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Synthesis of α,β-Unsaturated Lactams by Palladium-Catalysed Intramolecular Carbonylative Coupling

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Abstract: Amino vinyl triflates have been shown to undergo an intramolecular, carbonylative coupling in the presence of a palladium catalyst to afford α,β-unsaturated lactams.

INTRODUCTION

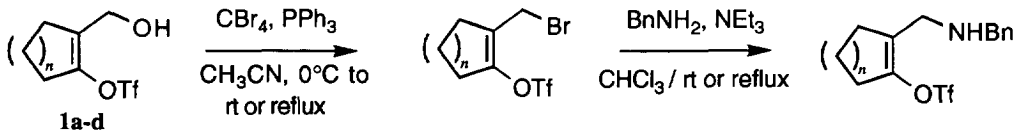
The palladium-catalysed incorporation of carbon-monoxide into organic substrates has been exploited often in organic synthesis.[1] Palladium-bound carbon monoxide is readily inserted into a carbon-palladium bond to afford an acyl-palladium complex[2] which can react with oxygen or nitrogen nucleophiles to afford, after elimination, esters[3] and amides[4]. Aryl halides have been shown to undergo intramolecular carbonylations to give 1,4-benzodiazepins[5], benzolactams[6] and lactams[7]. Vinyl halides under similar conditions give β-lactams[8] and α-methylene γ, δ, or ε-lactams[9]. Recently aryl and vinyl triflates have also been used for palladium-catalysed carbonylations with amines to afford amides[10] and a number of natural product syntheses, including dehydrotubifoline[11] and gelsemine,[12] have used this methodology as a key step.

We have recently reported on the palladium-catalysed, intramolecular carbonylation of hydroxy vinyl triflates to α,β-butenolides[13] and now report in this paper on the analogous conversion of amino vinyl triflates to α,β-unsaturated lactams.

RESULTS AND DISCUSSION

Preparation of amino vinyl triflates

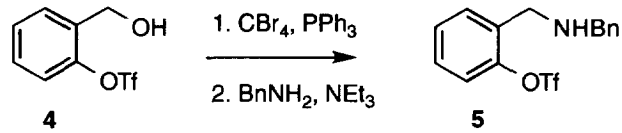
We have previously described the synthesis of cyclic hydroxy vinyl triflates **1a-d** from β-keto esters[13] and Scheme 1 describes their conversion to bromo vinyl triflates **2a-d** and subsequently into amino vinyl triflates **3a-d**. The hydroxyl group of **1a-d** can be converted into a bromide by the slow addition of triphenylphosphine to a solution of the alcohol and carbon tetrabromide in acetonitrile at 0°C, followed by heating at reflux.[14] The allylic bromide of compounds **2a-d** can be readily transformed into an amino group by a minor modification of a procedure[8] where benzylamine is added to a chloroform solution of **2a-d** and triethylamine at 0°C and, depending upon the substrate, either stirried at ambient temperature or heated to reflux for 2-3 hours. Treatment of 2-trifloxybenzyl alcohol **4** under the same conditions afforded *N*-benzyl-2-trifloxybenzylamine **5** in low yield (Scheme 2).



2a n=1 100%
2b n=2 100%
2c n=3 100%
2d n=4 95%

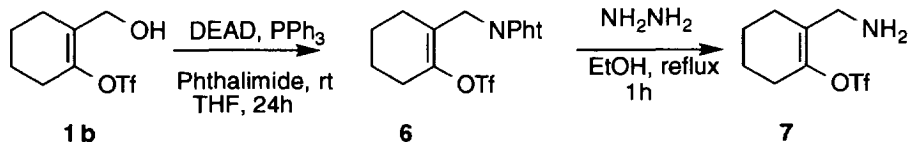
3a n=1 37%
3b n=2 57%
3c n=3 45%
3d n=4 70%

Scheme 1



Scheme 2

Compound **1b** can also also converted into the phthalimido protected amine **6** (96%) by the dropwise addition of diethylazodicarboxylate (DEAD) to a THF solution of **1b**, triphenylphosphine and phthalimide.[15] Hydrolysis of the phthalimido group was effected by heating an ethanol solution of **6** in the presence of an excess of hydrazine hydrate to give the primary amine derivative **7** in 71% (Scheme 3).[14,16]



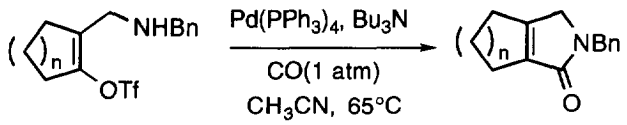
Scheme 3

Acyclic amino vinyl triflates **8-10** (see Table) were conveniently prepared by the addition of triflic acid to the corresponding alkynyl triflate followed by reaction with benzylamine as described previously.[17]

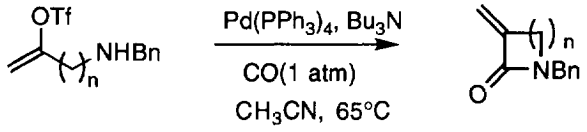
Palladium-catalysed intramolecular carbonylations of amino vinyl triflates

The carbonylation reactions of amino vinyl triflates were conducted under one atmosphere of carbon monoxide in the presence of tributylamine and a palladium catalyst (Scheme 4). The results are summarized in the Table. The ring size of the cyclic amino vinyl triflates **3a-d** appears to have little influence on the isolated yield of 3,4-disubstituted α,β-unsaturated γ-lactams **11a-d** (entries 1-4, Table). Cyclohexenyl triflate **7**, containing the primary amino group, was similarly converted to the corresponding γ-lactam **13** in good yield (entry 6, Table). The acyclic amino vinyl triflates also underwent the carbonylation reaction with ease and in good to excellent yields, although the reaction times were found to be considerably longer than the cyclic cases (enteries 7-9, Table).

However, it was found that to effect the transformation of aryl triflate **5** the addition of the chelating ligand 1,1'-bis(diphenylphosphino)ferrocene(dppf) was necessary (Entry 5, Table). In fact, in its absence palladium precipitated from the mixture and a ^{1}H NMR analysis revealed that the reaction was only one-third complete. This observation is similar to that reported by Cacchi and Ortar[18] who reported in their synthesis of arene carboxylic acid derivatives from aryl triflates that 1,3-bis(diphenylphosphino)propane (dppp) was necessary to produce effective rates in the carbonylation reactions of aryl triflates.



3a-d **11a-d**



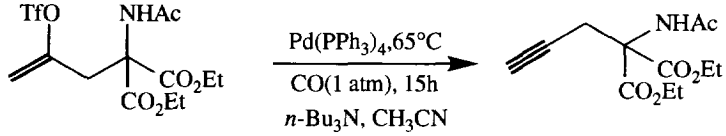
8 n=1 **14** n=1
9 n=2 **15** n=2
10 n=3 **16** n=3

Scheme 4

Synthesis of an α,β-unsaturated amide derivative of proline

Non-proteinogenic α-amino acids bearing a vinylic or acetylenic group in the α-side chain constitute an important class of molecules since many are known to act as irreversible mechanism based inhibitors of pyridoxal phosphate and flavin dependent enzymes.[19] Their mode of action lies in their ability to deactivate specific target enzymes *via* the target enzyme catalytically unmasking a latent functional group at a point in the catalytic cycle of the enzyme.

An attempted synthesis of an α,β-unsaturated amide derivative of proline, utilizing a palladium-catalyzed intramolecular carbonylation reaction is outlined in Scheme 5. Compound **17** was readily prepared from the sodium salt of diethyl acetamidomalonate and the appropriate allyl bromide. Subsequent carbonylation under the standard conditions for fifteen hours gave a black solution that showed upon TLC analysis a spot of an identical R_f to that of the starting triflate. Flash chromatography of the residue furnished quantitatively a clear viscous oil that was shown by ^1H NMR to be propargylmalonate derivative **18**. This was presumably formed by the elimination of triflic acid under the reaction conditions.

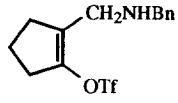
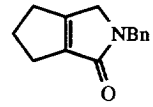
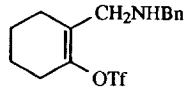
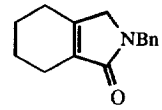
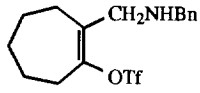
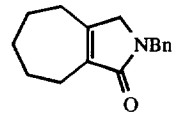
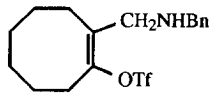
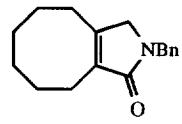
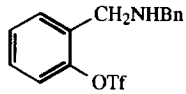
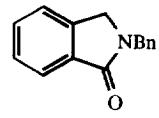
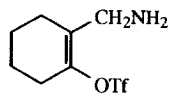
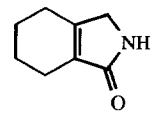
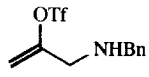
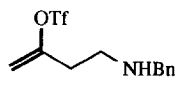
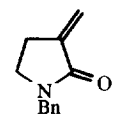
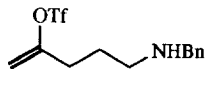
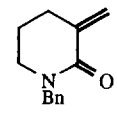


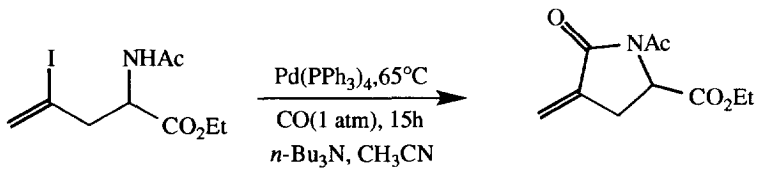
17 **18**

Scheme 5

To circumvent this problem the vinyl iodide derivative, γ-iodoallylglycinate **19** was carbonylated under these same conditions (Scheme 6) and the solution rapidly turned from the characteristic initial yellow colour to a dark brown in 30 minutes. Inspection of the mixture by TLC indicated the reaction had gone to completion and following two sets of flash chromatographic purifications (the presence of coloured impurities made this necessary) the desired proline derivative **20** was obtained in moderate yield (63%).

Table. Yields of α,β-Unsaturated Lactams as shown in Scheme 4.

Entry	Amino vinyl triflate	Catalyst /time	Product	Yield %
1	 **1a**	$Pd(PPh_3)_4$ / 2h	 **11a**	100
2	 **1b**	$Pd(PPh_3)_4$ / 2h	 **11b**	89
3	 **1c**	$Pd(PPh_3)_4$ / 2h	 **11c**	100
4	 **1d**	$Pd(PPh_3)_4$ / 2h	 **11d**	98
5	 **5**	$Pd(PPh_3)_4$ + dppf / 2h	 **12**	63
6	 **7**	$Pd(PPh_3)_4$ / 2h	 **13**	93
7	 **8**	$Pd(PPh_3)_4$ / 15h	 **14**	73
8	 **9**	$Pd(PPh_3)_4$ / 15h	 **15**	100
9	 **10**	$Pd(PPh_3)_4$ / 15h	 **16**	72



19 **20**

Scheme 6

In conclusion amino vinyl trflates can be readily converted into α,β-unsaturated lactams by an intramolecular, palladium-catalysed carbonylation.

EXPERIMENTAL

General: Infrared spectra were obtained using a Jasco A102 or a Hitachi 270-30 infrared spectrophotometer, as a neat film or a nujol mull . ^{1}H NMR spectra and ^{13}C NMR spectra were recorded using an ACP 300 Fourier Transform NMR spectrometer. All NMR samples were prepared in deuterochloroform with tetramethylsilane as the internal standard. Electron impact mass spectra and accurate mass measurements were obtained using a AEI-GEC MS3074 mass spectrometer. Where the electron impact technique was unsuccessful in giving a molecular ion, mass spectra were obtained using the FAB technique using a VG ZAB 2HF mass spectrometer. All solvents were distilled prior to use. The analytical tlc plates used were Merck Alufolien Kieselgel 60 PF_{254} and were visualized by UV light (254 nm), by staining with iodine vapour or by staining with phosphomolybdic acid followed by development with heat. Preparative radial chromatography plates were prepared using Merck Kieselgel 60 PF_{254} containing gypsum. Melting points were recorded using a Reichert hot stage melting point apparatus and are uncorrected.

The following compounds were prepared by literature procedures: 2-[(trifluoromethanesulfonyl) oxy]-1-cyclopentenyl methanol (**1a**)[13], 2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexenyl methanol (**1b**)[13], 2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptenyl methanol (**1c**)[13], 2-[(trifluoromethanesulfonyl) oxy]-1-cyclooctenyl methanol (**1d**)[13], N-benzyl 2-[(trifluoromethanesulfonyl)oxy]-2-propenylamine (**8**)[17], N-benzyl 3-[(trifluoromethanesulfonyl)oxy]-3-butenylamine (**9**)[17], N-benzyl 4-[(trifluorometanesulfonyl) oxy]-4-pentenylamine (**10**)[17], ethyl *N*-acetyl-4-iodoallylglycinate (**19**)[20], tetrakis(triphenylphosphine) palladium(0)[21].

2-Bromomethylcyclopent-1-enyltrifluoromethanesulfonate (2a)

To a solution of **1a** (0.44g, 1.79mmol) and carbon tetrabromide (1.19g, 3.57mmol) in acetonitrile (35ml) was added triphenylphosphine (0.94g, 3.57mmol) portionwise at 0°C. The solution was then subsequently refluxed for 15h. Evaporation of the solvent *in vacuo* was followed by flash chromatography (hexanes:ethyl acetate, 49:1) of the residue to yield the title compound as a pale yellow liquid (0.55g, 100%). A small sample was distilled by kugelrohr (50-60°C/0.01mm) for analytical purposes. ^{1}H NMR: δ2.04 (*p*, 2H, *J*7.76Hz), 2.55 (*m*, 2H, CH_2C=C), 2.68 (*m*, 2H, CH_2C=C), 2.68 (*m*, 2H, CH_2C=C), 4.00 (*s*, 2H, CH_2Br); ^{13}C NMR: δ19.1, 21.0, 23.4, 31.2, 118.3 (*q*, J_{CF}320.0Hz), 127.8, 145.3; IR (neat): ν_{max}2950m, 1680*m* (C=C), 1420*s* (asym S=O), 1330*m*, 1295*m* (asym C-OSO_2), 1210*s* (C-F), 1130*s* (sym S=O), 990*s*, 905*w*, 840*s*, 760*m*cm^{-1}; MS m/z: 310/308 (M^+); HRMS Calc. for

$C_7H_8{}^{79}BrF_3O_3S$: 307.93296; Found: 307.93196; Anal. calc. for $C_7H_8BrF_3O_3S$: C, 27.2%; H, 2.61%; Found: C, 27.5%; H, 2.82% .

1-(Benzylamino)methyl-2-[(trifluoromethanesulphonyl)oxy]-1-cyclopentene(3a)

To a chloroform (25ml) solution of **2a** (0.45g, 1.46mmol) at 0°C was added triethylamine (0.41ml, 2.91mmol) and benzylamine (0.32ml, 2.91mmol) dropwise. Stirring at room temperature for 15h was then followed by a 2h reflux upon which the reaction solution changed from yellow to orange in colour. The solvent was then removed in vacuo and the residue purified by flash chromatography (hexanes:ethyl acetate; 9:1) to yield the title compound as a yellow oil (0.18g, 37%). A small sample was distilled by kugelrohr (150-160°C/0.06mm). ^{1}H NMR: 1.98 (*p*, 2H, *J*7.16Hz), 2.47 (*m*, 2H, CH_2C=C), 2.63 (*m*, 2H, CH_2C=C), 3.37 (*s*, 2H, $C\underline{H}_2$Ph), 3.74 (*s*, 2H, $C\underline{H}_2$NH); ^{13}C NMR: δ19.4, 29.9, 30.9, 44.4, 53.5, 118.3 (J_{CF}319.9Hz), 127.1, 128.1, 128.4, 131.0, 139.7, 143.9; IR(neat): ν_{max}3350*w* (N-H), 2930*m*, 1700*m* (C=C), 1605*w*, 1590*w*, 1500*m*, 1460*m*, 1425*s* (asym S=O), 1335*m*, 1300*m*, 1250*s* (asym C-OSO_2), 1210*s* (C-F), 1140*s* (sym S=O), 1025*m*, 1005*m*, 905*m*, 860*s*, 740*m*, 700*m*, 610*s*cm^{-1}; MS m/z: 336 (M^++1), 335(M^+); HRMS Calc. for $C_{14}H_{16}F_3NO_3S$: 335.0803; Found: 335.07982; Anal. calc. for $C_{14}H_{16}F_3NO_3S$: C, 50.14%; H, 4.81%; N, 4.18%; Found: C, 50.39%; H, 4.56%; N, 4.18%.

2-Bromomethylcyclohex-1-enyltrifluoromethanesulfonate(2b)

This compound was prepared from **1b** in an analogous manner to that described for compound **2a** except that three equivalents of both CBr_4 and PPh_3 were used. Flash chromatography (hexanes:ethyl acetate; 49:1) yielded the title compound as a clear oil (100%). A small sample was distilled by kugelrohr (90-100°C/0.07mm). ^{1}H NMR: δ1.70 (*m*, 2H, homallylic CH_2), 1.79 (*m*, 2H, homoallylic CH_2), 2.36 (*m*, 4H, CH_2C=C), 4.02 (*s*, 2H, CH_2Br); ^{13}C NMR: δ21.3, 22.8, 27.4, 27.8, 28.1, 118.2 (*q*, J_{CF}319.8), 126.8, 145.4; IR (neat): ν_{max}2950m, 1680m (C=C), 1410s (asymS=O), 1250m (asymC-OSO_2), 1210s (C-F), 1120s (symS=O), 1080m, 1015s (S-O), 905s (symC-OSO_2), 845m, 795s, 750m, 650cm^{-1}; HRMS Calc. for $C_8H_8{}^{79}BrF_3O_3S$: 321.94861; Found: 321.94763; Anal. calc. for $C_8H_8BrF_3O_3S$: C, 29.74%; H, 3.12%; Found: C, 29.35%; H, 3.35%.

1-(Benzylamino)methyl-2-[(trifluoromethanesulphonyl)oxy]-1-cyclohexene (3b)

This compound was prepared from **2b** in an analogous manner to that described for compound **3a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (58%). A small sample was distilled by kugelrohr (120-130°C/0.07mm). ^{1}H NMR: δ1.63 (*m*, 2H, homoallylic CH_2), 1.73 (*m*, 2H, homoallylic CH_2), 2.30 (*m*, 4H, CH_2C=C), 3.35 (*s*, 2H, $C\underline{H}_2$Ph), 3.75 (*m*, 2H, $C\underline{H}_2$NH), 7.22-7.33 (*m*, 5H, Ph); ^{13}C NMR: δ21.6, 23.0, 27.4, 27.6, 47.9, 53.6, 118.3 (*q*, J_{CF}319.9Hz), 127.0, 128.1, 128.4, 129.2, 139.9, 144.6; IR (neat); ν_{max}3350*w* (N-H), 3025*m*, 2950*s*, 1700*m* (C=C), 1600*w*, 1500*m*, 1460*s*, 1420*s* (asymS=O), 1360*m*, 1250*s* (asymC-OSO_2), 1210*s* (C-F), 1140*s* (symS=O), 1030*s* (S-O), 935*m* (symC-OSO_2), 900*s*, 820*s*, 770*m*, 740*s*, 700*s*, 620*s* cm^{-1}; MS m/z: 349 (M^+, 4%), 348 ([M-1]$^+$, 4), 272 ([M-C_6H_5)$^+$, 2), 258 ([M-C_7H_7]$^+$, 13), 243 (2), 217 (14), 216 ([M-Tf]$^+$, 100); HRMS Calc. for $C_{15}H_{18}F_3NO_3S$: 349.09595; Found: 349.09675; Anal. calc. for $C_{15}H_{18}F_3NO_3S$: C, 51.57%; H, 5.19%; N, 4.01%; Found: C, 51.58%; H, 5.25%; N, 4.09%.

2-Bromomethylcyclohept-1-enyltrifluoromethanesulfonate (2c)

This compound was prepared from **1c** in an analogous manner to that described for compound **2a** except that within five minutes the reaction was complete as evidenced by the precipitation of Ph_3PO. Flash chromatography (hexanes:ethyl acetate; 49:1) yielded the title compound as a clear liquid (100%). A small

sample was distilled by kugelrohr (60-70°C/0.05mm). ^{1}H NMR: δ1.60 (*m*, 6H, ring CH_2), 2.33 (*m*, 2H, CH_2C=C), 2.56 (*m*, 2H, CH_2C=C), 4.03 (*s*, 2H, CH_2Br); ^{13}C NMR: 24.2, 25.7, 30.5, 30.6, 30.9, 33.0, 118.3 (*q*, J_{CF}319.7Hz), 131.5, 148.8; IR (neat): ν_{max}2930*s*, 1680*m* (C=C), 1415*s* (asymS=O), 1250*s* (asymC-OSO_2), 1220*s* (C-F), 1140*s* (symS=O), 1105*m*, 990, 935*s* (symC-OSO_2), 870*s*, 810*m*, 760*m*, 670*s* cm^{-1}; MS m/z: 338/336 (M^+, 2%), 257 ([M-Br]$^+$, 100), 203/205 (M-Tf]$^+$, 1), 187/189 ([M-OTf]$^+$, 1), 153 (33); HRMS Calc. for $C_9H_{12}{}^{79}BrF_3O_3S$: 335.96426; Found: 335.96519; Anal. calc. for $C_9H_{12}BrF_3O_3S$: C, 32.06%; H, 3.59%; Found: C, 32.08%; H, 3.67%.

1-(Benzylamino)methyl-2-[(trifluoromethanesulphonyl)oxy]-1-cycloheptene (3c)

This compound was prepared from **2c** in an analogous manner to that described for compound **3a** except that the reaction solution was refluxed for 3.5h. Flash chromatography (hexanes:ethyl acetate; 19:1) yielded the title compound as a viscous yellow oil (45%). A small sample was distilled by kugelrohr (110-120°C/0.06mm). ^{1}H NMR: δ1.52-1.77 (*m*, 6H, ring CH_2), 2.31 (*m*, 2H, CH_2C=C), 2.51 (*m*, 2H, CH_2C=C), 3.30 (*s*, 2H, $C\underline{H}_2Ph$), 3.74 (*s*, 2H, $C\underline{H}_2NH$), 7.21-7.34 (*m*, 5H, Ph); ^{13}C NMR: 24.5, 24.6, 29.4, 30.7, 32.8, 49.8, 53.6, 118.3 (*q*, J_{CF}319.7Hz), 127.0, 128.1, 128.3, 134.2, 140.1, 147.9; IR (neat): ν_{max}3025*m* (N-H), 1690*m* (C=C), 1605*w*, 1500*m*, 1455*s*, 1410*s* (asymS=O), 1360*s*, 1245*s* (C-OSO_2), 1210*s* (C-F), 1140*s* (symS=O), 985*s*, 910*s*, 880*s*, 780*m*, 740*s*, 700*s*,620*s* cm^{-1}; MS m/z: 364 (M^++1,1%), 363 (M^+, 1), 362 (M^+-1, 1), 272 ([M-C_7H_7]$^+$, 2), 230 ([M-Tf]$^+$, 59), 214 ([M-OTf]$^+$, 8); HRMS calc. for $C_{16}H_{20}F_3NO_3S$: 363.1116; Found: 363.11257; Anal. calc. for $C_{16}H_{20}F_3NO_3S$: C, 52.88%; H, 5.55%; N3.85%; Found: C, 52.74%; H, 5.62%; N, 3.88%.

2-Bromomethylcyclooct-1-enyltrifluoromethanesulfonate (2d)

This compound was prepared from **1d** in an analogous manner to that described for compound **2a** except that the reaction mix was refluxed for only 1.5h and gave a solution black in colour. Flash chromatography (hexanes:ethyl acetate; 97:3) yielded the title compound as an unstable yellow liquid. ^{1}H NMR: δ1.57 (*m*, 4H, ring CH_2), 1.74 (*m*, 4H, ring CH_2), 2.36 (*m*, 2H, CH_2C=C), 2.53 (*m*, 2H, CH_2C=C), 4.04 (*s*, 2H, CH_2Br); ^{13}C NMR: 25.8, 27.8, 28.3, 29.3, 29.7, 29.9, 31.6, 118.4 (*q*, J_{CF}319.8Hz), 128.8, 147.2; IR (neat): ν_{max}2930*s*, 1680*m* (C=C), 1470*m*, 1450*m*, 1415*s* (asymS=O), 1240*s* (asymC-OSO_2), 1215*s* (C-F), 1140*s* (symS=O), 1105*m*, 1070*m* (S-O), 1030*m*, 935*s*, 865*s*, 820*s*, 655*s* cm^{-1}; MS m/z: 352/350 (M^+, 1%), 271 ([M-Br]$^+$, 5), 171 (100); HRMS calc. for $C_{10}H_{14}{}^{79}BrF_3O_3S$: 349.97991; Found: 349.97853; Compound unsuitable for microanalysis.

1-(Benzylamino)methyl-2-[(trifluoromethanesulphonyl)oxy]-1-cyclooctene (3d)

This compound was prepared from **2d** in an analogous manner to that described for **3a** except that the reaction mix was refluxed for 3h. Flash chromatography (hexanes:ethyl acetate; 19:1) yielded the title compound as a clear oil (70%). A small sample was distilled by kugelrohr (120-130°C/0.01mm). ^{1}H NMR: δ1.53 (m, 4H, ring CH_2), 1.67 (m, 4H, ring CH_2), 2.34 (m, 2H, CH_2C=C), 2.49 (m, 2H, CH_2C=C), 3.33 (s, 2H, $C\underline{H}_2Ph$), 3.76 (s, 2H, $C\underline{H}_2NH$), 7.22-7.33 (m, 5H, Ph); ^{13}C NMR: δ25.8, 26.1, 27.9, 28.7, 29.2, 29.9, 47.6, 53.8, 118.4 (*q*, J_{CF}319.7Hz), 127.0, 128.1, 128.4, 131.6, 140.0, 145.6; IR (neat): ν_{max}3025 (N-H) *w*, 2925*s*, 1685*w* (C=C),1605*w*, 1500*w*, 1455*m*, 1410*s* (asymS=O), 1250*m* (asymC-OSO_2), 1215*s* (C-F), 1140*s* (symS=O), 110*m*, 1065*m*, 1025*m* (S-O), 920*s*, 870*s*, 735*s*, 700*m*, 625*m* cm^{-1}; MS m/z: 378 ([M+1]$^+$, 22%), 376 ([M-1]$^+$, 3), 244 ([M-Tf]$^+$, 70), 142 (70), 91 ([C_7H_7]$^+$, 100); HRMS calc. for $C_{17}H_{22}F_3NO_3S$: 378.13508 ([M+1]$^+$); Found: 378.13418; Anal. calc. for $C_{17}H_{22}F_3NO_3S$: C, 54.10%; H, 5.88%; N, 3.71%; Found: C,54.15%; H, 5.80%, N, 3.79%.

2-[(Trifluoromethanesulphonyl)oxy]benzyl bromide (4)

This compound was prepared from 2-trifloxy benzyl alcohol[13] in an analogous manner to that described for **2a**. Flash chromatography (hexanes:ethyl acetate; 49:1) yielded the title compound as a clear oil (100%). A small sample was distilled by kugelrohr (60-70°C/0.05mm). ^{1}H NMR: δ4.53 (*m*, 2H, CH_2Br), 7.25-7.55 (*m*, 4H, Ph); ^{13}C NMR: δ25.6, 118.5 (*q*, J_{CF}320.2), 121.7, 128.8, 130.5, 132.2, 147.1, 171.1; IR (neat): ν_{max}2910w, 1605m, 1580w, 1500w, 1420s (asymS=O), 1250s (asymC-OSO_2), 1210s (C-F), 1140s (symS=O), 1075m (S-O),1040m, 900s, 860m, 805m, 760s, 710m; HRMS calc. for $C_8H_6{}^{79}BrF_3O_3S$: 319.9171; Found: 319.91663; Anal. calc. for $C_8H_6BrF_3O_3S$: C, 30.11%; H, 1.90%; Found: C, 30.34%; H, 1.81%.

N-Benzyl-2-[(trifluoromethanesulphonyl)oxy]-benzylamine (5)

This compound was prepared from **4** in an analogous manner to that described for **3a** except that the reaction was stirred at ambient temperature for 36 hours. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (20%). A small sample was distilled by kugelrohr (100-110°C/0.04mm). ^{1}H NMR: δ3.82 (*s*, 2H, NCH_2Ph), 3.91 (*s*, 2H, CH_2N), 7.25-7.35 (m, 9H, Ar); ^{13}C NMR: δ47.3, 53.4, 118.5 (*q*, J_{CF}319.9Hz), 121.3, 127.1, 128.2, 128.3, 128.4, 128.8, 131.0, 133.2, 139.8, 147.0; IR (neat): ν_{max}3025 (N-H) m, 2925 m, 1600 w, 1580 w, 1500 m, 1460 m, 1420 s (asymS=O), 1250 m (asymC-OSO_2), 1210 s (C-F), 1140 s (symS=O), 1080 m (S-O), 890 s, 770 m, 750 m, 740 m, 700 m; MS m/z: 345 (M^+) ; HRMS calc. for $C_{15}H_{14}F_3NO_3S$: 345.0553; Found: 345.06514; Anal. calc. for $C_{15}H_{14}F_3NO_3S$: C, 52.17%; H, 4.09%; N, 4.06%; Found: C, 52.14%; H, 4.23%; N, 4.02%.

1-(Phthalimido)methyl-2-[(trifluoromethanesulphonyl)oxy]-1-cyclohexene (6)

A solution of **1b** (0.1g, 0.38mmol), PPh_3 (0.15g, 0.58mmol) and phthalimide (0.07g, 0.46mmol) in THF (2ml) was placed under vigorous stirring. To this was added dropwise a solution of diethylazodicarboxylate (91μl, 0.58mmol) in THF (0.5ml) (to give a yellow solution) and the reaction mixture allowed to stir at ambient temperature for 15h. The solvent was then removed *in vacuo* and the residue purified by flash chromatography (hexanes:ethyl acetate; 9:1) to yield the title compound as a white crystalline solid (96%). Mpt.: 127-130°C. ^{1}H NMR: δ1.60 (*m*, 2H, cyclohexenyl CH_2), 1.73 (*m*, 2H, cyclohexenyl CH_2), 2.05 (*m*, 2H, CH_2C=C), 2.40 (*m*, 2H, CH_2C=C), 4.50 (*br s*, 2H, CH_2N), 7.75 (*m*, 2H, aromatic), 7.86 (*m*, 2H, aromatic); ^{13}C NMR: 21.1, 22.6, 25.9, 27.5, 36.7, 118.3 (*q*, J_{CF}=319.6Hz), 123.4, 124.9, 131.8, 134.1, 145.0, 167.8; IR (nujol mull): ν_{max}2920 *s*, 1770 *s* (C=O), 1615 *w*, 1465 *s*, 1400 *m*, 1380 *m*, 1250 *m*, 1200 *m*, 1140 *m*, 1030 *m*, 970 *m*, 935 *m*, 730 *m*, 710 *m* cm^{-1}; MS, m/z: 391 ($[M+1]^+$, 1%), 390 (M^+, 4), 320 ($[M-C_4H_2]^+$, 1), 257 ($[M-Tf]^+$, 20), 256 (100), 240 ($[M-HOTf]^+$, 52), 160 (55), 148 (50), 130 (38), 109 (65), 81 (63); HRMS Calc. for $C_{16}H_{14}F_3NO_5S$ (M+1): 390.06231; Found: 390.06117; Anal. calc. for $C_{16}H_{14}F_3NO_5S$: C, 49.36%; H, 3.62%; N, 3.60%; Found: C, 48.96%; H, 3.62%; N, 3.60%.

1-Aminomethyl-2-[(trifluoromethanesulphonyl)oxy]-1-cyclohexene (7)

Hydrazine hydrate (0.46ml, 9.25mmol) was added to a suspension of **6** (0.36g, 0.93mmol) in ethanol (30ml). The solution was heated at 60°C for two hours and then allowed to cool to ambient temperature with subsequent removal of the solvent *in vacuo*. The residue was dissolved in dichloromethane and the resultant white solid removed by filtration. Kugelrohr distillation (100-110°C/0.04mm) of the residue yielded the title compound as a colourless liquid (71%). ^{1}H NMR: δ1.68 (*m*, 2H, cyclohexenyl CH_2), 1.78 (*m*, 2H, cyclohexenyl CH_2), 2.30 (*m*, 4H, CH_2C=), 3.39 (*s*, 2H, CH_2N); ^{13}C NMR: δ21.6,

23.0, 26.8, 27.6, 41.0, 118.3 (*q*, J_{CF}319.2Hz), 131.1, 143.3; IR (neat): ν_{max}3395 *m* (N-H), 3305*m* (N-H), 2935 *s*, 1695 *m* (C=O), 1595 *m*, 1410 *s* (asymS=O), 1245 *s* (asymC-OSO_2), 1215 *s* (C-F), 1145 *s* (symS=O), 1070 *m* (S-O), 1020 *s*, 900 *s*, 815 *s*, 765 *m* cm^{-1}; MS, m/z: 260 ($[M+1]^+$, 12%), 243 (9), 233 (6), 126 ($[M-Tf]^+$, 100), 109 ($[M-HOTf]^+$, 55); HRMS Calc. for $C_8H_{12}F_3NO_3S$: 260.05711 (for M+1); Found: 260.05634; Anal. calc. for $C_8H_{12}F_3NO_3S$: C, 37.06%; H, 4.67%; N, 5.40%; Found: C, 36.84%; H, 4.94%; N, 5.58%.

N-Benzyl-3,4,5,6-tetrahydro-1H-cyclopenta[c]pyrolid-1-one (11a)

Carbon monoxide was bubbled through a solution of **3a** (0.12g, 0.36mmol), $Pd(PPh_3)_4$ (0.041g, 0.036mmol), tri-n-butylamine (0.17ml, 0.72mmol) in acetonitrile (15ml) for 25 min. The reaction mixture was then heated to 65°C under one atmosphere of carbon monoxide (supplied by the placement of a balloon over the reflux condenser) for 2h. The solution was then allowed to cool to room temperature upon which ether (15ml) was added and the solution filtered through a pad of kenite. The pad was subsequently thoroughly rinsed with ether (3x10ml). The solvent was then removed *in vacuo* and the residue taken up in dichloromethane and purified by flash chromatography (hexanes:ethyl acetate; 5:1) to yield the title compound as a pale yellow oil (100%). A small sample was distilled by kugelrohr (150-160°C/0.06mm). ^1H NMR: δ2.36 (*m*, 2H, cyclopentenyl CH_2), 2.53 (*m*, 4H, CH_2C=C), 3.74 (*s*, 2H, CH_2Ph), 4.62 (*s*, 2H, $ArCH_2N$), 7.24-7.36 (*m*, 5H, Ph); ^{13}C NMR: δ25.8, 27.7, 29.4, 46.4, 49.1, 127.3, 127.9, 128.6, 137.8, 142.3, 161.4, 168.8; IR (neat): ν_{max}3025 *w*, 2950 *s*, 1670 *s* (C=O), 1600 *w*, 1580 *w*, 1490 *m*, 1440 *s*, 1400 *s*, 1350 *m*, 1230 *m*, 1260 *m*, 1220 *m*, 1170 *m*, 1120 *m*, 740 *m*, 700 *m* cm^{-1}; MS m/z: 214 ($[M+1]^+$, 11%), 213 (M^+, 100), 212 ($[M-1]^+$, 14), 195 ($[M-H_2O]^+$, 4), 185 ($[M-CO]^+$, 4), 136 ($[M-C_6H_5]^+$, 8), 110 (60), 109 (84), 108 (24), 91 ($C_7H_7^+$, 45); HRMS calc. for $C_{14}H_{15}NO$: 213.11536; Found: 213.11511; Anal. calc. for $C_{14}H_{15}NO$: C, 78.84%; H, 7.09%; N, 6.57%; Found: C, 78.64%; H, 7.11%; N, 6.49%.

N-Benzyl-1,3,4,5,6,7-hexahydroisoindolin-1-one (11b)[22]

This compound was prepared from **3b** in an analogous manner to that described for compound **11a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (89%). ^1H NMR: δ1.71 (*m*, 4H, cyclohexenyl CH_2), 2.22 (*m*, 4H, CH_2C=C), 3.65 (*s*, 2H, CH_2Ph), 4.61 (*s*, 2H, CH_2N), 7.23-7.35 (*m*, 5H, Ph); ^{13}C NMR: δ20.3, 21.8, 22.0, 24.1, 45.9, 52.5, 127.3, 127.9, 128.5, 131.8, 137.9, 150.0, 171.8; IR (neat): 3025 *w*, 2950 *s*, 1670 *s* (C=O), 1600 *w*, 1580 *w*, 1500 *m*, 1460 *s*, 1420 *s*, 1360 *m*, 1280 *m*, 1260 *m*, 1220 *m*, 1140 *m*, 1110 *m*, 1090 *m*, 750 *s*, 700 *s* cm^{-1}; MS m/z: 228 ($[M+1]^+$, 11%), 227 (M^+, 63), 226 ($[M-1]^+$, 21), 142 (100), 91 ($C_7H_7^+$, 56); HRMS Calc. for $C_{15}H_{17}NO$: 227.13101; Found: 227.13168.

1,2,3,4,5,6,7,8-Octahydro-1H-cyclohepta[c]pyrolid-1-one (11c)

This compound was prepared from **3c** in an analogous manner to that described for compound **11a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (100%). A small sample was distilled by kugelrohr (150-160°C/0.02mm). ^1H NMR: δ1.57-1.82 (2*m*, 6H, cycloheptenyl CH_2), 2.32 (*m*, 2H, CH_2C=C), 2.45 (*m*, 2H, CH_2C=C), 3.62 (*s*, 2H, CH_2Ph), 4.60 (*s*, 2H, CH_2N), 7.23-7.34 (*m*, 5H, Ph); ^{13}C NMR: 24.9, 26.9, 27.0, 29.4, 30.7, 45.9, 53.0, 127.1, 127.8, 128.4, 137.4, 152.3, 172.3; IR (neat): ν_{max}3025 *w*, 2920 *s*, 1680 *s* (C=O), 1605 *w*, 1580 *w*, 1500 *m*, 1455 *s*, 1410 *s*, 1290 *s*, 1230 *m*, 1145 *m*, 1080 *m*, 960 *m*, 920 *m*, 730 *s*, 700 *s* cm^{-1}; MS m/z: 242 ($[M+1]^+$, 23%), 241 (M^+, 100), 240 ($[M-1]^+$, 16), 198 (15), 91 ($C_7H_7^+$, 73); HRMS Calc. for $C_{16}H_{19}ON$:

241.14666; Found: 241.14748; Anal. calc. for $C_{16}H_{19}ON$: C, 79.63%; H, 7.94%; N, 5.80%; Found: C, 79.83%; H, 8.11%; N, 5.61%.

1,3,4,5,6,7,8,9-Octahydro-3H-cycloocta[c]pyrolid-1-one (11d)

This compound was prepared from **3d** in an analogous manner to that described for compound **11a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a pale yellow oil (98%). A small sample was distilled by kugelrohr (130-140°C/0.03mm). ^{1}H NMR: δ1.50 (*m*, 4H, cyclooctenyl CH_2), 1.70 (*m*, 4H, cyclooctenyl CH_2), 2.41 (*m*, 2H, CH_2C=C), 2.49 (*m*, 2H, CH_2C=C), 3.63 (*s*, 2H, CH_2Ph), 4.63 (*s*, 2H, CH_2N), 7.21-7.35 (*m*, 5H, Ph); ^{13}C NMR: δ22.2, 25.6, 25.8, 26.6, 27.4, 27.5, 46.1, 52.5, 127.3, 127.9, 128.6, 132.5, 137.7, 151.0, 172.3; IR (neat): ν_{max}3030 *m*, 2925 *s*, 1670 *s* (C=O), 1605 *m*, 1590 *w*, 1500 *m*, 1450 *s*, 1410 *s*, 1360 *m*, 1320 *m*, 1295 *m*, 1280 *m*, 1250 *m*, 1150 *m*, 1110 *m*, 1075 *m*, 1030 *m*, 735 *s*, 700 *s* cm^{-1}; MS m/z: 256 ([M+1]$^+$, 15%), 255 (M$^+$, 78), 254 ([M-1]$^+$, 9), 198 (17), 91 ($C_7H_7^+$, 100); HRMS Calc. for $C_{17}H_{21}NO$: 255.16231; Found: 255.16345; Anal. calc. for $C_{17}H_{21}NO$: C, 79.96%; H, 8.29%; N, 5.49%; Found: C, 80.01%; H, 8.50%; N, 5.43%.

N-Benzylisoindolin-1-one (12)[6]

To a solution that had been saturated with carbon monoxide for 20 minutes was added N-benzyl-2-(trifluoromethanesulphonyl)oxy-benzylamine (**X**) (25mg, 0.007mmol), $Pd(PPh_3)_4$ (8.4mg, 0.0007mmol), *n*-Bu_3N (0.05ml, 0.014mmol) and diphenylphosphinoferrocene (8mg, 0.014mmol). The mixture was heated at 65°C under one amoshere of carbon monoxide for 3h. The residue was purified by flash chromatography (hexanes:ethyl acetate; 4:1) to yield the title compound as white "dendritic-like" crystals (93%). M.pt.: 90-91°C. ^{1}H NMR: δ4.26 (s, 2H, CH_2Ph), 4.81 (s, 2H, CH_2N), 7.26-7.52 (m, 5H, Ph); ^{13}C NMR: δ46.3, 49.4, 122.7, 123.9, 127.6, 128.0, 128.1, 128.8, 131.3, 132.6, 137.0, 141.2, 168.5; IR (solution $CHCl_3$): ν_{max} 2920 *w*, 1680 *s* (C=O), 1620 *m*, 1495 *w*, 1470 *m* 1455 *m*, 1360 *m*, 1305 *m*, 1145 *m*, 980 *m*, 900 *m*, 770 *w* cm^{-1};; MS, m/z: 224 ([M+1]$^+$, 17%), 223 (M$^+$, 100), 222 ([M-1]$^+$, 34), 181 (10), 169 (10), 145 ([M-C_6H_6]$^+$, 17), 132 ([M-C_7H_7]$^+$, 34), 119 (79), 91 ($C_7H_7^+$, 76), 69 (57), 65 (17); HRMS Calc. for $C_{15}H_{13}NO$: 223.09971; Found: 223.09959.

4,5,6,7-Tetrahydrophthalimidine (13)[23]

This compound was prepared from **7** in an analogous manner to that described for compound **11a**. The resultant black/brown residue was dissolved in dichloromethane (20ml), washed with 10% hydrochloric acid (20ml) and distilled by kugelrohr (100-110°C/0.05mm) to give a yellow solid. Recrystallization (dichloromethane/hexanes) yielded the title compound as colourless prisms (63%). M pt.: 115-116°C, lit.[23] 113-114°C. ^{1}H NMR: δ1.73 (m, 4H, cyclohexenyl CH_2), 2.22 (m, 2H, CH_2C=), 2.28 (m, 2H, m, CH_2C=); ^{13}C NMR: δ20.0, 22.0, 24.5, 48.9, 131.5, 153.3, 175.4; IR (nujol mull): 3250 *m* (NH), 2930 *m*, 1680 *s* (C=O), 1490 *w*, 1450 *s*, 1405 *w*, 1350 *m*, 1120 *m*, 975 *m*, 895 *m*, 865 *m* cm^{-1}; MS, m/z: 138 ([M+1]$^+$, 12%), 137 (M$^+$, 100), 136 ([M-1]$^+$, 7), 109 ([M-CO]$^+$, 25), 108 (26), 96 (19), 95 (30), 94 (25); HRMS Calc. for $C_8H_{11}O$: 137.08406; Found: 137.08461.

1-Benzyl-3-methyleneazetidin-2-one (14)[8]

This compound was prepared from **8** in an analogous manner to that described for compound **11a** except that the reaction was heated at 65°C for 5 h. Flash chromatography (hexanes:ethyl acetate; 19:1) twice yielded the title compound as a white amorphous solid (73%). ^{1}H NMR: δ3.65 (*dd*, *J*1.5, 1.3Hz, 2H, CH_2C=), 4.52 (*s*, 2H, NCH_2Ph), 5.17 (*dt*, *J*1.1, 1.3Hz, 1H, vinyl), 5.74 (*dt*, *J*1.7, 1.5Hz, 1H, vinyl), 7.25-7.39 (*m*, 5H, aromatic); ^{13}C NMR: δ46.1, 47.9, 109.7, 127.8, 128.2, 128.9, 135.3, 145.1,

163.6; IR (nujol mull): ν_{max}3025 *w*, 2920 *s*, 1745 *s* (C=O), 1675 *w* (C=C), 1500 *w*, 1455 *m*, 1400 *s*, 1355 *m*, 1260 *m*, 1220 *m*, 1105 *m*, 1075 *m*, 1030 *m*, 930 *m*, 800 *m*, 750 *w*, 700 *s* cm^{-1}; MS, m/z: 174 ($[M+1]^+$, 9%), 173 (M^+, 33), 172 ($[M-1]^+$, 22), 133 (40), 132 (18), 105 (22), 104 (22), 91 ($C_7H_7^+$, 100); HRMS Calc. for $C_{11}H_{11}NO$: 173.08406; Found: 173.08475.

1-Benzyl-3-methylene-2-pyrrolidone (15)[9]

This compound was prepared from **9** in an analogous manner to that described for compound **11a** except that the reaction mixture was heated for 15h. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a pale yellow oil (100%). ^1H NMR: δ2.74 (*m*, 2H, CH_2C=), 3.28 (*dd*, *J*=7.0, 6.4Hz, 2H, CH_2N), 4.55 (*s*, 2H, NCH_2Ph), 5.36 (*dt*, *J*0.6, 2.4Hz, 1H, vinyl), 6.04 (*dt*, *J*0.7, 2.9Hz, 1H, vinyl), 7.25-7.37 (*m*, 5H, aromatic); ^{13}C NMR: 23.9, 43.4, 47.2, 115.7, 127.6, 128.2, 128.7, 136.2, 139.5, 167.9; IR (neat): ν_{max}3030 *w*, 2925 *m*, 1690 *s* (C=O), 1605 *w*, 1495 *m*, 1450 *s*, 1430 *m*, 1305 *s*, 1265 *m*, 1190 *w*, 1160 *w*, 910 *s*, 805 *w*, 735 *s*, 700 *s* cm^{-1}; MS, m/z: 188 ($[M+1]^+$, 19%), 187 (M^+, 100), 186 ($[M-1]^+$, 24), 158 (14), 143 (24), 91 ($C_7H_7^+$, 81); HRMS Calc. for $C_{12}H_{13}NO$: 187.09971; Found: 187.09915.

1-Benzyl-3-methylene-2-piperidone (16)[24]

This compound was prepared from **10** in an analogous manner to that described for compound **11a** except that the reaction was heated for 15h. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (70%). ^1H NMR: δ1.84 (*m*, 2H, CH_2), 2.58 (*m*, 2H, CH_2C=), 3.30 (*dd*, *J*6.0, 5.8Hz, 2H, CH_2N), 4.67 (*s*, 2H, CH_2Ph), 5.33 (*dt*, *J*1.8, 1.6Hz, 1H, vinyl), 6.28 (*dt*, *J*1.7, 1.6Hz, 1H, vinyl), 7.24-7.35 (*m*, 5H, aromatic); ^{13}C NMR: δ23.1, 30.1, 47.7, 50.7, 122.0, 127.3, 128.0, 128.5, 137.1, 137.7, 164.3; IR (neat): ν_{max}3050 *w*, 2925 *m*, 1655 *s* (C=O), 1615 *s*, 1490 *m*, 1455 *m*, 1340 *m*, 1265 *m*, 1220 *m*, 1200 *m*, 975 *m*, 735 *s*, 700 *s* cm^{-1}; MS, m/z: 202 ($[M+1]^+$, 26%), 201 (M^+, 100), 200 ($[M-1]^+$, 7), 172 (21), 110 ($[M-C_7H_7]^+$, 25), 104 (25), 91 ($C_7H_7^+$, 57); HRMS Calc. for $C_{13}H_{15}NO$: 201.11536; Found: 201.11591.

Attepted carbonylation of 17

Compound **17**[25] was treated in an analogous manner to that described for **11a** except that the reaction was heated for 15h. The dark residue was purified by gradient flash chromatography (hexanes:ethyl acetate; 49 to 9:1) to give the terminal alkyne **18**[20].

Ethyl 1-acetyl-3-methylene-2-pyrolidone-5-carboxylate (20)

This compound was prepared from **19** (0.2g, 0.66mmol) in an analogous manner to that described for **11a** except that the reaction was heated for 30 min. The dark red residue was purified twice by gradient flash chromatography (hexanes:ethyl acetate; 49 to 9:1) to give the title compound as an orange oil (90mg, 63%). A small sample was distilled by kugelrohr (130-140°C/0.005mm) to give a colourless viscous oil. ^1H NMR: δ1.28 (*t*, *J*7.0Hz, 3H, $CH_2C\underline{H}_3$), 2.61 (*s*, 3H, $COCH_3$), 2.75 [*dq*, *J*17.6, 2.4Hz, 1H, H-C(4)], 3.1 [*ddt*, *J*17.6Hz, 10.2, 3.0Hz, 1H, H-C(4)], 4.21 (*q*, *J*7.0Hz, 2H, $C\underline{H}_2CH_3$), 4.74 (*dd*, *J*3.2, 3.2Hz, 1H, CHN), 5.60 (*t*, *J*2.5Hz, 1H, vinylic), 6.29 (*t*, *J*2.6Hz, 1H, vinylic); ^{13}C NMR: δ14.0, 24.7, 27.5, 54.5, 61.8, 121.9, 137.1, 166.6, 170.6, 171.5; IR (neat): ν_{max}2985 *m*, 1740 *s* (C=O), 1705 *s* (C=O), 1660 *m* (C=C), 1445 *m*, 1380 *s*, 1320 *s*, 1280 *s*, 1200 *s*, 1125 *m*, 1020 *s*, 955 *m*, 910 *w*, 860 *w*, 810 *m*, 610 *s* cm^{-1}; MS, m/z: 212 ($[M+1]^+$, 15%), 211 (M^+, 54), 183 ($[M-CO]^+$, 4), 169 (63), 166 ($[M-EtO]^+$, 31), 165 ($[M-EtOH]^+$, 25), 139 (53), 138 ($[M-CO_2Et]^+$, 63), 97 (65), 96 (100); HRMS calc. for $C_{10}H_{13}NO_4$: 211.08446; Found: 211.08375. Compound unsuitable for microanalysis.

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