **157** in >95% conversion and purity.

More recently, the group of Rutjes applied a similar 'click strategy' in the synthesis of triazole-linked glycosidic amino acids and peptides.[46] The Cu(I)-catalysed formation of glycopeptides **159** from azidoglycosides with the general structure **158** and the acetylenic amino acids **2** proceeded smoothly with yields varying from 30 to 98% (Scheme 33). The enantiomeric purity of the starting amino acids was conserved during the reactions, and no C-1 epimerisation of the sugars was reported. The same reaction conditions were successfully applied to couple oligopeptides and disaccharides.



Scheme 33 *Reagents and conditions*: $Cu(OAc)_2$ (cat.), sodium ascorbate, H_2O–*t*-BuOH (1 : 1), rt, 16 h.

A library of triazole-linked glycopeptides was accessed by Lin and Walsh.[47] They started from the antibiotic cyclic decapeptide tyrocidine (Tyc) and sought to introduce sugar moieties in order to improve the therapeutic value of Tyc. In their approach, they made use of a chemoenzymatic pathway using the thioesterase (TE) domain from tyrocidine synthetase which enacts the cyclisation of Tyc's ten-membered precursor[48] (Scheme 34). Various Tyc derivatives with acetylenic handles were obtained by substituting up to three amino acids of the precursor by propargylglycine at different positions (for example, **162**) and subjecting them to TE-mediated cyclisation. The acetylenic Tyc derivatives were allowed to react in 'click reactions' with a range of azido sugars to give an array of Tyc-based glycopeptides that were tested for their therapeutic value.



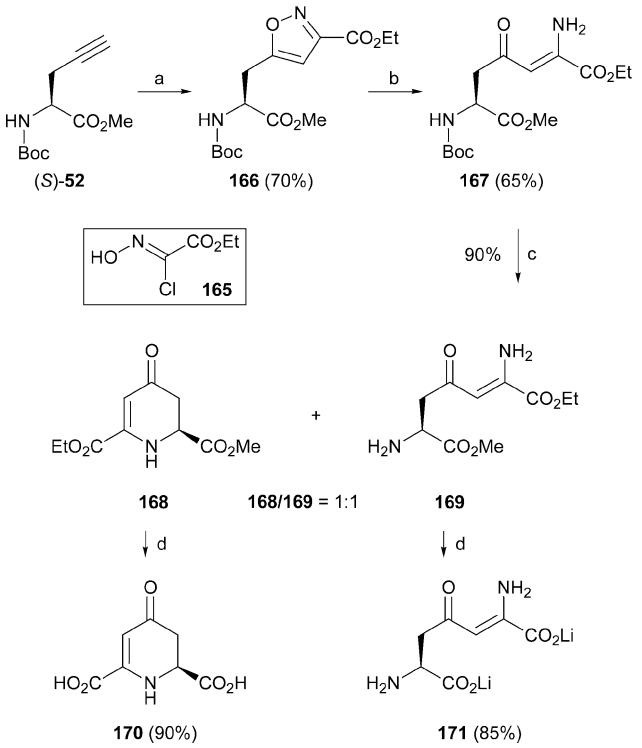
Scheme 34 Exemplified preparation of a Tyc-derived glycoprotein.

The group of Vederas used a 1,3-dipolar cycloaddition on protected propargylglycine (*S*)-**52** as the key step in the synthesis of the vinylogous amides **170** and **171** (Scheme 35).[49]

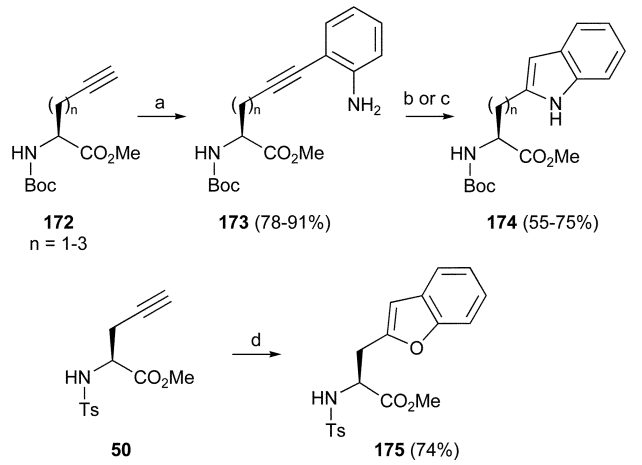
Cycloaddition reaction of (*S*)-**52** with ethyl chloroximidoacetate (**165**) under basic conditions afforded isoxazole **166** as a single regioisomer. Ring opening by the action of molybdenum hexacarbonyl and water afforded the vinylogous amide **167**, which was subsequently exposed to TFA to give a 1 : 1 mixture of cyclic and open-chain products (**168** and **169**) in 90% yield. Hydrolysis of both compounds using LiOH gave the targeted vinylogous amides **170** and **171** (only stable as dilithium salt) in good yields, both of which were then evaluated as inhibitors of enzymes involved in bacterial lysine biosynthesis.

Amino acids bearing a 2-substituted indole or benzofuran moiety were prepared by van Esseveldt *et al.* utilising Ag- or Pd-catalysed cyclisation reactions on acetylenic precursors (**172**).[50] The 2-aniline-substituted amino acids **173** were accessed *via* Sonogashira-type couplings (Scheme 36). Subsequent Ag(I)-($n = 1$) or Pd(II)-catalysed reaction ($n = 2,3$) provided enantiopure isotryptophan and its homologues **174** in moderate to good yields.

When applying the same strategy for the synthesis of benzo[*b*]furan-containing amino acid, it was found that subjecting the Ts-protected propargylglycine methyl ester **50** to 2-iodophenol under modified Sonogashira conditions (Et_2NH as base and solvent) afforded the desired benzofuran derivative **175** in a single step while preserving the optical purity of the starting material.



Scheme 35 *Reagents and conditions*: (a) **165**, Et_2O, then Na_2CO_3, H_2O, rt, 3 h; (b) $Mo(CO)_6$, H_2O, MeCN, 80 °C; (c) TFA, CH_2Cl_2, rt, 1 h; (d) LiOH, MeCN–H_2O (1 : 1), rt, 17 h.

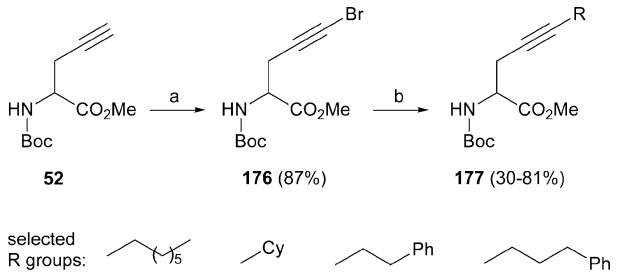


Scheme 36 *Reagents and conditions*: (a) 2-iodoaniline, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, Et_2O, rt, 2 h; (b) $n =$ 1: AgOTf, MeCN, reflux, 20 h; (c) $n =$ 2,3: $PdCl_2(MeCN)_2$, MeCN, reflux; (d) 2-iodophenol, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, reflux, 4 h.

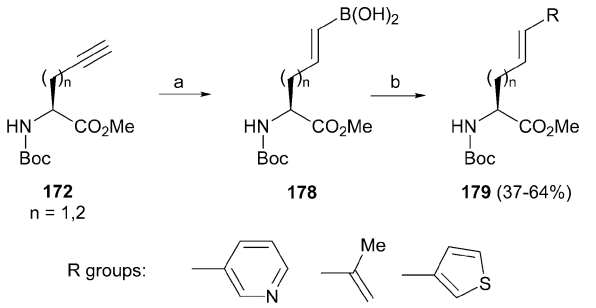
In contrast to the abundance of examples where the terminal acetylene is functionalised *via* coupling to an sp^2 carbon atom, functionalisation with alkyl groups is much less straightforward. One approach was pursued by IJsselstijn *et al.*, who applied a strategy previously published by Yeh and Knochel,[51] to introduce a variety of R groups at the terminal acetylene carbon relying on organozinc coupling reactions.[52] The organozinc chemistry requires an iodo- or bromo-acetylene as the coupling partner; therefore, propargylglycine derivative **52** was first brominated using *N*-bromosuccinimide and a catalytic amount of $AgNO_3$ to provide **176** in 87% yield (Scheme 37).

Brominated propargylglycine was then reacted with an *in situ*-generated organozinc/copper species to give the amino acids **177** with different alkyl side chains in reasonable to good yields.

Another way of modifying the acetylenic side chain was developed by the group of Danion,[53] shown in Scheme 38. They reported that the enantiopure propargyl- and homopropargyl-



Scheme 37 *Reagents and conditions*: (a) NBS, $AgNO_3$, acetone; (b) Riecke Zn, CuCN, LiCl, RI, DMF, rt.

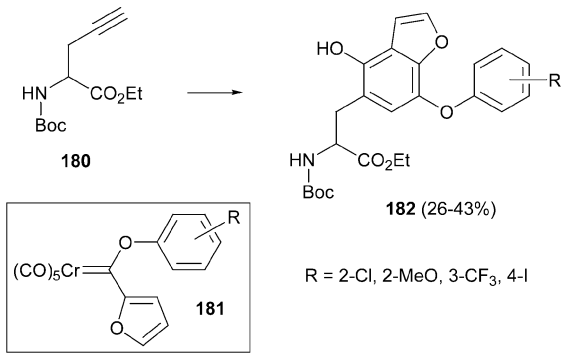


Scheme 38 *Reagents and conditions*: (a) (i) Ipc_2BH, THF, rt, (ii) MeCHO, rt, (iii) H_2O, rt; (b) RBr, $Pd(PPh_3)_4$, CsF, DME, 80 °C.

glycine derivatives **172** could be transformed into the corresponding (*E*)-vinylboronic acids (**178**). The methodology involved a hydroboration with diisopinocampheylborane (Ipc_2BH), followed by oxidation of the resulting boranes using acetaldehyde and, finally, hydrolysis leading to geometrically pure **178**.

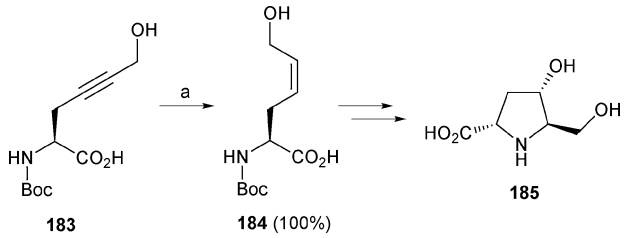
The amino acids **178** could be deprotected in an almost quantitative manner to give the corresponding free amino acids. These compounds are potential mimics of (*S*)-arginine and were evaluated as active site probes of the enzymes arginase and nitric oxide synthase. In addition, the boronic acids **178** readily underwent Suzuki-type couplings with aromatic or vinylic bromides to give the stereodefined unsaturated amino acids **179** in reasonable yields.[54]

The group of Pulley synthesised several phenylalanine analogues starting from propargylglycine derivative **180**. They used a benzannulation strategy that formally involved a [3 + 2 + 1] cycloaddition between aryloxy-substituted Fischer chromium carbenes of type **181** and the acetylenic side chain of the amino acid. These cycloadditions led to the formation of diaryl ether-containing phenylalanines **182** in moderate yields (Scheme 39).[55]



Scheme 39 *Reagents and conditions*: compound **181**, THF, 55 °C.

Holt *et al.* devised a concise and scalable route to the enantiopure *cis*-allylglycine derivative **184** and its optical antipode, starting from 2-butyne-1,4-diol (Scheme 40).[56] The synthesis proceeded *via* the propargylglycine derivative **183** which could be conveniently transformed into target **184** *via* a stereoselective

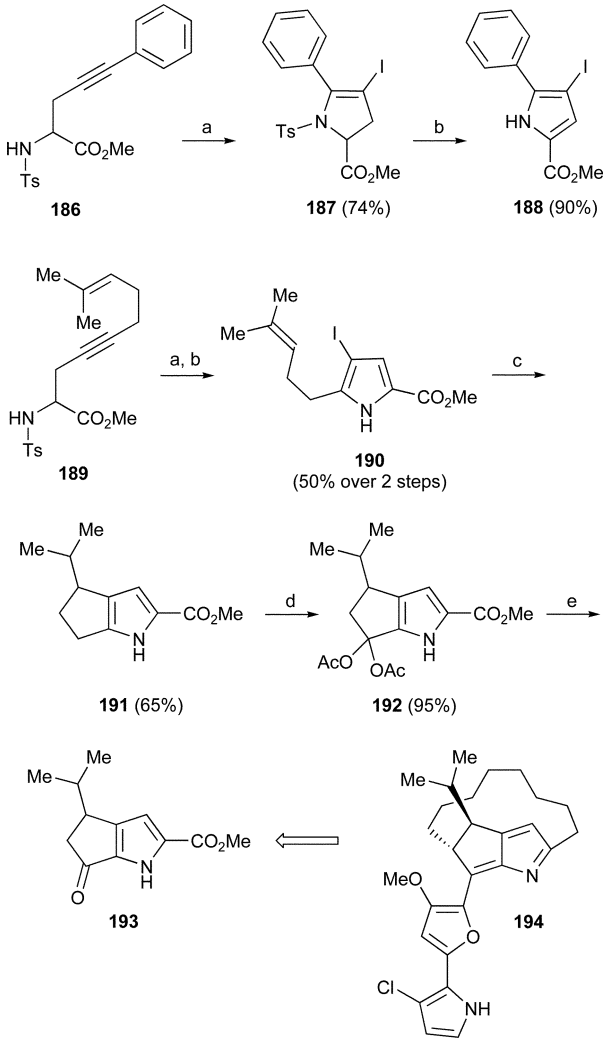


Scheme 40 *Reagents and conditions*: (a) Lindlar catalyst, H_2 (1 bar), MeOH, 20 °C.

reduction using Lindlar's catalyst. Compound **184** proved to be a key intermediate in the synthesis of (−)-bulgecinine (**185**).

3. Direct cyclisations

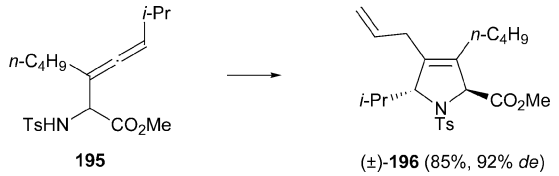
Knight *et al.* found that propargylglycine derivatives such as **186** smoothly undergo an iodine-mediated 5-*endo*-*dig* cyclisation to give the corresponding iodinated proline derivative **187**.[57] Subsequent treatment of **187** with DBU (2 equiv.) in DMF at room temperature resulted in the elimination of *p*-toluenesulfinic acid to provide the iodopyrrole **188** in 90% yield (Scheme 41).



Scheme 41 *Reagents and conditions*: (a) I_2, K_2CO_3, MeCN, rt; (b) DBU, DMF, rt; (c) Bu_3SnH, AIBN, benzene, 80 °C; (d) $Pb(OAc)_4$, $CHCl_3$, 60 °C; (e) 1 M HCl, rt.

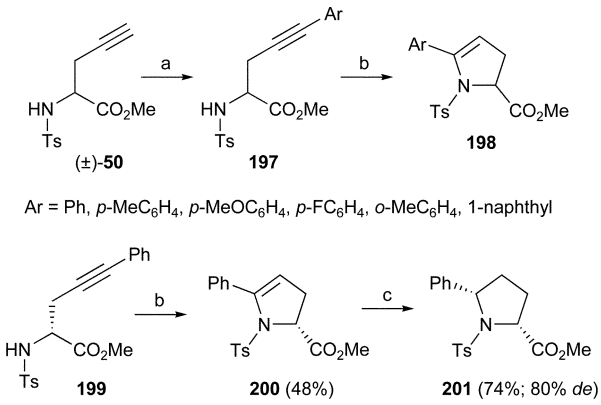
This procedure was applied by the same group in a synthetic approach towards the core of the natural product roseophilin (**194**).[58] In this route, the appropriately substituted propargylglycine derivative **189** first underwent the previously mentioned iodocyclisation, followed by elimination to give iodopyrrole **190**. This compound was reacted with tributyltin hydride and AIBN to bring about a radical cyclisation affording the annulated pyrrole **191** in 65% yield. Oxidation using lead(IV) acetate gave acetal **192**, which was hydrolysed to ketone **193**, representing part of the bicyclic core of roseophilin.

The group of Ma reported the synthesis of allyl-substituted 2,5-dihydro-1*H*-pyrroles commencing with α-amino allenes.[59] A Pd-catalysed cyclisation–coupling reaction provided the *N*-heterocycles in one step, simply by reacting the allene with an allylic halide in the presence of the catalyst. For example, the allenic amino acid **195** was treated with allyl bromide and $PdCl_2$ to afford the functionalised dihydropyrrole **196** in 85% yield as a 96 : 4 mixture of diastereomers with the *trans* isomer as the main product (Scheme 42).



Scheme 42 *Reagents and conditions*: allyl bromide, $PdCl_2$ (cat.), DMA, rt, 44 h.

Van Esseveldt presented a route to 5-substituted proline derivatives starting from the aryl-substituted acetylenic amino acids **197** (Scheme 43).[60] These precursors were readily available *via* a Sonogashira reaction between protected propargylglycine and the appropriate aryl iodides. Cyclisation was induced by treatment of the precursors with $PdCl_2(MeCN)_2$ in refluxing MeCN affording the pyrrolines **198** in moderate yields.

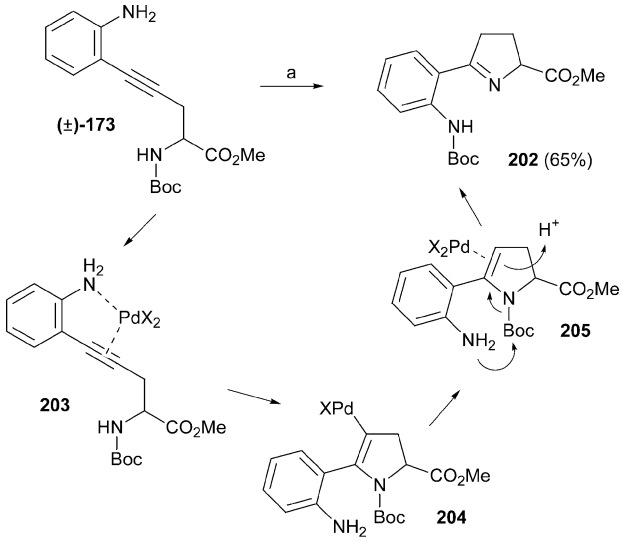


Scheme 43 *Reagents and conditions*: (a) ArI, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, Et_2O, rt; (b) $PdCl_2(MeCN)_2$, MeCN, reflux; (c) Et_3SiH, TFA, TFAA, CH_2Cl_2, 0 °C to rt, 1.5 h.

The reaction was found to be sensitive towards electronic effects since propargylglycines substituted with electron-poor aromatic substituents such as 4-nitrophenyl, 2-pyridinyl or 3-pyridinyl refused to react. Optically pure compounds underwent cyclisation without detectable racemisation. As an example, the (*R*)-propargylglycine derivative **199** gave rise to the enantiopure substituted pyrroline **200**. Subsequent reduction by means of TFA and Et_3SiH *via* the intermediate *N*-sulfonyliminium ion yielded the corresponding proline derivative **201** with 80% de in favour of the *syn* isomer.

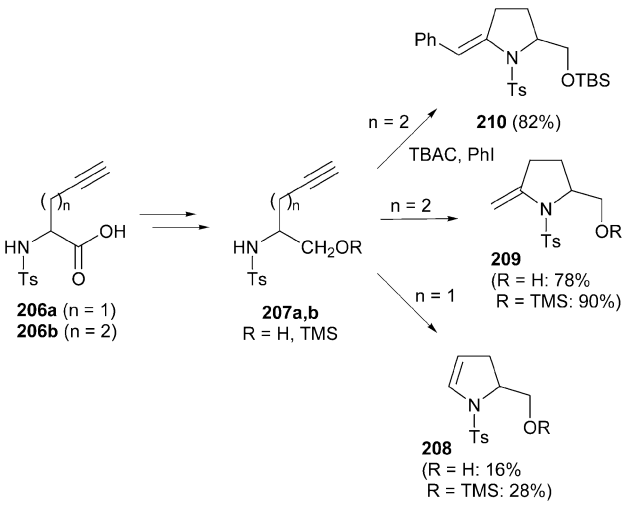
Interestingly, subjection of the Boc-protected, 2-aniline-substituted propargylglycine derivative (±)-**173** to aminopalladation conditions effected a cycloisomerization.[50] This proceeds presumably *via* the cyclic vinylpalladium species **204**, which may then undergo a migration of the Boc-group (Scheme 44).

Wolf *et al.* utilised *N*-protected amino alcohols derived from propargylglycine or homopropargylglycine to synthesise hydroxymethyl-substituted pyrrolidine derivatives.[61] The optionally protected pentynols **207a** (n = 1) underwent



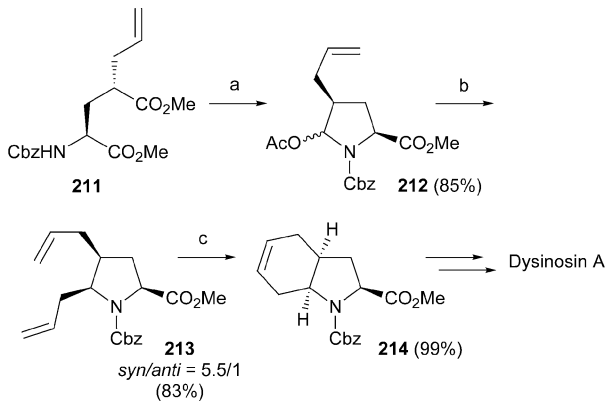
Scheme 44 *Reagents and conditions*: (a) $PdCl_2(MeCN)_2$, MeCN, reflux, 3 h.

Pd(0)-catalysed cyclisation reactions to arrive at the cyclic enamides **208** in low yields (Scheme 45). Under similar conditions, the hexynols **207b** ($n = 2$) gave access to the heterocycles **209** carrying an exocyclic double bond in much more satisfying yields. The TMS-protected amino alcohols generally were higher yielding than their unprotected pendants. Subjection of the *O*-protected hexynol **207b** to cyclisation conditions in the presence of tetrabutylammonium chloride (TBAC) and phenyliodide caused a tandem cyclisation coupling reaction to occur and afforded the benzylidene pyrrolidine **210** in 82% yield. With unprotected starting material the yields of this particular reaction were lower than 5% (not shown).



Scheme 45 Cyclisation. *Reagents and conditions*: Pd(0)-catalyst [$Pd(PPh_3)_4$ or $Pd(dba)_3$], K_2CO_3, THF or DMF.

In the endeavor of the total synthesis of the marine serine protease inhibitor dysinosin A, the Hanessian group employed the (*S*)-glutamic acid-derived olefinic amino acid **211** for the construction of one of the necessary fragments.[62] Acidic deprotection of **211** followed by heating resulted in the formation of the corresponding (*S*)-pyroglutamate (Scheme 46). Cbz protection and subsequent partial reduction of the lactam and acetylation afforded the proline derivative **212** thereby setting the stage for the introduction of a second allyl rest at C-5 in *syn* fashion. A careful selection of reaction conditions allowed for the formation of diene **213** with a 5.5 : 1 *syn*/*anti* selectivity *via* *N*-acyliminium ion chemistry using allyltributylstannane and cataytic $BF_3{\cdot}Et_2O$ in toluene. Treatment of this diene with Grubbs catalyst

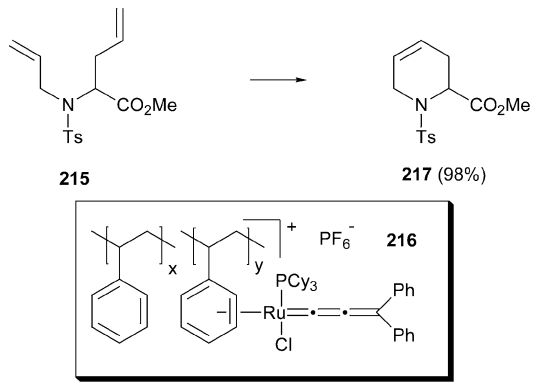


Scheme 46 *Reagents and conditions*: (a) (i) TFA, CH_2Cl_2, then neutralisation, (ii) Δ, toluene, (iii) LiHMDS, CbzCl, THF, −78 °C, (iv) $LiHBEt_3$, THF, −78 °C, (v) Ac_2O, DMAP, CH_2Cl_2; (b) $BF_3{\cdot}Et_2O$, $CH_2{=}CHCH_2SnBu_3$, toluene, −78 °C; catalyst **65**, CH_2Cl_2.

65 gave the targeted hexahydroindole **214** in outstanding yield (99%).

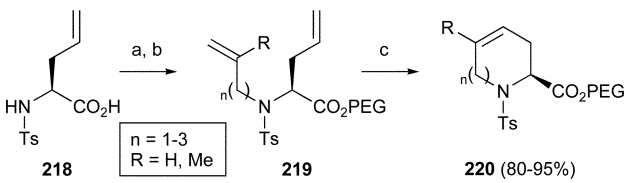
4. Cyclisations *via* a functional group on the nitrogen atom

Olefinic amino acids have been the subject of ring-closing metathesis (RCM) ever since this reaction became more widely used, and nowadays they often serve as test substrates for novel metathesis catalysts and conditions. A number of reports have recently emerged on this topic.[63] For example, Akiyama and Kobayashi cyclised *N*-allyl allylglycine **215** with a novel, polymer-supported allenylidene–ruthenium catalyst (**216**), to afford **217** in 98% yield (Scheme 47).[64]



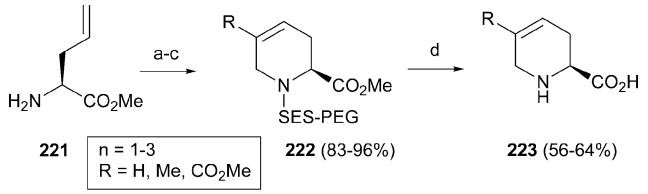
Scheme 47 *Reagents and conditions*: catalyst **216** (20 mol%), hexane–toluene (10 : 1), reflux, 12 h.

In the group of Lamaty, RCM of polymer-bound allylglycines was studied. For example, allylglycine **218** was attached to a poly(ethylene glycol) (PEG) linker *via* an ester functionality using the Mitsunobu reaction (Scheme 48).[65] *N*-Alkylation of the sulfonamide with various alkenyl bromides afforded the precursors of type **219**.



Scheme 48 *Reagents and conditions*: (a) PEG–OH, PPh_3, DEAD, THF (83%); (b) $CH_2{=}CHR(CH_2)_nBr$ or propargyl bromide, K_2CO_3, DMF; (c) catalyst **65** (20–40 mol%), CH_2Cl_2, rt.

The best RCM conditions were found to be 40 mol% of catalyst **65** at room temperature, leading to the cyclic amino acids of type **220**. Applying this protocol, various ring-sizes ($n = 1$–3 for R = H) could be synthesised. Furthermore, a substituted double bond (R = Me) was also successfully cyclised in the case of a six-membered ring. Enyne metathesis with a propargyl residue on the nitrogen afforded the product with R = vinyl. A similar type of metathesis was performed by the same group on systems with the PEG resin attached to the nitrogen *via* a silylethylsulfonyl (SES) linker (Scheme 49).[66] The required polymer-bound precursors were obtained by sulfonylation of allylglycine **221** with PEG–SES–Cl, followed by alkylation with olefinic bromides.

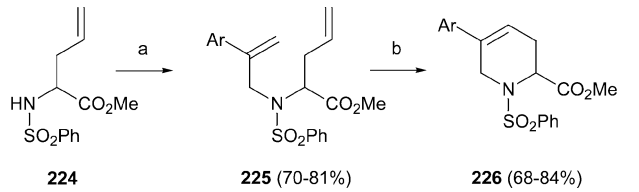


Scheme 49 *Reagents and conditions*: (a) PEG–SES–Cl, THF, rt; (b) CH_2=CHR$(CH_2)_n$Br, or propargyl bromide, K_2CO_3, DMF, 48 h; (c) catalyst **65** (20–40 mol%), CH_2Cl_2, rt; **66** (20 mol%, rt, 14 h) was used for R = CO_2Me; (d) 6 M aqueous HCl, 100 °C, 24 h.

RCM employing catalyst **65** gave very good yields (83–96%) of the cyclic amino acids **222**. Also in this case, enyne metathesis with *N*-propargyl-substituted species gave product **222** (R = vinyl) in good yield. For the precursor with R = CO_2Me, the 2nd generation Grubbs catalyst **66** was necessary to obtain the product in a satisfactory yield. Standard SES-cleavage conditions (fluoride, DMF) were not suitable for the cleaving products off the resin. Therefore, complete hydrolysis was necessary to afford the free cyclic amino acids **223**.

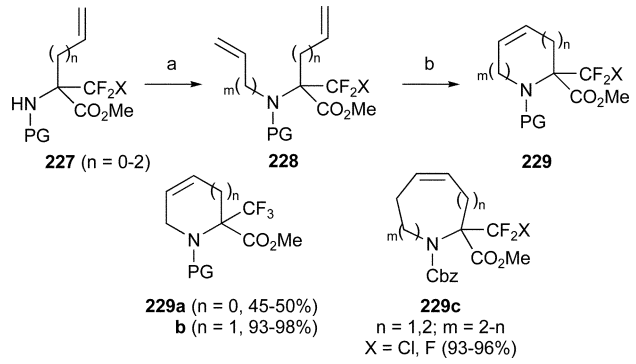
The same group also attached the Hoveyda–Grubbs ruthenium catalyst to a PEG-solid support. Metathesis of SES-protected allylglycines was studied with this recyclable polymer-bound catalyst.[67]

Closely related to these metathesis reactions is the work of Dondas *et al.* in which the required diene precursors were obtained *via* a palladium-catalysed coupling of allylglycine with an aryl iodide and an allene.[68] Benzenesulfonyl-protected allylglycine **224** was reacted with allene (1 bar) in the presence of $Pd(OAc)_2$ and an aryl iodide (Scheme 50). Through this protocol, the metathesis precursors **225** (Ar = phenyl, 2-thiophenyl, 4-nitro-3-methylphenyl, 1-naphthyl, 3-tolyl and 1-methyl-1*H*-indol-5-yl) were obtained in yields ranging from 70 to 81%. RCM using the 2nd generation Grubbs catalyst **66** in toluene at 80 °C afforded the unsaturated cyclic 5-aryl-substituted pipecolic acid derivatives **226**.



Scheme 50 *Reagents and conditions*: (a) ArI, allene (1 bar), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3, toluene, 80 °C, 24 h; (b) catalyst **66**, toluene 80 °C, 3 h.

α,α-Disubstituted allylglycines and homologues, with a trihalomethyl moiety as the additional substituent at the α-position, were subjected to RCM by Osipov *et al*.[69] Such fluorinated amino acids are known to function as selective inhibitors of pyridoxal phosphate dependent enzymes. Five- to seven-membered ring formations were studied through metathesis with allyl or butenyl substituents on the nitrogen (Scheme 51). The

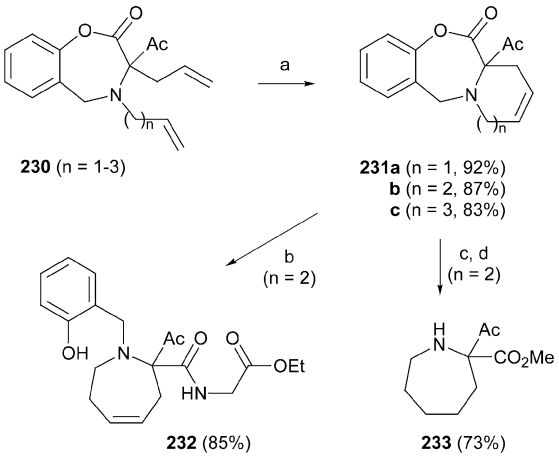


Scheme 51 *Reagents and conditions*: (a) NaH, DMF, −5 °C to rt, allyl bromide ($m = 1$) or butenyl bromide ($m = 2$); (b) catalyst **65** (10 mol%), CH_2Cl_2, rt, 3–5 h (60 h for **229a**).

RCM precursors (**228**) were obtained by alkylation of the amino acids **227** (PG = SO_2Ph, Boc, Cbz, X = F, Cl) which in turn were obtained from Grignard addition to the corresponding fluorinated 2-iminopropanoates.

RCM took place with the ruthenium catalyst **65** in dichloromethane at room temperature. Moderate yields (45–50%) were obtained for five-membered rings (**229a**), even at prolonged reaction times. In contrast, excellent yields (93–98%) were observed for the six- (**229b**) and seven-membered (**229c**) ring systems.

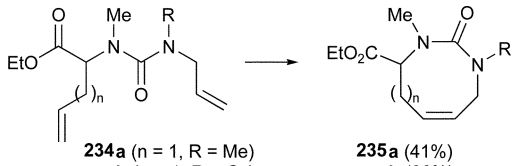
The metathesis of α,α-disubstituted allylglycine-containing substrates as a way to obtain cyclic α,α-disubstituted amino acids was also addressed by Clark and Middleton.[70] The diolefinic systems **230** served as RCM precursors and provided compound **231a** in 92% yield with catalyst **65** in dichloromethane, and **231b** and **231c** in 83–87% yield with catalyst **66** in toluene at elevated temperatures (Scheme 52).



Scheme 52 *Reagents and conditions*: (a) catalyst **65**, CH_2Cl_2, rt, 24 h (for **231a**), or catalyst **66**, toluene, 80 °C, 45 min (for **231b**,**c**); (b) $EtO_2CCH_2NH_2$·HCl, DMAP, Et_3N, DMF, 120 h; (c) NaOMe, MeOH; (d) HCO_2H, Pd/C, rt.

Peptide **232** (85%) was obtained by reaction of compound **231b** with glycine ethyl ester. The cyclic, free amino acid **233** was produced in 73% yield by cleavage of the benzoic lacton and subsequent hydrogenation of the double bond followed by hydrogenolysis of the nitrogen substituent.

Mesocyclic ureas **235a**–**d** (Scheme 53) were prepared by Hoffman and Madan *via* RCM of the linear olefinic precursors **234a**–**d**.[71] Both urea nitrogens needed to be fully substituted (*i.e.* tertiary) for the cyclisation to proceed. In the case of **234a**, methyl substituents were sufficient to make the ring closing possible (41%); however, replacing methyl on the external nitrogen by cyclohexyl resulted in a greatly improved yield of 86%. With

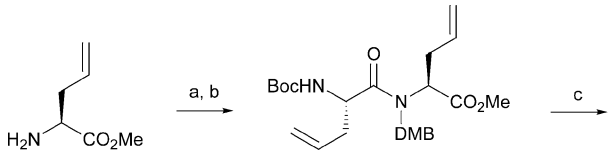


234a (n = 1, R = Me) **235a** (41%)
b (n = 1, R = Cy) **b** (86%)
c (n = 2, R = Me) **c** (0%, dimer)
d (n = 2, R = Cy) **d** (61%)

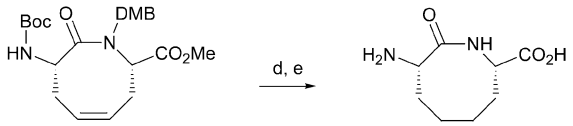
Scheme 53 *Reagents and conditions*: catalyst **65**, CH_2Cl_2, reflux or **65**, benzene, 55 °C.

the homologous precursors ($n = 2$) the *N*,*N*′-dimethylurea **234c** refused to ring-close, and dimerisation was observed instead. The cyclohexyl-substituted analogue **234d** on the other hand could be transformed to the nine-membered cyclic urea **235d** in 61% yield. These results suggest that, by virtue of the urea's planar rigidity, the bulkiness of the substituent on the external nitrogen induces a conformational preorder of the precursors, thereby facilitating the ring-closing reaction.

Creighton and Reitz[72] utilised ring-closing metathesis as a way to cyclise the bis-allylglycine amide **236** into an eight-membered pseudodipeptide (Scheme 54).



221 **236** (71%)

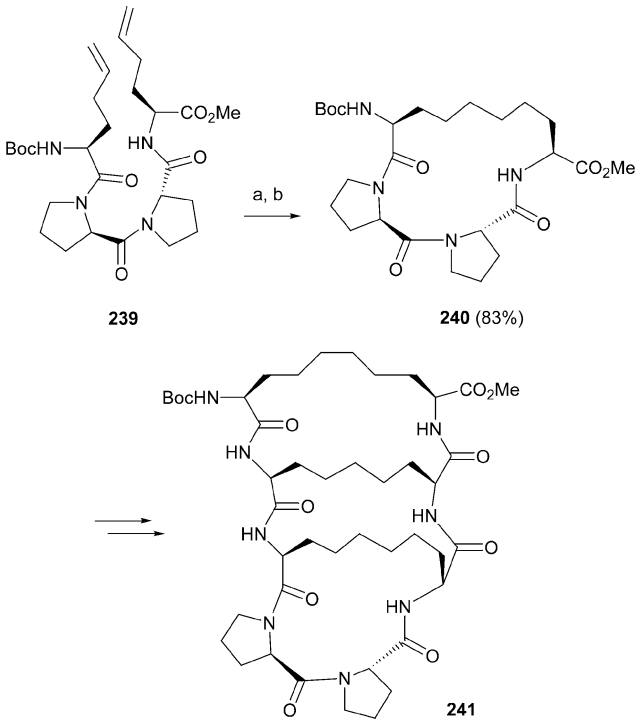


237 (80%) **238** (78%)

Scheme 54 *Reagents and conditions*: (a) 2,4-dimethoxybenzaldehyde, $NaBH(OAc)_3$; (b) Boc–allylglycine–OH, HATU, NEM (*N*-ethylmaleimide); (c) catalyst **65**, CH_2Cl_2, reflux, 60 h; (d) (i) LiOH, MeOH–H_2O, (ii) 10% TFA in CH_2Cl_2, 3 h, (iii) 1 M aqueous HCl, then lyophilise; (e) Pd/C, H_2.

Alkylation of allylglycine **221** *via* reductive amination with 2,4-dimethoxybenzaldehyde and coupling with Boc-protected allylglycine afforded the diolefin **236**. The dimethoxybenzyl (DMB) moiety on the nitrogen caused the amide to adopt both the *cis*- and the *trans*-amide conformation. While without the benzylic moiety no metathesis occurred, compound **236** could be ring-closed to the cyclic amide **237** in 80% yield using Grubbs catalyst **65** in refluxing dichloromethane. Saponification, deprotection and hydrogenation led to the free, eight-membered ring amino acid **238** in 78% yield over these steps. This type of compound may serve as a peptidomimetic for the corresponding cystine eight-membered ring. The topic of pseudopeptide mimetics has also been addressed by Hanessian and Angiolini, studying the synthesis of conformationally stable and constrained mimics of β-hairpin structures.[73] The homoallylglycine-derived peptide **239** underwent RCM by the action of catalyst **65** in dichloromethane at room temperature (Scheme 55).

The cyclic product was obtained as a 1 : 1 mixture of double bond isomers, which was hydrogenated to afford the peptide **240** in 83% over both steps. Repetitive deprotection, coupling, metathesis and hydrogenation afforded ultimately the saturated, bridged pseudo-octapeptide **241** as a mixture of four conformers, thus providing a synthetic route towards carbocyclic analogues of β-hairpin and β-sheet model systems.



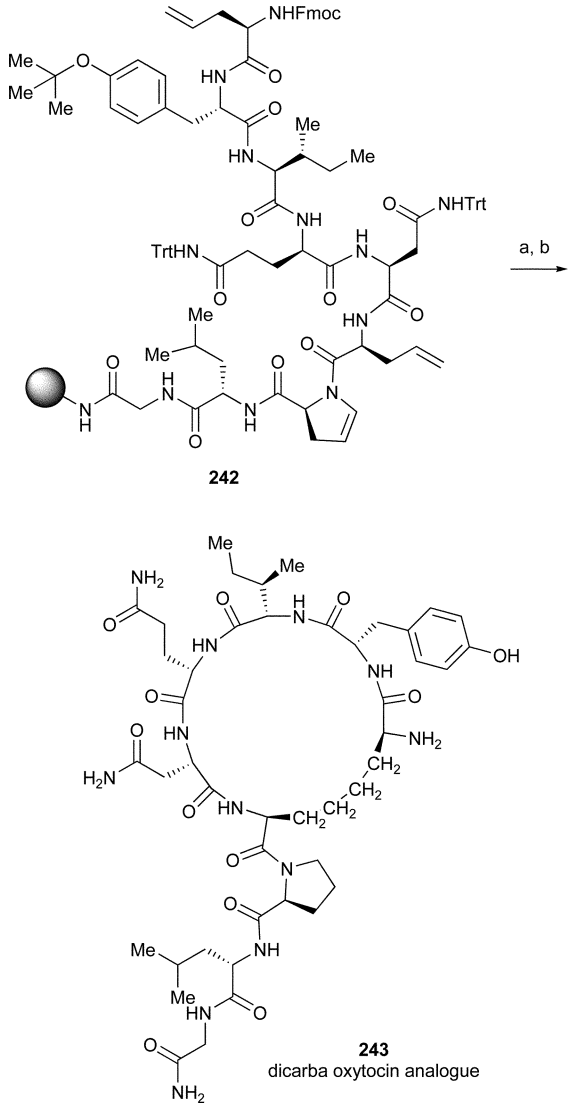
239 **240** (83%) **241**

Scheme 55 *Reagents and conditions*: (a) catalyst **65** (10 mol%), CH_2Cl_2, rt, 5 h; (b) Pd/C, H_2, MeOH, 16 h.

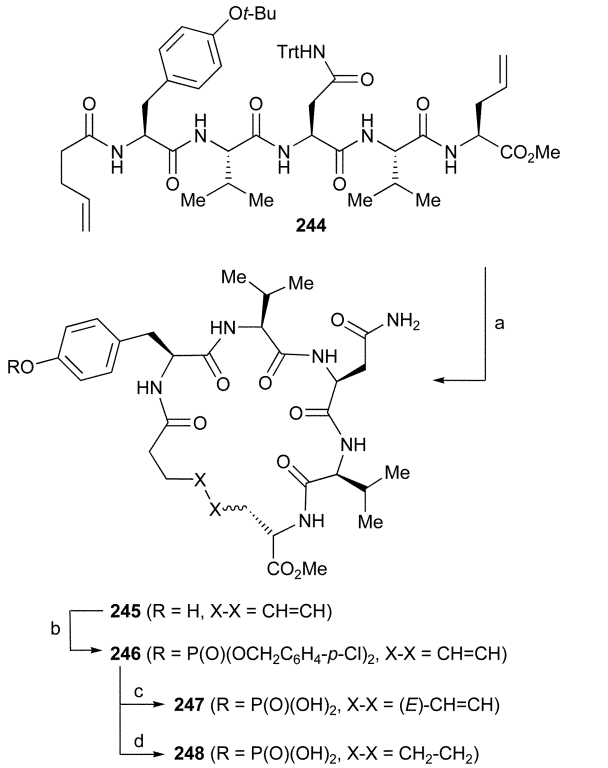
An RCM entry into biologically active dicarba analogues of the peptide hormone oxytocin was reported by the group of Vederas.[74] The strategy commenced with the solid phase synthesis of the diolefinic linear peptide backbone **242** (Scheme 56). Cyclisation of the resin-bound linear peptide using catalyst **65** afforded a mixture of cyclic olefinic products. DMSO was added to avoid ruthenium-containing contaminants, followed by Fmoc removal and acidic cleavage from the resin together with side chain deprotection. This led in *ca.* 45% yield to the cyclic product after reversed phase HPLC purification. Hydrogenation then afforded the desired target **243**, which was tested for biological activity and compared with oxytocin. The dicarba analogue (EC_{50} 38 ng mL^{-1}) showed a 14-fold less activity than oxytocin (EC_{50} 2.7 ng mL^{-1}) itself.

The group of Liskamp set out to prepare cyclic phosphopeptides resembling the conformation of –pTyr–Val–Asn–Val– bound to the SH2 domain of Grb2, a signal transduction protein involved in cell proliferation.[75] A solid phase synthesis provided the open chain precursor **244** that could be cyclised without the need for further conformational preordering measures using the 2nd generation Grubbs catalyst **66** in refluxing 1,1,2-trichloroethane (Scheme 57). Upon deprotection, the unsaturated macrocycle **245** was obtained in 21% yield displaying a 1 : 3 (*E*)/(*Z*) ratio. Phosphitylation of the Tyr residue followed by *m*-chloroperoxybenzoic acid (*m*-CPBA) oxidation accomplished the synthesis of the phosphate ester **246** in 66% yield. Hydrolysis by means of TFA–EDT–TIS–water (EDT = 1,2-ethanedithiol; TIS = triisopropylsilane) gave access to the unsaturated phosphopeptide **247** of which only the *trans* isomer could be isolated (32%). The saturated analogue was made available by hydrogenolysis of **246** yielding 45% of the peptide **248**. Cyclic peptides **247** and **248** showed affinities for the Grb2 SH2 that were comparable to those of the open chain parent compounds.

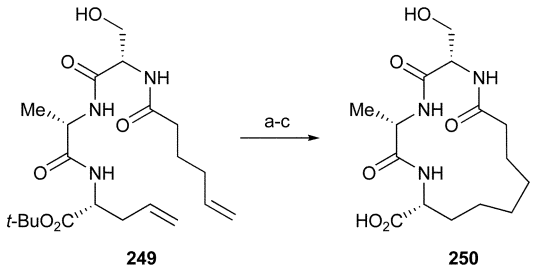
Inhibitors of Mur D, an enzyme involved in bacterial cell wall biosynthesis, were targeted by Horton *et al*.[76] From computer-based molecular design studies, they derived a series of peptidic macrocycles that were prepared and tested for their inhibition



Scheme 56 *Reagents and conditions*: (a) (i) catalyst **65** (10 mol%), CH_2Cl_2, Δ, 24 h, (ii) DMSO (50 equiv.), rt, 12 h, (iii) 20% piperidine–DMF, rt, 5 min, (iv) TFA–CH_2Cl_2–anisole (90 : 5 : 5), 1 h, (v) RP-HPLC (*ca.* 45%); (b) H_2, Pd/C, EtOH, rt, 36 h.



Scheme 57 *Reagents and conditions*: (a) (i) catalyst **66**, 2,6-dichlorotoluene, 1,1,2-TCE, (ii) TFA–EDT–TIS–water (90 : 2.5 : 2.5 : 5); (b) (i) bis(4-chlorobenzyl)-*N*,*N*-diisopropylphosphoramidite, 1*H*-tetrazole, MeCN–dioxane, (ii) *m*-CPBA, H_2O–MeCN; (c) TFA–EDT–TIS–water (90 : 2.5 : 2.5 : 5); (d) H_2, Pd/C, *t*-BuOH–H_2O.



Scheme 58 *Reagents and conditions*: (a) catalyst **65**; (b) hydrogenation; (c) saponification.

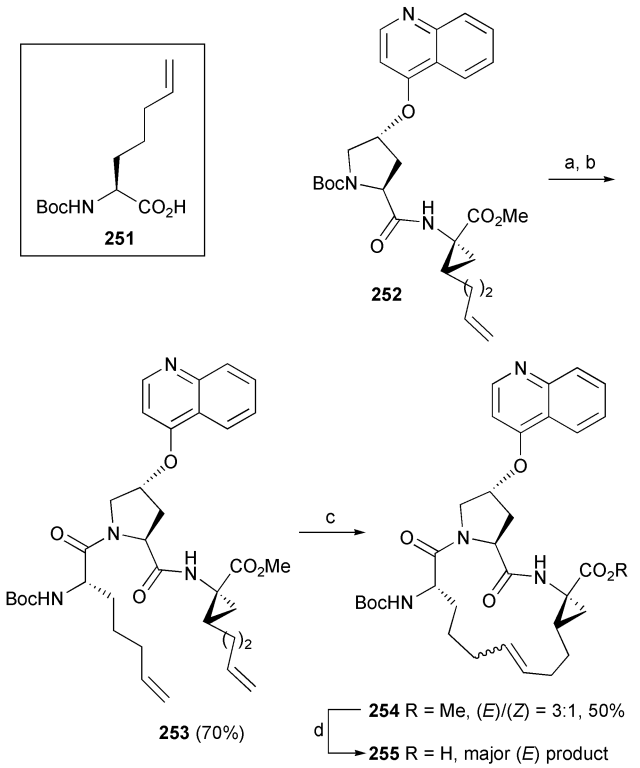
potential. Shown in Scheme 58 are the final synthetic steps of the most potent inhibitor, which displayed an IC_{50} of 0.7 ± 0.3 μM. Thus, subjection of the *N*-acylated diolefinic tripeptide **249** to the sequence of RCM using catalyst **65**, hydrogenation, and saponification gave access to the Mur D inhibitor **250**.

Researchers from Boehringer Ingelheim reported the synthesis of a series of 15-membered ring β-strand mimics that are active as competitive inhibitors of the hepatitis C virus NS3 serine protease.[77] The last steps of the preparation of one of the inhibitors are displayed in Scheme 59. The unusual tripeptide **253**, serving as an RCM precursor, was constructed from bis-homoallylglycine **251** and the olefinic dipeptide **252** in 70% yield. Ring closing using the 1st generation Grubbs catalyst **65** succeeded to give the cyclopeptide **254** as a 3 : 1 mixture of (*E*)/(*Z*) isomers, respectively, of which the (*E*)-form (**255**) could be isolated after saponification by reversed phase HPLC.

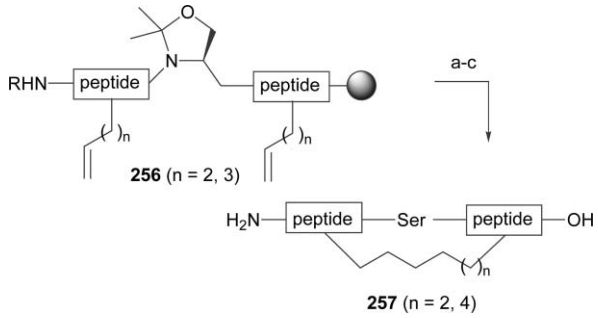
Schmiedeberg and Kessler employed RCM to further shorten and rigidify a previously identified decapeptide serving as a receptor binding domain mimic derived from the serine protease uPA.[78] It was found that successful ring closing of the resin-bound substrate required a peptide chain turning motif to preorder the diolefinic precursor. Since a bend-introducing proline residue was undesired in their target molecules, the authors relied on the incorporation of Mutter's pseudoproline into the RCM precursor (**256**), effectively enabling the intended RCM reactions (Scheme 60). Reduction and deprotection were applied to arrive at the constrained macrocycles **257**.

A study towards a better theoretical understanding of cyclic peptide formation *via* RCM was performed by Toniolo and co-workers.[79] In this study, X-ray diffraction analysis and conformational energy computations of β-turn and 3_{10}-helical peptides based on olefinic α-amino acids were used. The reported findings established a better picture of the feasibility of ring-closing metathesis in turn/helical peptides. An application of this principle was published in which the tetrapeptide benzylamide **258** was cyclised using RCM of the two pre-organized (intramolecularly H-bonded, type-II β-turn motif) allylglycine fragments, catalysed by Nolan's catalyst **67** to afford the four-carbon cross-linked β-turn **259** in 70% yield after hydrogenation (Scheme 61).[80]

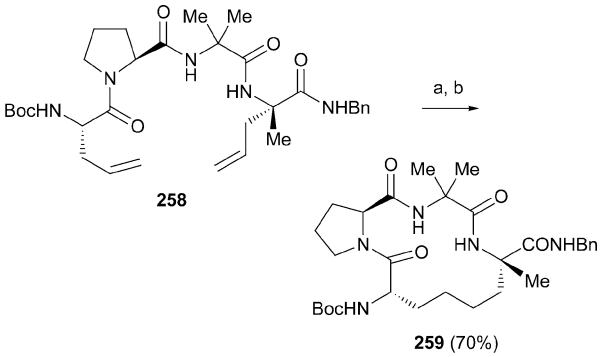
Allylglycine has also been used in a ring-opening, ring-closing metathesis sequence (ROM–RCM) by Voigtmann and Blechert.[81] The palladium-catalysed allylation of racemic allylglycine **47** with the enantiopure allylic acetate **260** gave the precursor **261** in 71% yield (Scheme 62). Subjection of this olefin to Grubbs catalyst **65** led completely to the rearranged pipecolic acid derivative **262**. Upon treatment of this 1 : 1 diastereoisomeric mixture with catalytic base, the thermodynamically most stable compound **263** was obtained. Protective



Scheme 59 *Reagents and conditions*: (a) 4 M HCl–dioxane; (b) **251**, HATU, *N*-methylmorpholine (NMM), CH_2Cl_2, rt; (c) catalyst **65**, CH_2Cl_2, reflux; (d) LiOH, H_2O, MeOH, rt.

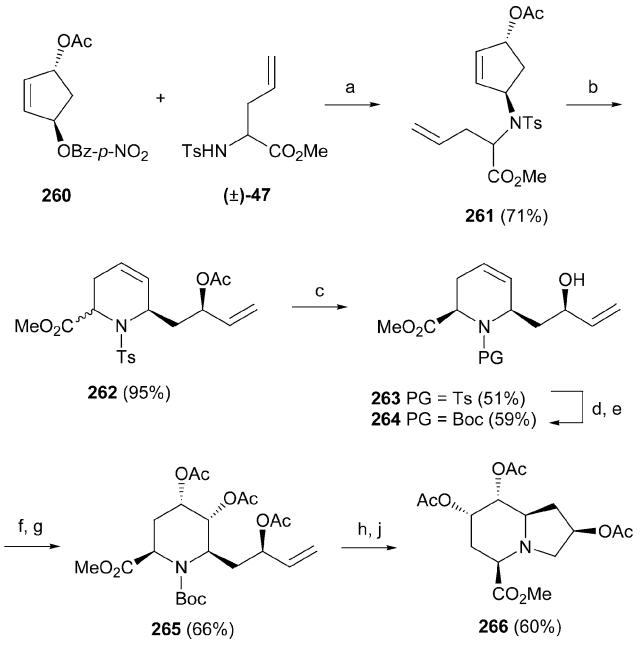


Scheme 60 *Reagents and conditions*: (a) catalyst **65**; (b) reduction; (c) deprotection.



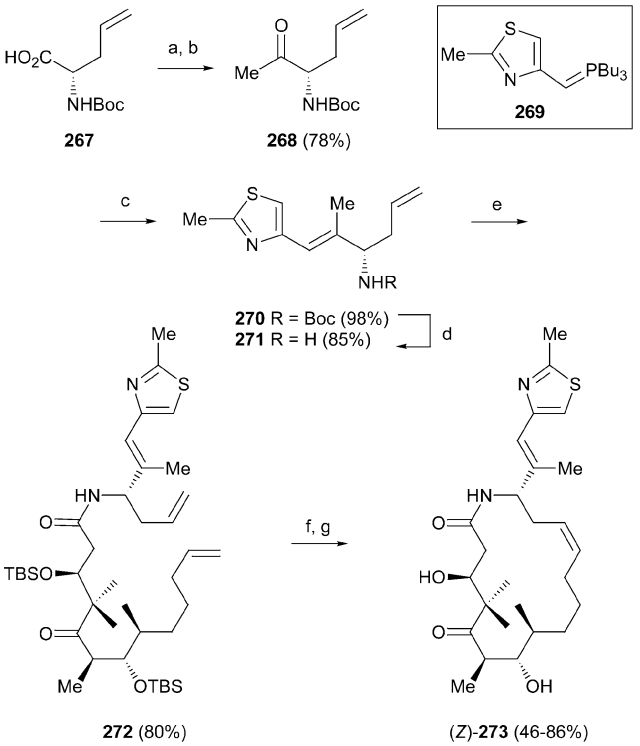
Scheme 61 *Reagents and conditions*: (a) catalyst **67** (5 mol%), toluene, 80 °C, 16 h; (b) H_2, PtO_2, EtOAc, rt, 20 h.

group exchange, followed by site-selective OsO_4 oxidation of the tetrahydropyridine double bond and subsequent acetylation gave the triacetate **265**. Double bond cleavage using the OsO_4/$NaIO_4$ couple produced the aldehyde, which cyclised to the imine after standard Boc deprotection. Imine reduction with $NaCNBH_3$ at pH 7 afforded the target indolizidine **266** in 60% yield over the two final steps.



Scheme 62 *Reagents and conditions*: (a) $Pd(OAc)_2$, PPh_3, NaH, DMF, rt to 40 °C; (b) catalyst **65** (5 mol%), CH_2Cl_2, rt; (c) NaOMe, MeOH, rt; (d) Na, naphthalene, THF; (e) Boc_2O, *i*-Pr_3N, CH_2Cl_2; (f) OsO_4, NMO, acetone–H_2O, rt; (g) Ac_2O, Et_3N, CH_2Cl_2; (h) OsO_4, $NaIO_4$, acetone–H_2O, rt; (j) (i) TFA, CH_2Cl_2, (ii) K_2CO_3, pH 7, $NaCNBH_3$, MeOH, rt.

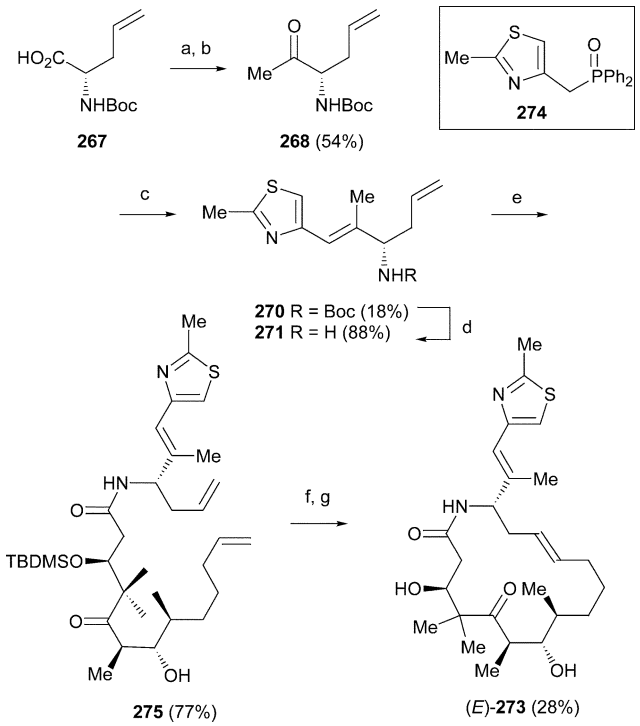
In recent synthetic approaches towards aza-epothilones, allylglycine was used as a key building block for the introduction of the thiazole moiety and for the metathesis-based ring formation. In the approach of Schinzer *et al.*, Boc-protected allylglycine **267** was subjected to Weinreb amide formation, followed by the addition of methyllithium to afford **268** in 78% yield (Scheme 63).[82]



Scheme 63 *Reagents and conditions*: (a) HCl·HNMe(OMe), 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDC), CH_2Cl_2; (b) MeLi (2 equiv., THF, −78 °C; (c) **269**, THF; (d) TFA; (e) RCO_2H (R = substituted olefinic chain), PyBOP, DIPEA, DMF; (f) (i) catalyst **65**, (*E*)/(*Z*) = 1 : 1, (ii) separation; (g) HF·pyr.

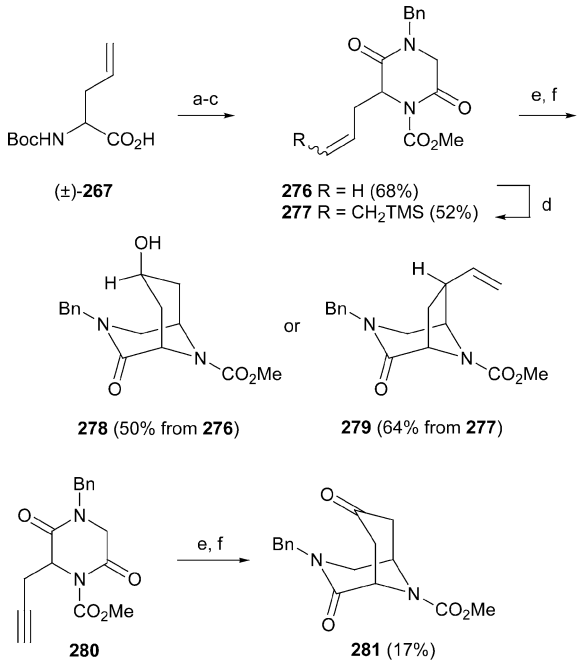
The thiazole moiety of **270** was introduced by reacting **268** with ylide **269**. Deprotection of the nitrogen afforded the free amine **271** in 85% yield, which was coupled to the second enantiopure olefinic fragment using PyBOP (*O*-benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate) in DMF affording the metathesis precursor **272** in 80% yield. RCM using catalyst **65** gave the cyclic olefin in 56% yield as a 1 : 1 mixture of (*E*)/(*Z*)-isomers, which could be separated by chromatography. Deprotection of the (*Z*)-isomer afforded the desired aza-epothilone (*Z*)-**273** in 82% yield.

The closely related approach by Borzilleri *et al.* surprisingly delivered the (*E*)-isomer in excess (5 : 1).[83] Following approximately the same route, the metathesis precursor **275** was synthesised, starting from allylglycine **267** (Scheme 64). After coupling amine **271** to a second olefinic fragment, the only difference with the previous approach was the free hydroxyl group present in compound **275** as opposed to a silyl ether in **272**. Deprotection led to (*E*)-**273**, a product that was actually undesired because of the known lower biological activity of the comparable (*E*)-olefin epothilones C and A.



Scheme 64 *Reagents and conditions*: (a) HCl·HNMe(OMe), EDC, HOBt, NMM, $CHCl_3$, 0–25 °C (71%); (b) MeMgBr, THF, 0 °C; (c) *n*-BuLi, THF, −78 °C to rt (18%, 30–40% recovered SM); (d) 4 M HCl, dioxane, 0 °C, 0.5 h; (e) RCO_2H (R = olefinic fragment), EDC, HOBt, DMF, 15 h; (f) catalyst **65** (0.7 mol%), benzene, 22 h, (*E*)/(*Z*) = 5 : 1 (41%); (g) TFA, CH_2Cl_2, 0 °C, 4 h.

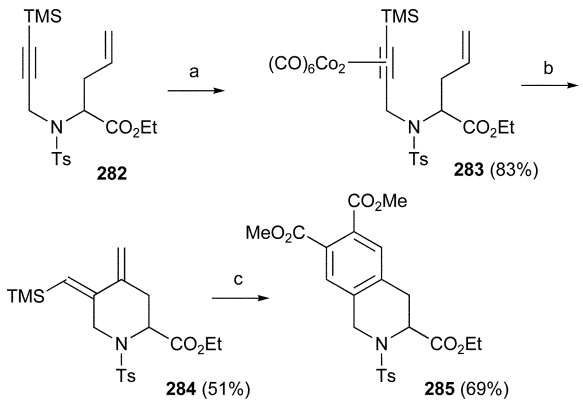
Besides the use of ring-closing metathesis, cross-metathesis with allylglycine derivatives has also found applications. The group of Hiemstra made use of unsaturated amino acids for the construction of 2,6-bridged piperazidine-3-ones *via* cyclisations of (substituted) diketopiperazine-derived *N*-acyliminium ions.[84] Coupling of Boc-allylglycine (±)-**267** to *N*-benzylglycine methyl ester, followed by Boc-deprotection and *in situ* cyclisation built up the diketopiperazine motif (Scheme 65). Methoxycarbonyl protection of the lactam gave **276** in 68% yield over three steps. Cross-metathesis with allyltrimethylsilane (ATMS) catalysed by ruthenium catalyst **66** afforded the allylsilane **277** in 52% yield. Both racemic precursors were subjected to chemoselective reduction with $NaBH_4$ in methanol, followed by formic acid-mediated cyclisation. This resulted in the bridged piperazinones **278** (50%, after formate aminolysis) and **279** (64%) as single diastereomers. Employing propargylglycine as the starting material in this



Scheme 65 *Reagents and conditions*: (a) $BnHNCH_2CO_2Me$, EDC, 1-hydroxy-7-azabenzotriazole (HOAt), CH_2Cl_2; (b) TFA–CH_2Cl_2 (1 :1); (c) MeO_2CCl, Et_3N, DMAP, CH_2Cl_2; (d) ATMS, catalyst **66** (10 mol%), toluene; (e) $NaBH_4$, MeOH; (f) HCO_2H, then NH_3–MeOH (only for **278**).

reaction sequence gave rise to the ketone-bridged piperazinone **281** *via* the acetylenic diketopiperazine **280**. The same product could be obtained by the oxidation of alcohol **278** (not shown).

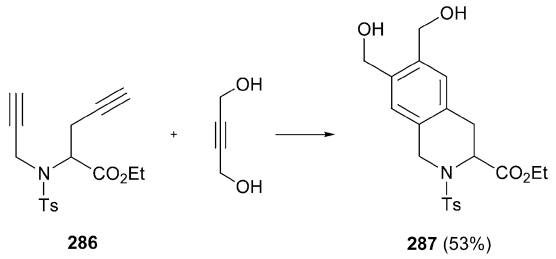
Besides ruthenium-based metathesis catalysts, other transition metals play an important role in ring-closing reactions of amino acid derivatives. Kotha and co-workers reported the transformation of allylglycine derivative **282** into the cobalt complex **283** in 83% yield (Scheme 66).[85a,b]



Scheme 66 *Reagents and conditions*: (a) $Co_2(CO)_8$, Et_2O, rt; (b) (i) toluene, reflux, (ii) NMO, $CHCl_3$; (c) (i) DMAD, toluene, hydroquinone (cat.), sealed tube, 150 °C, (ii) DDQ, toluene, reflux.

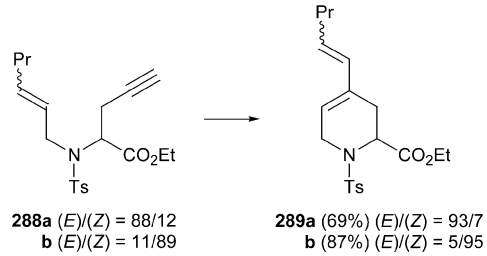
Heating this organometallic species in refluxing toluene and subsequent oxidative decomposition with 4-methylmorpholine *N*-oxide (NMO) yielded diene **284** in 51% yield. A small amount (11%) of the corresponding Pauson–Khand side-product was also formed. Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD) followed by DDQ oxidation afforded the targeted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivative **285** in 69% yield.

Other approaches towards Tic derivatives using [2 + 2 + 2] cycloaddition reactions as the key step were reported by the same group.[85b,c] A representative example is the cyclotrimerisation of diyne **286** with 2-butyn-1,4-diol using Wilkinson's catalyst, providing Tic derivative **287** in 53% yield (Scheme 67).



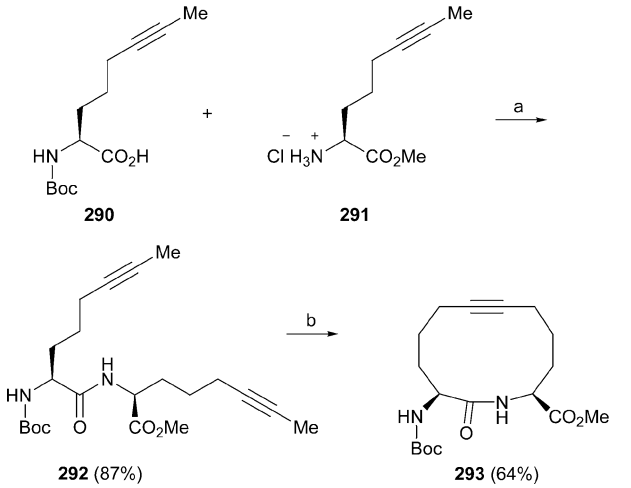
Scheme 67 *Reagents and conditions*: $RhCl(PPh_3)_3$, EtOH, reflux.

Chatani's group reported the transformation of enynes to vinylcycloalkenes mediated by $GaCl_3$.[86] This main group metal halide catalysed the skeletal rearrangement of the propargylglycine-derived enynes **288a**,**b** into the corresponding pipecolic acid derivatives **289a**,**b** (Scheme 68). The products were formed in 69 and 87% yield, respectively.



Scheme 68 *Reagents and conditions*: $GaCl_3$, toluene, 40–60 °C.

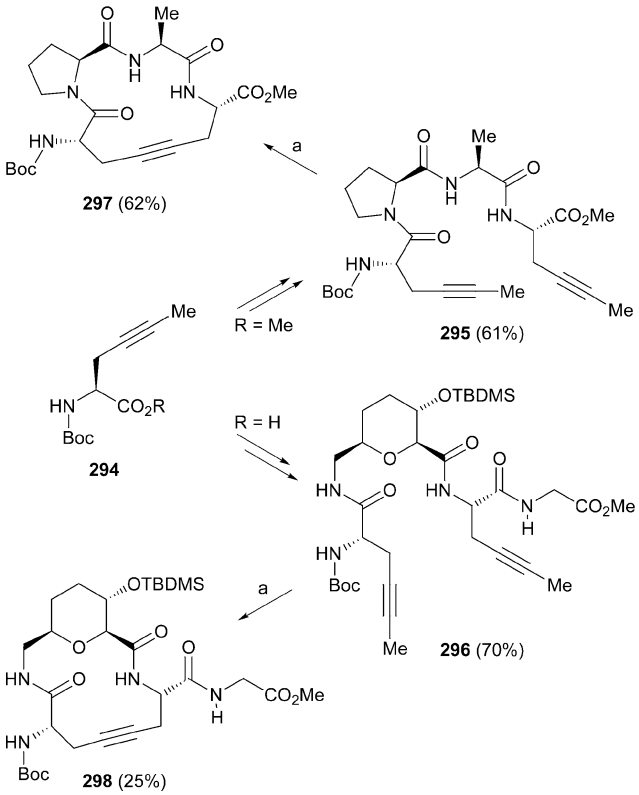
The group of Rutjes investigated the viability of ring-closing alkyne metathesis (RCAM) in the synthesis of cyclic dipeptides derived from acetylenic amino acids.[52] Dipeptide **292** was selected as a substrate to test the RCAM strategy, and it was obtained *via* coupling of the bis-homopropargylglycine derivatives **290** and **291** (Scheme 69). Subjection of precursor **292** to the tungsten catalyst **112** (*viz.* Scheme 22) afforded the corresponding 12-membered lactam **293** in 64% yield (based on 50% conversion), thereby demonstrating the potential of RCAM on these highly functionalised substrates.



Scheme 69 *Reagents and conditions*: (a) *i*-BuO_2CCl, Et_3N, CH_2Cl_2; (b) catalyst **112**, PhCl, 80 °C.

This methodology was further elaborated by the groups of Overkleeft and Rutjes in the synthesis of cyclic β-turn mimetics.[87] Among several examples, they prepared the acetylenic amino acid-containing oligopeptides **295** and **296** using standard solution phase peptide coupling procedures (Scheme 70).

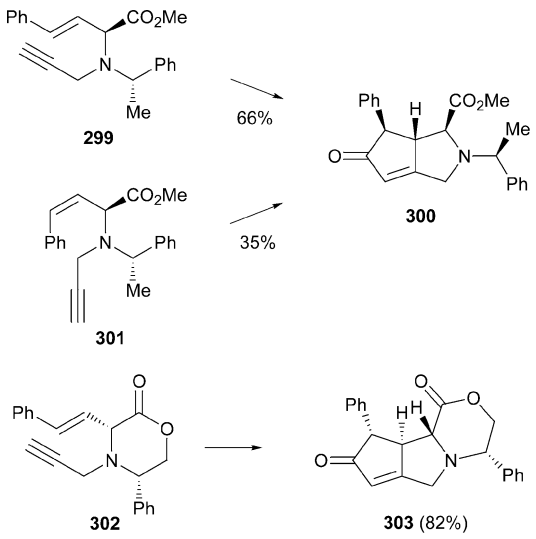
Both peptidic diynes were then subjected to the aforementioned RCAM conditions affording the cyclic tetrapeptides **297** and **298** in 62 and 25% yield, respectively. The structure of



Scheme 70 *Reagents and conditions*: (a) catalyst **112**, PhCl, 80 °C.

compound **298** was investigated by 2D NMR measurements and compared with its cystine-containing counterpart. This structural analysis indicated that the replacement of a disulfide bridge by an acetylene moiety gave rise to a more rigid cyclic peptide.

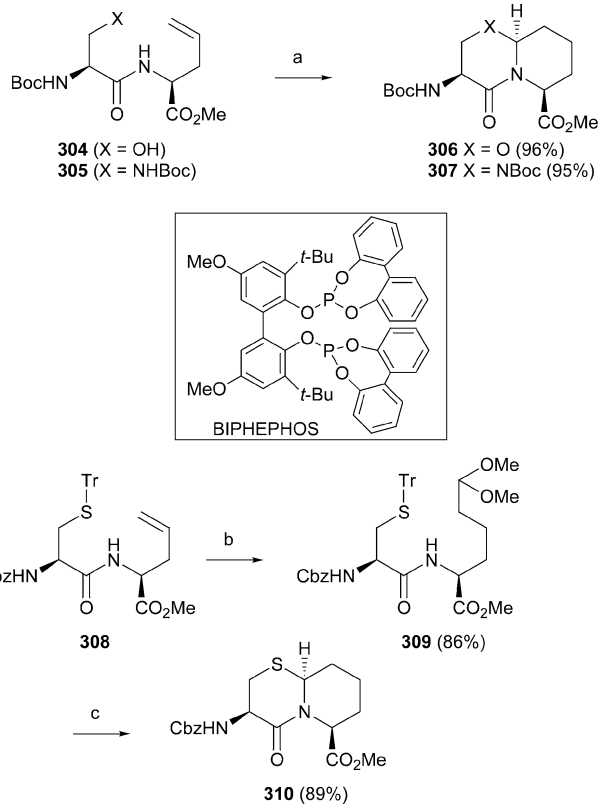
The Pauson–Khand reaction of vinylglycine derivatives was studied by Jiang and Xu.[88] Heating precursor **299** in benzene at 70 °C for 4 h in the presence of 10 mol% $Co_2(CO)_8$ and 60 mol% of Bu_3PS as co-catalyst under an atmosphere of carbon monoxide afforded the Pauson–Khand product **300** as a single diastereoisomer in 66% yield (Scheme 71).



Scheme 71 *Reagents and conditions*: $Co_2(CO)_8$ (10 mol%), Bu_3PS (60 mol%), benzene, 70 °C, CO (1 atm), 4 h.

Double bond isomer **301** gave the same product but in lower yield. The best yield was obtained by applying identical conditions to a cyclic precursor (**302**) affording diastereoisomerically pure **303** in 82% yield.

An efficient hydroformylation of olefinic α-amino acid-containing dipeptides was published by the Ojima group using a rhodium-catalysed process.[89] Heating dipeptide **304** in toluene under a syngas atmosphere (H_2/CO) in the presence of $Rh(acac)(CO)_2$ (2 mol%) with BIPHEPHOS (4 mol%) as ligand afforded the aldehyde-hydrocarbonylation product, which cyclised spontaneously in toluene to afford **306** in 96% yield (Scheme 72).



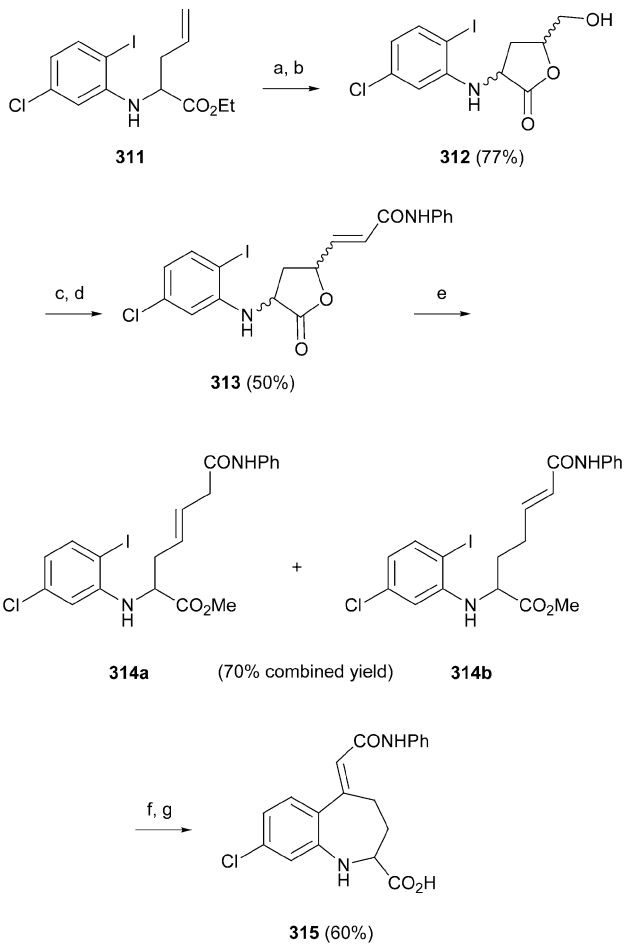
304 (X = OH)
305 (X = NHBoc)
306 X = O (96%)
307 X = NBoc (95%)
308
309 (86%)
310 (89%)

Scheme 72 *Reagents and conditions*: (a) 2 mol% $Rh(acac)(CO)_2$, 4 mol% BIPHEPHOS, H_2 (2 atm), CO (2 atm), PTSA, toluene, 65 °C, 20 h; (b) 2 mol% $Rh(acac)(CO)_2$, 4 mol% BIPHEPHOS, H_2 (2 atm), CO (2 atm), MeOH, 65 °C, 20 h; (c) TFA (cat.), CH_2Cl_2, rt, 30 min.

This process was accelerated by the addition of a catalytic amount of PTSA. In THF or in the presence of base, the cyclisation was suppressed, allowing the isolation of the intermediate aldehyde. Applying the same conditions to precursor **305** resulted in the formation of bicyclic compound **307** in 95% yield. Sulfide **308** could be transformed stepwise into a similar bicyclic system by performing the hydroformylation in methanol to give the acetal **309** in 86% yield. The acetal was cyclised with a catalytic amount of TFA to afford the bicyclic dipeptide **310** in 89% yield. These products can serve as peptide β-turn mimetics.

Researchers of GlaxoSmithKline studied 2-carboxybenzazepine **315** which was recognised as a potential antagonist of the strychnine-insensitive glycine binding site associated with the NMDA receptor (Scheme 73).[90]

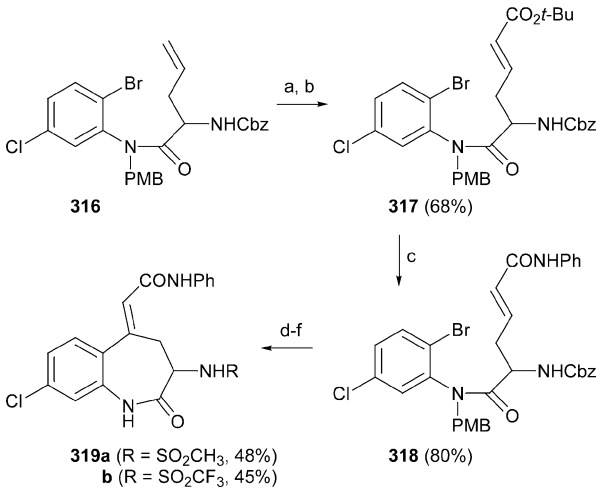
The route to **315** went *via* allylglycine derivative **311**, which was dihydroxylated[91] and cyclised to give **312** in 77% yield. Swern oxidation and a Wittig coupling of the aldehyde with the required phosphorus ylide afforded intermediate **313** in 50% yield over these two steps as an 8 : 2 mixture of *syn*- and *anti*-diastereoisomers and with a 84 : 16 (*E*)/(*Z*) ratio. Treatment with Bu_3SnH in the presence of $Pd(PPh_3)_4$ led to reductive ring opening of the γ-lactone, after which methylation provided the methyl esters **314a**,**b** in a combined yield of 70%. A Heck-type cyclisation with $Pd(PPh_3)_4$ in DMF, followed by saponification gave the desired benzazepine derivative **315** in 60% yield over these two steps.



311
312 (77%)
313 (50%)
314a (70% combined yield) **314b**
315 (60%)

Scheme 73 *Reagents and conditions*: (a) OsO_4, NMO, THF–H_2O, rt, 5 h; (b) (i) LiOH, EtOH–H_2O, rt, 2 h, (ii) 1 M HCl, THF, 24 h; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (d) $(Ph_3PCHCONHPh)^+Br^-$, DBU, MeCN, rt, 1 h; (e) (i) Bu_3SnH, $Pd(PPh_3)_4$, THF, rt, 4 h, (ii) $TMSCHN_2$, CH_2Cl_2–MeOH, rt, 30 min; (f) $Pd(PPh_3)_4$, TEA, DMF, 80 °C, 1 h; (g) LiOH, EtOH–H_2O, rt, 1 h.

More recently, researchers of the same company published a different approach to similar benzo[*b*]azepines bearing a sulfonamide moiety in the C-3 position (**319**, Scheme 74).[92] Allylglycine derivative **316** was converted to the aldehyde by ozonolysis followed by a Wittig-type reaction to arrive at the (*E*)-configured α,β-unsaturated *t*-butyl ester **317**. Sequential deprotection and amide formation with aniline gave the intermediate **318** in

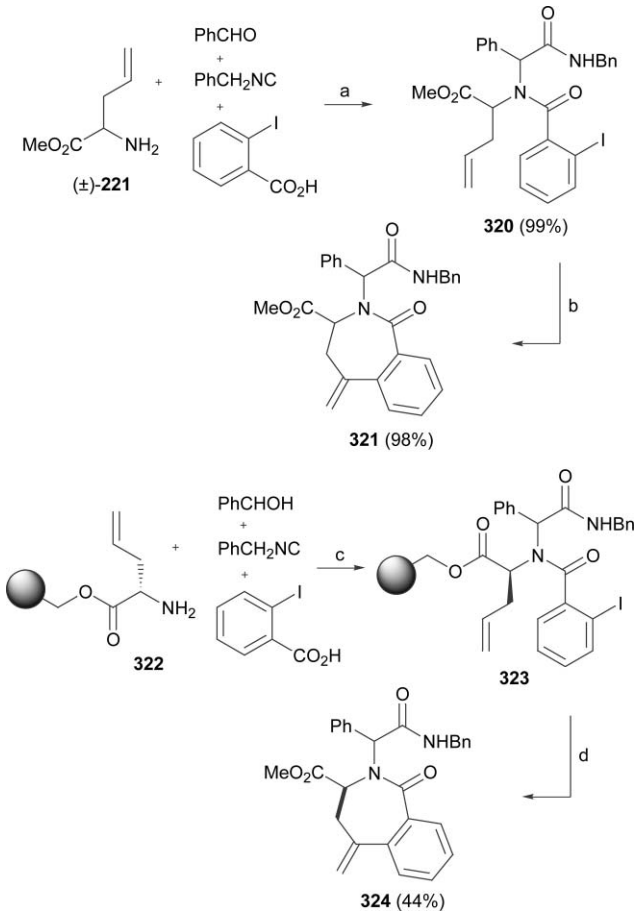


316
317 (68%)
319a (R = SO_2CH_3, 48%)
b (R = SO_2CF_3, 45%)
318 (80%)

Scheme 74 *Reagents and conditions*: (a) (i) ozone, −78 °C, (ii) PPh_3; (b) $Ph_3P{=}CHCO_2t$-Bu, toluene, reflux; (c) (i) HCO_2H, (ii) HOBt, DCC, aniline, DMF; (d) $Pd(PPh_3)_4$, DMF, Et_3N, 110 °C; (e) CF_3CO_2H, anisole, H_2SO_4; (f) Tf_2O, Et_3N, THF, −78 °C or MsCl, Et_3N, THF, 0 °C.

80% yield. In the next pivotal step, a Heck reaction was used to effect the assembly of the seven-membered ring, yielding 60% of the azepinone. After complete deprotection, the amine in the C-3 position was transformed to either the methylsulfonamide **319a** or the trifluoromethylsulfonamide **319b**.

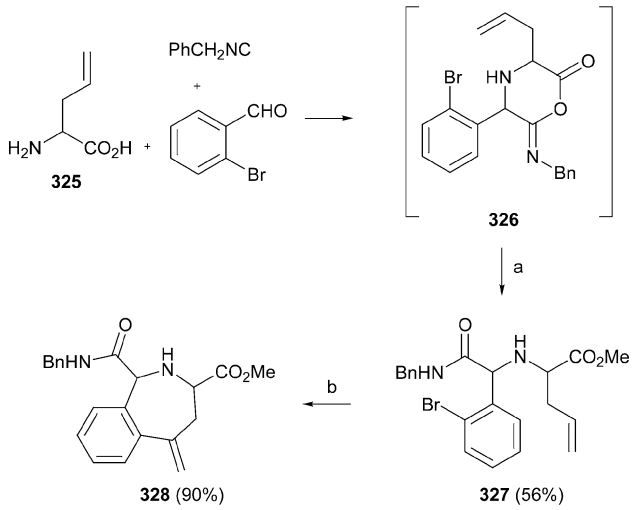
In the group of Gracias, a sequential Ugi/Heck cyclisation strategy was applied in the synthesis of nitrogen-containing heterocycles. The Ugi reaction was used to construct a tertiary amine containing an olefin as well as an aryl halide, both of which were coupled in the following intramolecular Heck reaction.[93] Thus, benzaldehyde, benzylisocyanide, and 2-iodobenzoic acid were reacted with allylglycine methyl ester **221** in its role as amine component to give Ugi product **320** as a 1 : 1 mixture of diastereomers (Scheme 75). In a microwave-assisted Heck reaction **320** readily formed the corresponding benzazepinone **321**. Besides the classic solution phase approach, the researchers also demonstrated the viability of this reaction sequence in a solid phase protocol, involving (*S*)-allylglycine immobilized on a Wang resin *via* an ester linkage. Thus, resin-bound amino acid **322** was converted to the Ugi product **323** followed by a Heck reaction to close the seven-membered ring. Acidic cleavage of the substrate off the resin and esterification afforded the enantiopure benzazepine **324**.



Scheme 75 *Reagents and conditions*: (a) MeOH; (b) $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, microwaves, 25 min; (c) MeOH–CH_2Cl_2 (1 : 1); (d) (i) KOAc, Bu_4NCl, $Pd(OAc)_2$, PPh_3, MeCN, (ii) TFA, (iii) $TMSCHN_2$.

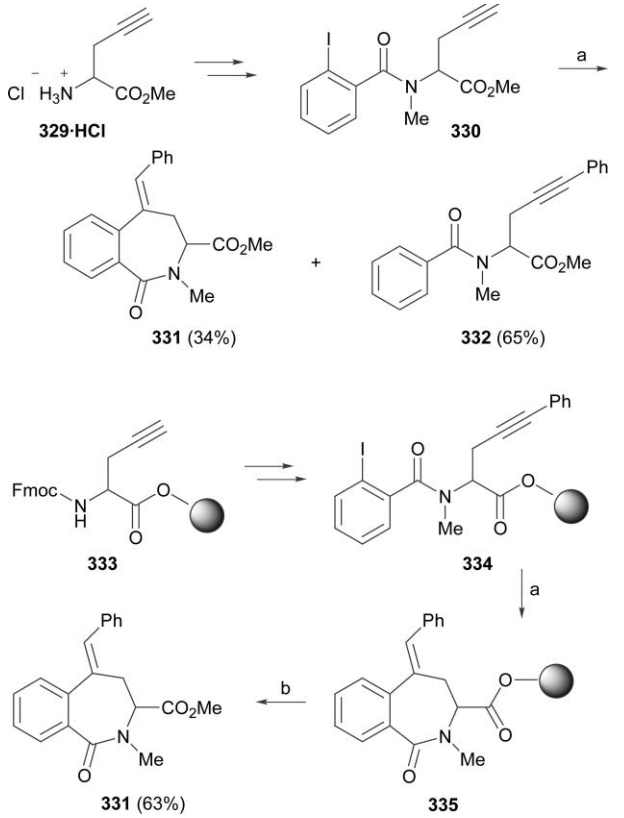
Intriguingly, amino acids can serve both as the amine and the acid component in an Ugi 5-centre–4-component reaction. The same researchers let allylglycine **325** react with 2-bromobenzaldehyde and benzylisocyanide in methanol yielding the secondary amine **327** (Scheme 76). A microwave-assisted Heck reaction afforded the cyclised product **328** in good yield.

Bolton and Hodges studied the intramolecular Heck cyclisation on propargylglycine derivatives for the construction of substituted benzazepines.[94] Initially, they investigated a



Scheme 76 *Reagents and conditions*: (a) MeOH; (b) $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, microwaves, 2 h.

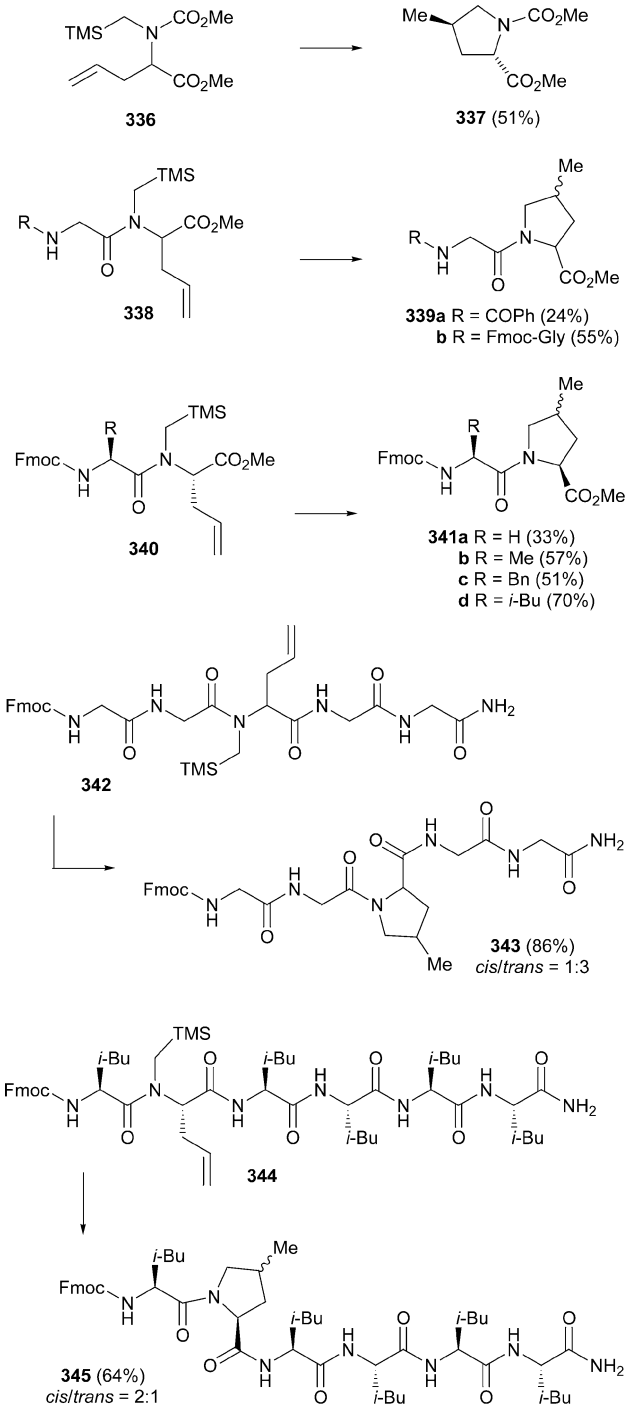
solution phase pathway towards benzazepinone **331** starting from propargylglycine methyl ester (**329**, Scheme 77). After derivatization, the resulting amide **330** was subjected to typical Heck cyclisation conditions providing the desired azepinone **331** in a modest yield of 34%, together with the deiodinated precursor **332** as the major product (65%).



Scheme 77 *Reagents and conditions*: (a) $Pd(OAc)_2$, PPh_3, Bu_4NCl, HCO_2Na, DMF, 70 °C; (b) (i) TFA, CH_2Cl_2, (ii) CH_2N_2.

The same researchers translated the solution phase sequence to the solid phase. This pathway commenced with Wang resin-linked, Fmoc-protected propargylglycine **333**, which was transformed in several steps into the immobilized Heck substrate **334**. In this case, subjection of compound **334** to similar cyclisation conditions as used before in solution afforded azepinone **331** as the sole product in 63% overall yield after cleavage from the resin.

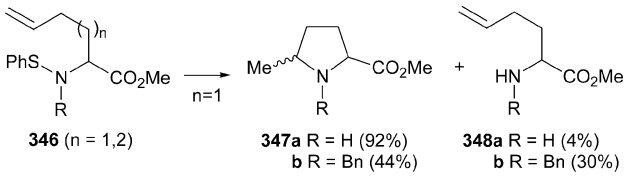
A radical cyclisation reaction of allylglycines was developed by Blechert and co-workers.[95] Irradiation of the compounds **336**, **338** and **340** in a mixture of methanol–acetonitrile with photoexcited 9,10-anthracene dicarbonitrile (ADC) and biphenyl (BP) as co-sensitiser led to a desired photochemically-induced electron transfer reaction (PET, Scheme 78).



Scheme 78 *Reagents and conditions*: BP (20 mol%), ADC (30 mol%), MeOH–MeCN, irradiation $\lambda > 345$ nm.

In this way, the proline derivatives **337** (51%), **339a**,**b** (24–55%) and **341a**–**d** (33–70%) were isolated. This radical cyclisation protocol was applied to the olefinic oligopeptides **342** and **344**. The cyclisation led to the proline-containing oligomers **343** (86% yield) and **345** (64% yield), thereby causing a structural rearrangement of the peptide backbone.

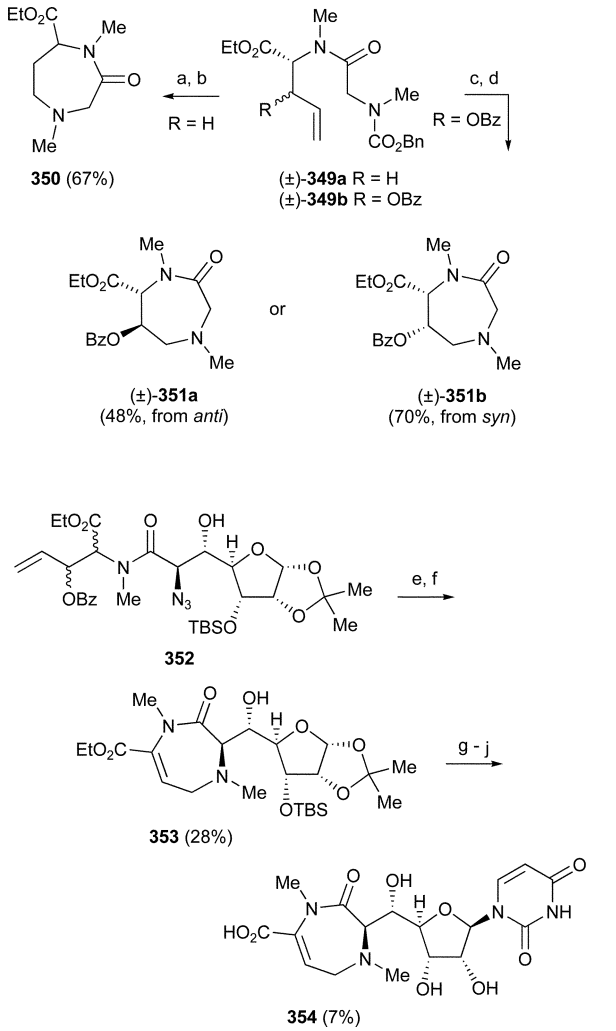
A study of Bowman *et al.* focused on the cyclisation of α-chiral aminyl radicals derived from reactions of sulfenamides with tributyltin.[96] The homo- and bis-homo-allylglycine-derived sulfenamides **346** were evaluated (Scheme 79).



Scheme 79 *Reagents and conditions*: Bu_3SnH, AMBN, cyclohexane, reflux, 6 h.

In the case of $n = 1$ and R = H, successful radical cyclisation induced by AMBN {2-[(*E*)-2-(1-cyano-1-methylpropyl)-1-diazenyl]-2-methylbutanonitrile} and Bu_3SnH in cyclohexane at reflux temperature led to the formation of **347a** in 92% yield. For the *N*-benzyl derivative **347b** the yield was substantially lower, with concomitant formation of **348b** (30%). No cyclisation was observed for the homologous precursor ($n = 2$).

Knapp and co-workers reported the oxidation of allylglycine derivatives and subsequent cyclisation to form 1,4-diazepan-2-ones (Scheme 80).[97]

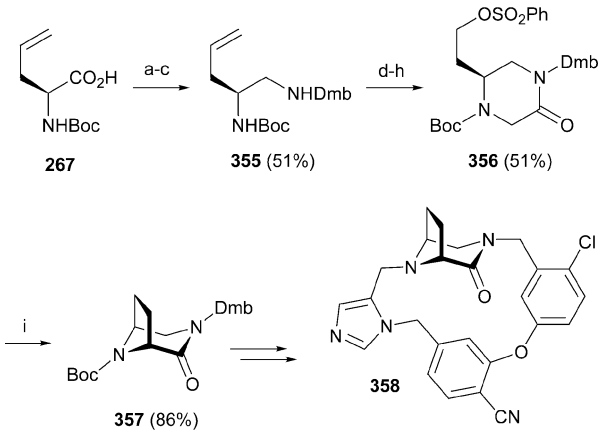


Scheme 80 *Reagents and conditions*: (a) OsO_4, $NaIO_4$, aqueous THF; (b) H_2, Pd/C, MeOH; (c) (i) O_3, CH_2Cl_2, −78 °C, (ii) Me_2S, rt; (d) H_2, Pd/C, MeOH; (e) (i) O_3, CH_2Cl_2, −78 °C, (ii) PPh_3, THF; (f) $NaBH(OAc)_3$, THF; (g) Ac_2O, MsOH; (h) HCl-salt formation, then bis(trimethylsilyl)uracil, TMSOTf, MeCN, reflux; (j) 0.5 N LiOH, EtOH, RP-HPLC.

For example, oxidative cleavage of the double bond of allylglycine derivative **349a** led to the formation of diazepanone **350** in 67% yield after deprotection/reductive amination. In the case of precursor **349b**, both diastereoisomers were separately cyclised using ozone-oxidation and subsequent reductive amination of the resulting aldehydes. This led to **351a**

(48% yield) and **351b** (70% yield) starting from the *anti*- and *syn*-precursors, respectively. The same methodology was applied in the synthesis of the Liposidomycin diazepanone nucleoside. Thus, key intermediate **352** was prepared and treated with ozone at −78 °C. The intermediate azido ozonide could be separated and reduced with PPh_3. The resulting imine was then reduced with triacetoxyborohydride, which also caused elimination of the benzoyl moiety. During these steps, the nitrogen was also methylated (**353**), presumably due to the presence of formaldehyde liberated in the ozonide reduction. Acetylation, coupling with uracil, and saponification led to the desired Liposidomycin degradation product **354**, useful for the establishment of the absolute stereochemistry of liposidomycins B and C.

A conformationally restricted farnesyltransferase inhibitor was targeted by Dinsmore *et al.*,[98] starting from *N*-Boc-allylglycine **267** (Scheme 81).

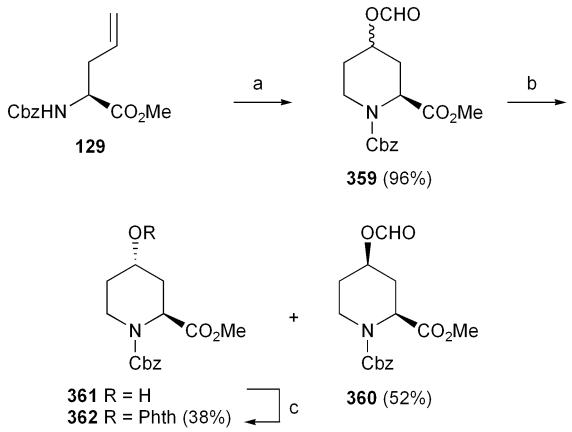


Scheme 81 *Reagents and conditions*: (a) MeO(Me)NH·HCl, EDC, HOBt, DMF, 0 °C, 24 h; (b) $LiAlH_4$, Et_2O, −50 to 5 °C, 3 h; (c) 2,4-$(MeO)_2BnNH_2$, $NaBH(OAc)_3$, 4 Å MS, 1,2-dichloroethane, 16 h; (d) $ClCH_2COCl$, $NaHCO_3$, EtOAc–H_2O, 0 °C, 30 min; (e) Cs_2CO_3, DMF, 65 °C, 16 h; (f) OsO_4, NMO, *t*-BuOH, THF, H_2O, 7 h, then $NaIO_4$, $NaHCO_3$, 1.5 h; (g) $NaBH_4$, EtOH, 0 °C to rt, 1 h; (h) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (i) LiHMDS, THF, −78 to 0 °C, 40 min.

Following a straightforward sequence of eight steps, the allylglycine derivative was transformed into the benzenesulfonate-functionalised piperazinone **356**, which was cyclised by the addition of LiHMDS in THF to afford the bicyclic framework **357** in 86% yield. Eventually, this compound was transformed in a series of steps into the targeted cyclophane **358**. This compound was found to be more potent than the parent, unbridged system in the inhibition of FTase-catalysed incorporation of [^{3}H]-farnesylpyrophosphate into recombinant Ras-CVIM.

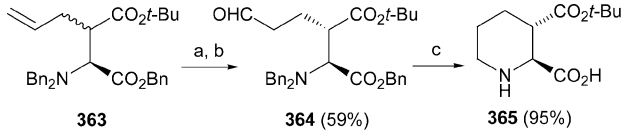
Process chemists from Chirotech Technology developed a large-scale preparation method for all four diastereoisomers of 4-hydroxypipecolic acid.[99] They utilised a known procedure for the cyclisation of protected allylglycines *via* an *N*-acyliminium ion intermediate.[100] Allylglycine **129** was reacted with paraformaldehyde in formic acid to afford a 1 : 1 diastereomeric mixture of **359** in 96% yield (Scheme 82).

The diastereomers were separated by subjection to lipase AY30 that selectively hydrolyzed the (*S*,*S*)-isomer. Treatment of the resulting inseparable 1 : 1 mixture of the 4-hydroxy- and 4-formyloxypipecolic acid with phthalic anhydride, to form the hemiphthalate ester derivative **362**, enabled separation by partitioning between the aqueous and organic layers. Enantiomerically pure **362** was obtained in 38% yield *via* this procedure, and the pure formate **360** was obtained in 52% yield, providing an entry into the corresponding alcohol by facile hydrolysis. The remaining two stereoisomers were prepared *via* a similar strategy.



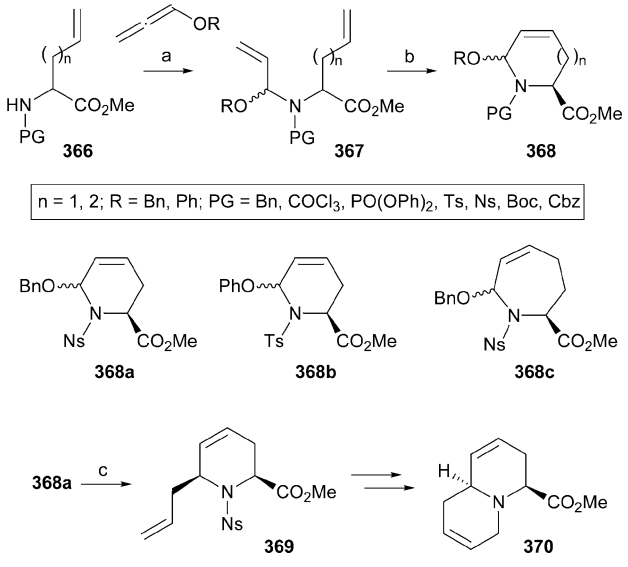
Scheme 82 *Reagents and conditions*: (a) paraformaldehyde, HCO_2H; (b) lipase AY30; (c) phthalic anhydride.

The piperidine skeleton was also targeted by Xue *et al.* using a reductive amination approach (Scheme 83).[101] Hydroboration of the aspartic acid derivative **363** afforded a mixture of diastereoisomeric alcohols that could be separated from each other. Oxidation to the aldehyde level using pyridinium dichromate (PDC) gave **364** in 59% yield over these steps. Hydrogenation removed the benzyl groups and led to reduction of the resultant cyclic imine to afford the desired pipecolic aid derivative **365** in 95% yield.



Scheme 83 *Reagents and conditions*: (a) (i) 9-BBN, THF, (ii) separation; (b) PDC, CH_2Cl_2; (c) H_2, Pd/C, MeOH.

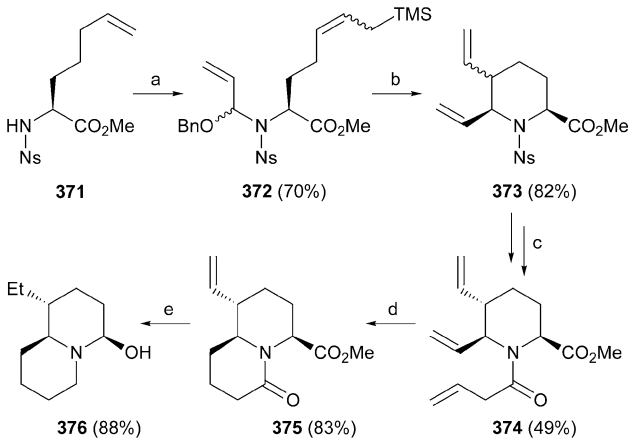
Iminium ion-mediated ring-closing reactions of olefinic *N*,*O*-acetals comprise a practical approach to create *N*-heterocycles. Kinderman *et al.* addressed the synthesis of allylic *N*,*O*-acetals *via* a Pd-catalysed nucleophilic addition of protected olefinic amino acids to alkoxyallenes. This reaction allowed the creation of an array of *N*,*O*-acetals differing in amino acid side chain length, alkoxy substituent and amine protecting group (Scheme 84).[102] The less acidic carbamates required



Scheme 84 *Reagents and conditions*: (a) for general amidopalladation, $Pd(OAc)_2$/dppp (5 mol%), base (Et_3N or DBU), MeCN; (b) catalyst **65**, CH_2Cl_2, rt; (c) $BF_3{\cdot}Et_2O$, allyltributylstannane, CH_2Cl_2, −78 °C to rt, 4 h.

a stronger base (DBU) as compared to their sulfonamide analogues where triethylamine appeared to be sufficient. In the case of the enantiopure starting material, it was demonstrated that no racemisation occurred in the course of the reaction. Starting from protected allylglycine or homoallylglycine (**366**), the diolefinic acetals **367** were prepared and subjected to RCM conditions providing the corresponding *N*-heterocycles **368** of which the pipecolic acid derivative **368a** was used in the synthesis of a quinolizidine-based amino acid (**370**).[102a] Thus, an *N*-sulfonyliminium-mediated diastereoselective alkylation of **368a** afforded the diene **369** that could be converted into the desired amino acid in four steps.

Another synthetic application of such *N*,*O*-acetals was presented by the same researchers in the preparation of a precursor of the poisonous frog alkaloid quinolizidine 233A.[102b] Treatment of protected bis-homoallylglycine **371** with allyltrimethylsilane (ATMS) and the Hoveyda–Grubbs catalyst **68** caused an unusual double bond isomerization followed by cross-metathesis with ATMS (Scheme 85). The coupling product was converted to the *N*,*O*-acetal **372** by amidopalladation with benzyl propadienyl ether and thereafter subjected to Lewis acid-mediated ring-closing conditions arriving at the cyclic diene **373** as a mixture of diastereomers. Deprotection and *N*-acylation led to triene **374** that in turn was ring-closed by catalyst **66** to give the bicyclic product **375** as a mixture of separable diastereomers. Subjection of the *trans* isomer to two reduction steps completed a formal synthesis of quinolizidine 233A (**376**).



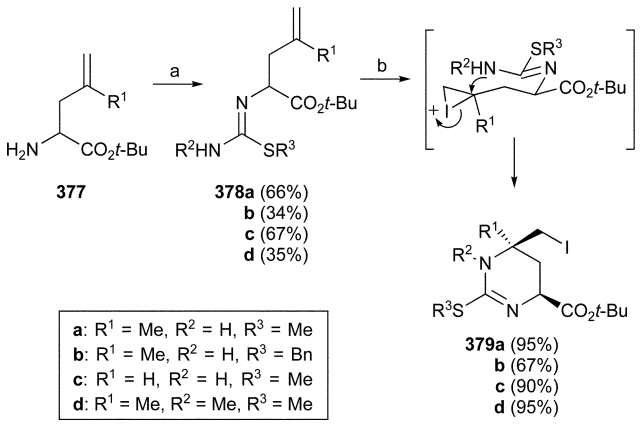
Scheme 85 *Reagents and conditions*: (a) (i) ATMS, catalyst **68**, CH_2Cl_2, reflux, 16 h, (ii) benzyl propadienyl ether, $Pd(OAc)_2$/dppp, Et_3N, MeCN, rt, 16 h; (b) $Sn(OTf)_2$, CH_2Cl_2, 0 °C to rt, 2 h; (c) deprotection, *N*-acylation; (d) catalyst **66**, CH_2Cl_2, reflux, 4 h; (e) (i) PtO_2, H_2, MeOH, 2 h, (ii) $LiAlH_4$, THF, 70 °C, 20 h.

Woo and MacKay prepared key intermediates from allylglycine derivatives to be used in the total synthesis of manzidins.[103] The allylglycine ester derivatives **377** were converted to the isothiourea compounds **378** which in turn were subjected to iodocyclisation conditions. The targeted tetrahydropyrimidines **379** were obtained in a good diastereomeric ratio (20 : 1), probably due to a chair-like transition state for attack on the intermediate iodonium ion (Scheme 86).

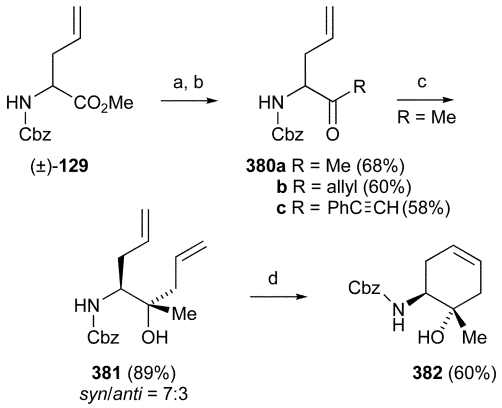
5. Cyclisations involving the ester substituent

In the group of Hiemstra and Rutjes, a diastereoselective synthesis of β-amino alcohols was developed, starting from Cbz-protected allylglycine **129** (Scheme 87).[104]

Weinreb amide formation, followed by Grignard addition led to the ketones **380a**–**c** in 58–68% yield over the two steps. A second Grignard addition of allylmagnesium bromide to ketone **380a** (R = Me) resulted in the formation of **381** in 89% yield as a 7 : 3 mixture of *syn*/*anti* diastereoisomers. Upon RCM of the diolefin to give cyclohexene derivative **382**, the *trans*-relationship of the main product was established by NMR.

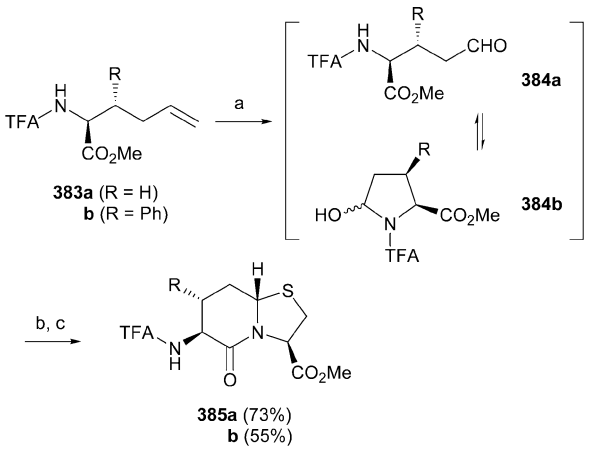


Scheme 86 *Reagents and conditions*: (a) (i) Im_2CS, CH_2Cl_2, (ii) NH_2R^2, CH_2Cl_2, (iii) MeI or BnBr, MeCN; (b) IBr, −78 °C, 2 h.



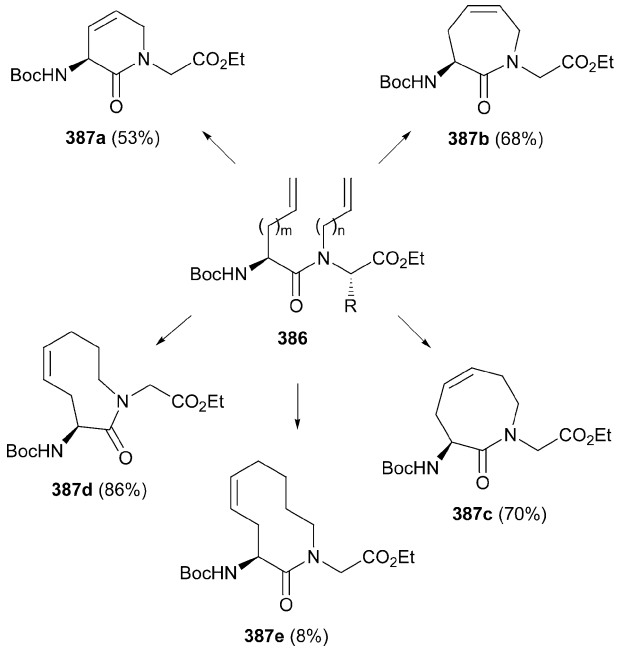
Scheme 87 *Reagents and conditions*: (a) HCl·HNMe(OMe), $AlMe_3$, CH_2Cl_2; (b) RMgBr, THF; (c) allylMgBr, THF, −78 °C, 70 : 30 (*syn*/*anti*); (d) catalyst **65**, CH_2Cl_2.

Another type of cyclisation, involving the ester substituent and the olefin side chain, was performed by the group of Hruby, in which they targeted the synthesis of bicyclic β-turn dipeptides.[105] Access to the enantiopure homoallylglycine intermediates **383** was gained through an asymmetric alkylation involving a chiral template nickel(II)-complex. Oxidative cleavage of the double bond of **383** resulted in the formation of **384** as a mixture of ring and chain isomers which was subjected to cysteine in the presence of pyridine at 50 °C for 4 days to form the *N*,*S*-acetal (Scheme 88). Essential for this process was the use of the TFA protective group for the starting amino acid. Esterification completed the synthesis of the [4.3.0]bicyclic β-turn dipeptides, yielding **385a** and **385b** in 73 and 55% yield, respectively, over the three steps.



Scheme 88 *Reagents and conditions*: (a) OsO_4, $NaIO_4$, THF, H_2O; (b) cysteine, pyridine, 50 °C, 4 d; (c) CH_2N_2, CH_2Cl_2.

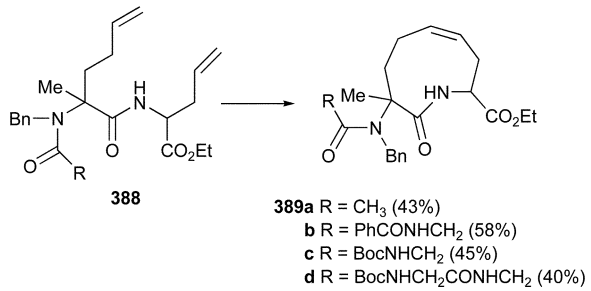
Gmeiner and co-workers reported on the synthesis of dehydro-Freidinger lactams *via* RCM of allylglycine-derived dipeptides and homologues.[106] RCM of the precursors **386** was successful in most cases with ruthenium catalyst **65** in refluxing 1,2-dichloroethane (Scheme 89).



Scheme 89 Ring-closing. *Reagents and conditions*: catalyst **65** (10 mol%) or **66** (5 mol% for **387e**), 1,2-dichloroethane, reflux.

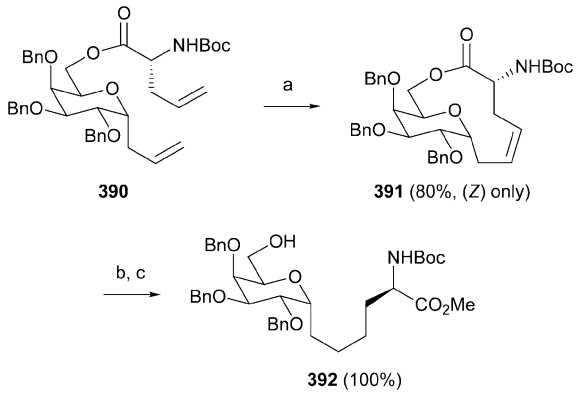
The ring-closed products **387** were generally obtained in good yields except for the ten-membered ring lactam **387e** which probably contained the (*E*)-isomer as a minor impurity. Noteworthy is the excellent yield of the nine-membered dehydro-Freidinger lactam **387d** in 86% isolated yield. The cyclic lactams were used to investigate the conformational preferences of these β-turn models.

In a related study, the group of Banfi prepared nine-membered cyclic lactams for the potential use as external reverse turn inducers.[107] An Ugi-4-centre reaction incorporating unsaturated substrates provided the diolefins **388** that were transformed into the mesocycles **389a**–**d** *via* an RCM reaction using Grubbs catalyst **65** (Scheme 90). Remarkably, all ring-closed products possessed the (*Z*)-configuration, while analogous ten-membered rings constructed by RCM are capable of forming both (*E*)-[108] and (*Z*)-isomers (*vide supra*). After ring closure, the *cis*/*trans* diastereoisomers resulting from the unselective Ugi reaction could be separated by chromatography in most cases. Scheme 90 shows a selection of the lactams produced *via* this Ugi/RCM reaction sequence.



Scheme 90 *Reagents and conditions*: catalyst **65** (20 mol%), CH_2Cl_2, reflux, 48 h.

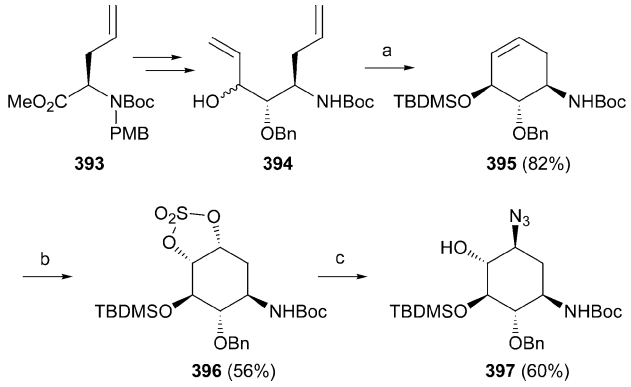
Westermann and Walter used RCM as the key transformation for the construction of *C*-glycosidic neoglycoconjugates.[109] Glyco-allylglycine **390** was subjected to RCM conditions using



Scheme 91 *Reagents and conditions*: (a) catalyst **65**, CH_2Cl_2, reflux, 48 h; (b) NaOMe; (c) $TsNHNH_2$, 1 M aqueous NaOAc, DME.

Grubbs catalyst **65** in refluxing dichloromethane (Scheme 91). Only the (*Z*)-product **391** was isolated after 48 h in 80% yield. Lactone opening and chemoselective double bond reduction with tosylhydrazine afforded the *C*-glycosidic neoglycoconjugate **392**.

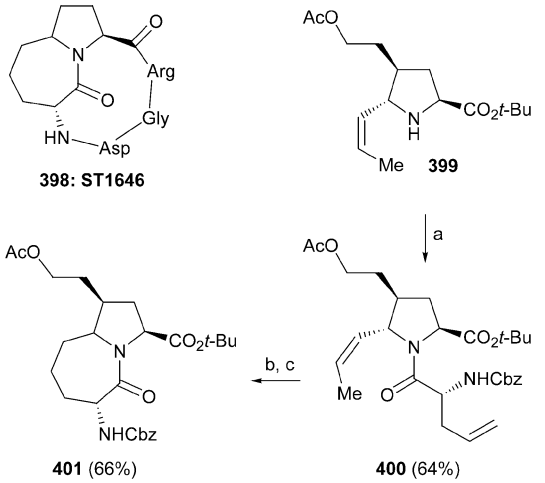
Busscher *et al.* employed (*R*)-allylglycine **393** as starting material in the asymmetric synthesis of orthogonally protected 2-deoxystreptamine **397** (Scheme 92).[110] A series of transformations converted the starting material into diene **394**. Upon ring-closing metathesis of **394** using the 2nd generation Grubbs catalyst **66**, the cyclic olefin **395** was formed. Epoxidation in order to introduce the azide and alcohol functionality of 2-deoxystreptamine appeared to be an awkward strategy due to the formation of inseparable distereomers. Instead, it was decided to make use of a cyclic sulfate. Thus, dihydroxylation of **395** yielded the facial diol exclusively which in turn was treated with $SOCl_2$ followed by a Ru-catalysed oxidation to give sulfate **396**. Ring opening with lithium azide and hydrolysis of the sulfate resulted in the enantiopure desymmetrised 2-deoxystreptamine derivative **397**.



Scheme 92 *Reagents and conditions*: (a) (i) catalyst **66**, CH_2Cl_2, rt, 2 h, (ii) TBDMSOTf, Et_3N, CH_2Cl_2, rt, 2 h; (b) (i) $RuCl_3$, $NaIO_4$, EtOAc–MeCN–H_2O (3 : 3 : 1), 0 °C, 3 min, (ii) $SOCl_2$, pyridine, EtOAc, 0 °C, 30 min, (iii) $NaIO_4$, $RuCl_3 \cdot H_2O$, CH_2Cl_2–MeCN–H_2O (2 : 2 : 3), 0 °C, 1 h; (c) (i) LiN_3, DMF, Δ, 4 h, (ii) H_2SO_4, THF, H_2O, rt, 30 min.

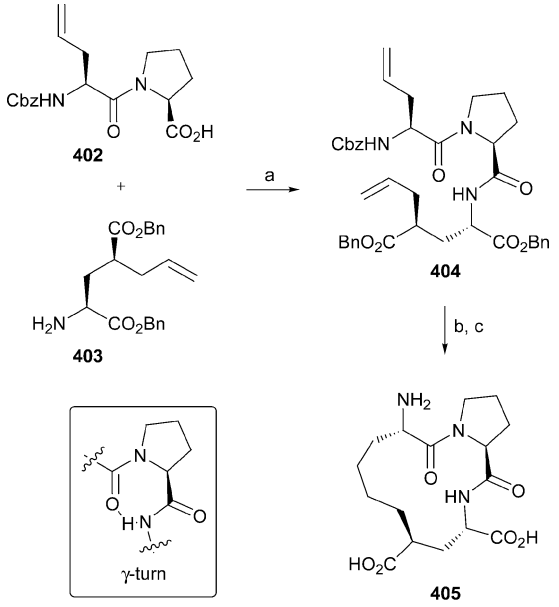
The cyclic pseudopeptide ST1646 (**398**, Scheme 93) has been shown to be a highly active $\alpha_v\beta_3$ integrin antagonist. A synthesis of the azabicyclo[5.3.0] motif equipped with a handle for further derivatization was presented by Bracci *et al.*[111] The key step was the mixed anhydride-mediated coupling of racemic *N*-Cbz allylglycine to the proline derivative **399**. This reaction proceeded with complete kinetic resolution, and employing 3.3 equiv. of allylglycine resulted in amide **400** as a single enantiomer in 64% yield. Ring-closing metathesis using **65** followed by double bond reduction completed the synthesis of the bicyclic scaffold **401**.

The synthesis of a series of bicyclic proline-containing peptides *via* olefin RCM has been described by Harris *et al.*[112]



Scheme 93 *Reagents and conditions*: (a) *N*-Cbz allylglycine, NMM, *i*-PrOCOCl, THF, −30 °C to rt; (b) catalyst **65**, CH_2Cl_2; (c) $NaBH_4$–$NiCl_2$, MeOH.

Among several targets, the 13-membered macrocycle **405** (Scheme 94) was prepared which emerged as the *trans* amide (Pro) rotamer exclusively. The researchers rationalized this conformational preference by the small ring size of the peptide and its ability to arrange in a γ-turn motif around the proline residue. As depicted, linkage of the dipeptide **402** to the glutamic acid derivative **403** provided the diolefinic precursor **404** that upon ring closure and reduction gave rise to the cyclic product **405**.

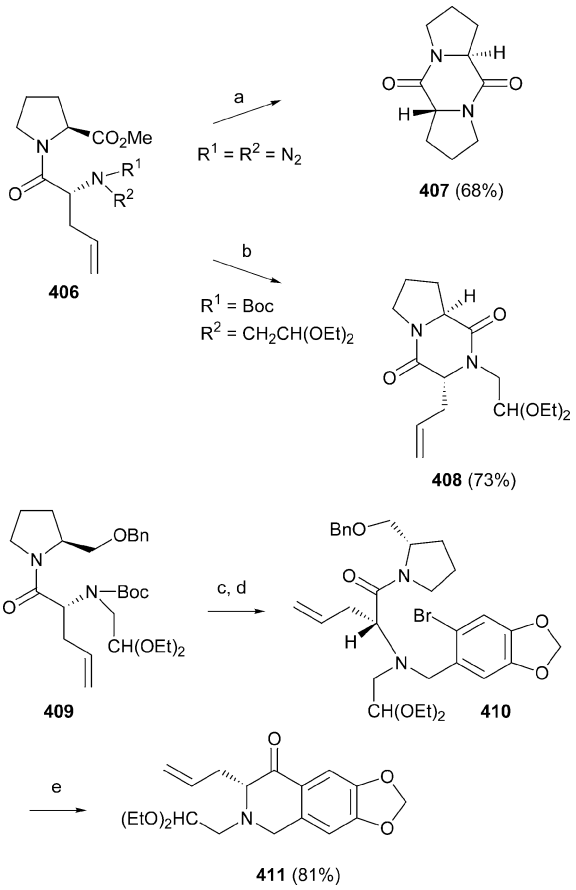


Scheme 94 *Reagents and conditions*: (a) EtOCOCl; (b) catalyst **65**, CH_2Cl_2, reflux, 48 h; (c) H_2, Pd/C.

6. Miscellaneous applications

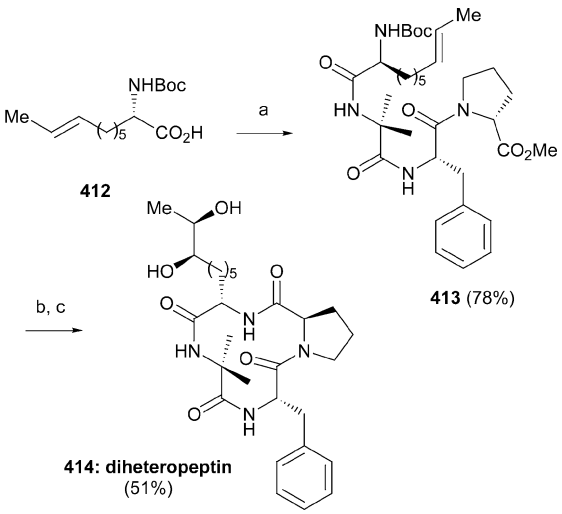
Nubbemeyer and Zhang reported on the synthesis of optically active allylglycine derivatives by using a proline-derived unit as chiral auxiliary.[113]

Several building blocks were synthesised *via* the intermediates **406** (proline as auxiliary) and **409** (prolinol as auxiliary), which had been obtained with high diastereoselectivity *via* a zwitterionic aza-Claisen rearrangement (Scheme 95). Among the targets synthesised from **406** were piperazinediones **407** (68%) and **408** (73%, 1 : 15 *cis*/*trans* mixture). With the prolinol-derived allylglycine derivative **409** in hand, the intermediate **410** was obtained by removal of the Boc-group and benzylation with the required bromide. Finally, the isoquinoline **411** was synthesised through lithiation of bromide **410** and subsequent cyclisation.



Scheme 95 *Reagents and conditions*: (a) Cy_2BH, CH_2Cl_2, 0 °C to rt, then NH_4Cl, MeOH; (b) MeOH, SiO_2, rt; (c) $SOCl_2$, EtOH, rt; (d) $ArCH_2Br$, K_2CO_3, MeCN, 80 °C; (e) BuLi, THF, −78 °C.

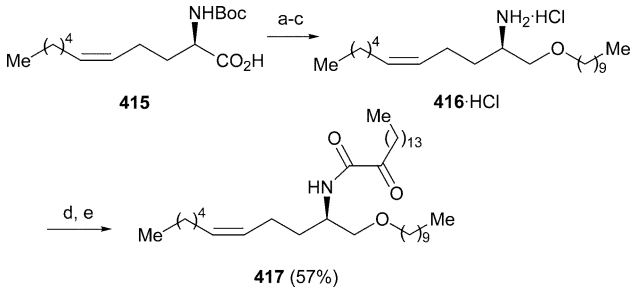
Durand *et al.* targeted the asymmetric synthesis of natural diheteropeptin (**414**), a cyclic tetrapeptide displaying TGF-β-like (transforming growth factor) biological properties.[114] The strategy was based on the construction of the linear peptide **413**, starting from the olefinic α-amino acid **412** (Scheme 96).



Scheme 96 *Reagents and conditions*: (a) Aib–(L)-Phe–(D)-Pro–OMe, PyBOP, DIEA, CH_2Cl_2, rt; (b) (i) LiOH, DME, H_2O, rt, (ii) TFA, CH_2Cl_2, (iii) PyBOP, DIEA, CH_2Cl_2; (c) AD-mix-β, $CH_3SO_2NH_2$, H_2O, *t*-BuOH, 0 °C, 2 h.

After deprotection and macrolactamization of **413**, the double bond was asymmetrically dihydroxylated using the Sharpless method to afford the desired enantiopure diheteropeptin **414** in 51% yield over these two steps.

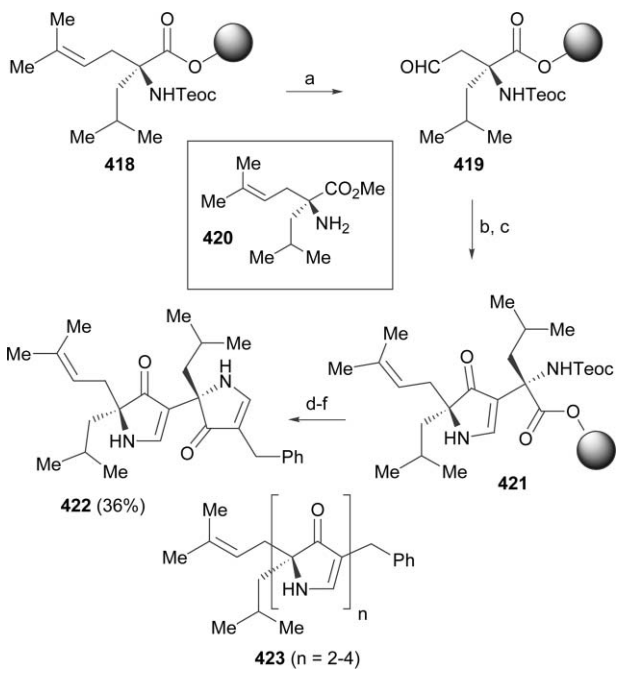
Kokotos and co-workers used the olefinic α-amino acid **415** for the synthesis of a lipophilic α-keto amide, a novel inhibitor of pancreatic lipase.[115] Acyl fluoride formation of the acid followed by reduction to the amino alcohol, alkylation with *n*-decyl bromide, and Boc-deprotection afforded the HCl-salt of amine **416** (Scheme 97).



Scheme 97 *Reagents and conditions*: (a) (i) 2,4,6-trifluoro-[1,3,5]-triazine, pyridine, (ii) $NaBH_4$, MeOH; (b) $Me(CH_2)_9Br$, 50% NaOH, Bu_4NHSO_4, benzene; (c) 4 M HCl, THF; (d) EDC, HOBt, Et_3N; (e) PDC, AcOH.

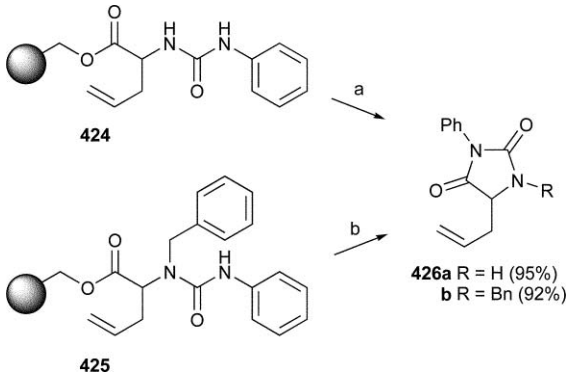
Coupling of **416** with 2-hydroxyhexadecanoic acid using EDC and HOBt (1-hydroxybenzotriazole hydrate), followed by pyridinium dichromate oxidation afforded the desired α-keto amide **417** in 57% yield over all the steps. The inhibition of pancreatic lipase was studied using this lipophilic compound.

The polypyrrolinone structural motif was synthesised by Smith *et al.* making use of the prenyl-containing acid **418** on solid support.[116] The Wang resin-bound amino acid **418** was oxidatively cleaved with ozone to afford aldehyde **419** (Scheme 98). Imine formation of **419** with amino acid **420**, followed by treatment with KHMDS, led to the metallo-enamine cyclisation product **421**. Removal of the Teoc group and subsequent imine formation with hydrocinnamaldehyde, followed by metallo-enamine formation with KHMDS led to cyclisation and concomitant release of **422** from the resin in 36% overall yield. This principle, and the use of key building block **419**, gave rise to a strategy for the synthesis of oligopyrrolinones **423** on the solid support.



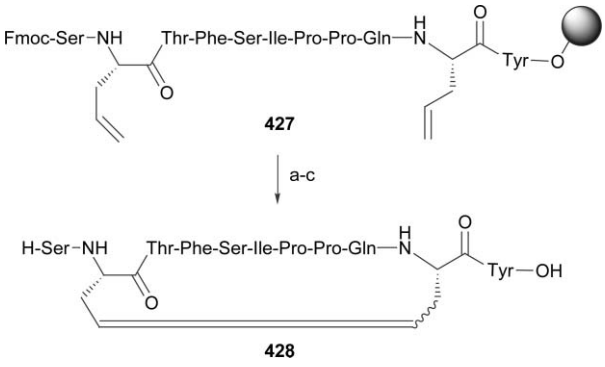
Scheme 98 *Reagents and conditions*: (a) O_3, PPh_3; (b) **420**, $(MeO)_3CH$, THF; (c) KHMDS; (d) TBAF; (e) $PhCH_2CH_2CHO$, $(MeO)_3CH$–THF; (f) KHMDS.

Another application of allylglycine attached to the solid support was given by Kurth and Park.[117] They reported a protocol for the synthesis of the Merrifield-resin-bound allylglycine derivatives **424** and **425** (Scheme 99). Cyclisation–cleavage led to the release of the hydantoins **426a**,**b** in 95 and 92% yield, respectively.



Scheme 99 *Reagents and conditions*: (a) Et_3N, 60 °C; (b) rt, no Et_3N necessary.

Leatherbarrow and co-workers made use of allylglycine and homoallylglycine in the preparation of Bowman–Birk inhibitor (BBI) analogues.[118] This family of serine protease inhibitors naturally displays a nine-residue, disulfide-linked peptide loop. Replacement of the flanking serine residues in the open chain precursor by various olefinic amino acids and subjection of these diolefins to RCM conditions provided an array of inhibitor analogues that was passed through activity tests. Scheme 100 shows an example of the synthesis of a carbon-linked BBI based on (*S*)-allylglycine. Treatment of the Wang-bound oligopeptide **427** with the 2nd generation Grubbs catalyst **66** along with microwave irradiation led to the formation of ring-closed product **428**. Similar reaction sequences were successfully carried out using homoallylglycine.

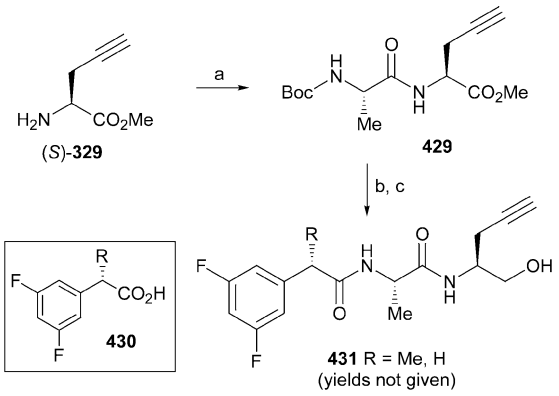


Scheme 100 *Reagents and conditions*: (a) catalyst **66**, CH_2Cl_2, 120 °C, microwaves, 10 min, 4 iterations; (b) 20% piperidine; (c) 95% TFA.

Without utilising the acetylenic side chain for structural modifications, propargylglycine has recently also been applied as a building block in the synthesis of (biologically active) peptides or peptidomimetics. For example, researchers at Elan and Eli Lilly used propargylglycine **329** as starting material in the synthesis of the amino alcohol dipeptides **431**, which were designed to inhibit formation of β-amyloid peptide (Scheme 101).[119]

Propargylglycine **329** was first coupled with Boc-protected (*S*)-alanine to give dipeptide **429**. Subsequent cleavage of the Boc-group and coupling with acids **430** (R = Me or H) provided *N*-terminated dipeptides. These esters were then reduced to the targeted amino alcohol analogues **431**, which were screened for the desired biological activity.

In order to investigate the importance of the terminal peptidic moiety for the biological activity of the natural antibiotic



Scheme 101 *Reagents and conditions*: (a) Boc–Ala–OH, EDC, HOBt, NMM, THF; (b) (i) TFA, (ii) **430**, EDC, HOBt, NMM, THF; (c) $LiBH_4$, THF.

pyloricidin C (**432**, Fig. 3), Hasuoka *et al.* prepared several derivatives in which the terminal leucine residue was substituted with various amino acids.[120] As part of this study, derivative **433** was prepared in which the leucine moiety was replaced by (*S*)-propargylglycine.

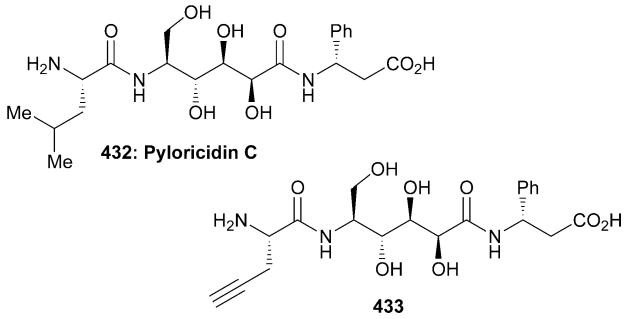
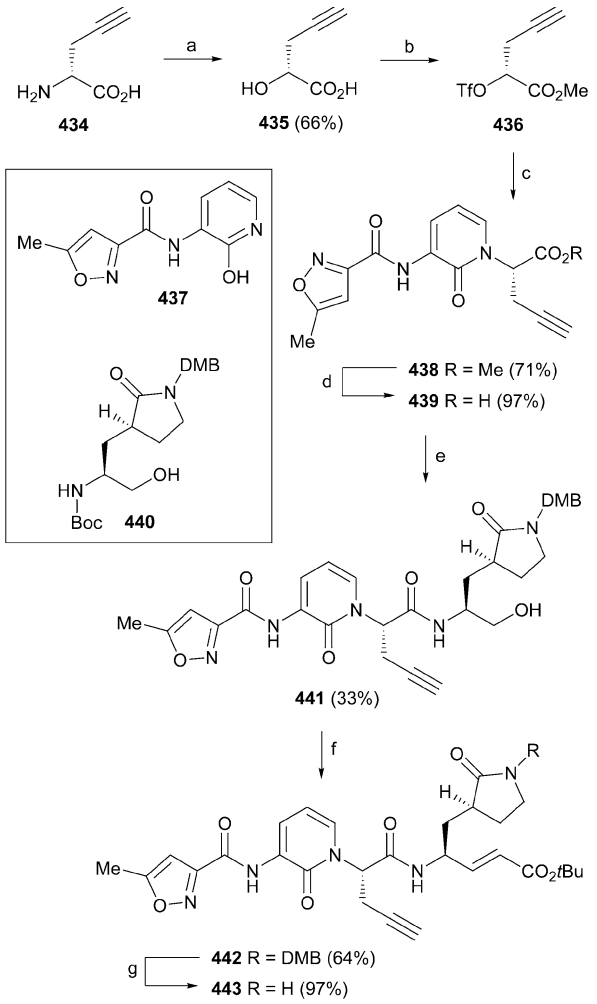


Fig. 3 Natural antibiotic pyloricidin C (**432**) and derivative (**433**).

The propargylglycine-containing derivative **433** was evaluated for antibacterial activity against *H. pylori* NCTC11637 and turned out to be 30-fold more active than the parent compound pyloricidin C.

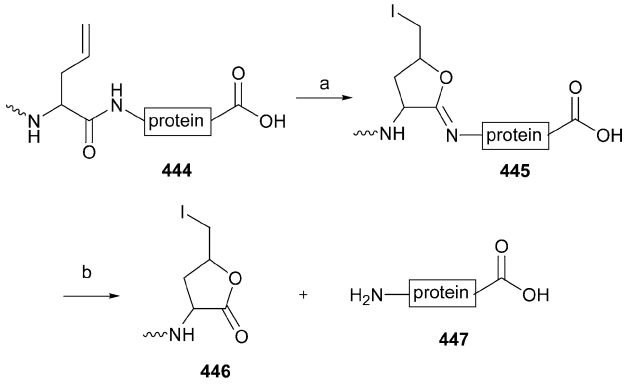
At Pfizer, a variety of 2-pyridone-containing peptidomimetics were synthesised and tested as inhibitors of the human rhinovirus 3C protease.[121] In several synthetic routes towards the targeted compounds, enantiopure propargylglycine **434** proved to be a versatile starting material, which is illustrated by the example in Scheme 102.

Thus, (*R*)-propargylglycine **434** was first converted into the α-hydroxy acid **435** in 66% yield. This compound was then esterified and transformed into the corresponding triflate **436**, which was reacted with hydroxypyridine **437** to afford *N*-alkylated pyridone **438** in 71% yield over three steps. Subjection of methyl ester to LiI in refluxing pyridine gave carboxylic acid **439**, which was coupled with amino alcohol **440** to provide compound **441**. This product was oxidised using Dess–Martin periodinane, and the intermediate aldehyde underwent olefination to give **442** in 64% yield. Finally, oxidative removal of the DMB group led to the desired inhibitor **443** in good yield.



Scheme 102 *Reagents and conditions*: (a) $NaNO_2$, H_2SO_4, rt; (b) (i) HCl, MeOH, rt, (ii) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) **437**, NaH, THF, rt; (d) LiI, pyridine, reflux; (e) HCl, dioxane, rt, then **440**, HOBt, DIPEA, EDC, CH_2Cl_2, rt; (f) (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C, (ii) $PPh_3{=}CHCO_2t$-Bu, THF, reflux; (g) DDQ, $CHCl_3$, H_2O, 65 °C.

Hecht and co-workers reported on the site-specific cleavage of proteins, using the chemoselective iodination at the allylglycine position (Scheme 103).[123]



Scheme 103 *Reagents and conditions*: (a) I_2; (b) H_2O.

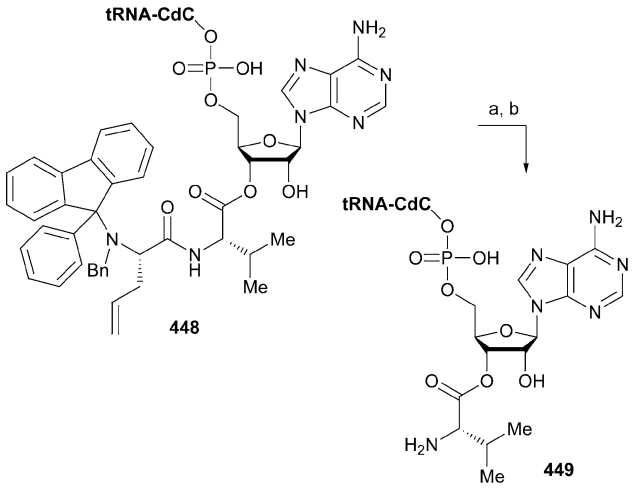
In this way, allylglycine-containing rat trypsinogen could be activated with iodine. Iodolactonization of the allylglycine-containing protein **444** led to intermediate **445** that could be hydrolysed to release the protein **447**. The same principle was applied in the construction of an iodine-labile trypsin inhibitor. An allylglycine-containing ecotin derivative was prepared and complexed to trypsin. Treatment of this complex with iodine

7. Biosynthetic applications

Numerous, recently published applications have been detailed in which olefinic α-amino acids are applied in the synthesis of organic compounds. In addition, these amino acids can be used in the formation of organometallic complexes,[122] but, more importantly, they can also play a specific role in the biochemistry of proteins.

induced a cleavage of the ecotin derivative thereby delivering active trypsin.[123c]

The same group further exploited this principle by using a bulky *N*-protected allylglycine amino acid as a protective moiety for valyl-tRNA (Scheme 104).[124] Consequently, site-specific cleavage of **448** with iodine, followed by hydrolysis, resulted in the release of the valine-loaded tRNA **449**.



Scheme 104 *Reagents and conditions*: (a) I_2; (b) H_2O.

Verdine and co-workers made special use of ring-closing metathesis to generate an all-hydrocarbon-type of cross-linking in α-helical peptides, which enhances the metabolic stability.[125] α-Methyl-α-allylglycine amino acids (and homologues) were incorporated in α-helices across either one or two turns. RCM in 1,2-dichloroethane with Grubbs catalyst **65** caused cross-linking within the helix.

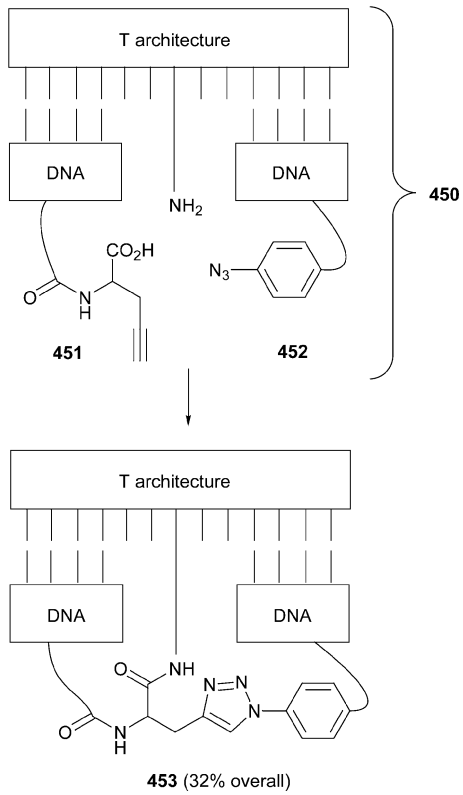
An increase in the targeted ring size generally led to a better conversion in the metathesis reaction. Large effects on the efficiency of cross-linking were observed upon small variations of ring sizes. An example was given in which the cross-linking leading to a 30-membered macrocycle failed, while the corresponding 31-membered cycle was formed in 50% yield. Furthermore, the effects of the incorporation of α-methyl-α-allylglycine amino acids into α-helices and the effect of the cross-linking on the helicity was studied.

Expanding the scope of DNA-templated organic synthesis, the research group of Liu developed a novel DNA-template, the so-called T architecture.[126] In contrast to previously used DNA-templates, the T architecture offers the possibility to perform two DNA-templated reactions on a single template in one step. The viability of the T architecture in sequential DNA-templated reactions was, for example, demonstrated by combining the amine-linked T architecture with the complementary DNA-linked propargylglycine **451** and phenylazide **452** (Scheme 105).

Subjection of a buffered solution of system **450** to 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)–4-methylmorpholinium chloride (DMT–MM) led to amide formation, after which addition of $CuSO_4$ and sodium ascorbate induced a 1,3-dipolar cycloaddition ('click reaction') to give the triazole adduct **453** in 32% overall yield.

The incorporation of non-proteinogenic amino acids into proteins is an important strategy in altering the chemical and physical properties of natural and artificial proteins. This can be achieved *via* conventional synthetic methods such as solid phase synthesis; however, one of the most efficient means employs the *in vivo* translation of non-natural amino acids into proteins. The latter strategy utilises the ability of the cell's translation machinery to incorporate structurally-related analogues of the proteinogenic amino acids into proteins.

The group of Tirrell has been actively involved in this field. They showed that several methionine analogues could



Scheme 105 *Reagents and conditions*: aqueous buffer pH 7.0, DMT–MM, 25 °C, then $CuSO_4$, sodium ascorbate, 25 °C.

be incorporated into proteins using the translation system in methionine-depleted *E. coli* cells that overexpressed methionyl-tRNA synthetase (MetRS).[127] In particular, 2-butynylglycine proved to be an excellent methionine mimic, which could be incorporated into proteins with extents of substitution of methionine of up to 98%.[127d] Also, *E. coli* cells harboring a mutant of LeuRS with impaired proof reading were reported to tolerate several unsaturated amino acids (allylglycine, homoallylglycine, propargylglycine and 2-butynylglycine) in protein synthesis.[128]

At a more basic level, Forster *et al.* utilised the cell's translation system to produce a pentapeptide containing three non-natural amino acids in succession. In their *in vitro* approach, the researchers extended the genetic code by assigning three arbitrarily chosen codons to code for one of the amino acids *O*-methylserine, propargylglycine, and allylglycine.[129] Aminoacyl-tRNAs (aa-tRNAs) derived from *E. coli* were equipped with the novel anti-codons and chemoenzymatically charged with the matching non-natural amino acids. These artificial aa-tRNAs were put to use in a translation system thoroughly cleansed of natural aa-tRNAs but with other necessary translation factors present. In this set-up, the researchers were able to translate an mRNA template containing the *de novo* codons and by this means successfully obtained a pentapeptide featuring the sequence of propargylglycine, *O*-methylserine, and allylglycine.

8. Conclusions

Unsaturated amino acids have been recognised as versatile starting materials in the preparation of a diversity of subtances, ranging form small functionalised molecules to peptides. Among them, many therapeutically useful targets can be found, a fact that does not come as a surprise in the light of the functional richness of unsaturated amino acids together with the long-standing use of proteinogenic amino acids in organic synthesis.

Owing to their unsaturation they offer the possibility to combine the inherent acid and amine functionalities with a plethora of possible derivatizations. Those range from functional group interconversions and couplings (Heck, Stille, cross-metathesis,

RCM, click-reactions, *etc.*) to the preparation of isosteres and carba analogues of known natural compounds, often providing additional rigidity by virtue of unsaturations or ring systems. In particular, the latter examples rank among the most important applications of unsaturated amino acids. Of future importance are the recent efforts of employing nature's translational system to incorporate unsaturated amino acids in peptides. The trend of equipping polypeptides and proteins with the synthetic possibilities of unsaturation is set and will undoubtedly prove fruitful in the chemical biology field.

It must be clear that unsaturated amino acids have only just begun to unfold their potential in synthetic chemistry, not in the least due to the rather limited availability, high pricing or cumbersome synthesis even in racemic form of most of their members. Improved access will therefore certainly further increase their applications in the field of synthetic chemistry and chemical biology.

References and notes

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