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Elaboration of the Side Chain of α-Amino Acids Containing a Vinyl Iodide by Palladium-Catalysed Coupling

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Abstract: The palladium-catalysed coupling of a γ-iodoallylglycine derivative and an *E*-δ-iodoallylglycine derivative with various organic nucleophiles is described.

Unnatural and non-proteinogenic α-amino acids are important as enzyme inhibitors, therapuetic agents and chiral synthons.[1a-e] An important class of non-proteinogenic α-amino acids is that based on allylglycines, many of these compounds have been reported to act as irreversible, mechanism-based, inhibitors of pyridoxal phosphate dependent enzymes.[2a-d] Allylglycine derivatives have been prepared previously by routes such as allyl electrophiles reacting with glycine anions[3a-d], allyl nucleophiles reacting with glycine cations[4a-d] and Wittig reactions of *L*-aspartic acid semialdehyde derivatives.[5]

Palladium coupling of vinyl iodides with organometallic nucleophiles has been used extensively and should be ideally suited for the elaboration of the side-chain of α-amino acids since the reactions take place under mild conditions and are tolerant of a wide variety of functionality.[6] Palladium-catalysis has been used previously for the synthesis of allylglycine derivatives including allyl acetate coupling with glycine anions[3d,7], vinyl electrophiles coupling with an organozinc derivative of β-iodoalanine [8], rearrangements of imino acid allyl ester derivatives[9] and a Stille and Suzuki coupling of a bromoallylglycine derivative.[10]

We have previosly reported on the palladium-catalysed elaboration of tri-*n*-butylstannylallylglycine derivatives via palladium-catalysis with organic electrophiles.[11]

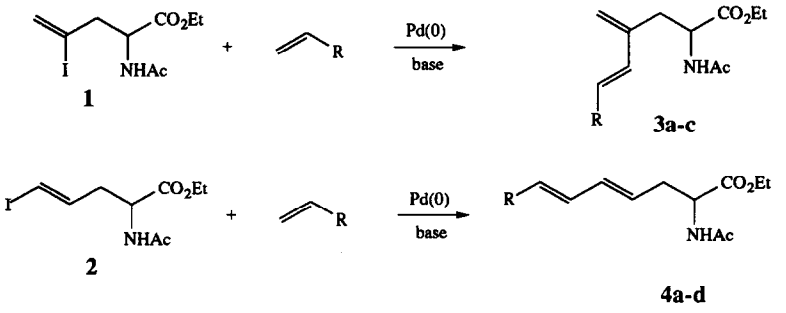
In this paper we report that iodoallylglycine derivatives also undergo coupling with organic nucleophiles in the presence of palladium catalysts and we have explored the scope and limitations of this methodology for the preparation of modified allylglycines.

RESULTS AND DISCUSSION

Heck reactions of ethyl N-acetyl-γ-iodoallylglycinate(1) and ethyl E,N-acetyl-δ-iodo allylglycinate(2)

The preparation of ethyl N-acetyl-*D,L*-4-iodoallylglycinate (**1**) and ethyl-*E*-*D,L*-5-iodoallyl glycinate(**2**) from the corresponding vinyl stannanes by electrophilic iodination has been briefly reported.[12] In order to determine the efficacy of these vinyl iodides for carbon-carbon bond formation the Heck

reactions of **1** and **2** were investigated with a number of alkenes (Scheme 1). The alkenes chosen as coupling partners were the electron deficient ethyl acrylate, acrylonitrile and methyl vinyl ketone. Ethyl acrylate was investigated under a variety of reaction conditions in order to optimize the coupling yield. The results are summarised in Table 1 (entries 1-4). Using the Jeffery conditions[13] (entry 1, condition A) all the vinyl iodide (**1**) was consumed but only a low yield of coupled product (**3a**) was obtained. The use of the traditional Heck catalyst system[14] (entry 2, condition B) gave a more stable catalyst and a higher yield. The ^{1}H nmr spectrum of the product (**3a**) confirmed the stereochemistry of the double bond (δ6.98, d, *J* 15.9Hz; δ7.25, d, *J*16.0Hz)



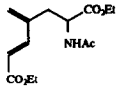
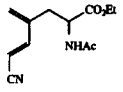
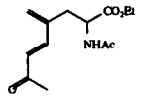
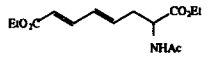
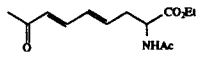
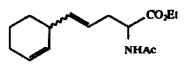
Scheme 1

The use of silver salts in Heck reactions of vinyl halides was developed by Hallberg[15a,b] and Overman[16] and has been shown to improve the rate and yield of the coupling and the isomeric purity of the products. The presence of silver salts results in the formation of cationic palladium(II) intermediates in the catalytic cycle. The use of Overman's catalyst system [$Pd(OAc)_2$, Ag_2CO_3][16] for the reaction of **1** with ethyl acrylate (entries 3 and 4) gave the expected product **3a** in both DMF and THF as solvents. The yields were similar to those obtained using the traditional catalyst system. The use of THF is unusual for successful Heck coupling which normally requires a coordinating solvent such as DMF or acetonitrile.[17a-c]

Acrylonitrile gave no product when reacted under the Jeffery conditions (entry 5), but gave a low yield of the expected 1,3-diene (**3b**) when coupled using the more traditional conditions (entry 6). Freshly distilled methyl vinyl ketone coupled with **1** under both the traditional (entry 7) and silver carbonate (entry 8) conditions, but a pure product (**3c**) could not be isolated after flash chromatography. The product obtained in both cases contained an aromatic impurity which could not be separated or identified. This unidentified side product could not be derived from the triphenylphosphine ligand since none was used in entry 8. Perhaps a Diels-Alder reaction or an electrocyclic ring closure occurs with **3c** followed by aromatisation. Methyl vinyl ketone is notorious for polymerisation under the conditions of Heck reactions,[17a] and **3c** may also have undergone polymerisation.

In order to determine whether these Heck reactions were occurring with any significant degree of racemisation at the α-centre, the reaction of ethyl acrylate was repeated with the enantiomerically enriched

Table 1. Heck coupling between ethyl N-acetyl-*D,L*-γ-iodoallylglycinate (**1**) and ethyl-*E*-N-acetyl-*D,L*-δ-iodoallylglycinate (**2**) and alkenes.

Entry	Alkene	Iodide	Catalyst[a]	Product	Yield
1		**1**	A		29
				3a	
2			B	**3a**	41
3			C	**3a**	44
4			C[b]	**3a**	44
5		**1**	A		0
				3b	
6			B	**3b**	27
7		**1**	B		78[c]
				3c	
8		**1**	C	**3c**	78[c]
9		**2**	C[b]		73
				4a	
10		**2**	C[b]		78
				4b	
11		**2**	C[b]		69
				4c	
12		**2**	C[b]		43
				4d	

Reactions carried out with alkene (*ca* 10 eq) and catalyst system A, B or C in DMF unless otherwise noted.

a A : $Pd(OAc)_2$ (5mol%), K_2CO_3 (5 eq), Bu_4NCl (1.0 eq); B : $PdCl_2(PPh_3)_2$ (5mol%), Et_3N (2 eq); C : $Pd(OAc)_2$ (5mol%), Ag_2CO_3 (1.5 eq).

b THF solvent.

cThe isolated product contained an aromatic impurity.

vinyl iodide (*L*-**1**) using the conditions of entry 2 of Table 1. Optically active product was obtained in 48% yield and a chiral shift ^{1}H nmr experiment with Eu(hfc)$_3$ showed no evidence for any racemization.

The Heck reactions were repeated with the *E*-δ-iodide (**2**) and in addition coupling with cyclohexene was also studied. Overman's conditions of palladium acetate and silver carbonate in THF[16] with excess alkene were used in all cases. Generally the reactions proceeded to give good yields of coupled products (Table 1, entries 9-12). In all cases the reactions were very clean as ajudged by tlc with just one new spot formed. Ethyl acrylate and methyl vinyl ketone reacted cleanly to furnish the expected coupled products (**4a** and **4c**) as *E,E*-isomers in good yields (entries 9 and 11). Acrylonitrile gave a moderate yield of product which was a 58:42 mixture of 6-*E* and 6-*Z*-isomers (*E* ,*E* and *E,Z*-**4b**) (*i.e.* isomers about the bond which is formed by β-hydride elimination). The corresponding reaction of acrylonitrile with the γ-iodide (**1**) gave only the *E*-isomer (**3b**) (Table 1, entry 6) although a different catalyst and solvent was used in that case. Acrylonitrile is known to produce various amounts of *Z*-isomers as products in a number of Heck reactions.[18]

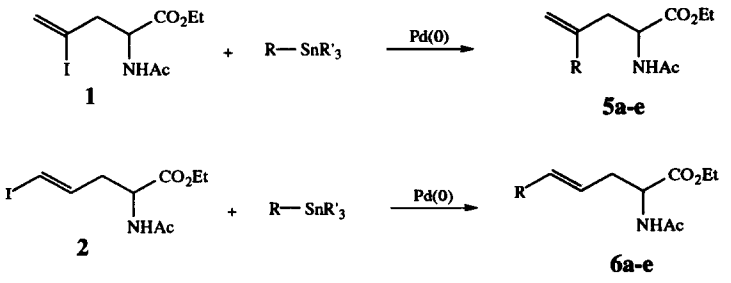
Cyclohexene was also investigated as a coupling partner (entry 12). Under the standard conditions a low yield of product was obtained which was a complex, inseparable mixture of isomers, which we presume to be the diastereomeric pair of 1,4-dienes (**4d**). The ^{13}C nmr spectrum showed the presence of eight olefinic resonances which would support the presence of the two diastereomers. The 1,4-dienes are the expected products as the double bond insertion occurs in a *syn*-manner and *syn*-β-hydride elimination is then only possible with the one hydrogen of this cyclohexyl intermediate which leads to formation of the 1,4-dienes (**4d**). The product did not contain any 1,3-diene since that compound had been synthesised previously[11] and comparison of spectra clearly indicated that it was not present in the mixture.

The observations gained in this section of the work supports the view that the *E*-δ-iodoallylglycinate (**2**) is the more reactive of the two. The reasons for this are most likely the increased steric hindrance of **1** compared to **2** since the rates of Heck reactions are known to favour the least hindered vinyl halide and the intermediate palladium(II) species resulting from oxidative addition of the vinyl iodide may be stabilised in **1** intramolecularly by the amide nitrogen or the carbonyl oxygens ligated to the palladium.

Stille coupling reactions of ethyl N-acetyl-γ-iodoallylglycinate(1) and ethyl E,N-acetyl-δ-iodoallylglycinate(2)

The Stille reaction has an inherent advantage over many forms of carbon-carbon bond formation in that the nucleophilic and electrophilic partners in the coupling can be interchanged.[19a,b,20] We explored this complementarity by carrying out the coupling of iodoallylglycinates (**1** and **2**) with a range of organostannanes (vinyl, allyl and phenyl) as an alternative to the Stille coupling of the two corresponding stannylallyl glycinates with organic halides and triflates.[11] The coupling reactions of the general type shown in Scheme 2 proved to be quite limited in terms of reactivity of the γ-iodoallylglycinate (**1**). The yields obtained for coupled products were variable (Table 2). For instance, under the conditions developed by Farina [21] using Pd(AsPh$_3$)$_4$ as the catalyst, reaction with 2-trimethylstannylpropene yielded no product and unreacted vinyl iodide was recovered (entry 1). Varying the reaction conditions such as the use of DMF as solvent or changing the catalyst to Pd(CH$_3$CN)$_2$Cl$_2$ had no effect on the poor reactivity. However, in the reactions with other organostannanes product was isolated in each case (entries 2-4).

In some instances, the product could not be separated from **1** by flash chromatography on silica gel. This was a disadvantage since it became difficult to follow the course of these particular reactions by tlc.

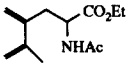
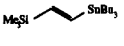
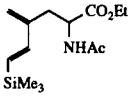
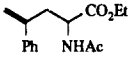
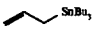
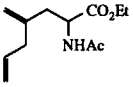
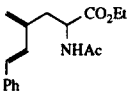
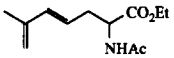
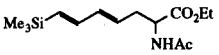
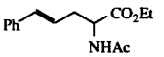
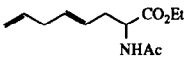
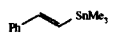
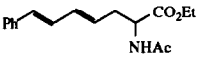


Scheme 2

Generally the reactions were carried out by the addition of the palladium catalyst to a solution of **1** and organostannane in DMF at room temperature. This caused the solution to turn deep purple in colour, presumably the result of formation of an intermediate palladium(0) or (II) π-complex with the organostannane. After stirring overnight at room temperature the solutions became clear and pale canary yellow in colour, possibly because of π-coordination of the product to palladium(0) (*i.e.* catalyst did not decompose). Since it was difficult to ascertain whether the reactions had proceeded to completion by tlc, the solutions were heated to 80-90° for 1-2 hours by which time palladium black precipitated. Chromatography of the mixtures gave the products as shown in Table 2. The electron rich *E*-1-(trimethyl silyl)-2-(tributylstannyl)ethylene (entry 2) was a reactive substrate and the coupled product (**5b**) was isolated in high yield. Phenyltributylstannane gave a moderate yield of coupled product (**5c**) which could not be separated from unreacted vinyl iodide (entry 3). Allyltributylstannane reacted poorly and only a small amount of product (**5d**) was obtained as a mixture with recovered vinyl iodide (entry 4). No product could be detected from the reaction of *E*-β-(trimethylstannyl)styrene under these conditions (entry 5).

Reactions of the general type shown in Scheme 2 were undertaken with *E*-δ-iodoallylglycinate (**2**) with the same selection of organostannanes as discussed above. Generally, low to moderate yields of coupled products were obtained in all instances (Table 2). Again, reactions performed with $Pd(AsPh_3)_4$ gave none of the desired products, yet those catalysed by $PdCl_2(CH_3CN)_2$ in DMF were successful (entries 6-10). Using THF rather than DMF gave none of the desired product so presumably a solvent which coordinates quite strongly to palladium is necessary. Separation of products from unreacted vinyl iodide was often difficult. 2-(Trimethyl stannyl)propene reacted quite well with **2** to form **6a** (entry 6) whereas no product could be detected from its Stille reaction with the γ-iodide (**1**) and this is presumably because the vinyliodide **2** is less sterically demanding. Conversely, a poor yield of product (**6b**) was obtained by reaction of *E*-1-(trimethylsilyl)-2-(tributylstannyl) ethylene, which had coupled surprisingly well with **1**, but this appeared to be the result of catalyst instability (entry 7).

Table 2. Stille coupling between ethyl N-acetyl-γ-iodoallyglycinate (**1**) and ethyl-*E*-N-acetyl-δ-iodoallyglycinate (**2**) and organostannanes.

Entry	Alkene	Catalyst[a]	Temp./Time	Product		Yield[b]
1		A or B			**5a**	0
2		B	15°/15h then 90°/60min		**5b**	86
3	PhSnBu3	B	15°/15h then 90°/2h		**5c**	56 (61[b])
4		B	15°/15h then 90°/2h		**5d**	7 (23[b])
5		B	15°/15h then 80°/1h		**5e**	0
6		B	40°/18h		**6a**	65
7		B	15°/15h		**6b**	23
8	PhSnBu3	B	15°/15h		**6c**	31 (53[b])
9		B	80°/4h		**6d**	41 (68[b])
10		B	40°/17h		**6e**	21

Reactions carried out with catalyst (A or B) (5mol%), organostannane (2 eq) and vinyliodide (1.0 eq) for the temperature and time shown (in DMF unless otherwise noted).

a. A = $Pd(AsPh_3)_4$; B = $PdCl_2(CH_3CN)_2$

b. Based on recovered iodide.

Coupling of ethyl N-acetyl-γ–odoallylglycinate(1) and ethyl E,N-acetyl-γ–iodoallyl glycinate(2) with terminal alkynes.

The organometallic coupling between aryl halides and terminal alkynes has been known for many years[22], later developments involved copper acetylides and the presence of palladium catalysts and base[23,24]. The method used in this paper uses catalytic quantities of copper(I) and palladium(0) as developed by Hagihara[25].

We initially examined the reaction of the γ-iodide (**1**) with a variety of terminal alkynes of varying electron density and the results are shown in Table 3. All the reactions were performed with $PdCl_2(PPh_3)_2$ (5mol%) and copper(I) iodide (10mol%) in THF at room temperature and monitored by tlc. Crystallisation of triethyl ammonium iodide from the reaction solution also gave a visual indication of the progress of the reaction. Most reactions were complete within one to two hours and produced the enynes (**7a, 7b, 7c, 7d**) in good to excellent yields. The products were easily assigned the structures shown since the terminal olefinic protons in the ^1H nmr spectra resonated as singlets in the region δ5.12 to 5.55 and the infrared spectra showed weak absorbances for the alkynes in the region 2144 to 2212cm^{-1}.

Although it was not expected, to ascertain whether these couplings were proceeding with any degree of racemisation at the α-carbon the reaction of phenylacetylene (entry 3) was repeated using the enantiomerically enriched γ-iodide (*L*-**1**). Optically active product was obtained in 91% yield and a chiral shift ^1H nmr experiment with $Eu(hfc)_3$ showed no evidence for any racemization.

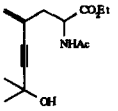
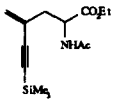
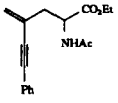
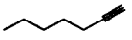
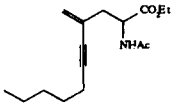
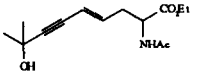
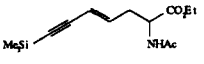
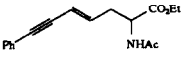
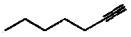
The correponding reactions of *E*-δ-iodoallylglycinate (**2**) were carried out under identical conditions to those used for the coupling reactions above and the results are given in Table 3. The rates of reaction were much faster than for the corresponding coupling reactions of the γ-iodide, and generally triethyl-ammonium iodide precipitated within 5 to 15 minutes, but the reactions were left overnight for convenience. The yields of the 4-en-6-ynes (**8a, 8b, 8c, 8d**) were good to excellent and the products were shown to have the indicated structures by the presence in their ^1H nmr spectra of doublets with *trans*-coupling constants (15.7-15.8Hz) in the region δ5.48 to 5.73 for the C5-protons and doublets of triplets for the C4-protons at δ5.86 to 6.02. Infrared spectra confirmed the presence of the alkynes by weak absorbances the region 2132 to 2236cm^{-1}.

These coupling reactions were amongst the simplest and cleanest reactions for the vinyl iodides **1** and **2** and seem to be of total generality in the synthesis of racemic and chiral amino acid derivatives bearing conjugated enynes in the side chain.

Carboethoxylation reactions of ethyl N-acetyl-γ–odoallylglycinate(1) and ethyl E,N-acetyl-γ–iodoallylglycinate(2)

The palladium catalysed carbonylation of organic halides, triflates and diazonium salts is an extremely effective method for the construction of carboxylic esters, amides and acids.[26] It is a safe, mild and catalytic alternative to the use of the highly toxic and volatile nickel tetracarbonyl. The reaction was initially pioneered independently by Heck[27] and Stille[28] for carbonylation of aryl, benzyl and vinyl halides.

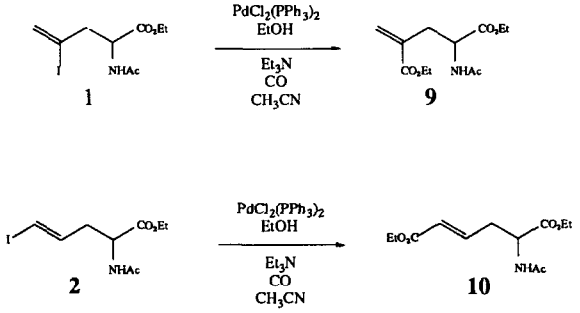
Table 3. Coupling between ethyl N-acetyl-γ-iodoallylglycinate (**1**) and ethyl-*E*,N-acetyl-δ-iodoallylglycinate (**2**) and terminal alkynes

Entry	Substrate	Time	% Yield	Product
1		1.5h	62	 **7a**
2		15h	79	 **7b**
3		15h	97	 **7c**
4		2h	93	 **7d**
5		15h	98	 **8a**
6		15h	96	 **8b**
7		2h	64	 **8c**
8		15h	80	 **8d**

Reactions carried out with $PdCl_2(PPh_3)_2$ (5mol%), Cu(I) iodide (10mol%), substrate (1.5 eq) and triethylamine (2 eq) in THF at room temperature.

We wished to investigate the two vinyl iodides (**1** and **2**) in carbonylative reactions for the formation of α,β-unsaturated esters (**9** and **10**, Scheme 3). These products are derivatives of the known compounds 4-methylene glutamic acid which occurs naturally in a number of plants,[29a,b] and 5-amino-2-hexenedioic acid which has been investigated as a conformationally restricted amino acid with respect to neuronal receptor excitation and dihydrofolate reductase inhibition (when incorporated as the amino acid side chain of methotrexate and aminopterin).[30a-c] Leanna has recently reported the carbomethoxylation of a γ-bromallylglycine derivative using a nickel carbonyl catalyst as a route to a 4-methyleneglutamic acid derivative .[29b]

Upon treatment of the γ-iodoallylglycinate (**1**) with $PdCl_2(PPh_3)_2$ and ethanol in the presence of triethylamine under an atmosphere of carbon monoxide in acetonitrile at 60° for 30 minutes (Scheme 3), tlc indicated that no vinyl iodide remained and one new spot had formed. This was isolated by flash chromatography in good yield (77%) and the structure confirmed as the expected diethyl N-acetyl-4-methylene glutamate (**9**). The reaction was repeated with the *E*-δ-iodoallylglycinate (**2**) under the same conditions as above and diethyl 5-amido-2-hexenedioate (**10**) was obtained in moderate yield (67%) (Scheme 3). In order to determine whether these carbonylation reactions were occurring with any significant degree of racemisation at the α-centre, the reaction was repeated with the enantiomerically enriched vinyl iodide (*L*-**1**) using the conditions described for **1** above. Optically active product *L*-**9**was obtained in 77% yield and a chiral shift ^1H nmr experiment with $Eu(hfc)_3$ showed no evidence for any racemization.



Scheme 3

In summary the palladium-catalysed couplings of α-amino acids containing vinyl iodide side chains has proved to be an expeditious route to a variety of modified amino acids.

Experimental

^1H and ^{13}C nuclear magnetic resonance spectra were recorded using a Bruker ACP-300 spectrometer as dilute solutions in deuteriochloroform. Nmrmultiplicities are abbreviated as follows: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *quin* = quintet, *m* = multiplet, *br* = broad. Infrared spectra were recorded using a Hitachi 270-30 spectrophotometer as neat films, nujol mulls or chloroform solutions as indicated. Electron impact mass spectra and accurate mass measurements were obtained using an AIG-GEC MS3074 spectrometer. Optical rotation data were obtained on a Perkin Elmer 141 Polarimeter measured with sodium D light (589nm). Melting points were determined using a Kofler hot stage with a Reichert microscope and are uncorrected.

Thin layer chromatography was carried out on Merck Alufolien Kieselgel 60 PF_{254} plates which were visualised by ultraviolet light (254nm) and by staining with an acidic aqueous solution of ammonium molybdate, a 5% ethanolic solution of phosphomolybdic acid or a 5% ethanolic solution of vanillin followed by development with heat. Flash and 'squat' column chromatographies were carried out using Merck Silica Gel 60 (230-400 mesh) and Merck Silica Gel 60 PF_{254} respectively.

All solvents were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone prior to use. Dimethyl formamide (DMF) was distilled from sodium sulphate under reduced pressure and stored over 4Å molecular sieves. Acetonitrile was distilled from calcium hydride and stored over 4Å molecular sieves. Light petroleum refers to the fraction of boiling point 66-69°. Organic extracts were dried with magnesium sulphate.

The following compounds were prepared according to known procedures: dichlorobis(triphenyl phosphine)palladium,[31] dichlorobis(acetonitrile)palladium,[32] tris(dibenzylidine)dipalladium chloroform complex,[33] trimethyl(2-propenyl)stannane,[34] *E*-1-(trimethylsilyl)-2-(trimethylstannyl)ethene,[35] and (β-styryl) trimethylstannane.[36]

Ethyl N-acetyl-*D,L*-4-iodoallylglycinate (1) Iodine (0.80g, 3.16mmol) was added to a solution of ethyl N-acetyl-*D,L*-4-(tributylstannyl)allylglycinate[11,12] (1.5g, 3.16mmol) in dichloromethane (20ml). The deep purple mixture was stirred under nitrogen for 90 minutes, then the solvent was evaporated. The residue was taken up in ether and washed with 10% potassium fluoride solution (50ml) and the aqueous phase was extracted with ether (4x40ml). The combined organic extracts were dried and the solvent evaporated. Flash chromatography of the residue gradient eluting with 40-50% ethyl acetate/light petroleum yielded the title compound (0.81g, 82%). ^1H nmr: 1.18 (*t*, *J*7.1Hz, 3H), 1.92 (*s*, 3H), 2.75 (*dd*, *J*7.6, 14.7Hz, 1H), 2.86 (*dd*, *J*5.3, 14.8Hz, 1H), 4.09 (*q*, *J*7.1Hz, 2H), 4.61 (*dt*, *J*5.5, 7.7Hz, 1H), 5.72 (*d*, *J*1.4Hz, 1H), 6.02 (*d*, *J*1.3Hz, 1H), 6.61 (*br d*, J7.6Hz, 1H); ^{13}C nmr: 13.92, 22.74, 46.40, 51.52, 61.50, 103.03 ($\underline{C}=CH_2$), 129.32 ($C=\underline{C}H_2$), 169.89, 170.84; IR (neat): 3280*s*, 3064*m*, 2980*m*, 2932*w*, 1740*s*, 1660*s*, 1548*s*, 1432*m*, 1376*m*, 1276*w*, 1222*m*, 1192*w*, 1148*m*, 1026*s*, 908*s*, 732*m*; MS: 311 (M^+, 100%, calc. for $C_9H_{14}NO_3I$: 311.0018, found: 311.0030), 293 (2), 269 (5), 265 (5), 237 ($[M\text{-}HCO_2Et]^+$, 5), 195 (9), 183 (82), 110 (9), 102 (7), 68 (11), 43 (23). Repetition of the reaction with enantiomerically enriched vinylstannane[11] using identical conditions gave the optically active product (*L*-**1**). $[\alpha]_D$ = +32.6° (*c*0.47, $CHCl_3$).

Ethyl *E*-N-acetyl-*D,L*-5-iodoallylglycinate (2) Reaction of ethyl (*E*)-N-acetyl-*D,L*-5-(tributyl stannyl)allyglycinate[11,12] (0.18g, 0.377mmol) with iodine (0.10g, 0.396mmol) in CH_2Cl_2 for 60min

yielded on workup the title compound as a clear oil (99mg, 84%). ^{1}H nmr: 1.15 (*t*, *J*7.2Hz, 3H), 1.90 (*s*, 3H), 2.40 (*m*, 2H), 4.07 (*m*, 2H), 4.50 (*dt*, *J*6.0, 7.7Hz, 1H), 6.05 (*d*, *J*14.3Hz, 1H), 6.30 (*dt*, *J*7.5, 14.4Hz, 1H), 6.72 (*br d*, *J*7.7Hz, 1H); ^{13}C nmr: 13.97, 22.72, 38.13, 50.91, 61.37, 78.58 (CH=CHI), 139.76 (CH=CHI), 169.81, 171.04; IR (neat): 3288*s*, 3052*m*, 2980*m*, 2932*w*, 1736*s*, 1660*s*, 1544*s*, 1436*m*, 1376*m*, 1342*w*, 1298*w*, 1272*m*, 1200*s*, 1128*m*, 1028*s*, 946*s*, 860*w*, 734*m*; MS: 311 (M^+, 2%, calc. for $C_9H_{14}NO_3I$: 311.0018, found: 311.0009), 265 (2), 252 ([M-AcNH$_2$]$^+$, 19), 238 ([M-CO2Et]$^+$, 20), 196 (40), 184 (41), 167 (7), 144 (12), 125 (24), 102 (100), 97 (51), 74 (31), 43 (26). Repetition of the reaction with enantiomerically enriched vinylstannane using identical conditions gave the optically active product (*L*-**2**). $[\alpha]_D$ = +68.1° (*c*0.50, $CHCl_3$).

Ethyl (*E*)-2-acetamido-4-methylene-6-(carboethoxy)hex-5-enoate (3a) A mixture of ethyl N-acetyl-*D*,*L*-4-iodoallylglycinate (**1**) (40mg, 0.129mmol), ethyl acrylate (100μl, 0.923mmol), triethylamine (36μl, 0.257mmol) and $PdCl_2(PPh_3)_2$ (4.5mg, 6.4μmol) in DMF was heated at 90° for 3h under a nitrogen atmosphere, then cooled to room temperature. Water (30ml) was added and the aqueous phase extracted with ether (4x50ml). The organic extracts were dried and the solvent evaporated. Flash chromatography of the residue gradient elution with mixtures of ethyl acetate and light petroleum (25-45%) gave the title compound as a thick oil (15mg, 41%). ^{1}H nmr: 1.24 (*t*, *J*7.1Hz, 3H), 1.25 (*t*, *J*7.1Hz, 3H), 1.96 (*s*, 3H), 2.65 (*dd*, *J*6.2, 14.1Hz, 1H), 2.73 (*dd*, *J*6.5, 14.0Hz, 1H), 4.13 (*m*, 2H), 4.14 (*q*, *J*7.0Hz, 2H), 4.71 (*dt*, *J*6.5, 7.8Hz, 1H), 5.29 (*s*, 1H), 5.45 (*s*, 1H), 6.98 (*d*, *J*15.9Hz, 1H), 6.04 (*br d*, *J*7.8Hz, 1H, NH), 7.25 (*d*, *J*16.0Hz, 1H); ^{13}C nmr: 14.07 ($OCH_2\underline{C}H_3$), 14.22 ($OCH_2\underline{C}H_3$), 23.05, 34.39, 51.19, 60.50 ($O\underline{C}H_2$), 61.69 ($O\underline{C}H_2$), 119.10, 126.01, 139.59 (quarternary olefinic), 145.41, 166.81 (conjugated $\underline{C}O_2Et$), 169.64, 171.67; IR ($CDCl_3$): 3444*m*, 2980*m*, 2936*w*, 1736*s*, 1712*s*, 1678*s*, 1634*m*, 1606*w*, 1512*s*, 1448*m*, 1376*m*, 1312*m*, 1278*s*, 1188*s*, 1034*s*, 986*m*; MS: 283 (M^+, <0.5%, calc. for $C_{14}H_{21}NO_5$: 283.1420, found: 283.1397), 212 (3), 170 (3), 127 (6), 102 (5), 86 (22), 84 (33), 49 (40), 32 (65), 31 (100), 29 (44). Reaction of the enantiomerically enriched vinyliodide (*L*-**1**) using identical conditions yielded the optically active product (*L*-**3a**). $[\alpha]_D$ = +24.6° (*c*0.18, $CHCl_3$).

Ethyl (*E*)-2-acetamido-4-methylene-6-cyanohex-5-enoate (3b) Reaction of **1** (40mg, 0.129 mmol), acrylonitrile (100μl, 1.52mmol), triethylamine (36μl, 0.257mmol) and 5mol% $PdCl_2(PPh_3)_2$ in DMF at 60-100° for 3h gave on workup the title compound as a thick oil (8.3mg, 27%). ^{1}H nmr: 1.24 (*t*, *J*7.3Hz, 3H), 1.98 (*s*, 3H), 2.65 (*d*, *J*6.6Hz, 2H), 4.16 (*m*, 2H), 4.64 (*br q*, *J*7.1Hz, 1H), 5.32 (*s*, 1H), 5.43 (*s*, 1H), 5.64 (*d*, *J*16.6Hz, 1H), 6.12 (*br d*, *J*7.0Hz, 1H, NH), 6.98 (*d*, *J*16.6Hz, 1H); ^{13}C nmr: 14.14, 23.06, 34.19, 51.17, 61.90, 117.82 (CN), 126.86, 139.30, 150.73, 151.31, 169.75, 171.36; IR ($CHCl_3$): 3436*w*, 2220*w* (CN), 1736*s*, 1672*s*, 1504*m*, 1378*m*, 1280*w*, 970*w*; MS: 236 (M^+, 0.5%, calc. for $C_{12}H_{16}N_2O_3$: 236.1161, found: 236.1152), 177 (2), 165 (9), 123 (20), 102 (16), 86 (18), 84 (28), 49 (33), 43 (100), 32 (39), 31 (95), 29 (90).

Ethyl (*E*,*E*)-2-acetamido-7-(carboethoxy)hepta-4,6-dienoate (4a) A solution of **2** (40mg, 0.129mmol) in dry THF was degassed by a stream of nitrogen. Ethyl acrylate (100μl, 0.923mmol), $Pd(OAc)_2$ (1.4mg, 6.5μmol) and silver carbonate (53mg, 0.194mmol) were added and the flask covered with aluminium foil. The mixture was heated to reflux for 19h then cooled to room temperature. Water (30ml) was added and the aqueous phase extracted with ethyl acetate (3x50ml). Flash chromatography of the residue gradient eluting with mixtures of ethyl acetate in light petroleum (30-45%) yielded the title

compound as a thick oil (27mg, 73%). ^{1}H nmr: 1.24 (*t*, *J*7.0Hz, 3H), 1.25 (*t*, *J*7.2Hz, 1H), 1.99 (*s*, 3H), 2.60 (*m*, 1H), 2.70 (*m*, 1H), 4.16 (*m*, 2H), 4.67 (*dt*, *J*5.7, 7.6Hz, 1H), 5.78 (*d*, *J*15.4Hz, 1H), 5.91 (*dt*, *J*7.4, 15.1Hz, 1H), 6.08 (*br d*, *J*7.7Hz, 1H), 6.17 (*ddd*, *J*0.7, 11.0, 15.1Hz, 1H, C5-H), 7.17 (*dd*, 1H, *J*10.9, 15.4Hz, 1H, C6-H); ^{13}C nmr: 14.20 ($OCH_2\underline{C}H_3$), 14.25 ($OCH_2\underline{C}H_3$), 23.18, 35.79, 51.64, 60.38 ($O\underline{C}H_2$), 61.78 ($O\underline{C}H_2$), 121.13, 131.97, 136.41, 143.62, 166.91 (conjugated ester CO), 169.71, 171.45; IR ($CDCl_3$): 3420*m*, 2970*m*, 1730*s*, 1700*s*, 1672*s*, 1618*w*, 1500*m*, 1368*m*, 1340*w*, 1300*w*, 1260*m*, 1198*w*, 1024*m*, 996*m*; MS: 284 ([M+H]$^+$, 1%, calc. for $C_{14}H_{22}NO_5$: 284.1498, found: 284.1503), 238 (2), 224 (5), 210 (4), 195 (11), 188 (13), 158 (11), 142 (11), 116 (17), 114 (22), 102 (46), 72 (43), 43 (100).

(*E*,*E*) and (*E*,*Z*)-Ethyl-2-acetamido-7-cyanohexa-4,6-dienoates (4b) Reaction of **2** (40mg, 0.129mmol), acrylonitrile (100µl, 1.52mmol), silver carbonate (53mg, 0.194mmol) and 5mol% $Pd(OAc)_2$ at reflux in THF overnight yielded on workup the title compounds as an inseparable mixture (21.1mg, 69%, ratio 58:42). ^{1}H nmr: (*E*,*E*)-**4c**: 1.23 (*t*, *J*7.0Hz, 1H), 1.98 (*s*, 3H), 2.59 (*m*, 1H, beta), 2.74 (*m*, 1H, beta), 4.19 (*m*, 2H), 4.67 (*m*, 1H, alpha), 5.26 (*d*, *J*16.1Hz, 1H, C7-H), 6.02 (*dt*, *J*7.5, 15.1Hz, 1H, C4-H), 6.15 (*ddd*, *J*0.7, 10.8, 15.1Hz, 1H, C5-H; overlapping with *br*, 1H, NH), 6.90 (*dd*, *J*10.7, 16.1Hz, 1H, C6-H); (*E*,*Z*)-**4c**: 1.25 (*t*, *J*7.2Hz, 1H), 1.99 (*s*, 3H), 2.59 (*m*, 1H), 2.74 (*m*, 1H), 4.19 (*m*, 2H), 4.67 (*m*, 1H), 5.15 (*d*, *J*10.8Hz, 1H), 5.94 (*dt*, *J*7.3, 15.2Hz, 1H, C4-H), 6.15 (*br*, 1H, NH), 6.53 (*ddd*, *J*0.9, 11.0, 15.1Hz, 1H, C5-H), 6.74 (*t*, *J*10.9Hz, 1H, C6-H); IR ($CHCl_3$): 3420*m*, 2976*m*, 2212*s* (CN), 1734*s*, 1672*s*, 1640*w*, 1596*w*, 1394*s*, 1374*m*, 1340*m*, 1018*m*, 984*m*, 942*w*, 900*w*, 850*w*; MS: 236 (M^+, 7%, calc. for $C_{12}H_{16}N_2O_3$: 236.1161, found: 236.1166), 177 (25), 163 (11), 144 (22), 121 (53), 102 (86), 94 (19), 93 (19), 74 (31), 43 (100).

Ethyl (*E*,*E*)-2-acetamido-8-oxonona-4,6-dienoate (4c) Reaction of **2** (40mg, 0.129mmol), methyl vinyl ketone (100µl, 1.20mmol), silver carbonate (53mg, 0.194mmol) and 5mol% $Pd(OAc)_2$ at reflux in THF overnight yielded on workup the title compound as a thick oil (25.5mg, 78%). ^{1}H nmr: 1.21 (*t*, *J*7.2Hz, 1H), 1.96 (*s*, 3H), 2.21 (*s*, 3H, methyl ketone), 2.57 (*br dt*, *J*7.3, 14.5Hz, 1H), 2.67 (*br dt*, *J*7.0, 14.5Hz, 1H), 4.14 (*m*, 2H), 4.65 (*br q*, 1H, alpha), 5.98 (*dt*, *J*7.5, 15.0Hz, 1H, C4-H), 6.01 (*d*, *J*15.6Hz, 1H, C7-H), 6.17 (*dd*, *J*10.7, 15.1Hz, 1H, C5-H), 6.24 (*br d*, 1H, NH), 6.99 (*dd*, *J*10.6, 15.7Hz, 1H, C6-H); ^{13}C nmr: 14.12, 23.03, 27.09 (methyl ketone CH_3), 35.86, 51.55, 61.70, 130.13, 132.22, 137.59, 141.58, 169.81, 171.36, 198.71 (ketone C=O); IR ($CHCl_3$): 3420*m*, 2970*m*, 1732*s*, 1606*vs*, 1588*w*, 1500*m*, 1372*m*, 988*m*, 900*w*; MS: 254 ([M+H]$^+$, 18%, calc. for $C_{13}H_{20}NO_4$: 254.1392, found: 254.1396), 206 (9), 194 (7), 188 (8), 165 (26), 145 (16), 102 (39), 72 (33), 43 (100).

Diastereotopic ethyl 2-acetamido-5-(cyclohex-2-en-1-yl)pent-4-enoates (4d) Reaction of **2** (40mg, 0.129mmol), cyclohexene (100µl, 0.987mmol), silver carbonate (53mg, 0.194mmol) and 5mol% $Pd(OAc)_2$ at reflux in THF overnight yielded on workup the title compound as a thick oil (25.5mg, 78%). ^{1}H n.m.r.: 1.23 (t, J7.1Hz, 3H), 1.30 (m), 1.49 (m), 1.60 (m), 2.44 (m, 2H, C3-H's), 2.68 (m), 4.14 (br q, 2H), 4.57 (br q, 1H, C2-H), 5.25 (br dt, 1H, C4-H), 5.38-5.50 (m), 5.61 (br s), 5.67 (m), 6.02 (br d, J7.2Hz, 1H); ^{13}C n.m.r.: 14.20, 20.33, 20.41, 23.16, 24.66, 24.95, 28.62, 29.13, 31.31, 35.41, 36.51, 38.18, 52.00, 61.39, 121.51, 122.62, 125.88, 126.89, 127.85, 127.85, 128.41, 139.35, 140.40; IR ($CHCl_3$): 3420m, 2980m, 2920m, 2850w, 1732s, 1668s, 1498s, 1432w, 1376m, 1342m, 1018w,

968m, 902w, 854w; MS: 266 (M+H, 44%, calc. for $C_{15}H_{24}NO_3$: 266.1756, found: 266.1758), 206 (41), 102 (100).

Ethyl (*E*)-2-acetamido-4-methylene-6-(trimethylsilyl)hex-5-enoate (5b) A solution of **1** (40mg, 0.129mmol) and (*E*)-1-(trimethylsilyl)-2-(tributylstannyl)ethylene (99mg, 0.257mmol) in DMF (2ml) was degassed with a stream of nitrogen. $PdCl_2(CH_3CN)_2$ (1.7mg, 6.4μmol) was added and the dark purple solution was stirred at ambient temperature overnight. After 15h the canary yellow solution was heated at 90° for 60min by which time palladium black had precipitated. Potassium fluoride solution (10%, 30ml) was added and the aqueous phase extracted with ether (3x50ml). The organic extracts were dried and the solvent evaporated. Flash chromatography of the residue yielded the title compound as a thick oil (31mg, 86%). ^{1}H nmr: 0.37 (*s*, 9H), 1.22 (*t*, *J*7.2Hz, 3H), 2.59 (*dd*, *J*6.9, 14.2Hz, 1H), 2.72 (*dd*, *J*5.7, 14.2Hz, 1H), 4.11(*m*, 2H), 4.65 (*br q*, 1H, alpha), 5.00 (*s*, 1H), 5.11 (*s*, 1H), 5.88 (*d*, *J* 19.2Hz, 1H), 6.01 (*br d*, *J*7.6Hz, 1H), 6.47 (*d*, *J*19.2Hz, 1H); ^{13}C nmr: -1.36 ($\underline{C}H_3Si$), 14.07, 23.03, 33.25, 51.50, 61.33, 119.20 (C=$\underline{C}H_2$), 129.85, 142.17 ($\underline{C}$=CH_2), 144.98, 169.57, 171.98; IR ($CHCl_3$): 3450*m*, 2900*m*, 1732*s*, 1670*s*, 1576*w*, 1504*m*, 1176*m*, 1238*m*, 1016*w*, 988*m*, 880*s*, 840*w*; MS: 283 (M^+, 14%, calc. for $C_{14}H_{25}NO_3Si$: 283.1604, found: 283.1611), 268 ([M-Me$^·$]$^+$, 13), 241 (4), 240 (4), 224 ([M-$AcNH_2$]$^+$, 4), 210 ([M-CO_2Et]$^+$, 19), 168 (13), 102 (41), 75 (31), 73 (43), 43 (38), 18 (100). Reaction of enantiomerically enriched vinyliodide (*L*-**1**) using an identical procedure yielded the optically active product (*L*-**5b**) (41%). $[\alpha]_D$ = +24.7° (*c*0.15, $CHCl_3$).

Ethyl 2-acetamido-4-phenylpent-4-enoate (5c) Reaction of **1** (40mg, 0.129mmol) and phenyl tributylstannane (94mg, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15h then 90° for 2h gave after workup the title compound (56%) contaminated with unreacted and inseparable vinyliodide (**1**) (8%) (*i.e.* 61% yield of **5c** based on recovered starting material). Spectra identical to that obtained for reference 11.

Ethyl 2-acetamido-4-methylenehept-6-enoate (5d) Reaction of **1** (40mg, 0.129mmol) and allyl tributylstannane (80μl, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15h then 90° for 2h gave after workup the title compound (7%) contaminated with unreacted and inseparable vinyliodide (**1**) (70%) (*i.e.* 23% yield of **5d** based on recovered starting material). Spectra identical to that obtained for reference 11.

Ethyl (*E*)-2-acetamido-6-methylhepta-4,6-dienoate (6a) Reaction of **2** (40mg, 0.129mmol) and prop-1-en-2-yl trimethylstannane (53mg, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 18h gave after workup the title compound as a thick oil (19mg, 65%). ^{1}H nmr: 1.22 (*t*, *J*7.1Hz, 3H), 1.76 (*br s*, 3H, C6-Me), 1.97 (*s*, 3H), 2.55 (*m*, 2H), 4.15 (*m*, 2H), 4.62 (*dt*, *J*5.8, 7.9Hz, 1H), 4.86 (*br s*, 1H), 4.88 (*br s*, 1H), 5.43 (*dt*, *J*7.4, 15.5Hz, 1H), 6.11 (*br*, 1H, NH, masked by doublet), 6.13, (*d*, *J*15.6Hz, 1H); ^{13}C nmr: 14.12, 18.47 (6-CH_3), 23.10, 35.61, 51.95, 61.42, 116.09, 123.26, 136.87, 141.35 ($\underline{C}$=CH_2), 169.66, 171.80; IR ($CHCl_3$): 3430*m*, 2970*m*, 1732*s*, 1670*s*, 1600*w*, 1498*s*, 1432*w*, 1374*m*, 1340*m*, 1120*w*, 1014*w*, 962*m*, 884*m*; MS: 226 ([M+H]$^+$, 23%, calc. for $C_{12}H_{20}NO_3$: 226.1443, found: 226.1453), 179 (10), 166 (52), 152 (10), 137 (29), 102 (63), 93 (100), 43 (50).

Ethyl (*E*,*E*)-2-acetamido-7-(trimethylsilyl)hepta-4,6-dienoate (6b) Reaction of **2** (40mg, 0.129mmol) and (*E*)-1-(trimethylsilyl)-2-(tributylstannyl)ethylene (74mg, 0.193mmol) with 5mol%

$Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15 minutes decomposed the catalyst and gave after workup the title compound as a thick oil (8.5mg, 23%). ^1H nmr: 0.02 (*s*, 9H), 1.23 (*t*, *J*7.2Hz, 3H), 1.97 (*s*, 3H), 2.53 (*m*, 2H), 4.16 (*m*, 2H), 4.62 (*dt*, *J*5.7, 7.7Hz, 1H), 5.50 (*dt*, *J*7.4, 15.1Hz, 1H), 5.74 (*d*, *J*18.4Hz, 1H), 6.05 (*dd*, *J*10.1, 15.2Hz, 1H), 6.07 (*br d*, 1H, NH, masked by previous *dd*), 6.40 (*dd*, *J*10.0, 18.4Hz, 1H); ^{13}C nmr: -1.41, 14.15, 23.13, 35.26, 51.82, 61.54, 127.45, 133.82, 137.26, 143.21, 169.77, 171.74; IR ($CHCl_3$): 3426*m*, 2900*m*, 1736*s*, 1662*s*, 1508*m*, 1374*m*, 1236*m*, 1012*w*, 858*m*, 838*m*; MS: 283 (M^+, 7%, calc. for $C_{14}H_{25}NO_3Si$: 283.1604, found: 283.1597), 268 (6), 224 (21), 210 (9), 209 (9), 188 (14), 168 (20), 106 (47), 102 (100), 74 (74), 72 (68), 43 (96).

Ethyl (*E*)-2-acetamido-5-phenylpent-4-enoate (6c) Reaction of **2** (40mg, 0.129mmol) and phenyl tributylstannane (94mg, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at ambient temperature for 15h gave after workup the title compound (31%) contaminated with unreacted and inseparable vinyliodide (**2**) (42%) (*i.e.* 53% yield of **6c** based on recovered starting material). Spectra identical to that obtained for reference 11.

Ethyl (*E*)-2-acetamidooctadien-4,7-oate (6d) Reaction of **2** (40mg, 0.129mmol) and allyl tributylstannane (80µl, 0.257mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at 80° for 4h gave after workup the title compound (41%) contaminated with unreacted and inseparable vinyliodide (**2**) (40%) (*i.e.* 68% yield of **6d** based on recovered starting material). Spectra identical to that obtained for reference 11.

Ethyl (*E*,*E*)-2-acetamido-7-phenylhepta-4,6-dienoate (6e) Reaction of e**2** (30mg, 96.4µmol) and E-β-(trimethylstannyl)styrene (51mg, 0.193mmol) with 5mol% $Pd(CH_3CN)_2Cl_2$ in DMF at 40° for 17h gave after workup the title compound (6mg, 21%). Spectra identical to that obtained for reference 11.

Ethyl 2-acetamido-4-methylene-7-hydroxy-7-methyloct-5-ynoate (7a) To a solution of **1** (40mg, 0.129mmol), 2-methyl but-3-yn-2-ol (19µl, 0.193mmol) and triethylamine (36µl, 0.256mmol) in dry THF (2ml) was added $PdCl_2(PPh_3)_2$ (4.5mg, 6.5µmol) and copper(I) iodide (2.5mg, 12.9µmol). The mixture was stirred at room temperature under a nitrogen atmosphere for 90min. Water (20ml) was added and the aqueous phase extracted with ethyl acetate (3x25ml). The combined organic extracts were dried and the solvent evaporated. The residue was subjected to flash chromatography on silica gel gradient eluting with a mixture of ethyl acetate and light petroleum (60-75%) to yield the title compound as a thick oil (21mg, 62%). ^1H nmr: 1.23 (*t*, *J*7.2Hz, 3H), 1.46 (*s*, 3H, diasteriotopic methyl), 1.47 (*s*, 3H, diasteriotopic methyl), 1.98 (*s*, 3H), 2.53 (*dd*, *J*7.5, 14.3Hz, 1H), 2.67 (*dd*, *J*5.2, 14.2Hz, 1H), 3.48 (*br*, 1H, OH), 4.15 (*q*, *J*7.1Hz, 2H), 4.80 (*m*, 1H, α), 5.19 (*d*, *J*1.2Hz, 1H), 5.33 (*d*, *J*1.2Hz, 1H), 6.34 (*br d*, *J*8.3Hz, 1H); ^{13}C nmr: 14.08, 23.09, 31.13 (diasteriotopic CH_3), 31.26 (diasteriotopic CH_3), 38.99, 51.03, 61.57, 64.94 (COH), 80.85 (C≡C), 95.81 (C≡C), 124.24 ($\underline{C}H_2$=C), 125.86 (CH_2=$\underline{C}$), 170.08, 171.77; IR (neat): 3292 (*vs*, *br*), 3080*w*, 2980*m*, 2928*w*, 2212*w*, 1736*s*, 1660*s*, 1544*s*, 1440*m*, 1376*m*, 1222 (*s*, *br*), 1024*m*, 954*w*, 910*w*, 860*w*, 754*w*; MS: 267 (M^+, <1%), 249 ([M-H_2O]$^+$, 15, calc. for $C_{14}H_{19}NO_3$: 249.1365, found: 249.1361), 176 (23), 134 (69), 102 (54), 43 (100); FAB: 268 (M+H).

Ethyl 2-acetamido-4-methylene-6-(trimethylsilyl)hex-5-ynoate (7b) Reaction of **1** (40mg, 0.129mmol) and trimethylsilyl acetylene (27µl, 0.194mmol) for 15h at ambient temperature under the conditions described for **7a** yielded on workup the title compound as a thick oil (28.8mg, 79%). ^1H nmr: 0.12 (*s*, 9H), 1.22 (*t*, *J*7.2Hz, 3H), 1.95 (*s*, 3H), 2.57 (*dd*, *J*6.2, 14.0Hz, 1H), 2.63 (*dd*, *J*5.3, 14.0Hz,

1H), 4.13 (*m*, 2H), 4.67 (*m*, 1H, α), 5.24 (*s*, 1H), 5.44 (*s*, 1H), 6.27 (*br d*, *J*7.3Hz, 1H); ^{13}C nmr: -0.23 (Me_3Si), 14.01, 23.04, 38.44, 51.52, 61.38, 95.30 (C≡C), 104.51 (C≡C), 125.97 (CH_2=C), 126.20 (CH_2=C), 169.56, 171.19; IR (neat): 3284 (*s*, *br*), 3068*w*, 2956*m*, 2144*m*, 1746*s*, 1658*s*, 1548*s*, 1440*w*, 1376*m*, 1250*m*, 1210*m*, 1134*w*, 1026*m*, 874*w*, 842*s*, 760*m*, 700*w*; MS: 281 (M^+, 26%, calc. for $C_{14}H_{23}NO_3Si$: 281.1447, found: 281.1454), 266 (M^+-Me·, 32), 248 (16), 212 (47), 208 (68), 207 (63), 192 (26), 166 (58), 150 (37), 123 (42), 102 (100), 73 (63), 43 (95).

Ethyl 2-acetamido-4-methylene-6-phenylhex-5-ynoate (7c) Reaction of **1** (42mg, 0.134mmol) and phenyl acetylene (21μl, 0.194mmol) for 15h at ambient temperature yielded on workup the title compound as a thick oil (37.8mg, 97%). ^{1}H nmr : 1.21 (*t*, *J*7.2Hz, 3H), 2.01 (*s*, 3H), 2.71 (*dd*, *J*6.0, 14.0, 1H), 2.79 (*dd*, *J*5.3, 13.9Hz, 1H), 4.14 (*m*, 2H), 4.78 (*br q*, 1H, α), 5.31 (*br s*, 1H), 5.50 (*d*, *J*1.3Hz, 1H), 6.57 (*br d*, *J*7.1Hz, 1H), 7.28 (*m*, 3H), 7.38 (*m*, 2H); ^{13}C nmr: 13.99, 22.71, 38.74, 51.64, 61.69, 88.40 (C≡C), 90.39 (C≡C), 122.45 (quarternary aromatic), 125.17 (CH_2=C), 125.80 (CH_2=C), 128.30, 128.50, 131.39; IR (neat): 3288 (*m*, *br*), 3060*w*, 2980*w*, 2928*w*, 2200*w* (C≡C), 1736*s*, 1656*s*, 1546*s*, 1492*w*, 1444*m*, 1376*m*, 1270*w*, 1200*s*, 1070*m*, 912*w*, 756*m*, 692*m*; MS: 285 (M^+, 42%, calc. for $C_{17}H_{19}NO_3$: 285.1365, found: 285.1376), 257 (17), 226 (50), 212 (36), 170 (92), 129 (39), 102 (78), 45 (56), 43 (100). Reaction of ethyl N-acetyl-*L*-4-iodoallylglycinate (*L*-**1**) (40mg, 0.129mmol) under identical conditions yielded *L*-**7c** (33.9mg, 91%). $[\alpha]_D$ = +56.9° (*c*0.34, $CHCl_3$).

Ethyl 2-acetamido-4-methylene-undec-5-ynoate (7d) Reaction of **1** (40mg, 0.129mmol) and 1-heptyne (26μl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (33.5mg, 93%). ^{1}H nmr: 0.83 (*t*, *J*6.6Hz, 3H), 1.21 (*t*, *J*7.2Hz, 3H), 1.27 (*m*, 4H), 1.46 (*m*, 2H, CH_2CH_2C≡C), 1.95 (*s*, 3H), 2.20 (*t*, *J*7.1Hz, 2H, CH_2C≡C), 2.53 (*dd*, *J*6.5, 13.9Hz, 1H), 2.59 (*dd*, *J*5.2, 13.9Hz, 1H), 4.12 (*m*, 2H), 4.66 (*br q*, 1H, α), 5.12 (*s*, 1H), 5.27 (*s*, 1H), 6.22 (*br d*, *J*7.5Hz, 1H); ^{13}C nmr: 13.84, 14.04, 19.17, 22.06, 22.95, 28.21, 31.00, 39.11, 51.38, 61.31, 79.85 (C≡C), 91.71 (C≡C), 123.46 (CH_2=C), 126.44 (CH_2=C), 169.69, 171.46; IR (neat): 3288 (*m*, *br*), 3068*w*, 2928*s*, 2856*w*, 2212*w*, 1744*s*, 1656*s*, 1546*s*, 1440*m*, 1376*m*, 1200*m*, 1134*w*, 1026*m*, 904*w*; MS: 279 (M^+, 26%, calc. for $C_{16}H_{25}NO_3$: 279.1834, found: 279.1839), 236 (26), 220 (23), 208 (31), 206 (45), 164 (69), 147 (40), 123 (57), 102 (71), 43 (100).

Ethyl 2-acetamido-8-hydroxy-8-methylnon-4-en-6-ynoate (8a) Reaction of **2** (43.1mg, 0.139mmol) and 2-methyl but-3-yn-2-ol (19μl, 0.194mmol) for 15h at ambient temperature yielded on workup the title compound as a thick oil (36.4mg, 98%). ^{1}H nmr: 1.22 (*t*, *J*7.1Hz, 3H), 1.45 (*s*, 6H), 1.97 (*s*, 3H), 2.54 (*m*, 2H, β), 2.28 (*br*, 1H, OH), 4.14 (*q*, *J*7.1Hz, 1H), 4.15 (*q*, *J*7.2Hz, 1H), 4.61 (*br q*, 1H, α), 5.48 (*dd*, *J*0.7, 15.8Hz, 1H), 5.86 (*dt*, *J*7.5, 15.8Hz, 1H), 6.35 (*br d*, *J*7.7Hz, 1H); ^{13}C nmr: 14.10, 22.00, 31.24 (CH_3COH), 35.50, 51.50, 61.67, 65.17 (COH), 79.64 (C≡C), 93.88 (C≡C), 113.30 (C=C), 137.09 (C=C), 170.01, 171.49; IR (neat): 3296 (*vs*, *br*), 3068*w*, 2980*m*, 2928*w*, 1736*s*, 1656*s*, 1548*s*, 1438*m*, 1378*s*, 1302*w*, 1216*s*, 1168*m*, 1136*m*, 1096*w*, 1026*m*, 954*s*, 860*m*; MS: 269 (M^+, <1%), 250 ($[M\text{-}OH]^+$, 3), 249 ($[M\text{-}H_2O]^+$, 4, calc. for $C_{14}H_{19}NO_3$: 249.1365, found: 249.1361), 206 (10), 203 (9), 176 (15), 161 (24), 134 (40), 106 (27), 102 (62), 43 (100).

Ethyl *E*-2-acetamido-7-(trimethylsilyl)hept-4-en-6-ynoate (8b) Reaction of **2** (40mg, 0.129mmol) and trimethylsilyl acetylene (27μl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (35.1mg, 96%). ^{1}H nmr: 0.12 (*s*, 9H), 1.23 (*t*, *J*7.0Hz, 3H),

1.97 (*s*, 3H), 2.55 (*m*, 2H, β), 4.16 (*q*, *J*7.1Hz, 1H), 4.17 (*q*, *J*7.1Hz, 1H), 4.62 (*dt*, *J*5.5, 7.7Hz, 1H), 5.50 (*d*, *J*15.7Hz, 1H), 5.96 (*dt*, *J*7.4, 15.8Hz, 1H), 6.18 (*br d*, *J*7.6Hz, 1H); ^{13}C nmr: -0.23 (CH_3Si), 14.10, 23.07, 35.53, 51.44, 61.68, 94.35 (C≡C), 102.80 (C≡C), 113.86 (C=C), 138.31 (C=C), 169.74, 171.37; IR (neat), 3292 (*s*, *br*), 3064*w*, 2956*m*, 2900*w*, 2132*m*, 1742*s*, 1656*s*, 1544*s*, 1436*w*, 1376*m*, 1250*m*, 1194*m*, 1134*m*, 1082*m*, 1026*m*, 956*m*, 846*s*, 760*m*, 700*w*, 656*w*; MS: 282 (M^+, 2%, calc. for $C_{14}H_{23}NO_3Si$: 281.1447, found: 281.1454), 266 (M^+-CH_4, 5), 222 (14), 207 (23), 206 (16), 193 (12), 178 (20), 166 (21), 150 (20), 136 (14), 102 (100), 73 (60), 43 (100).

Ethyl *E*-2-acetamido-7-phenylhex-4-en-6-ynoate (8c) Reaction of **2** (40mg, 0.129mmol) and phenyl acetylene (21μl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (23.7mg, 64%). ^{1}H nmr: 1.27 (*t*, *J*7.0Hz, 3H), 2.01 (*s*, 3H), 2.64 (*m*, 2H, β), 4.20 (*m*, 2H), 4.68 (*dt*, *J*5.6, 7.7Hz, 1H, α), 5.73 (*dt*, *J*1.3, 15.7Hz, 1H), 6.02 (*dt*, *J*7.6, 15.7Hz, 1H), 6.15 (*br d*, *J*7.8Hz, 1H), 7.25-7.30 (*m*, 3H), 7.35-7.40 (*m*, 2H); ^{13}C nmr: 14.20, 23.16, 35.79, 51.61, 61.75, 87.25 (C≡C), 89.30 (C≡C), 113.89 (C=C), 123.03 (quarternary aromatic), 128.22, 128.29, 131.44, 137.20 (C=C), 169.74, 171.45; IR ($CDCl_3$): 3420*m*, 2976*m*, 2236*m* (C≡C), 1736*s*, 1670*s*, 1590*w*, 1500*s*, 1440*w*, 1370*m*, 1340*m*, 1300*w*, 1210*m*, 1130*w*, 1010*m*; MS: 285 (M^+, 2%, calc. for $C_{17}H_{19}NO_3$: 285.1365, found: 285.1360), 252 (10), 238 (11), 226 (8), 196 (36), 184 (42), 144 (8), 141 (16), 125 (22), 105 (24), 102 (100), 97 (30), 86 (36), 84 (42), 43 (98).

Ethyl 2-(acetamido)dodec-4-en-6-ynoate (8d) Reaction of **2** (40mg, 0.129mmol) and 1-heptyne (26μl, 0.194mmol) for 2h at ambient temperature yielded on workup the title compound as a thick oil (28.9mg, 80%). ^{1}H nmr: 0.85 (*t*, *J*7.0Hz, 3H), 1.24 (*t*, *J*7.1Hz, 3H), 1.25-1.35 (*m*, 4H), 1.40-1.52 (*m*, 2H), 1.98 (*s*, 3H), 2.22 (*t*, *J*7.0Hz, 1H, diastereotopic C<u>H</u>C≡C), 2.23 (*t*, *J*7.0Hz, 1H, diastereotopic C<u>H</u>C≡C), 2.54 (*m*, 2H, β), 4.17 (*m*, 2H), 4.61 (*dt*, *J*5.5, 7.7Hz, 1H), 5.48 (*br d*, *J*15.7Hz, 1H), 5.80 (*dt*, *J*7.4, 15.7Hz, 1H), 6.09 (*br d*, *J*7.6Hz, 1H); ^{13}C nmr: 13.92, 14.15, 19.23, 22.14, 23.13, 28.31, 31.02, 35.50, 51.58, 61.63, 78.28 (C≡C), 90.54 (C≡C), 114.38 (C=C), 135.35 (C=C), 169.69, 171.50; IR (neat): 3280 (*br*, *s*), 3060*w*, 2950*w*, 2930*s*, 2860*m*, 2210*w* (C≡C), 1740*s*, 1660*s*, 1540*s*, 1462*w*, 1436*w*, 1376*m*, 1200 (*m*, *br*), 1020*m*, 750*w*, 856*w*; MS: 279 (M^+, 15%, calc. for $C_{16}H_{25}NO_3$: 279.1834, found: 279.1839), 252 (4), 250 (3), 236 (12), 220 (57), 206 (33), 191 (27), 164 (62), 163 (57), 147 (45), 105 (73), 102 (57), 99 (58), 79 (67), 77 (80), 75 (78), 60 (83), 55 (92), 43 (100).

Diethyl N-acetyl 4-methyleneglutamate (9) Carbon monoxide was bubbled through a solution of **1** (40mg, 0.129mmol), ethanol (100μl, 1.70mmol), and triethylamine (22μl, 0.154mmol) in acetonitrile (2ml) for 5 minutes. $Pd(PPh_3)_4$ (11.1mg, 9.6μmol) was added and the reaction mixture stirred at 60° for 60 minutes under 1 atmosphere of carbon monoxide (balloon). The solution was cooled and the solvent evaporated *in vacuo*. The residue was subjected to flash chromatography on silica gel to yield the title compound as a thick oil (25.7mg, 77%). ^{1}H nmr: 1.21 (*t*, *J*6.9Hz, 3H), 1.26 (*t*, *J*7.1Hz, 3H), 1.94 (*s*, 3H), 2.67 (*dd*, *J*7.8, 14.0Hz, 1H), 2.75 (*dd*, *J*5.4, 14.0Hz, 1H), 4.04-4.22 (*m*, 4H), 4.64 (*dt*, *J*5.4, 7.7Hz, 1H), 5.61 (*s*, 1H), 6.21 (*s*, 1H), 6.40 (*br d*, *J*6.9Hz, 1H); ^{13}C nmr: 14.05 (both <u>C</u>H_3CH_2O), 22.95, 34.41, 52.07, 61.10 (CH_2O), 61.39 (CH_2O), 128.43 (<u>C</u>H_2=C), 135.93 (CH_2=<u>C</u>), 166.95 (conjugated <u>C</u>O_2Et), 169.75, 171.53; MS: 257 (M^+, 2%, calc. for $C_{12}H_{19}NO_5$: 257.1263, found: 257.1260), 214 (2), 212 (1), 211 (1), 202 (2), 184 (25), 170 (8), 142 (18), 102 (63), 96 (19), 68 (7), 43

(16), 32 (100), 31 (40), 29 (83). The reaction was repeated with the enantiomerically enriched vinyl iodide (*L*-**1**) using identical conditions to yield the optically active product (*L*-**9**): $[\alpha]_D$ = +21.0° (*c*0.26, $CHCl_3$).

Ethyl (*E*)-2-acetamido-5-(carboethoxy)pent-4-enoate (10) Reaction of **2** (60mg, 0.193mmol), ethanol (100μl, 1.70mmol), and triethylamine (32μl, 0.231mmol) in acetonitrile (2ml) with 5mol% $Pd(PPh_3)_4$ in acetonitrile under 1 atmosphere of carbon monoxide for 3h at 80° yielded after workup the title compound as a thick oil (33mg, 67%). ^1H nmr: 1.21 (*t*, *J*7.2Hz, 6H), 1.96 (*s*, 3H), 2.61 (*br dtt*, 1H), 2.68 (*br dtt*, 1H), 4.11 (*q*, *J*7.1Hz, 2H), 4.13 (*m*, 2H), 4.66 (*br dt*, *J*5.7, 7.6Hz, 1H), 5.80 (*dt*, *J*1.2, 15.6Hz, 1H), 6.33 (*br d*, *J*7.5Hz, 1H), 6.72 (*dt*, *J*7.4Hz, 15.6Hz); ^{13}C: 14.04, 14.09, 22.97, 34.63, 51.20, 60.36, 61.75, 124.86, 141.97, 165.73 (conjugated $\underline{C}O_2Et$), 169.80, 171.12; IR (neat): 3296*m*, 3064*w*, 2984*m*, 2936*w*, 1722*s*, 1656*s*, 1542*m*, 1448*w*, 1374*m*, 1266*m*, 1184*s*, 1096*w*, 1034*m*, 982*w*, 862*w*; MS: 257 (M^+, 1%, calc. for $C_{12}H_{19}NO_5$: 257.1263, found: 257.1255), 214 (3), 212 (2), 211 (2), 184 (18), 170 (16), 144 (15), 142 (89), 114 (11), 102 (54), 96 (24), 43 (20), 29 (100).

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