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Indium mediated allylation of glyoxylate oxime ethers, esters and cyanoformates

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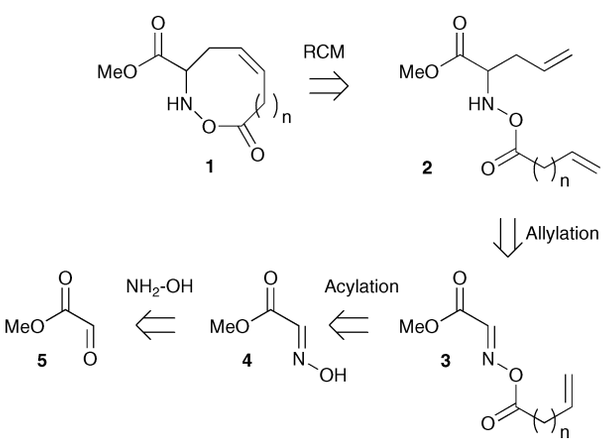
An indium mediated procedure has been developed for the allylation of activated *O*-functionalised oximes and nitriles as exemplified by a variety of glyoxylate derivatives. This method gives the corresponding free (or protected) amine in a one pot-process. The method is regiospecific and is carried out under remarkably mild conditions so that even oxime esters can be subjected to the typical reaction conditions.

Introduction

As part of a project to examine the synthesis of *N*-*O* containing heterocycles, such as **1**, by ring closing metathesis (RCM), we required a synthetic route to dienes of the type **2**. We considered that these compounds could be accessed by allylation of the corresponding oxime esters such as **3** which in turn could be made from glyoxylates **5** (Scheme 1).

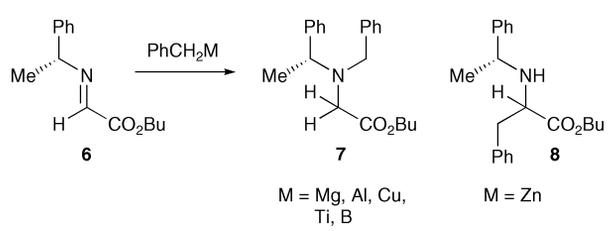


Scheme 1 Proposed route to cyclic hydroxylamines.

The key stage of this synthesis would be the nucleophilic addition of an allyl unit to the substituted oxime **3**. The addition of nucleophiles to imines and imine derivatives is a well known reaction but the low electrophilicity of imines as compared to aldehydes and ketones has necessitated the use of highly reactive reagents, often in conjunction with an activating agent.[1] Reports of ketimines undergoing 1,2-addition are rare, highlighting the low reactivity of this species.[2] Examples of aldimines reacting as electrophiles with organometallics are more prevalent. However, these reactions usually require a Lewis acid or activating agent to prevent the strongly basic nucleophiles deprotonating the α-position and forming azaenolates.[3]

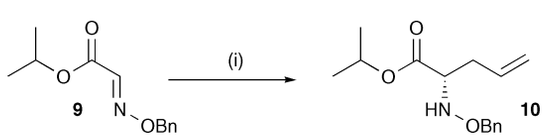
Nucleophilic additions to oximes and oxime ethers (R=N–OR′) have proven even more troublesome due to the increased acidity of the α-protons, giving rise to side products such as aziridines.[4] Furthermore, the lower electrophilicity of the iminyl bond of oximes, in comparison to imines, requires more forcing conditions to allow nucleophilic addition to occur. For example allyl boronates can add to aldimines but aldoximes require prolonged reaction times and elevated temperatures.[5,6] To achieve even moderate yields of *N*-alkyl *O*-alkyl hydroxylamines from oxime ethers demands the use of unstabilised organometallics (typically RLi or RMgX) often in the presence of a Lewis acid.[7] Given the harsh conditions required for the addition of nucleophiles to oxime ethers, it is of little surprise that 1,2-additions to oxime esters (R=N–O–C(O)R′) are prevented by competing addition at the ester carbon.

Despite the general difficulties experienced in adding nucleophiles to imines and oximes, it has been shown that electron-withdrawn species such as the α-imino esters **6** are more reactive to organometallics. However, few organometallics are compatible with α-imino esters as demonstrated by the fact that benzylzinc is the only reagent which adds regiospecifically to the desired position of **6** (Scheme 2).[8] This emphasises the fine balance between the reagents used and the reacting centre through which the reaction proceeds.



Scheme 2 Addition of organometallic reagents to α-carboxy imines.

Recently, Hanessian has reported allylations of glyoxylic acid and glyoxylate oxime ethers, such as **9**, using an allylzinc reagent under aqueous conditions (Scheme 3).[9] These workers reported yields up to 98% under mild conditions. We thus considered this method to be ideal for our required allylation of glyoxylate oxime esters.



Scheme 3 Hanessian's allylation of oxime ethers. *Reagents and conditions*: (i) Zn, CH_2=$CHCH_2Br$, NH_4Cl (aq), 98%.

Results

Glyoxylate derived oximes

Methyl glyoxylate **11** was reacted with hydroxylamine hydrochloride under basic aqueous conditions to afford the corresponding glyoxylate oxime **12** (Scheme 4). Carbodiimide

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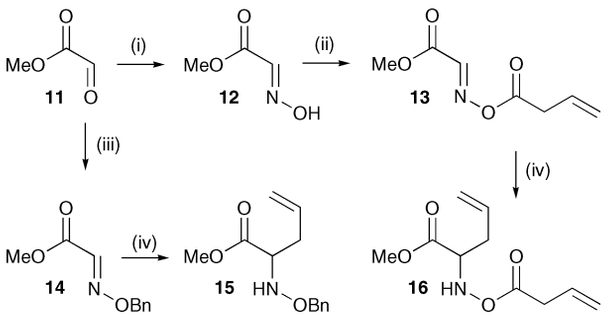
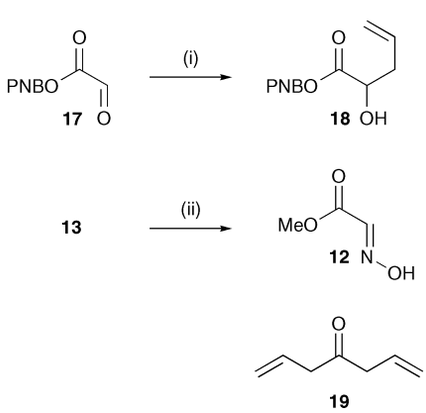


Scheme 4 Synthesis and reactions of oxime ether and ester. *Reagents and conditions*: (i) $HONH_3Cl$, $NaHCO_3$ (aq), RT, 52%; (ii) CH_2=$CHCH_2CO_2H$, EDCi, HOBt, THF, RT, 44%; (iii) $BnONH_3Cl$, pyr, MeOH, RT, 80%; (iv) Zn, CH_2=$CHCH_2Br$, THF–NH_4Cl (aq).

coupling with but-3-enoic acid, in the presence of hydroxybenzotriazole (HOBt), or treatment with but-3-enoic anhydride, then led to the required oxime ester **13**. The benzyl oxime ether **14** was formed by reaction of methyl glyoxylate with *O*-benzylhydroxylamine hydrochloride in methanol and pyridine. We first attempted allylation of **14** using the aqueous conditions developed by Hanessian. Thus treatment of **14** with allyl bromide and Zn in aqueous NH_4Cl gave the expected secondary amine **15** in 92% yield. However, under the same conditions the oxime ester **13** gave only a 38% yield of **16** (Scheme 4).

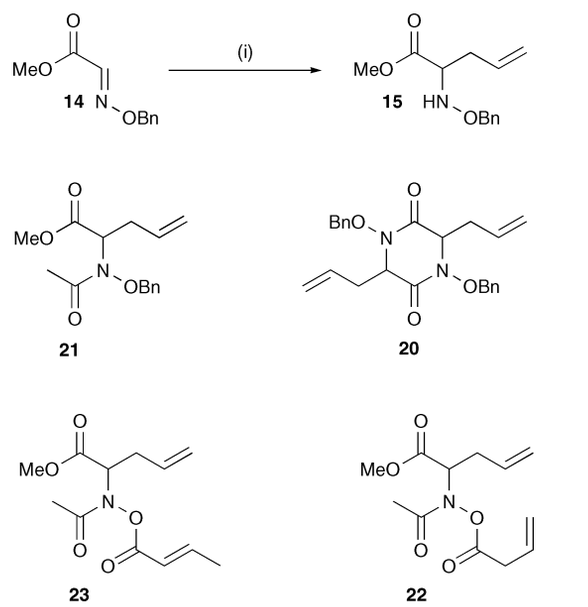
We next attempted an allylation of **13** using allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$. This reagent adds quickly to *p*-nitrobenzyl glyoxylate **17** to give the corresponding α-hydroxyester **18** (Scheme 5). However this reaction with the oxime ester **13** failed.[10] Grignard addition to **13** was also unsuccessful (with and without $BF_3{\cdot}OEt_2$). The major products of this reaction were the oxime **12** and the bisallyl ketone **19**, resulting from Grignard addition to the but-3-enoyl ester. The balance of the reaction was starting material **13** (Scheme 5). Predictably, the free oxime **12** did not react with either Grignard reagents or allyltrimethylsilane. These results dictated that an alternative means for the allylation of **13** had to be employed.



Scheme 5 Reactions with allylsilane and Grignard reagents. *Reagents and conditions*: (i) $TMSCH_2CH$=CH_2, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 78%; (ii) $BrMgCH_2CH$=CH_2, Et_2O.

Since the advent of indium mediated allyl additions to carbonyl compounds, as reported by Butsugan,[11] these reactions have become the method of choice for formation of homoallylic alcohols.[12] Although indium mediated allylations of imines are known (aldimines;[13] aryl/tosyl hydrazones and aldonitrones[14] all react) these reactions appear to demand an aromatic moiety adjacent to the imino group and there are no known examples of additions to oximes, oxime esters or oxime ethers.

We reasoned that the electron-withdrawn oxime glyoxylates such as **13** and **14** might react with allylindium reagents. In an initial experiment, indium powder was reacted with allyl bromide in DMF and addition of the oxime ester **13** provided the desired product **16** in 56% yield after aqueous workup. The less electrophilic oxime ether **14** was treated under the same conditions which, gratifyingly, gave **15** in > 80% yield. In an attempt to optimise the reaction we increased the concentration of the reacting species. Analysis of the reaction mixture indicated rapid consumption (typically conversion was complete in 15 min) of the starting material **14** and its conversion to product **15** (24%), the dimeric diketopiperazide **20** (19%) and polymeric material (Scheme 6).



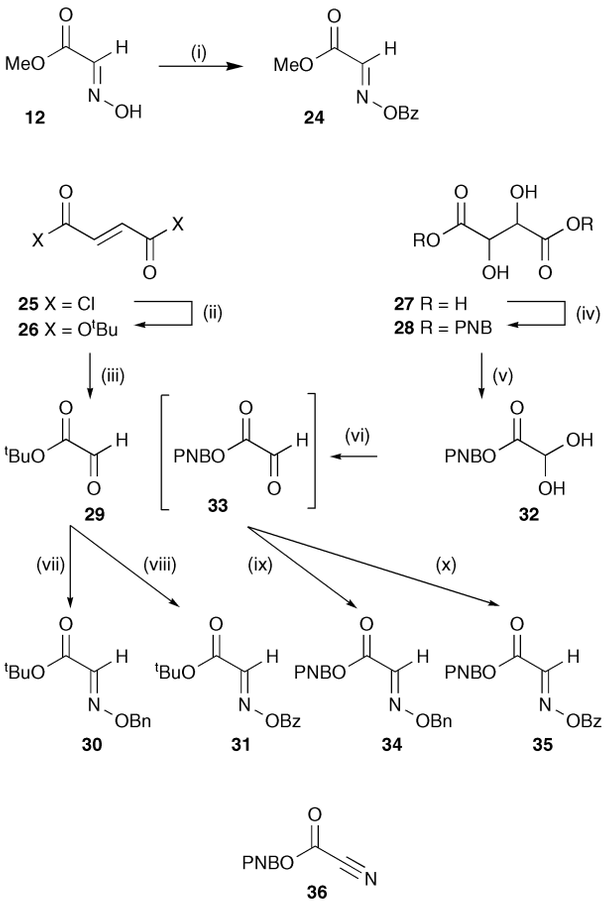
Scheme 6 Indium mediated allylation of oxime ether. *Reagents and conditions*: (i) In, CH_2=$CHCH_2Br$, THF–DMF.

In order to prevent the dimerisation we added acetic anhydride to the reaction mixture. Under these conditions two allylation products were recovered – the expected *N*-acetyl product **21** (42%) and the free amine **15** (40%) resulting from protonation of the amine intermediate by AcOH. The same reaction conditions were also successful with the glyoxylate oxime ester **13**, providing **22** in 57% and **16** in 21% overall yield (Scheme 6).

Addition of Et_3N to the reactions with acetic anhydride and the allylating reagent forced full reaction with the anhydride and gave 84% yield of the *N*-acetyl oxime ether **21**. However, although the oxime ester **13** reacted well under these conditions, we observed formation of the isomeric olefin **23**.

In order to examine the scope of this new allylation reaction we synthesised a range of oxime ethers and esters as potential substrates. We thus synthesised the benzoyl oxime ester **24** from **12** and benzoic anhydride. Fumaryl chloride **25** was converted to the corresponding *tert*-butyl ester **26**, and ozonolysis yielded *tert*-butyl glyoxylate **29**. In parallel, tartaric acid **27** was converted to its *p*-nitrobenzyl (PNB) ester **28**, and H_6IO_5 oxidation gave the PNB glyoxylate hydrate **32** which was dehydrated under Dean–Stark conditions to give the aldehyde **33** which was used immediately (Scheme 7).

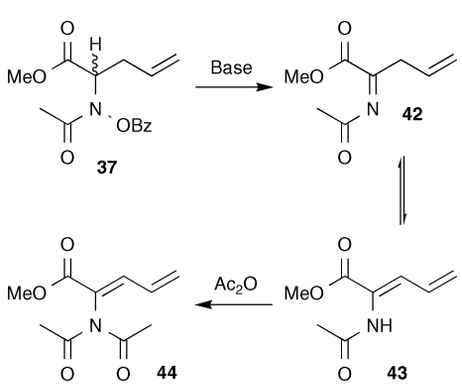
The glyoxylates **29** and **33** were then condensed with *O*-benzylhydroxylamine to give the oxime ethers **30** and **34**, or condensed with hydroxylamine and the products coupled with benzoic anhydride in the presence of pyridine to form the oxime esters **31** and **35** (Scheme 7). The PNB ester **35** proved to be unstable under basic conditions (pyr or dimethylaminopyridine, DMAP), eliminating to form the corresponding nitrile **36**. However, **35** was made by coupling benzoic acid to the oxime using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCi) and HOBt and it was isolated in good yield.



Scheme 7 Substituted glyoxylate oxime ethers and esters. *Reagents and conditions*: (i) $(PhCO)_2O$, pyr, CH_2Cl_2, DMAP, RT, 62%; (ii) ^tBuOH, BuLi, Et_2O, 0 °C, 39%; (iii) O_3, CH_2Cl_2, −78 °C, $(CH_3)_2S$, 50%; (iv) Et_3N, $O_2N(C_6H_4)CH_2Br$, DMF, 79%; (v) THF, H_6IO_5, RT, 63%; (vi) $PhCH_3$, Δ; (vii) $BnONH_3Cl$, pyr, MeOH, RT, 69%; (viii) $HONH_3Cl$, pyr, MeOH, 74%, then $(PhCO)_2O$, pyr, DMAP, CH_2Cl_2, 59%; (ix) $BnONH_3Cl$, pyr, MeOH, RT, 86%; (x) $HONH_3Cl$, pyr, MeOH, 81%, then $C_6H_5CO_2H$, EDCi, HOBt, MeCN, 65%.

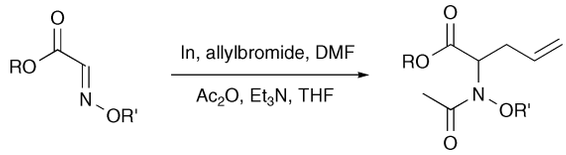
The standard allylation reaction consisted of premixing the oxime ether or ester with an excess of freshly distilled Ac_2O in anhydrous THF. This was followed by the addition of the allylating reagent consisting of 1.2 eq. indium and 1.8 eq. allyl bromide in dimethylformamide (DMF). After 2 h, to ensure acetylation was complete, an excess of Et_3N (10 eq.) was added followed by aqueous workup. For the oxime esters *one* equivalent of Et_3N was added to limit elimination (*vide infra*).

All the allylation reactions proceeded with good to excellent yields (Table 1). The yields of the oxime ester reactions are rather lower than those of the corresponding oxime ether reactions. The likely cause of this is the ability of the oxime esters to undergo elimination and tautomerisation to give enamines (Scheme 8). For example, under reaction conditions,



Scheme 8 Base catalysed elimination of oxime esters.

Table 1 Results of allylation reactions. Bn = Benzyl, Bz = Benzoyl



Oxime	R	R′	Product	Yield (%)[a]
14	Me	Bn	**21**	84
24	Me	Bz	**37**	81
30	^{t}Bu	Bn	**38**	80
31	^{t}Bu	Bz	**39**	72
34	PNB	Bn	**40**	86
35	PNB	Bz	**41**	47

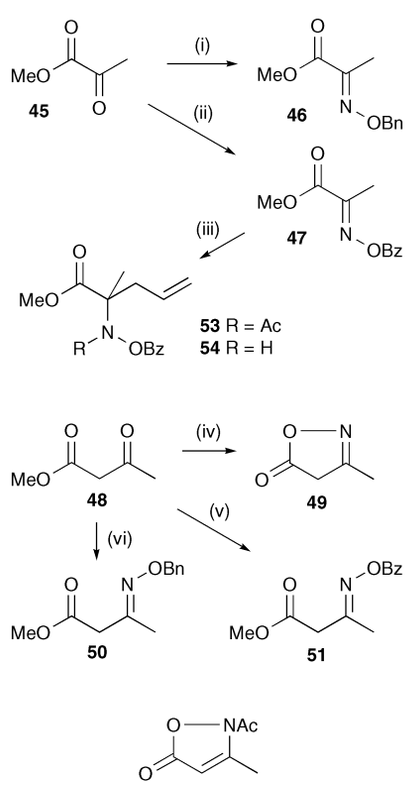
[a] Reaction conditions not optimised.

the oxime ester **24** gave the bis-acetamide **44** as a byproduct, *via* elimination of **37**. The PNB ester **41**, derived from **35**, proved particularly unstable in this respect.

Other oximes

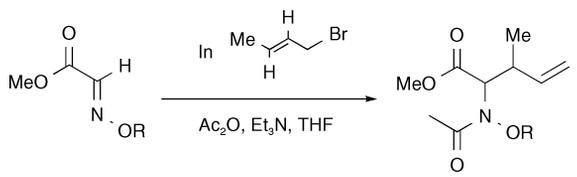
Methyl pyruvate **45** was also reacted with hydroxylamines to produce the corresponding oxime benzyl ether **46** and benzoyl ester **47**. Methyl acetoacetate **48** reacted with hydroxylamine to afford a mixture of the isoxazolone **49** and the corresponding oxime which was coupled to benzoic anhydride to give **51**. Reaction of methyl acetoacetate with *O*-benzylhydroxylamine gave the corresponding oxime ether **50**. These substrates were then reacted under the standard allylating conditions (Scheme 9).

The only ketoxime which reacted was the oxime ester **47**. The product was obtained as a mixture of the expected *N*-acetyl amide **53** (53%) and the corresponding free amine (38%) **54**. All



Scheme 9 Ketoxime ethers and esters. *Reagents and conditions*: (i) $BnONH_3Cl$, pyr, MeOH, RT, 87%; (ii) $HONH_3Cl$, pyr, MeOH, 83%, then $(PhCO)_2O$, pyr, DMAP, CH_2Cl_2, 97%; (iii) In, CH_2=$CHCH_2Br$, Ac_2O, Et_3N, THF–DMF, 53%; (iv) $HONH_3Cl$, pyr, MeOH, 51%; (v) $HONH_3Cl$, pyr, MeOH, 37% then $(PhCO)_2O$, pyr, DMAP, CH_2Cl_2, 78%; (vi) $BnONH_3Cl$, pyr, MeOH, RT, 77%.

Table 2 Addition of crotyl units

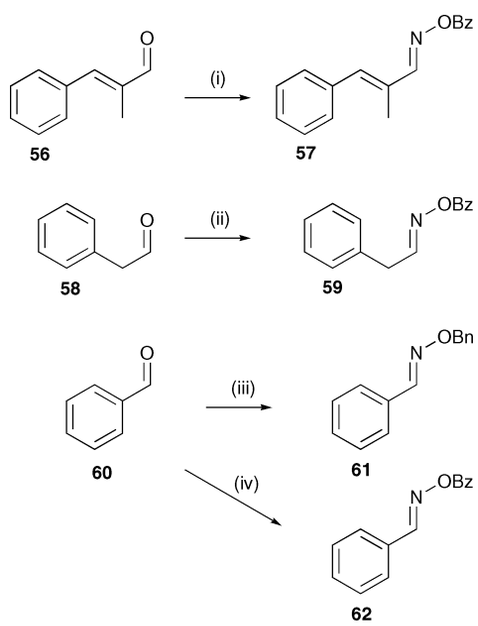


Oxime	R	Product	Yield (%)[a]	d.e.
14	Bn	**63**	77	11.8 : 1
24	Bz	**64**	75	1.3 : 1

[a] Reaction conditions not optimised.

starting material was consumed. This demonstrated that the iminyl carbons of the oxime esters were, as expected, more electrophilic than those of the analogous oxime ethers. The ketoxime ether **46** and the two acetoacetate derivatives **50** and **51** were not allylated. The isoxazolone **49** reacted with Ac_2O to give the known *N*-acetyl derivative **55**.

We also examined a range of unsaturated and aromatic aldehydes with the oxime ester derivatives as they had proven more reactive. *trans*-2-Methylcinnamaldehyde **56** was condensed with hydroxylamine hydrochloride (Scheme 10) after which the oxime was reacted with benzoic anhydride to give the conjugated aldoxime **57**, while phenylacetaldehyde **58** gave the corresponding oxime ester **59** (the acidic nature of the α-protons of phenylacetaldehyde, the corresponding oxime and oxime ester resulted in low yielding reactions). Benzaldehyde **60** was used to make the corresponding oxime ether and esters **61** and **62** in good yields. None of these compounds were allylated under the standard conditions, or in the presence of CF_3CO_2H (*vide infra*).

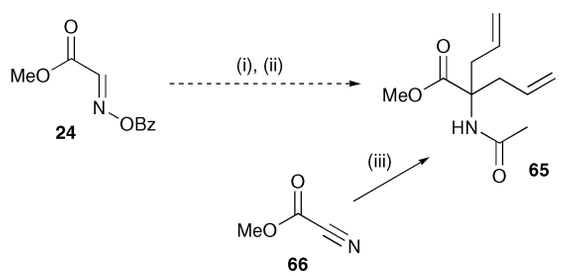


Scheme 10 Aldoxime esters and ethers. *Reagents and conditions*: (i) $HONH_3Cl$, pyr, MeOH, RT, 91% then $(PhCO)_2O$, pyr, DMAP, CH_2Cl_2, 50%; (ii) $HONH_3Cl$, pyr, MeOH, RT, 42% then $C_6H_5CO_2H$, EDCi, HOBt, CH_2Cl_2, 19%; (iii) $BnONH_3Cl$, pyr, MeOH, RT, 89%; (iv) $HONH_3Cl$, pyr, MeOH, RT, 33% then $(PhCO)_2O$, DMAP, CH_2Cl_2, 76%.

The reaction of substituted allyl bromide species was then investigated (Table 2). The use of crotyl bromide as the allylating agent did not impede the reaction with either oxime ethers or esters. Exclusive γ-addition was observed, and in the case of the oxime ethers some diastereoselectivity (11.8 : 1) was observed. In the case of the oxime esters much lower (1.3 : 1) diastereoselectivity was observed, most likely a product of the higher reactivity of the oxime esters overcoming a steric barrier in the transition state. Although crotyl bromide reacted well, we found that prenyl bromide was unreactive under our conditions.

Cyanoformates

When Et_3N was premixed with *O*-benzoyl methyl glyoxylate oxime ester **24** the reaction turned black and an exotherm was detected. The allylating suspension was decanted into the black solution whereupon another exotherm was observed. The solitary product was the bis-allylated amide **65**. This compound must have arisen *via* double addition to a nitrile formed by elimination of benzoate from **24**. To corroborate this finding commercial methyl cyanoformate **66** was subjected to a typical allylation procedure and this resulted in the same product (Scheme 11).



Scheme 11 Bis-allyl addition to methyl cyanoformate. *Reagents and conditions*: (i) Et_3N, DMF; (ii) In, allyl bromide, Ac_2O, DMF; (iii) In, allyl bromide, Ac_2O, Et_3N, DMF, 68%.

The only reported synthesis of amide **65** was by Hammer and Undheim in 4 steps with an overall yield of 46%.[15] Our method gives the same unnatural amino acid (which can be subjected to ring-closing metathesis conditions to produce conformationally restricted amino acids) in 68% yield in a single step. Other nitriles, such as acetonitrile and benzonitrile did not react under these conditions, however.

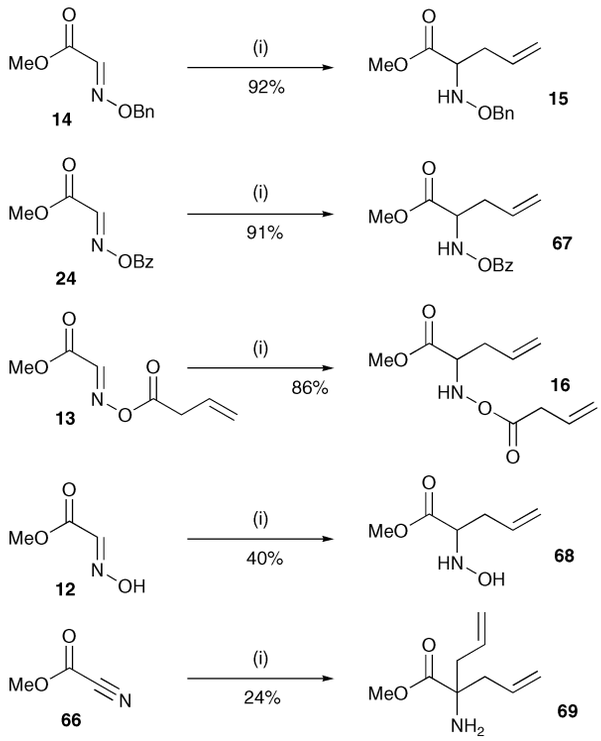
Acidic conditions

To allow synthesis of the unprotected amine the allylating reaction was carried out in the presence of one equivalent of CF_3CO_2H and the absence of Ac_2O and Et_3N. The oxime ether **14** and oxime esters **24** and **13** reacted smoothly with the allylating reagent to give the corresponding allylated products in excellent yields (Scheme 12). In contrast to the basic conditions described previously, the butenoyl oxime ester **16** did not undergo olefin isomerisation and neither oxime ester underwent elimination reactions. The *O*-benzoyl hydroxylamine **67** proved unstable, however, and degraded over time. The free oxime **12** and methyl cyanoformate **66** both underwent allyl additions, giving **68** and **69** respectively, in the acidic medium. This reinforces how weakly basic, and tolerant of functionality, the allylindium species is.

Discussion

The difficulty associated with the reaction of oximes with organometallic species has been highlighted recently. For example, Moody *et al.* have shown that while vinyllithium, generated from tetravinyltin, will add to oxime ethers, a variety of other species, including phenyllithium, vinyl Grignard, furyllithium, trimethylsilyl acetylide and cyanide (from Et_2AlCN) will not.[16] We have shown here that other species such as allylsilane also do not add to oxime ethers. In the case of oxime ethers derived from glyoxylate, and of oxime esters, the nucleophile generally attacks the ester carbonyl rather than the oxime.

In contrast to these results, allylindium reagents add smoothly, and in high yield to both oxime ethers and oxime



Scheme 12 Allylations carried out in an acidic environment. *Reagents and conditions*: (i) In, allyl bromide, TFA, THF–DMF.

esters. To some extent this mirrors the results of Hanessian who has shown that allylzinc species will also add to oxime ethers. However, the allylindium reagents described here will add smoothly to oxime esters, whereas allylzinc reagents add in lower yield. Furthermore, the allylindium reactions can be carried out under diverse conditions: in the presence of base and an acid chloride the resulting oxyamines are acylated; in the presence of acid, the oxyamines are protonated and protected from further reaction. The reaction works with allyl bromide and crotyl bromide equally well, but prenyl bromide does not add, perhaps due to adverse steric interactions. The reaction appears to rely on the presence of an ester α to the oxime. All the glyoxylate derived oximes reacted in good yield. In the case of the ketoxime derived from pyruvate, only the more reactive oxime ester reacted: it appeared that the allylindium reagent would not add to the benzyl oxime ether. Furthermore, oximes α to aromatic groups, olefins and methylene groups were unreactive.

In the presence of excess base, the oxime esters were prone to elimination to form the corresponding cyanoformates. These then underwent double allylation to form bis-allylglycine derivatives, again in good yields. Once again, only nitriles α to an ester reacted.

Overall the indium mediated allylation of glyoxylate derived oxime ethers and esters provides a rapid and convenient route to protected oxyaminoesters which we are investigating as substrates for ring closing metathesis. The facile double addition to cyanoformates provides rapid access to bis-allylglycine derivatives which are difficult to make by other routes.

Experimental

General

Commercially available reagents and solvents of ACS grade were used throughout without prior purification unless otherwise stated. Petrol refers to petroleum ethers 40/60. All anhydrous solvents were purchased from Fluka and were transferred under dried N_2.

NMR spectra were obtained using JEOL Δ-250, Δ-270, λ-300 and Δ-400 spectrometers operating at 270, 300 and 400 MHz (^{1}H) and 68, 76 and 101 MHz (^{13}C) respectively. Chemical shifts are quoted in ppm relative to TMS. IR spectra were obtained using a Perkin-Elmer FT-IR spectrometer. Mass spectra were obtained in the indicated mode using a VG analytical autospec instrument. Flash chromatography was performed using the method of Still *et al.*[17] or using an automated Biotage system. TLC analysis was performed using Merck glass backed 0.2 mm silica plates developed using the indicated solvent and visualised with UV and/or potassium permanganate.

Procedure A. General procedure for preparation of *O*-benzyl oxime ethers not containing a methyl ester

O-Benzylhydroxylamine hydrochloride (1.3 eq.) was added to the glyoxylate (1 eq.) in EtOH followed by pyridine (1.1 eq.). The reaction was heated to reflux for 40 min then allowed to cool and the solvent removed *in vacuo*. The residue was then dissolved in CH_2Cl_2 and washed with H_2O and the aqueous layer was further extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and the solvent was evaporated. Purification of the product was carried out by chromatography eluting with petrol–EtOAc.

Procedure B. General procedure for allylation of oxime ethers

In powder (100 mesh, 276 mg, 2.4 mmol) was weighed into a Wheaton vial. DMF (0.7 mL) was added followed by allyl bromide (310 μL, 435 mg, 3.6 mmol). A triangular stirrer bar was then dropped in and the mixture stirred vigorously. Within a few minutes an exotherm could be felt and the mixture turned into a very fine suspension that was dark green/black in colour. After 40 min the allylating mixture was pipetted into a solution of oxime derivative (2.0 mmol) and freshly distilled Ac_2O (4 mL) in anhydrous THF (14 mL) under a N_2 atmosphere. The Wheaton vial was washed out with dry THF (1 mL). After 2 h Et_3N (1 mL) was added and the reaction was left to stir overnight. The reaction was quenched with NH_4Cl (aq) (30 mL) and extracted with Et_2O (3 × 40 mL) which was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using petrol–EtOAc.

Procedure C. General procedure for allylation of oxime esters

In powder (100 mesh, 276 mg, 2.4 mmol) was weighed into a Wheaton vial. DMF (0.7 mL) was added followed by allyl bromide (310 μL, 435 mg, 3.6 mmol). A triangular stirrer bar was then dropped in and the mixture stirred vigorously. Within a few minutes an exotherm could be felt and the mixture turned into a very fine suspension that was dark green/black in colour. After 40 min the allylating mixture was pipetted into a solution of oxime derivative (2.0 mmol) and freshly distilled Ac_2O (4 mL) in anhydrous THF (14 mL) under a N_2 atmosphere. The Wheaton vial was washed out with dry THF (1 mL). After 2 h Et_3N (0.2 mL) was added and TLC monitoring began (if any of the less polar amine intermediate remained Et_3N was added in no more than 0.1 mL portions with a minimum of 1 h between additions). When complete, the reaction was quenched with NH_4Cl (aq) (30 mL) and extracted with Et_2O (3 × 40 mL) which was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using petrol–EtOAc.

Procedure D. General procedure for allylation of oxime ethers, esters and cyanoformates under acidic conditions

The oxime/nitrile derivative (2 mmol) was stirred in THF (14 mL) with TFA (2 mmol). In parallel, indium powder (100 mesh, 2.4 mmol for oxime/4.4 mmol for nitrile) was weighed into a Wheaton vial. DMF (0.7 mL for oxime/1.5 mL for nitrile) was added followed by allyl bromide (3.4 mmol for oxime/6.6 mmol for nitrile). A triangular stirrer bar was then

dropped in and the mixture stirred vigorously. Within a few minutes an exotherm could be felt and the mixture turned into a very fine suspension that was dark green/black in colour. After 40 min the allylating mixture was pipetted into the oxime/nitrile solution and was washed out with DMF (0.4 mL). The reaction was left to stir overnight then quenched with $NaHCO_3$ (30 mL) and Et_2O (40 mL) was added. The organics were collected and the aqueous layer extracted with Et_2O (3 × 40 mL). All organics were combined, dried ($MgSO_4$), filtered and concentrated.

Methyl glyoxylate oxime 12[18]

$NaHCO_3$ (1.924 g, 22.3 mmol) was dissolved in H_2O (15 mL) and hydroxylamine hydrochloride (1.73 g, 24.9 mmol) was slowly added with stirring. Stirring continued until effervescence had subsided, then methyl glyoxylate **11**[19] (2.00 g, 22.7 mmol) was added. The reaction was stirred for a further 7 h before being extracted with CH_2Cl_2 (3 × 25 mL). The aqueous layer was returned to the flask and stirring continued overnight. The solution was extracted again with CH_2Cl_2 (3 × 25 mL) and the organic layers were combined and dried (Na_2SO_4) and solvent removed *in vacuo* to give methyl glyoxylate oxime **12** as a colourless solid (1.21 g, 11.8 mmol, 52%). (7 : 3 Petrol–EtOAc, R_F 0.25); mp 56–58 °C (lit.[18] 48–51 °C); ν_{max} (solid)/cm^{-1} 3203 (OH), 1722 (CO); δ_H (270 MHz; $CDCl_3$) 9.09 (1H, s, OH), 7.58 (1H, s, CH), 3.87 (3H, s, OMe); δ_C (101 MHz; $CDCl_3$) 162.2 (CO), 142.1 (CN), 52.6 (OMe).

O-But-3-enoyl methyl glyoxylate oxime ester 13

Vinylacetic acid (1.21 mL, 1.18 g, 11.8 mmol) and EDCi (2.70 g, 14.1 mmol) were premixed in THF–Et_2O (1 : 1, 45 mL) with HOBt (cat.) for 20 min. Methyl glyoxylate oxime **12** (1.21 g, 11.7 mmol) was then added to the suspension and the reaction left to stir for 4 h. The reaction was diluted with EtOAc (25 mL), washed with H_2O (2 × 30 mL) and $NaHCO_3$ (aq. 40 mL), dried ($MgSO_4$), filtered and concentrated. The yellow oil was purified by column chromatography using 88 : 12 petrol–EtOAc (7 : 3 petrol–EtOAc, R_F 0.36) as the running solvent which provided *O-but-3-enoyl methyl glyoxylate oxime ester* **13** as a colourless oil (890 mg, 5.2 mmol, 44%). ν_{max} (neat)/cm^{-1} 3086 (CH), 2959 (CH), 1779 (CO), 1733 (CO); δ_H (400 MHz; $CDCl_3$) 7.78 (1H, s, NCH), 5.95 (1H, ddt, *J* 17.2, 10.3, 7, CH=), 5.26 (2H, m, $=CH_2$), 3.92 (3H, s, OMe), 3.29 (2H, dt, *J* 7.0, 1.5, $COCH_2$); δ_C (101 MHz; $CDCl_3$) 167.8 (CO), 161.4 (CO), 147.4 (CN), 128.6 (CH=), 119.9 (=CH_2), 53.1 (OMe), 37.3 (CH_2); *m/z* (FAB) 343 [$(M_2H)^+$, (27)], 194 [$(MNa)^+$, (34)], 172 [$(MH)^+$, (99%)]; (Found C, 48.99; H, 5.10; N, 8.37. $C_7H_9NO_4$ requires C, 49.12; H, 5.30; N, 8.18%).

13 was also synthesised by pretreatment of vinylacetic acid (2.1 mL, 2.06 g, 20.1 mmol) with EDCi (1.97 g, 10 mmol) in CH_2Cl_2 (18 mL) for 60 min at RT to form the anhydride *in situ*. The reaction ws diluted with CH_2Cl_2 (10 mL) and washed with water (20 mL) and satd. aqueous $NaHCO_3$ (15 mL). The organics were collected, dried ($MgSO_4$) and concentrated *in vacuo* and the crude anhydride was added to a solution of **12** (524 mg, 5.1 mmol) in CH_2Cl_2 (18 mL) and pyridine (565 μL, 554 mg, 7.0 mmol). The reaction was stirred overnight and worked-up and purified as before to afford **13** (559 mg, 3.3 mmol, 64%).

O-Benzyl methyl glyoxylate oxime ether 14[20]

To a solution of *O*-benzylhydroxylamine hydrochloride (4.90 g, 30.6 mmol) and pyridine (1.99 mL, 1.942 g, 24.5 mmol) in MeOH (22 mL) was added methyl glyoxylate **11** (1.80 g, 20.5 mmol) and the reaction refluxed for 3.5 h. The reaction was cooled and the MeOH removed *in vacuo*. The residue was then dissolved in CH_2Cl_2 (45 mL) and H_2O (30 mL) and the organic layer collected. The aqueous layer was extracted with CH_2Cl_2 (2 × 45 mL), the organics were combined and dried (Na_2SO_4) and the solvent was evaporated. The crude oil was purified by passing the oil through a plug of silica using 9 : 1 petrol–EtOAc as the solvent (7 : 3 petrol–EtOAc, R_F 0.50) to give the title compound **14** as a pale yellow oil (3.155 g, 16.3 mmol, 80%). δ_H (400 MHz; $CDCl_3$) 7.56 (1H, s, NCH), 7.38 (5H, m, 5 × ArH), 5.30, (2H, s, $PhCH_2$), 3.86 (3H, s, OMe); δ_C (68 MHz; $CDCl_3$) 162.4 (CO), 141.0 (CN), 136.0 (Ar*C*CH_2), 128.6 (4 × ArC), 78.2 ($PhCH_2$), 52.5 (OMe); *m/z* (CI) 194 [$(MH)^+$, (32%)], 91 [$PhCH_2^+$, (100)].

Methyl 2-[benzyloxy-amino]-pent-4-enoate 15

Using **14** (378 mg, 1.96 mmol) and general procedure B yielded a colourless oil (434 mg, 1.8 mmol, 92%). ν_{max} (neat)/cm^{-1} 3261.8 (NH), 3032 (CH), 2953 (CH), 1739 (CO); δ_H (400 MHz; $CDCl_3$) 7.33 (5 H, s, 5 × ArH), 5.95 (1 H, brs, NH), 5.70 (1 H, m, CH=), 5.10 (2 H, m, $=CH_2$), 4.71 (2 H, s, $PhCH_2$), 3.74 (3 H, s, OMe), 3.68 (1 H, t, *J* 6.8, COCH), 2.34 (2 H, m, $COCHCH_2$); δ_C (101 MHz; $CDCl_3$) 174.6 (CO), 138.9 (Ar*C*C), 134.3 (=CH), 129.6 (2 × ArCH), 129.4 (2 × ArCH), 128.9 (ArCH), 119.1 (=CH_2), 77.4 ($PhCH_2$), 64.4 (COCH), 53.0 (OMe), 35.0 (CH*C*H_2CH); *m/z* (CI) 236 [$(MH)^+$, (64%)]; HRMS (CI) calc. $(MH)^+$ 236.1287 found 236.1284.

Methyl 2-[but-3-enoyloxy-amino]-pent-4-enoate 16

In powder (100 mesh, 257 mg, 2.2 mmol) was weighed into a Wheaton vial. THF (1.0 mL) was added, followed by allyl bromide (300 μL, 419 mg, 3.5 mmol). A triangular stirrer bar was then dropped in and the mixture stirred vigorously. Within a few minutes an exotherm could be felt and the mixture turned into a very fine suspension that was dark green/black in colour. After 1.5 h *O*-but-3-enoyl methyl glyoxylate oxime ester **13** (189 mg, 1.1 mmol) was added. The reaction was stirred overnight before being quenched with NH_4Cl (aq) (25 mL) and extracted with Et_2O (3 × 40 mL) which was dried ($MgSO_4$), filtered and concentrated. Purity was achieved through flash chromatography eluting with 9 : 1 petrol–EtOAc (7 : 3 petrol–EtOAc, R_F 0.55) to give *methyl 2-[but-3-enoyloxy-amino]-pent-4-enoate* (133 mg, 0.6 mmol, 56%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3230 (NH), 3083 (CH), 2984 (CH), 1740 (CO); δ_H (400 MHz; $CDCl_3$) 7.68 (1 H, d, *J* 9.2, NH), 5.72–5.89 (2 H, m, 2 × CH=), 5.15 (4 H, m, 2 × $=CH_2$), 3.85 (1 H, m, COCH), 3.75 (3 H, s, OMe), 3.08 (2 H, m, $COCH_2$), 2.49 (2 H, m, $COCHCH_2$); δ_C (101 MHz; $CDCl_3$) 172.1 (CO), 170.3 (CO), 132.2 (CH=), 129.2 (CH=), 119.3 (=CH_2), 119.0 (=CH_2), 62.7 (COCH), 52.2 (OMe), 37.3 ($COCH_2$), 33.8 ($COCHCH_2$); *m/z* (FAB) 214 [$(MH)^+$, (100%)], 236 [$(MNa)^+$, (50)], 427 $(M_2H)^+$, (6)].

16 was also synthesised using **13** (342 mg, 2.0 mmol) and Procedure D to afford **16** (362 mg, 1.72 mmol, 84%) after chromatography eluting with 9 : 1 petrol–EtOAc.

p-Nitrobenzyl 2-hydroxypent-4-enoate 18

p-Nitrobenzyl glyoxylate (2.04 g, 9.8 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) and the reaction vessel was cooled to 0 °C. Boron trifluoride diethyl etherate (1.80 mL, 2.03 g, 14.3 mmol) was then added and allyltrimethylsilane (2.32 mL, 1.67 g, 14.6 mmol) was added to the solution 30 min later. After 1 h the reaction was warmed to RT and left to stir overnight. The reaction was washed with water (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated. The orange oil was purified by flash chromatography, eluting with 3 : 2 petrol–EtOAc (1 : 1 petrol–EtOAc, R_F 0.34), to give *p-nitrobenzyl 2-hydroxypent-4-enoate* as an orange oil (1.91 g, 7.6 mmol, 78%). ν_{max} (film)/cm^{-1} 3492 (OH), 3090 (CH), 2950 (CH), 1738 (CO), 1518 (NO_2), 1350 (NO_2); δ_H (270 MHz; $CDCl_3$) 8.24 (2 H, d, *J* 8.9, 2 × ArH), 7.57 (2 H, d, *J* 8.9, 2 × ArH), 5.79 (1 H, m, CH=), 5.3 (2 H, d, *J* 1.7, $PhCH_2$), 5.13 (2 H, m, $=CH_2$), 4.37 (1 H, td, *J* 6.3, 4.6, COCH), 2.72 (1 H, d, *J* 6.3, OH), 2.55 (2H, m, $CHCH_2CH$); δ_C (101 MHz; $CDCl_3$) 174.0 (CO), 147.6 (ArCN), 142.2 (Ar*C*C), 132.0

(CH=), 128.7 (2 × ArCH), 123.9 (2 × ArCH), 119.2 (=CH_2), 70.0 (COCH), 65.8 ($PhCH_2$), 38.7 (CH_2); *m/z* (CI) 252 [$(MH)^+$, (24%)], 206 [$(M-HO_2CCH(OH)CH_2CHCH_2)^+$, (100)]; HRMS (CI) calc [$(MH)^+$] 252.0872 found 252.0874.

Methyl 2-[acetyl-benzyloxy-amino]-pent-4-enoate 21

Using **14** (391 mg, 2.02 mmol), Procedure B and 9 : 1 Petrol–EtOAc as the solvent during chromatography (7 : 3 petrol–EtOAc, R_F 0.29) gave *methyl 2-[acetyl-benzyloxy-amino]-pent-4-enoate* **21** as a pale yellow oil (465 mg, 1.7 mmol, 84%). ν_{max} (neat)/cm^{-1} 3067 (CH), 2982 (CH), 1742 (CO), 1677 (CO); δ_H (270 MHz; $CDCl_3$) 7.38 (5H, s, 5 × ArH), 5.81 (1H, ddt, *J* 6.9, 10.2, 16.8, CH=), 5.15 (2H, m, =CH_2), 4.99 (1H, m, COCH), 4.98 (1H, d, *J* 10.6, PhCH*H*), 4.90 (1H, d, *J* 10.2, PhC*H*H), 3.75 (3H, s, OMe), 2.78 (2H, m, CH_2), 2.15 (3H, s, Me); δ_C (101 MHz; $CDCl_3$) 174.4 (CO), 170.4 (CO), 134.7 (Ar*C*C), 133.9 (CH=), 129.0 (2 × ArCH), 128.9 (ArCH), 128.7 (2 × ArCH), 118.2 (=CH_2), 78.3 ($PhCH_2$), 60.7 (CO*C*H), 52.4 (OMe), 32.7 (CH_2), 20.7 (Me); *m/z* (CI) 278 [$(MH)^+$, (59%)], 236 [$(MH_2-Ac)^+$, (87%)], 91 [$PhCH_2^+$, (100)]; HRMS (CI) calc. $(MH)^+$ 278.1392 found 278.1396.

Methyl 2-[acetyl-but-3′-enoyloxy-amino]-pent-4-enoate 22

In powder (100 mesh, 252 mg, 2.2 mmol) was weighed into a Wheaton vial. DMF (0.8 mL) was added, followed by allyl bromide (290 μL, 411 mg, 3.4 mmol). A triangular stirrer bar was then dropped in and the mixture stirred vigorously. Within a few minutes an exotherm could be felt and the mixture turned into a very fine suspension that was dark green/black in colour. After 40 min a solution of *O*-but-3-enoyl methyl glyoxylate oxime ester **13** (344 mg, 2.0 mmol) and freshly distilled Ac_2O (570 μL) in DMF (1.5 mL) were added to the allylating mixture. After 2.5 h the reaction was quenched with NH_4Cl (aq) (25 mL) and extracted with Et_2O (3 × 40 mL) which was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography eluting with petrol–EtOAc 4 : 1 (7 : 3 petrol–EtOAc, R_F 0.34) to yield *methyl 2-[acetyl-but-3′-enoyloxy-amino]-pent-4-enoate* **22** as a colourless oil (291 mg, 1.1 mmol, 57%). ν_{max} (neat)/cm^{-1} 3082 (CH), 2956 (CH), 1791 (CO), 1744 (CO), 1688 (CO); δ_H (270 MHz; $CDCl_3$) 5.91 (1H, ddt, *J* 16.8, 9.9, 7.0, CH=), 5.78 (1H, m, CH=), 5.07–5.33 (5H, m, 2 × =CH_2 and COC*H*CH_2), 3.74 (3H, s, OMe), 3.23 (2H, d, *J* 7.0, $COCH_2$), 2.57 (2H, m, CH_2), 2.05 (3H, s, COMe); δ_C (101 MHz; $CDCl_3$) 172.9 (CO), 169.3 (CO), 169.0 (CO), 133.0 (CH=), 128.1 (CH=), 120.3 (=CH_2), 118.4 (=CH_2), 59.3 (COCH), 52.5 (OMe), 36.6 ($COCH_2$), 32.7 (CH_2), 20.5 (Me); *m/z* (CI) 256 [$(MH)^+$, (16%)], 214 [$(MH_2-Ac)^+$, (100)]; HRMS (CI) calc. $(MH)^+$ 256.1185 found 256.1185.

***O*-Benzoyl methyl glyoxylate oxime ester 24**

Pyridine (2.15 g, 2.20 mL, 27.2 mmol) and benzoic anhydride (6.69 g, 29.6 mmol) were added to a solution of the oxime **12** (2.37 g, 26.9 mmol) in CH_2Cl_2 (75 mL). 4-Dimethylamino-pyridine (10 mol%) was then added and the reaction left to stir until complete by TLC. CH_2Cl_2 (30 mL) was added and the solution washed with H_2O (2 × 50 mL) then 0.5 M HCl (50 mL). The organics were collected, dried (Na_2SO_4) and purified twice by flash chromatography (7 : 3 petrol–EtOAc, R_F 0.33) to yield *O-benzoyl methyl glyoxylate oxime ester* **24** as a colourless solid (3.45 g, 16.7 mmol, 62%). mp 73–75 °C; ν_{max} (solid)/cm^{-1} 3062 (CH), 2955 (CH), 1729 (CO); δ_H (400 MHz; $CDCl_3$) 8.11 (2H, m, 2 × ArH), 7.97 (1 H, s, NCH), 7.65 (1H, m, ArH), 7.51 (2H, t, *J* 7.7, 2 × ArH), 3.95 (3H, s, OMe); δ_C (101 MHz; $CDCl_3$) 162.7 (CO), 161.5 (CO), 147.9 (NCH), 134.1 (ArCH), 130.1 (2 × ArCH), 128.8 (2 × ArCH), 127.5 (Ar*C*C), 53.1 (OMe); *m/z* (FAB) 230 [$(MNa)^+$, (25)], 207 [$(M)^+$, (27%)]; (Found C, 58.35; H, 4.33; N, 6.86. $C_{10}H_9NO_4$ requires C, 57.97; H, 4.38; N, 6.76%).

Di-*tert*-butyl fumarate 26[21]

tert-Butyl alcohol (10.0 mL, 105 mmol) was added under dry N_2 to a dry flask and the vessel was cooled to 0 °C. ^{n}BuLi (2.5 M, 24 mL, 60 mmol) was added over 10 min and the suspension stirred for 40 min at 0 °C. A solution of fumaryl chloride **25** (6.12 mL, 60 mmol) in anhydrous Et_2O (20 mL) was added through a dropping funnel over 40 min, the temperature of the reaction was maintained at room temperature. After 4 h the reaction was quenched with water (20 mL) and the organics were collected then washed with $NaHCO_3$ (aq., 2 × 25 mL), brine (2 × 20 mL) and dried ($MgSO_4$). The brown solution was filtered, concentrated and recrystallised from hexane to afford pale brown needles. These were dissolved in 95 : 5, petrol–EtOAc and passed through a plug of silica to yield **26** as a colourless solid. The recrystallisation mother liquors were purified by chromatography 96 : 4, petrol–EtOAc (9 : 1 petrol–EtOAc, R_F 0.55) to give the title compound as a colourless solid which was combined with the rest of the material (5.40 g, 23.7 mmol, 39%). mp softened at 67 °C, melted at 68–70 °C (lit.[21] 71–72 °C); ν_{max} (solid)/cm^{-1} 3006 (CH), 2939 (CH), 1704 (CO); δ_H (400 MHz; $CDCl_3$) 6.67 (2H, s, 2 × CH), 1.50 (18H, s, 6 × CH_3); δ_C (101 MHz; $CDCl_3$) 164.5 (2 × CO), 134.6 (2 × CH), 81.7 (2 × *C*$(CH_3)_3$), 28.0 (6 × CH_3); *m/z* (FAB) 251 [$(MNa)^+$, (7)], 229 [$(MH)^+$, (22%)], 173 [$(MH_2-C(CH_3)_3)^+$, (100)].

Di-*p*-nitrobenzyl tartrate 28[22]

Tartaric acid **27** (3.15 g, 21 mmol) was dissolved in DMF (40 mL) then cooled to 0 °C. Triethylamine (7.0 mL) was added over 5 min. After 30 min of stirring, 4-nitrobenzyl bromide (10.00 g, 46.3 mmol) in DMF (30 mL) was added dropwise at 0 °C. The solution was allowed to warm to RT and was then stirred overnight. The reaction was decanted into ice/water (*ca.* 300 mL) and stirred for 30 min before the white precipitate was filtered off under vacuum, washed with H_2O (4 × 30 mL) and air-dried. The colourless solid was then slurried in EtOH (270 mL) and after 16 h the suspension was filtered, air-dried then dried under reduced pressure to yield the title compound as a colourless solid (6.96 g, 16.6 mmol, 79%). mp softened at 162 °C, melted at 164–165 °C (lit.[22] 163–164 °C); ν_{max} (solid)/cm^{-1} 3472 (OH), 3089 (CH), 2939 (CH), 1712 (CO); δ_H (270 MHz; DMSO) 8.20 (2 H, d, *J* 8.6, 4 × ArH), 7.66 (2 H, d, *J* 8.6, 4 × ArH), 5.82 (2 H, m, 2 × CH), 5.32 (4 H, s, 2 × CH_2), 4.65 (2 H, m, 2 × OH); δ_C (68 MHz; DMSO) 171.9 (2 × CO), 147.9 (2 × ArCN), 144.0 (2 × Ar*C*C), 129.4 (4 × ArCH), 124.5 (4 × ArCH), 73.6 (2 × CH), 65.8 (2 × CH_2); (Found C, 51.43; H, 3.54; N, 6.49. $C_{18}H_{16}N_2O_{10}$ requires C, 51.43; H, 3.84; N, 6.66%).

***tert*-Butyl glyoxylate 29**[22]

Di-*tert*-butyl fumarate **26** (1.50 g, 6.6 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C. O_3 was bubbled through until an excess was observed then the reaction was stirred for another 30 min. Excess ozone was removed by passing O_2 through the solution. Dimethyl sulfide (0.50 mL, 6.8 mmol) was added and the reaction was warmed to RT. After 2 h the solution was washed with brine (1 × 35 mL), dried (Na_2SO_4) and the solvent evaporated. The crude product was applied to a silica column and the product eluted with 3 : 2 petrol–EtOAc to afford *tert*-butyl glyoxylate **29** as a colourless oil and as a mixture of the aldehyde and hydrate (948 mg, 6.5 mmol, 50%). ν_{max} (neat)/cm^{-1} 3452 (OH), 2981 (CH), 1733 (CO); δ_H (270 MHz; $CDCl_3$) 9.3 (0.5 H, s, CH), 5.13 (0.5 H, m, CH), 1.57 (9 H, m, 3 × CH_3); *m/z* (CI) 131 [$(MH)^+$, (3%)], 75 [$(MH_2-C(CH_3)_3)^+$, (7)], 57 [$(^tBu)^+$, (100)].

***O*-Benzyl *tert*-butyl glyoxylate oxime ether 30**[23]

Using **29** (600 mg, 4.6 mmol), procedure A and 9 : 1 petrol–EtOAc (9 : 1 petrol–EtOAc, R_F 0.45) as the running solvent

during chromatography gave *O*-benzyl *tert*-butyl glyoxylate oxime ether **30** as a pale yellow oil (748 mg, 3.2 mmol, 69%). δ_H (270 MHz; $CDCl_3$) 7.46 (1 H, s, CH), 7.37 (5 H, s, 5 × ArH), 5.27 (2 H, s, CH_2), 1.53 (9 H, s, 3 × CH_3); δ_C (101 MHz; $CDCl_3$) 161.1 (CO), 142.5 (CN), 136.1 (Ar*C*C), 128.6 (5 × ArCH), 82.7 ($C(CH_3)_3$), 77.9 (CH_2), 28.1 (3 × CH_3); *m*/*z* (CI) 180 [$(MH_2-C(CH_3)_3)^+$, (30%)], 57 [$(^tBu)^+$, (100)].

O-Benzoyl *tert*-butyl glyoxylate oxime ester 31

To a solution of **29** (948 mg, 7.3 mmol) in MeOH (12 mL) was added hydroxylamine hydrochloride (585 mg, 8.5 mmol) then pyridine (580 μL, 565 mg, 7.1 mmol). The reaction was stirred (with heating, if neccessary) after which the MeOH was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (30 mL) and water (30 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). All the organics were combined, dried (Na_2SO_4), filtered then concentrated and the resultant material purified by flash chromatography (9 : 1 petrol–EtOAc) to yield the oxime as a colourless oil (787 mg, 5.4 mmol, 74%). ν_{max} (neat)/cm^{-1} 3317 (OH), 2937 (CH), 1714 (CO); δ_H (270 MHz; $CDCl_3$) 8.69 (1 H, s, OH), 7.47 (1 H, s, CH), 1.54 (9 H, s, $(CH_3)_3$); δ_C (68 MHz; $CDCl_3$) 161.2 (CO), 143.1 (CN), 83.1 ($C(CH_3)_3$), 28.0 (3 × CH_3).

Pyridine (430 μL, 421 mg, 5.3 mmol) and benzoic anhydride (1.22 g, 5.4 mmol) were added to a solution of the oxime (787 mg, 5.4 mmol) in CH_2Cl_2 (15 mL). 4-Dimethylaminopyridine (10 mol%) was then added and the reaction left to stir until complete by TLC. CH_2Cl_2 was added and the solution washed with H_2O (2 × 25 mL) then 0.5 M HCl (30 mL). The organics were collected and dried (Na_2SO_4). The product was purified by flash chromatography using 9 : 1 petrol–EtOAc as the running solvent (9 : 1 petrol–EtOAc, R_F 0.22) and the colourless solid was then recrystallised from EtOAc–petrol to give *O-benzoyl tert-butyl glyoxylate oxime ester* **31** as colourless needles (798 mg, 3.2 mmol, 59%). mp 107 °C; ν_{max} (solid)/cm^{-1} 3026 (CH), 2987 (CH), 1743 (CO), 1716 (CO); δ_H (400 MHz; $CDCl_3$) 8.08 (2 H, m, 2 × ArH), 7.87 (1 H, s, CH), 7.63 (1 H, m, 1 × ArH), 7.49 (2 H, t, *J* 7.8, 2 × ArH), 1.58 (9 H, s, 3 × CH_3); δ_C (101 MHz; $CDCl_3$) 163.0 (CO), 159.9 (CO), 149.8 (CN), 133.9 (ArCH), 130.0 (2 × ArCH), 128.7 (2 × ArCH), 127.8 (Ar*C*C), 84.4 ($C(CH_3)_3$), 28.0 (3 × CH_3); *m*/*z* (FAB) 521 [$(M_2Na)^+$, (26%)], 499 [$(MH_2)^+$, (8)], 272 [$(MNa)^+$, (14)], 250 [$(MH)^+$, (20)], 194 [$(MH_2-C(CH_3)_3)^+$, (76)]; HRMS (CI) calc. $(MH_2-C(CH_3)_3)^+$ 194.0453 found 194.0452.

p-Nitrobenzyl glyoxylate hydrate 32[22]

Di-*p*-nitrobenzyl tartrate **28** (6.94 g, 16.5 mmol) was suspended in THF (70 mL) and stirred for 5 min. Periodic acid (4.52 g, 19.8 mmol) was added over 10 min and after 1.5 h the reaction was filtered. The solid inorganics were washed with THF (2 × 10 mL), the organics were combined and then water (150 mL) was poured into the flask which was subsequently left for 3 days at 4 °C. The precipitated crystals were filtered off under vacuum, washed with H_2O (2 × 50 mL) and hexane (2 × 50 mL) then dried to afford *p*-nitrobenzyl glyoxylate hydrate **32** as very pale yellow plates (4.70 g, 20.7 mmol, 63%). mp softened at 96 °C, melted at 103–105 °C (lit.[22] 100–102 °C); δ_H (270 MHz; DMSO) 8.23 (2 H, d, *J* 8.9, 2 × ArH), 7.63 (2 H, d, *J* 8.9, 2 × ArH), 6.81 (2 H, d, *J* 7.6, 2 × OH), 5.28 (2 H, s, CH_2), 5.12 (1 H, t, *J* 7.6, CH); δ_C (101 MHz; DMSO) 170.7 (CO), 147.7 (ArCN), 144.3 (ArCH), 129.0 (2 × ArCH), 124.0 (2 × ArCH), 87.5 (CH), 64.8 (CH_2); *m*/*z* (CI) 210 [$(MH-H_2O)^+$, (100%)], 136 [$(M-HO_2CCH(OH)_2)^+$, (95)]; (Found C, 47.56; H, 3.86; N, 6.05. $C_9H_9NO_6$ requires C, 47.58; H, 3.99; N, 6.17%).

O-Benzyl *p*-nitrobenzyl glyoxylate oxime ether 34

p-Nitrobenzyl glyoxylate hydrate **32** (2.54 g, 11.2 mmol) was dehydrated under Dean–Stark conditions before oxime formation. Using aldehyde **33** (1.21 g, 5.81 mmol), procedure A and 82 : 18 petrol–EtOAc as the solvent during flash chromatography (4 : 1 petrol–EtOAc, R_F 0.30) gave *O-benzyl p-nitrobenzyl glyoxylate oxime ether* **34** as a pale yellow solid (1.57 g, 5.0 mmol, 86%). ν_{max} (solid)/cm^{-1} 3081 (CH), 2953 (CH), 1720 (CO), 1514 (NO_2), 1348 (NO_2); δ_H (300 MHz; $CDCl_3$) 8.23 (2H, d, *J* 9, 2 × ArH), 7.60 (1H, s, NCH), 7.55 (2H, d, *J* 9, 2 × ArH), 7.37 (5H, s, 5 × ArH), 5.37 (2H, s, $PhCH_2$), 5.31 (2H, s, $PhCH_2$); δ_C (76 MHz; $CDCl_3$) 161.5 (CO), 147.9 ($ArCNO_2$), 142.3 (Ar*C*C), 140.3 (HCN), 135.7 (Ar*C*C), 128.6 (5 × ArCH + 2 × ArCH), 123.8 (2 × ArCH), 78.4 ($PhCH_2$), 65.5 ($PhCH_2$); *m*/*z* (CI) 315 [$(MH)^+$, (34%)], 91 [$PhCH_2^+$, (100)]; HRMS (CI) calc. $(MH)^+$ 315.0981 found 315.0973.

O-Benzoyl *p*-nitrobenzyl glyoxylate oxime ester 35

p-Nitrobenzyl glyoxylate hydrate **32** (2.54 g, 11.2 mmol) was dehydrated under Dean–Stark conditions before oxime formation. To a solution of the carbonyl compound **33** in MeOH (25 mL) was added hydroxylamine hydrochloride (1.01 g, 14.5 mmol) then pyridine (1.0 mL, 978 mg, 12.4 mmol). The reaction was heated to reflux for 40 min after which the MeOH was removed *in vacuo* and the residue dissolved in EtOAc (30 mL) and water (30 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 × 30 mL). All the organics were combined, dried ($MgSO_4$), filtered then concentrated. The residue was recrystallised from EtOAc–Petrol to afford *p-nitrobenzyl glyoxylate oxime* as pale yellow plates (2.03 g, 9.1 mmol, 81%). mp softened at 150 °C melted at 156–157 °C; ν_{max} (solid)/cm^{-1} 3272 (OH), 3020 (CH), 1713 (CO); δ_H (400 MHz; DMSO) 8.25 (2 H, d, *J* 8.8, 2 × ArH), 7.67 (3 H, m, 2 × ArCH + CH), 5.39 (2 H, s, CH_2); δ_C (101 MHz; $CDCl_3$) 162.5 (CO), 147.8 (ArCN), 144.0 (Ar*C*C), 141.2 (CN), 129.2 (2 × ArCH), 124.1 (2 × ArCH), 65.4 (CH_2); *m*/*z* (CI) 225 [$(MH)^+$, (82%)], 136 [$O_2N(C_6H_4)CH_2^+$, (100)]; HRMS (CI) calc. $(MH)^+$ 225.0511 found 225.0516; (Found C, 48.30; H, 3.45; N, 12.16. $C_9H_8N_2O_5$ requires C, 48.22; H, 3.60; N, 12.50%).

p-Nitrobenzyl glyoxylate oxime (244 mg, 1.0 mmol) was dissolved in MeCN (10 mL) to which benzoic acid (145 mg, 1.2 mmol), EDCi (246 mg, 1.3 mmol) and HOBt (catalytic amount) were added. After 1.5 h the reaction was diluted with EtOAc (30 mL) and the organics were washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and concentrated. The crude product was recrystallised from EtOAc–petrol to give *O-benzoyl p-nitrobenzyl glyoxylate oxime ester* **35** as pale yellow plates (236 mg, 0.7 mmol, 65%). mp 121–124 °C; ν_{max} (solid)/cm^{-1} 3077 (CH), 1748 (CO), 1718 (CO); δ_H (400 MHz; $CDCl_3$) 8.26 (2 H, d, *J* 8.8, 2 × ArH), 8.10 (2 H, m, 2 × ArH), 8.01 (1 H, s, CHN), 7.66 (1 H, m, ArH), 7.62 (2 H, d, *J* 8.8, 2 × ArH), 7.51 (2 H, t, *J* 7.8, 2 × ArH), 5.47 (2 H, s, CH_2); δ_C (101 MHz; $CDCl_3$) 162.6 (CO), 160.7 (CO), 148.2 (ArCN), 147.6 (CN), 141.7 (Ar*C*C), 134.2 (ArCH), 130.1 (2 × ArCH), 128.9 (2 × ArCH), 128.8 (2 × ArCH), 126.7 (Ar*C*C), 124.0 (2 × ArCH), 66.4 (CH_2); *m*/*z* (CI) 329 [$(MH)^+$, (4%)], 207 [$(M-HO_2CC_6H_5)^+$, (25)]; HRMS (CI) calc. $(M-HO_2CC_6H_5)^+$ 207.0406 found 207.0404; (Found C, 58.44; H, 3.32; N, 8.35. $C_{16}H_{12}N_2O_6$ requires C, 58.54; H, 3.68; N, 8.53%).

p-Nitrobenzyl cyanoformate **36** was also obtained as a yellow solid. ν_{max} (solid)/cm^{-1} 3113 (CH), 3081 (CH), 1741 (CO), 2252 (CN); δ_H (400 MHz; $CDCl_3$) 8.28 (2 H, d, *J* 8.8, 2 × ArH), 7.58 (2 H, d, *J* 8.8, 2 × ArH), 5.42 (2 H, s, CH_2); δ_C (101 MHz; $CDCl_3$) 180.1 (CO), 143.9 (ArCN), 139.4 (Ar*C*C), 129.3 (2 × ArCH), 124.2 (2 × ArCH), 108.9 (CN), 68.6 (CH_2); *m*/*z* (CI) 207 [$(MH)^+$, (74%)], 136 [$(M-HO_2CCN)^+$, (100)].

Methyl 2-[acetyl-benzoyloxy-amino]-pent-4-enoate 37

Using oxime ester **24** (407 mg, 1.98 mmol), procedure C and 85 : 15 petrol–EtOAc (4 : 1 petrol–EtOAc, R_F 0.15) as the chromatography solvent gave *methyl 2-[acetyl-benzoyloxy-amino]-pent-4-enoate* **37** as a yellow oil (473 mg, 1.6 mmol,

81%). ν_{max} (neat)/cm^{-1} 3075 (CH), 2954 (CH), 1769 (CO), 1747 (CO), 1693 (CO); δ_H (400 MHz; $CDCl_3$) 8.07 (2 H, m, 2 × ArH), 7.67 (1 H, m, ArH), 7.52 (2 H, t, *J* 7.8, 2 × ArH), 5.84 (1 H, m, CH=), 5.32 (1 H, brs, COCH), 5.15 (1 H, m, =CH*H*), 5.08 (1 H, d, *J* 10.2, =C*H*H), 3.77 (3 H, s, OMe), 2.67 (2 H, m, $COCHCH_2$), 2.13 (3 H, s, Me); δ_C (101 MHz; $CDCl_3$) 174.1 (CO), 169.8 (CO), 164.8 (CO), 135.0 (ArCH), 133.5 (CH_2CHCH_2), 130.5 (2 × ArCH), 129.4 (2 × ArCH), 126.9 (Ar*C*C), 118.9 (CH_2CHCH_2), 60.0 (COCH), 52.8 (OMe), 33.2 (CH_2CHCH_2), 21.1 (Me); *m*/*z* (ESMS) 332 [(M.MeCN)$^+$, (85%)], 314 [(MNa)$^+$, (10)], 250 [(MH_2−Ac)$^+$, (100)]; HRMS calc. (MNa)$^+$ 314.0999 found 314.0997.

Using oxime ester **24** (407 mg, 1.98 mmol), procedure B and 4 : 1 petrol–EtOAc for the running solvent in chromatography provided *methyl 2-[diacetylamino]-penta-2,4-dienoate* **44** as a yellow oil (140 mg, 0.7 mmol, 33%). δ_H (400 MHz; $CDCl_3$) 7.43 (1 H, d, *J* 11.2, CC*H*CH), 6.35 (1 H, ddd, *J* 16.8, 11.2, 10.2, CHC*H*CH_2), 5.82 (1 H, d, *J* 16.8, CHCH*H*), 5.68 (1 H, d, *J* 10.2, CHC*H*H), 3.82 (3 H, s, OMe), 2.34 (6 H, s, 2 × COMe); *m*/*z* (CI) 250 [(MK)$^+$, (21%)], 212 [(MH)$^+$, (31)], 170 [(MH_2−Ac)$^+$, (87)], 128 [(MH_3−2 × Ac)$^+$, (78)].

tert-Butyl 2-[acetyl-benzyloxy-amino]-pent-4-enoate 38

Using oxime ether **30** (465 mg, 1.98 mmol), procedure B and 9 : 1 petrol–EtOAc (9 : 1 petrol–EtOAc, R_F 0.19) as the chromatography solvent gave *tert-butyl 2-[acetyl-benzyloxy-amino]-pent-4-enoate* **38** as a yellow oil (511 mg, 1.6 mmol, 81%). ν_{max} (neat)/cm^{-1} 2979 (CH), 1733 (CO), 1679 (CO); δ_H (400 MHz; $CDCl_3$) 7.38 (5 H, s, 5 × ArH), 5.8 (1 H, m, CH=), 5.15 (1 H, dtd, *J* 17.2, 2.9, 1.5, =CH*H*), 5.10 (1 H, m, =C*H*H), 5.00 (1 H, d, *J* 10.6, PhCH*H*), 4.91 (1 H, d, *J* 10.6, PhC*H*H), 2.75 (2 H, m, $COCHCH_2$), 1.46 (9 H, s, 3 × CH_3); δ_C (101 MHz; $CDCl_3$) 174.7 (CO), 168.8 (CO), 134.9 (Ar*C*C), 134.3 (*C*H=), 128.8 (5 × ArCH), 117.8 (=*C*H_2), 82.1 (*C*$(CH_3)_3$), 78.2 ($PhCH_2$), 61.8 (COCH), 32.8 ($COCHCH_2$), 28.0 (3 × CH_3), 20.8 (Me); *m*/*z* 320 [(MH)$^+$, (1%)], 264 [(MH_2−C$(CH_3)_3$)$^+$, (32)], 222 [(MH_3−C$(CH_3)_3$−Ac)$^+$, (27)]; HRMS (CI) calc. (MH_2−C$(CH_3)_3$)$^+$ 264.1236 found 264.1226.

tert-Butyl 2-[acetyl-benzoyloxy-amino]-pent-4-enoate 39

Using oxime ester **31** (484 mg, 1.94 mmol), procedure C and 9 : 1 petrol–EtOAc (7 : 3 petrol–EtOAc, R_F 0.51) as the chromatography solvent afforded *tert-butyl 2-[acetyl-benzoyloxy-amino]-pent-4-enoate* **39** as a yellow oil (478 mg, 1.4 mmol, 72%). ν_{max} (neat)/cm^{-1} 2980 (CH), 1768 (CO), 1734 (CO), 1694 (CO); δ_H (400 MHz; $CDCl_3$) 8.05 (2 H, dd, *J* 8.3, 1.5, 2 × ArH), 7.64 (1 H, t, *J* 7.3, ArH), 7.50 (2 H, m, 2 × ArH), 5.85 (1 H, m, CH=), 5.2 (1 H, brs, COCH), 5.13 (1 H, dd, *J* 17.1, 1.5, =CH*H*), 5.06 (1 H, d, *J* 10.3, =C*H*H), 2.52–2.73 (2 H, m, $COCHCH_2$), 2.12 (3 H, s, Me), 1.46 (9 H, s, 3 × CH_3); δ_C (101 MHz; $CDCl_3$) 173.8 (CO), 167.9 (CO), 164.4 (CO), 134.3 (ArCH), 133.5 (*C*H=), 130.0 (2 × ArCH), 128.9 (2 × ArCH), 118.1 (=*C*H_2), 82.5 (*C*$(CH_3)_3$), 61.0 (COCH), 33.0 ($COCHCH_2$), 28.0 (3 × CH_3), 20.8 (Me); *m*/*z* (CI) 236 [(MH_3−Ac−C$(CH_3)_3$)$^+$, (66%)], 156 [(MH−C$(CH_3)_3$−$HO_2CC_6H_5$)$^+$, (12)]; HRMS (CI) calc. [(MH_3−Ac−C$(CH_3)_3$)$^+$] 236.0923 found 236.0922.

p-Nitrobenzyl 2-[acetyl-benzyloxy-amino]-pent-4-enoate 40

Using oxime ether **34** (624 mg, 1.99 mmol), procedure B and 84 : 16 petrol–EtOAc as the eluting solvent during flash chromatography (7 : 3 petrol–EtOAc, R_F 0.25) gave *p-nitrobenzyl 2-[acetyl-benzyloxy-amino]-pent-4-enoate* **40** as a yellow oil (679 mg, 1.71 mmol, 86%). ν_{max} (neat)/cm^{-1} 3080 (CH), 2945 (CH), 1745 (CO), 1674 (CO), 1520 (NO_2), 1341 (NO_2); δ_H (300 MHz; $CDCl_3$) 8.14 (2 H, d, *J* 8.8, 2 × ArH), 7.47 (2 H, d, *J* 8.8, 2 × ArH), 7.35 (5 H, m, 5 × ArH), 5.82 (1 H, m, C*H*=), 5.33 (1 H, d, *J* 13.4, PhC*H*H), 5.2 (1 H, d, *J* 13.6, PhCH*H*), 5.16 (2 H, m, =CH_2), 5.05 (1 H, dd, *J* 6.0, 9.2, COCH), 4.94 (1 H, d, *J* 10.5, PhC*H*H), 4.90 (1 H, d, *J* 10.2, PhCH*H*), 2.82 (2 H, m, CHCH_2CH), 2.15 (3 H, s, Me); δ_C (76 MHz; $CDCl_3$) 169.4 (CO), 147.8 (CO), 142.6 (ArCN), 134.3 (Ar*C*C), 133.5 (*C*H=), 129.1 (ArCH + Ar*C*C), 129.0 (2 × ArCH), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 123.8 (2 × ArCH), 118.5 (=*C*H_2), 78.5 ($ArCH_2$), 65.6 ($ArCH_2$), 60.8 (CO*C*H), 32.7 (COCH*C*H_2), 20.8 (Me); *m*/*z* (CI) 399 [(MH)$^+$, (66%)], 357 [(MH_2−Ac)$^+$, (69)], 293 [(MH_2−OBn)$^+$, (12)], 249 [(MH−Ac−OBn)$^+$, (14)]; HRMS (CI) calc. (MH)$^+$ 399.1556 found 399.1557. Found C, 63.32; H, 5.34; N, 7.09. $C_{21}H_{22}N_2O_6$ requires C, 63.31; H, 5.57; N, 7.03%).

p-Nitrobenzyl 2-[acetyl-benzoyloxy-amino]-pent-4-enoate 41

Using oxime ester **35** (663 mg, 2.02 mmol), procedure C and 4 : 1 petrol–EtOAc (7 : 3 petrol–EtOAc, R_F 0.29) during chromatography gave *p-nitrobenzyl 2-[acetyl-benzoyloxy-amino]-pent-4-enoate* **41** as a very viscous yellow oil (390 mg, 0.95 mmol, 47%). δ_H (400 MHz; $CDCl_3$) 8.21 (2 H, d, *J* 8.8, 2 × ArH), 7.99 (2 H, d, *J* 7.7, 2 × ArH), 7.68 (1 H, t, *J* 7.7, ArH), 7.51 (4 H, m, 4 × ArH), 5.84 (1 H, m, CH=), 5.09–5.46 (5 H, m, $PhCH_2$ + COCH + =CH_2), 2.71 (2 H, m, CH_2), 2.12 (3 H, s, Me); δ_C (101 MHz; $CDCl_3$) 168.6 (CO), 164.2 (CO), 147.8 (ArCN), 142.5 (Ar*C*C), 134.6 (ArCH), 132.7 (CH=), 130.0 (2 × ArCH), 129.0 (2 × ArCH), 128.7 (2 × ArCH), 126.6 (Ar*C*C), 123.8 (2 × ArCH), 123.8 (=CH_2), 65.8 ($PhCH_2$), 59.8 (COCH), 32.9 (COCH*C*H_2), 20.6 (Me); *m*/*z* (CI) 413 [(MH)$^+$, (32%)], 371 [(MH_2−Ac)$^+$, (68)], 291 [(M−$HO_2CC_6H_5$)$^+$, (60)]; HRMS calc. (MH)$^+$ 413.1349 found 413.1337.

O-Benzyl methyl pyruvate oxime ether 46[24]

To a solution of *O*-benzylhydroxylamine hydrochloride (4.90 g, 30.6 mmol) and pyridine (1.99 mL, 1.942 g, 24.5 mmol) in MeOH (22 mL) was added methyl pyruvate **45** (1.02 g, 10.0 mmol) and the reaction stirred for 3.5 h at RT. The MeOH was removed *in vacuo* and the residue was then dissolved in CH_2Cl_2 (45 mL) and H_2O (30 mL) and the organic layer collected. The aqueous layer was extracted with CH_2Cl_2 (2 × 45 mL), the organics were combined and dried (Na_2SO_4) and the solvent was evaporated. The crude oil was purified by flash chromatography using petrol–EtOAc 9 : 1 (9 : 1 petrol–EtOAc, R_F 0.28) as the running solvent to give *O*-benzyl methyl pyruvate oxime ether **46** as a colourless solid (1.80 g, 8.7 mmol, 87%). mp 41–45 °C; ν_{max} (solid)/cm^{-1} 3063 (CH), 2951 (CH), 1721 (CO); δ_H (270 MHz; $CDCl_3$) 7.37 (5 H, s, 5 × ArH), 5.31 (2 H, s, $PhCH_2$), 3.86 (3 H, s, OMe), 2.09 (3 H, s, Me); δ_C (101 MHz; $CDCl_3$) 164.3 (CO), 149.3 (CN), 136.8 (Ar*C*C), 128.5 (2 × ArCH), 128.3 (3 × ArCH), 77.6 ($PhCH_2$), 52.7 (OMe), 11.7 (Me); *m*/*z* (CI) 208 [(MH)$^+$, (16%)].

O-Benzoyl methyl pyruvate oxime ester 47

To a solution of methyl pyruvate **45** (1.03 g, 10.0 mmol) in MeOH (18 mL) was added hydroxylamine hydrochloride (905 mg, 13.0 mmol) then pyridine (890 μL, 870 mg, 11.0 mmol). The reaction was stirred for 4 h after which the MeOH was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (30 mL) and water (30 mL). The layers were separated and the aqueous layer extracted twice with CH_2Cl_2 (30 mL). All the organics were combined, dried (Na_2SO_4), filtered then concentrated and the resultant material purified by flash chromatography; 7 : 3 petrol–EtOAc was used as the running solvent (7 : 3 petrol–EtOAc, R_F 0.22) which gave *methyl pyruvate oxime* as a colourless solid (967 mg, 8.3 mmol, 83%). mp 75–76 °C; ν_{max} (solid)/cm^{-1} 3228 (OH), 2964 (CH), 1722 (CO); δ_H (270 MHz; $CDCl_3$) 8.50 (1 H, s, OH), 3.89 (3 H, s, OMe), 2.12 (3 H, s, Me); δ_C (101 MHz; $CDCl_3$) 164.2 (CO), 149.4 (CN), 52.7 (OMe), 10.5 (Me); *m*/*z* (CI) 118 [(MH)$^+$, (100%)]; HRMS (CI) calc. (MH)$^+$ 118.0504 found 118.0504; (Found C, 41.34; H, 6.28; N, 12.09. $C_4H_7NO_3$ requires C, 41.03; H, 6.03; N, 11.96%).

Pyridine (610 μL, 599 mg, 7.6 mmol) and benzoic anhydride (2.05 g, 9.1 mmol) were added to a solution of the oxime (900

mg, 7.7 mmol) in CH_2Cl_2 (20 mL). 4-Dimethylaminopyridine (10 mol%) was then added and the reaction left to stir until complete by TLC. CH_2Cl_2 (10 mL) was added and the solution washed with H_2O (2 × 20 mL) then 0.5 M HCl (20 mL). The organics were collected, dried (Na_2SO_4) and purified by flash chromatography. The running solvent used for chromatography was 4 : 1 petrol–EtOAc (7 : 3 petrol–EtOAc, R_F 0.31) which gave *O-benzoyl methyl pyruvate oxime ester* **47** as a colourless solid (1.613 g, 7.3 mmol, 97%). mp 104–106 °C; ν_{max} (solid)/cm^{-1} 3060 (CH), 2960 (CH), 1760 (CO), 1724 (CO); δ_H (400 MHz; $CDCl_3$) 8.10 (2 H, m, 2 × ArH), 7.64 (1 H, m, ArH), 7.51 (2 H, t, *J* 7.8, 2 × ArH), 3.94 (3 H, s, OMe), 2.38 (3 H, s, Me); δ_C (101 MHz; $CDCl_3$) 163.7 (CO), 162.8 (CO), 156.7 (CN), 133.9 (ArCH), 129.9 (2 × ArCH), 128.8 (2 × ArCH), 128.2 (Ar*C*C), 53.3 (OMe), 13.2 (Me); *m*/*z* (CI) 222 [$(MH)^+$, (10%)], 123 [$(MH_2-MeO_2CC(CH_3)N)^+$, (94)]; HRMS (CI) calc. $(MH)^+$ 222.0766 found 222.0769; (Found C, 59.77; H, 4.92; N, 6.33. $C_{11}H_{11}NO_4$ requires C, 59.73; H, 5.01; N, 6.33%).

O-Benzyl methyl acetoacetate oxime ether 50

Using methyl acetoacetate **48** (870 mg, 7.5 mmol) and procedure A yielded a crude product which was purified using a Horizon Biotage automated column eluting with 9 : 1 petrol–EtOAc (7 : 3 petrol–EtOAc R_F 0.59) to give *methyl acetoacetate O-benzyl oxime ether* **50**, as a mixture of geometric isomers 1 : 1.8 **a** and **b**, as a colourless oil (1.28 g, 5.8 mmol, 77%). ν_{max} (neat)/cm^{-1} 3031 (CH), 2953 (CH), 1741 (CO); δ_H (270 MHz; $CDCl_3$) 7.34 (5 H, m, 5 × ArH, isomers **a** and **b**), 5.11 (2 H, s, $PhCH_2$, isomer **b**), 5.08 (2 H, s, $PhCH_2$, isomer **a**), 3.71 (3 H, s, OMe, isomer **b**), 3.66 (3 H, s, OMe, isomer **a**), 3.38 (2 H, s, CH_2, isomer **a**), 3.23 (2 H, s, CH_2, isomer **b**), 1.97 (3 H, s, Me, isomer **a**), 1.96 (3 H, s, Me, isomer **b**); δ_C (101 MHz; $CDCl_3$) 170.1 (CO, isomer **b**), 169.2 (CO, isomer **a**), 151.9 (CN, isomer **b**), 150.7 (CN, isomer **a**), 137.9 (Ar*C*C, isomers **a** and **b**), 128.3 (2 × ArCH, isomers **a** and **b**), 128.0 (2 × ArCH, isomers **a** and **b**), 127.8 (ArCH, isomers **a** and **b**), 75.6 ($PhCH_2$, isomers **a** and **b**), 52.1 (OMe, isomers **a** and **b**), 41.2 (CH_2, isomer **b**), 35.3 (CH_2, isomer **a**), 20.6 (Me, isomer **a**), 14.8 (Me, isomer **b**); *m*/*z* (ESMS) 222 [$(MH)^+$, (25%)], 190 [$(M-MeOH)^+$, (20)], 162 [$(M-MeCO_2H)^+$, (100)]; HRMS calc. $(MNa)^+$ 244.0944 found 244.0944.

O-Benzoyl methyl acetoacetate oxime ester 51 and 3-methyl-isoxazolin-5-one 49[25]

To a solution of methyl acetoacetate **48** (1.16 g, 10.0 mmol) in MeOH (18 mL) was added hydroxylamine hydrochloride (694 mg, 10.0 mmol) then pyridine (810 μL, 791 mg, 10.0 mmol). The reaction was stirred for 10 min after which the MeOH was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (30 mL) and water (30 mL). The layers were separated and the aqueous layer extracted twice with CH_2Cl_2 (2 × 30 mL). All the organics were combined, dried (Na_2SO_4), filtered then concentrated. The residue was purified using 7 : 3 petrol–EtOAc as the running solvent for chromatography by a Horizon Biotage (7 : 3 petrol–EtOAc R_F 0.25) which afforded methyl acetoacetate oxime as a colourless oil in a mixture of geometric isomers **a** and **b** (494 mg, 3.8 mmol, 37%). ν_{max} (neat)/cm^{-1} 3342 (OH), 2956 (CH), 1741 (CO); δ_H (270 MHz; $CDCl_3$) 7.73 (1 H, s, OH), 3.73 (3 H, s, OMe), 3.24 (2 H, s, CH_2), 1.97 (3 H, s, Me); δ_C (101 MHz; $CDCl_3$) 170.0 (CO, isomer **a**), 169.4 (CO, isomer **b**), 152.6 (CN, isomer **a**), 151.3 (CN, isomer **b**), 52.2 (OMe, isomers **a** and **b**), 41.1 (CH_2, isomer **a**), 34.5 (CH_2, isomer **b**), 20.5 (Me, isomer **b**), 14.0 (Me, isomer **a**).

3-Methylisoxazolin-5-one **49**[26] was purified by a Horizon Biotage instrument eluting using a gradient from 9 : 1 to 4 : 1 petrol–EtOAc to give 3-methyl-2-isoxazolin-5-one **49** as a red/brown oil (506 mg, 5.1 mmol, 51%). δ_H (250 MHz; $CDCl_3$) 3.40 (2 H, s, CH_2), 2.16 (3 H, s, Me).

Pyridine (380 μL, 368 mg, 4.6 mmol) and benzoic anhydride (1.26 g, 5.6 mmol) were added to a solution of the oxime (609 mg, 4.6 mmol) in CH_2Cl_2 (12 mL). 4-Dimethylaminopyridine (10 mol%) was then added and the reaction left to stir until complete by TLC. CH_2Cl_2 (20 mL) was added and the solution washed with H_2O (2 × 20 mL) then 0.5 M HCl (20 mL). The organics were collected, dried (Na_2SO_4) and purified by a Horizon Biotage eluting from 9 : 1 to 4 : 1 petrol–EtOAc (7 : 3 petrol–EtOAc, R_F 0.31) to give *methyl acetoacetate O-benzoyl oxime ester* **51** as a yellow oil and a 1 : 3.8 mixture of geometric isomers **a** and **b** (846 mg, 3.6 mmol, 78%). ν_{max} (neat)/cm^{-1} 3004 (CH), 2955 (CH), 1741 (CO); δ_H (270 MHz; $CDCl_3$) 8.10 (2 H, m, 2 × ArH, isomers **a** and **b**), 7.58 (1 H, m, ArH, isomers **a** and **b**), 7.47 (2 H, m, 2 × ArH, isomers **a** and **b**), 3.76 (3 H, s, OMe, isomer **b**), 3.74 (3 H, s, OMe, isomer **a**), 3.57 (2 H, s, CH_2, isomer **a**), 3.52 (2 H, s, CH_2, isomer **b**), 2.26 (3 H, s, Me, isomer **a**), 2.25 (3 H, s, Me, isomer **b**); δ_C (101 MHz; $CDCl_3$) 169.1 (CO, isomer **b**), 167.8 (CO, isomer **a**), 163.6 (CO, isomer **b**), 163.1 (CO, isomer **a**), 133.5 (ArCH, isomers **a** and **b**), 129.7 (2 × ArCH, isomers **a** and **b**) 128.9 (Ar*C*C, isomers **a** and **b**), 128.6 (2 × ArCH, isomers **a** and **b**), 52.4 (OMe, isomers **a** and **b**), 41.0 (CH_2, isomer **b**), 36.9 (CH_2, isomer **a**), 21.3 (Me, isomer **a**), 16.3 (Me, isomer **b**); *m*/*z* (ESMS) 258 [$(MNa)^+$, (100%)]; HRMS calc. $(MNa)^+$ 258.0736 found 258.0736.

Methyl 2-[acetyl-benzoyloxy-amino]-2-methyl-pent-4-enoate 53

Using oxime ester **47** (459 mg, 2.08 mmol), procedure C and flash chromatography eluting with 85 : 15 petrol–EtOAc (4 : 1 petrol–EtOAc, R_F 0.21) gave *methyl 2-methyl-2-[acetyl-benzoyloxy-amino]-pent-4-enoate* **53** as a yellow oil (325 mg, 1.1 mmol, 53%). ν_{max} (neat)/cm^{-1} 3010 (CH), 2952 (CH), 1766 (CO), 1743 (CO), 1679 (CO); δ_H (400 MHz; $CDCl_3$) 8.12 (2 H, d, *J* 8.3, 2 × ArH), 7.70 (1 H, m, ArH), 7.54 (2 H, m, 2 × ArH), 5.76–5.96 (1 H, m, CH=), 5.13 (2 H, m, $=CH_2$), 3.77 (3 H, s, OMe), 2.71–2.99 (1 H, m, C(Me)CH*H*), 2.67 (1 H, m, C(Me)C*H*H), 2.07 and 2.03 (3 H, s, COMe, 2 conformers); δ_C (101 MHz; $CDCl_3$) 172.2 and 171.8 (CO), 171.5 (CO), 165.0 and 164.8 (CO), 134.7 (ArCH), 132.2 and 132.5 (CH), 130.1 (2 × ArCH), 129.1 (2 × ArCH), 126.6 and 126.4 (Ar*C*C), 119.4 and 119.0 (CH_2CHCH_2), 68.7 and 68.3 (C(Me)), 52.6 (OMe), 41.2 and 40.2 ($C(Me)CH_2$), 21.7 and 21.4 (COMe), 21.4 and 20.1 (Me); *m*/*z* (CI) 264 [$(MH_2-Ac)^+$, (50%)], 142 [$(MH-Ac-HO_2CC_6H_5)^+$, (17)]; HRMS (CI) calc. $(MH_2-Ac)^+$ 264.1236 found 264.1238.

After elution with 85 : 15 petrol–EtOAc *methyl 2-methyl-2-[benzoyloxy-amino]-pent-4-enoate* **54** was recovered as a yellow oil (198 mg, 0.8 mmol, 38%). δ_H (400 MHz; $CDCl_3$) 8.03 (1 H, s, NH), 7.95 (2 H, dd, *J* 1.0, 8.3, 2 × ArH), 7.56 (1 H, m, ArH), 7.44 (2 H, m, 2 × ArH), 5.82 (1 H, m, $CHCH_2$), 5.17 (2 H, m, $CHCH_2$), 3.71 (3 H, s, OMe), 2.57 (2 H, m, $C(Me)CH_2$), 1.46 (3 H, s, C(Me)).

2-Acetyl-3-methylisoxazol-5-one 55[27]

Attempted allylation of **49** (398 mg, 2.0 mmol) using procedure B yielded crude material which was purified by flash chromatography, eluting with 7 : 3 petrol–EtOAc to give 2-acetyl-3-methylisoxazol-5-one as a yellow oil (313 mg, 1.3 mmol, 63%). δ_H (270 MHz; $CDCl_3$) 5.30 (1 H, q, *J* 1.0, CH), 2.59 (3 H, d, *J* 1.0, CMe), 2.44 (3 H, s, COMe); δ_C (68 MHz; $CDCl_3$) 166.1 (CO), 165.0 (CO), 158.7 (CH_3CCH), 95.0 (COCH), 22.6 (Me), 15.4 (Me); *m*/*z* (CI) 142 [$(MH)^+$, (25%)], 98 [$(M-Ac)^+$, (90)].

O-Benzoyl 2-methyl-*trans*-cinnamaldehyde oxime ester 57

2-Methyl-*trans*-cinnamaldehyde **56** (1.46 g, 10.0 mol) was dissolved in EtOH (18 mL) to which hydroxylamine hydrochloride (1.04 g, 15 mmol) and pyridine (970 μL, 949 mg, 12.0 mmol) were added. The reaction was stirred at RT for 2 h and the solvent was evaporated then the residue was dissolved in

CH_2Cl_2 (30 mL) and H_2O (25 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) before the organics were combined and washed with 1 M HCl (40 mL) and dried (Na_2SO_4). The inorganics were filtered off and the solvent removed *in vacuo* then the crude material was purified on a Horizon Biotage automated column. 9 : 1 Petrol–EtOAc was used as the running solvent (7 : 3 petrol–EtOAc, R_F 0.47) which gave *2-methyl-trans-cinnamaldehyde oxime* as a colourless solid (1.47 g, 9.1 mmol, 91%). mp 129–131 °C; ν_{max} (solid)/cm^{-1} 3216 (OH), 2986 (CH); δ_H (400 MHz; $CDCl_3$) 8.08 (1 H, s, OH), 7.91 (1 H, s, NCH), 7.30 (5 H, m, 5 × ArH), 6.69 (1 H, m, ArCH), 2.10 (3 H, d, *J* 1.1, Me); δ_C (101 MHz; $CDCl_3$) 155.2 (CN), 136.7 (*C*HC(Me)), 136.3 (*C*Me), 131.8 (Ar*C*C), 129.3 (2 × ArCH), 128.3 (2 × ArCH), 127.6 (ArCH), 13.1 (Me).

2-Methyl-*trans*-cinnamaldehyde oxime (1.46 g, 9.1 mmol) was suspended in CH_2Cl_2 (25 mL) and pyridine (730 μL, 714 mg, 9.0 mmol) and benzoic anhydride (2.47 g, 10.9 mmol) were added. 4-Dimethylaminopyridine (10 mol%) was added and the reaction left to stir for 18 h before it was diluted (CH_2Cl_2, 10 mL). The reaction was washed with H_2O (2 × 20 mL) and $NaHCO_3$ (aq., 25 mL) and then dried (Na_2SO_4). The solvent was removed and the resultant material purified with a Quad 3 Biotage automated column using a 9 : 1 mixture of petrol–EtOAc as the elutant (7 : 3 petrol–EtOAc, R_F 0.55) which afforded *O-benzoyl 2-methyl-trans-cinnamaldehyde oxime ester* **57**. The solid was recrystallised from Et_2O–petrol to yield the desired compound as colourless plates (1.21 g, 4.6 mmol, 50%). mp 88–90 °C; δ_H (400 MHz; $CDCl_3$) 8.30 (1 H, d, *J* 0.7, NCH), 8.13 (2 H, dd, *J* 1.5, 8.4, 2 × ArH), 7.30–7.63 (7 H, m, 7 × ArH), 6.89 (1 H, q, *J* 0.7, ArCH), 2.30 (3 H, d, *J* 1.5, Me); δ_C (101 MHz; $CDCl_3$) 164.1 (CO), 161.7 (CN), 141.1 (*C*HC(Me)), 135.9 (Ar*C*C), 133.4 (ArCH), 131.4 (Ar*C*C), 129.8 (2 × ArCH), 129.6 (2 × ArCH), 129.0 (CH*C*(Me)), 128.6 (2 × ArCH), 128.5 (2 × ArCH), 128.4 (ArCH), 13.3 (Me).

O-Benzoyl phenylacetaldehyde oxime ester 59

Phenylacetaldehyde (1.81 g, 15.0 mmol) was dissolved in MeOH (30 mL) and hydroxylamine hydrochloride (1.25 g, 18.0 mmol) and pyridine (1.19 mL, 1.16 g, 14.7 mmol) were added. After 2.5 h the MeOH was removed *in vacuo* and the material was suspended in CH_2Cl_2 (40 mL) and washed with H_2O (2 × 30 mL) and 1 M HCl (30 mL). The organics were dried (Na_2SO_4) then concentrated and purified with a Horizon Biotage automated column eluting through a gradient from 100% petrol to 4 : 1 petrol–EtOAc which gave phenylacetaldehyde oxime[28] as a colourless solid and a 1.9 : 1 mixture of geometric isomers **a** and **b** (859 mg, 6.4 mmol, 42%). ν_{max} (solid)/cm^{-1} 3203.3 (OH), 3085 (CH), 2854 (CH); δ_H (250 MHz; $CDCl_3$) 9.05 (1 H, br s, OH, isomer **a**), 8.49 (1 H, br s, OH, isomer **b**), 7.54 (1 H, t, *J* 6.3, ArH, isomer **b**), 7.27 (4 H, m, 4 × ArH, isomers **a** and **b**), 6.90 (1 H, t, *J* 5.3, ArH, isomer **a**), 3.74 (2 H, d, *J* 5.3, CH_2, isomer **a**), 3.54 (2 H, d, *J* 6.3, CH_2, isomer **b**); δ_C (101 MHz; $CDCl_3$) 150.9 (CN, isomer **a**), 150.7 (CN, isomer **b**), 136.9 (Ar*C*C, isomer **a**), 136.6 (Ar*C*C, isomer **b**), 128.8 (2 × ArCH + ArCH, isomers **a** and **b**), 126.9 (2 × ArCH, isomer **b**), 126.7 (2 × ArCH, isomer **a**), 35.9 (CH_2, isomer **b**), 31.7 (CH_2, isomer **a**).

To a solution of phenyacetaldehyde oxime (859 mg, 6.4 mmol) in CH_2Cl_2 (25 mL) was added benzoic acid (781 mg, 6.4 mmol), EDCi (1.35 g, 7.0 mmol) and HOBt hydrate (10 mol%). The reaction was stirred overnight. The reaction was then washed with H_2O (2 × 20 mL) and $NaHCO_3$ (aq., 30 mL), dried (Na_2SO_4) and concentrated. The crude material was purified on a Horizon Biotage eluting through a gradient from 100% petrol to 9 : 1 petrol–EtOAc which gave *O-benzoyl phenylacetaldehyde oxime ester* as a yellow oil (289 mg, 1.2 mmol, 19%). ν_{max} (neat)/cm^{-1} 3026 (CH), 1734 (CO); δ_H (400 MHz; $CDCl_3$) 8.05 (2 H, dd, *J* 1.6, 7.2, 2 × ArH), 7.98 (1 H, t, *J* 6.8, NCH), 7.57 (1 H, t, *J* 7.6, ArH), 7.26–7.47 (7 H, m, 7 × ArH), 3.79 (2 H, d, *J* 6.8, CH_2); δ_C (101 MHz; $CDCl_3$) 164.1 (CO), 158.2 (CN), 134.6 (Ar*C*C), 133.4 (ArCH), 129.7 (2 × ArCH), 129.0 (2 × ArCH + 2 × ArCH), 128.5 (2 × ArCH + Ar*C*C), 127.3 (ArCH), 35.9 (CH_2).

O-Benzyl benzaldehyde oxime ether 61[29]

Using benzaldehyde **60** (1.27 g, 12.0 mmol), procedure A and 96 : 4 petrol–EtOAc as the solvent for flash chromatography yielded *O*-benzyl benzaldehyde oxime ether **61** as a colourless oil (2.26 g, 10.7 mmol, 89%). δ_C (101 MHz; $CDCl_3$) 149.1 (CH), 137.8 (Ar*C*C), 132.5 (Ar*C*C), 130.0 (ArCH), 128.8 (2 × ArCH), 128.6 (2 × ArCH), 128.5 (2 × ArCH), 128.1 (ArCH), 127.3 (2 × ArCH), 76.6 (CH_2); *m/z* (CI) 212 [$(MH)^+$, (50%)], 104 [$(M-C_6H_5CH_2OH)^+$, (56)] (Found C, 79.88; H, 6.66; N, 6.77. $C_{14}H_{13}NO$ requires C, 79.59; H, 6.20; N, 6.63%).

O-Benzoyl benzaldehyde oxime ester 62[30]

To a solution of benzaldehyde **60** (1.60 g, 15.1 mmol) in MeOH (25 mL) was added hydroxylamine hydrochloride (1.36 g, 19.6 mmol) then pyridine (1.33 mL, 1.31 g, 16.5 mmol). The reaction was stirred for 23 h after which the MeOH was removed *in vacuo* and the resulting residue dissolved in CH_2Cl_2 (40 mL) and water (30 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 40 mL). All the organics were combined, dried (Na_2SO_4), filtered then concentrated and the resultant material purified by flash chromatography eluting with 9 : 1 petrol–EtOAc (4 : 1 petrol–EtOAc, R_F 0.34) to give benzaldehyde oxime[31] as a pale yellow oil (605 mg, 5 mmol, 33%). ν_{max} (neat)/cm^{-1} 3278 (OH), 3063 (CH), 2983 (CH); δ_C (68 MHz; $CDCl_3$) 150.6 (CN), 132.0 (Ar*C*C), 130.2 (ArCH), 128.9 (2 × ArCH), 127.2 (2 × ArCH); *m/z* 122 [$(MH)^+$, (92%)], 104 [$(M-H_2O)^+$, (100)].

Benzoic anhydride (1.05 g, 4.6 mmol) was added to a solution of benzaldehyde oxime (514 mg, 4.2 mmol) in CH_2Cl_2 (12 mL). 4-Dimethylaminopyridine (10 mol%) was then added and the reaction left to stir until complete by TLC. CH_2Cl_2 (20 mL) was added and the solution washed with H_2O (2 × 25 mL) then $NaHCO_3$ (aq., 25 mL). The organics were collected, dried (Na_2SO_4) and purified by flash chromatography. Product eluted through a column of pre-slurried silica using 95 : 5 petrol–EtOAc as the solvent (7 : 3 petrol–EtOAc, R_F 0.49) to afford the title compound **62** as a colourless solid (714 mg, 3.2 mmol, 76%). mp 99–101 °C; δ_H (400 MHz; $CDCl_3$) 8.57 (1 H, s, CH), 8.13 (2 H, dd, *J* 1.5, 8.3, 2 × ArH), 7.81 (2 H, m, 2 × ArH), 7.62 (1 H, m, ArH), 7.48 (5 H, m, 5 × ArH); δ_C (68 MHz; $CDCl_3$) 164.0 (CO), 156.9 (CN), 133.5 (ArCH), 131.8 (ArCH), 130.2 (Ar*C*C), 129.8 (2 × ArCH), 128.9 (2 × ArCH), 128.7 (Ar*C*C), 128.6 (2 × ArCH), 128.6 (2 × ArCH); (Found C, 74.96; H, 5.22; N, 6.23. $C_{14}H_{11}NO_2$ requires C, 74.65; H, 4.92; N, 6.22%).

Methyl 2-[acetyl-benzyloxy-amino]-3-methyl-pent-4-enoate 63

Using oxime ether **14** (376 mg, 1.95 mmol), crotyl bromide in place of allyl bromide and procedure B yielded a product which was purified by flash chromatography using 9 : 1 petrol–EtOAc (4 : 1 petrol–EtOAc, R_F 0.24) as the solvent to give *methyl 2-[acetyl-benzyloxy-amino]-3-methyl-pent-4-enoate* **63** as a very pale yellow oil and a 11.8 : 1 mixture of diastereomers **a** and **b** (446 mg, 1.5 mmol, 77%). ν_{max} (neat)/cm^{-1} 3006 (CH), 2953 (CH), 1743 (CO), 1675 (CO); δ_H (400 MHz; $CDCl_3$) 7.40 (5 H, m, 5 × ArH, dias. **a** + **b**), 5.72–5.91 (1 H, m, CHC*H*CH_2, dias. **a** + **b**), 4.86–5.22 (5 H, m, COCH + $CHCH_2$ + $PhCH_2$, dias. **a** + **b**), 3.73 (3 H, s, OMe, dias. **a** + **b**), 3.08 (1 H, m, CH(Me), dias. **a** + **b**), 2.20 (3 H, s, COMe, dias. **a**), 2.14 (3 H, s, COMe, dias. **b**), 1.23 (3 H, d, *J* 6.8, CH(Me), dias. **b**), 1.05 (3 H, d, *J* 6.8, CH(Me), dias. **a**); δ_C (101 MHz; $CDCl_3$) Diastereomer **a**: 174.3 (CO), 170.4 (CO), 139.4 (CH(Me)*C*HCH_2), 134.6 (Ar*C*C), 129.2 (2 × ArCH), 128.9 (ArCH), 128.7 (2 × ArCH), 116.2 (CH(Me)$CHCH_2$), 78.1 ($PhCH_2$), 64.1 (COCH), 52.0 (OMe),

37.6 (*C*H(Me), 20.5 (COMe), 17.2 CH(Me); *m/z* (CI) 292 [$(MH)^+$, (14%)], 250 [$(MH_2-Ac)^+$, (57)]; HRMS (CI) calc. $(MH)^+$ 292.1549 found 292.1538.

Methyl 2-[acetyl-benzoyloxy-amino]-3-methyl-pent-4-enoate 64

Using oxime ester **24** (414 mg, 2.0 mmol), procedure C and crotyl bromide in place of allyl bromide gave a residue which was purified on a silica column eluting with 85 : 15 petrol–EtOAc (4 : 1 petrol–EtOAc, R_F 0.24) to give *2-[acetyl-benzoyloxy-amino]-3-methyl-pent-4-enoate* **64** as a yellow solid and a 1 : 1.3 mixture of diasteromers **a** and **b.** The solid was passed through a column once again to give a colourless solid (455 mg, 1.5 mmol, 75%). mp 59–61 °C; ν_{max} (solid)/cm^{-1} 2965 (CH), 1766 (CO), 1740 (CO), 1675 (CO); δ_H (270 MHz; $CDCl_3$) 8.08 (2 H, m, 2 × ArH, dias. **a** + **b**), 7.65 (1 H, m, ArH, dias. **a** + **b**), 7.51 (2 H, m, 2 × ArH, dias. **a** + **b**), 5.74 (1 H, m, CH(Me)C*H*CH_2, dias. **a** + **b**), 5.01–5.30 (3 H, m, COCH + CH_2, dias. **a** + **b**), 3.73 (3 H, s, OMe, dias. **a**), 3.68 (3 H, s, OMe, dias. **b**), 2.87–3.15 (1 H, m, CH(Me), dias. **a** + **b**), 2.12 (3 H, s, COMe, dias. **b**), 2.06 (3 H, s, COMe, dias. **a**), 1.18 (3 H, d, *J* 6.9, CH(Me), dias. **b**), 1.10 (3 H, d, *J* 6.9, CH(Me), dias. **a**); δ_C (101 MHz; $CDCl_3$) 172.9 (CO, dias. **a** + **b**), 168.9 (CO, dias. **a**), 168.7 (CO, dias. **b**), 164.4 (CO, dias. **a** + **b**), 139.0 (*C*HCH_2, dias. **a**), 138.5 (*C*HCH_2, dias. **b**), 134.4 (ArCH, dias. **a** + **b**), 130.1 (2 × ArCH, dias. **a** + **b**), 128.9 (2 × ArCH, dias. **a** + **b**), 126.9 (Ar*C*C, 2 × ArCH, dias. **a** + **b**), 116.7 (CH*C*H_2, dias. **b**), 116.5 (CH*C*H_2, dias. **a**), 62.9 (COCH, dias. **a** + **b**), 52.3 (OMe, dias. **a**), 52.1 (OMe, dias. **b**), 37.8 (*C*H(Me), dias. **a**), 37.6 (*C*H(Me), dias. **b**), 20.4 (COMe), 17.0 (Me, dias. **b**), 16.7 (Me, dias. **a**); *m/z* (CI) 306 [$(MH)^+$, (40%)], 264 [$(MH_2-Ac)^+$, (77)], 184 [$(M-HO_2CPh)^+$, (45)]; HRMS (CI) calc. $(MH)^+$ 306.1341 found 306.1338.

Methyl 2-acetamido-2-allylpent-4-enoate 65[15]

In powder (100 mesh, 505 mg, 4.4 mmol) was weighed into a Wheaton vial. DMF (1.7 mL) was added followed by allyl bromide (570 μL, 799 mg, 6.6 mmol). A triangular stirrer bar was then dropped in and the mixture stirred vigorously. Within a few minutes an exotherm could be felt and the mixture turned into a very fine suspension that was dark green/black in colour. After 40 min the allylating mixture was pipetted into a solution of the nitrile **66** (2.0 mmol) and freshly distilled Ac_2O (4 mL) in anhydrous THF (14 mL) under a N_2 atmosphere. The Wheaton vial was washed out with dry THF (1 mL). After 2 h Et_3N (1 mL) was added and the reaction was left to stir overnight. The reaction was quenched with NH_4Cl (aq) (30 mL) and extracted with Et_2O (3 × 40 mL) which was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using petrol–EtOAc 7 : 3 as the elutant (7 : 3 petrol–EtOAc, R_F 0.18) which provided a yellow solid. The chromatography was repeated to yield the title compound **65** as a colourless solid (288 mg, 1.4 mmol, 68%). mp 58–59 °C (lit. 60 °C);[15] δ_H (300 MHz; $CDCl_3$) 6.27 (1 H, s, NH), 5.56 (2 H, ddt, *J* 17.6, 9.5, 7.3, 2 × CH=), 5.08 (4 H, m, 2 × =CH_2), 3.76 (3 H, s, OMe), 3.19 (2 H, ddt, *J* 13.8, 7.3, 1.1, 2 × CC*H*H), 2.52 (2 H, dd, *J* 7.3, 13.9, 2 × CCH*H*), 1.99 (3 H, s, Me); δ_C (76 MHz; $CDCl_3$) 173.5 (CO), 169.2 (CO), 132.3 (2 × *C*H=), 119.0 (2 × =*C*H_2), 64.4 (C), 52.7 (OMe), 39.0 (2 × CCH_2), 24.0 (Me); *m/z* (CI) 212 [$(MH)^+$, (57%)], 168 [$(MH_2-Ac)^+$, (26)], 152 [$(M-MeO_2C)^+$, (21)].

Methyl 2-[benzoyloxy-amino]-pent-4-enoate 67

Using oxime ester **24** (409 mg, 1.98 mmol), procedure D and an aqueous $NaHCO_3$ work-up gave the unstable *methyl 2-[benzoyloxy-amino]-pent-4-enoate* **67** as a yellow solid (455 mg, 1.8 mmol, 91%). δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, m, 2 × ArH), 7.56 (1 H, m, ArH), 7.44 (2 H, m, 2 × ArH), 5.82 (1 H, m, CH=), 5.19 (2 H, =C*H*$_2$), 4.01 (1 H, m, COCH), 3.75 (3 H, s, OMe), 2.56 (2 H, m, $CHCH_2CH$).

Methyl 2-hydroxyaminopent-4-enoate 68

Using oxime **12** (206 mg, 2.0 mmol), procedure D and purification by flash chromatography eluting with a 3 : 2 mixture of petrol–EtOAc gave *methyl 2-hydroxyaminopent-4-enoate* **68** as a colourless solid (115 mg, 0.8 mmol, 40%). mp 43–46 °C; ν_{max} (solid)/cm^{-1} 3261 (OH), 3138 (NH), 3077 (CH), 2955 (CH), 1741 (CO); δ_H (400 MHz; $CDCl_3$) 5.75 (1 H, ddt, *J* 17.1, 10.3, 7.3, CH_2CHCH_2), 5.35 (1 H, s, br, NH), 5.12 (2 H, m, CH_2CHCH_2), 3.78 (3 H, s, OMe), 3.72 (1 H, m, COCH), 2.30–2.50 (2 H, m, CH_2CHCH_2); δ_C (68.0 MHz; $CDCl_3$) 173.4 (CO), 132.9 (CH_2CHCH_2), 118.6 (CH_2CHCH_2), 64.5 (COCH), 52.1 (OMe), 33.7 (CH_2CHCH_2); *m/z* (CI) 146 [$(MH)^+$, (18%)], 128 [$(M-H_2O)^+$, (23)], [$(M-MeCO_2H)^+$, (100)]; HRMS (CI) calc. $(MH)^+$ 146.0817 found 146.0823.

Methyl 2-allyl-2-aminopent-4-enoate 69[15]

Using methyl cyanoformate (177 mg, 2.08 mmol), procedure D and purification by preparative chromatography eluting with 3 : 2 petrol–EtOAc gave the title compound **69** as a yellow oil (82 mg, 0.5 mmol, 24%). ν_{max} (neat)/cm^{-1} 3382 (NH), 33.17 (NH), 3078 (CH), 2952.0 (CH), 1730.6 (CO); δ_H (400 MHz; $CDCl_3$) 5.69 (2 H, m, 2 × C*H*$_2$CHCH$_2$), 5.13 (4 H, m, 2 × CH_2CHCH_2), 3.72 (3 H, s, OMe), 2.55 (2 H, m, 2 × COCCH*H*), 2.28 (2 H, dd, *J* 13.5, 8.1, 2 × COCC*H*H); δ_C (101 MHz; $CDCl_3$) 176.7 (CO), 132.6 (CH_2CHCH_2), 119.4 (CH_2CHCH_2), 60.7 (COC), 52.1 (OMe), 44.1 (CCH_2).

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