Tetrahedron Vol. 44, No 17, pp. 5451 to 5466, 1988
Printed in Great Britain

0040-4020/88 $3.00+.00
Pergamon Press plc

SYNTHESIS OF α-AMINO ACIDS WITH β,γ-UNSATURATED SIDE CHAINS[1]

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(Received in USA 12 February 1988)

Abstract: α-Amino acids with allenyl, vinyl, and acetylenic side chains can be synthesized using non-enolate based strategies. The ester enolate-Claisen rearrangement applied to propargylic esters of N-protected α-amino acids is of limited utility since only poor yields of allenic product are obtained with the N-Boc glycine esters, the system which give the most reproducible results. However, α-allenyl-α-amino acids that are fully functionalized on the α-carbon are available through the agency of 4-allenyl-2-phenyloxazolones 4 (obtained from propargyl esters of N-benzoyl protected amino acids via cyclization and Claisen rearrangement) provided that Meerwein's reagent is used to facilitate hydrolysis of the benzamide function in 5. A variety of α-substituted glycinates, including those with α-vinyl and α-acetylenic functions, can be prepared using a two-step sequence involving condensation of the cationic glycine synthon 22 with various organomagnesium reagents, followed by hydrolysis.

Despite long-standing interest in the preparation of unnatural amino acids, the synthesis of α-amino acids with β,γ-unsaturated side chains has been pursued vigorously for only a little over a decade.[2] It is now recognized that α-ethynyl[3] and α-vinyl[4] substituents can profoundly perturb the biological properties of certain natural amino acids, converting them from enzyme substrates to irreversible inhibitors with potential therapeutic utility. This knowledge, coupled with related theoretical and mechanistic interest, has stimulated recent synthetic activity.[5]

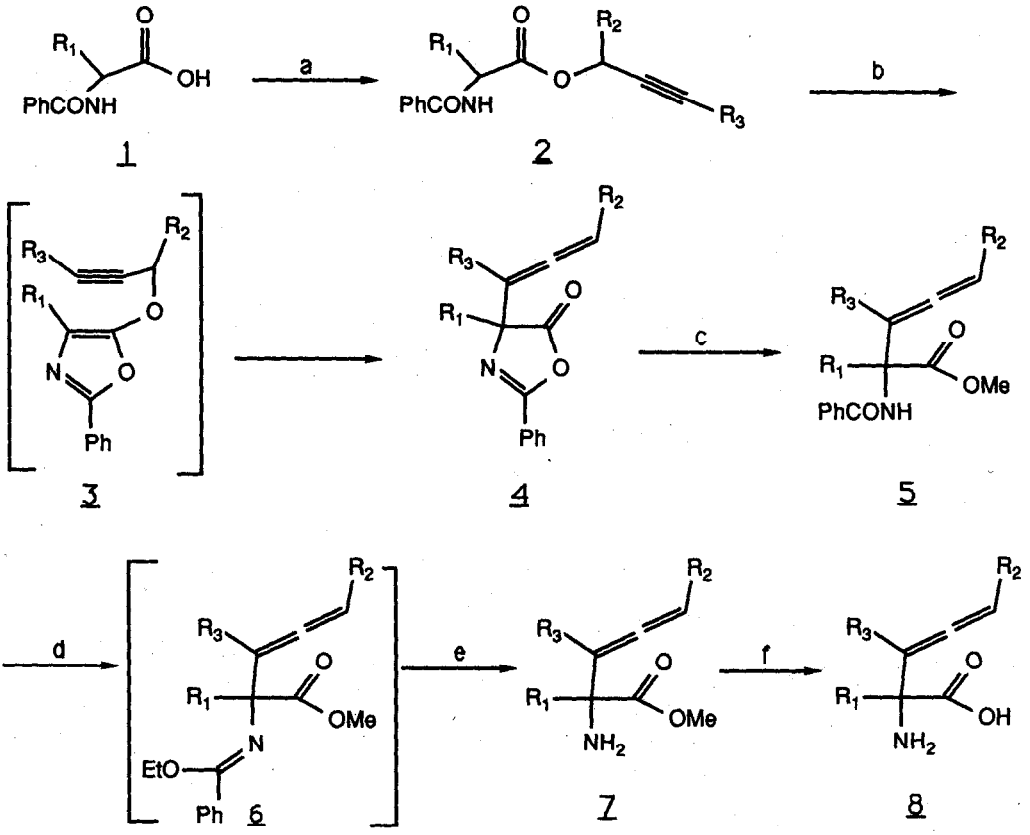
Our efforts have been directed towards the synthesis of α-allenyl-α-amino acids[4] and other novel amino acids that could be envisaged on theoretical grounds to function as specific inhibitors of vitamin B_6 dependent enzymes.[7,8] Prior to our work, there was not a single example of an α-allenyl-α-amino acid reported in the literature.[9] During the course of our studies, it became apparent that very few β,γ-unsaturated glycinates were known as well, and we sought to remedy this situation by adapting existing methodologies to the production of such novel amino acids. Steglich's clever manipulation of acyl imine intermediates[10] and his discovery of the Claisen rearrangement of propargyloxyoxazolones,[11] along with our own synthesis of γ-allenyl GABA,[12] provided a conceptual basis for our efforts.

α-Allenyl-α-Amino acids: Oxazolone Route

Some time ago Steglich[11] reported that the cyclization of propargyl

esters of N-acylamino acids promoted by dehydrating agents led to 4-substituted-4-allenyl-2-oxazolin-5-ones 4 (R_1 = phenyl, isopropyl) (Scheme 1), undoubtedly through the intermediacy of the corresponding propargyloxyoxazolone 3. The availability of 4 evokes the prospect of hydrolysis as a direct route to the free amino acids. However, the harsh conditions required for conventional hydrolysis of the benzamide group do not leave the allene moiety intact. In fact, Bartlett and Barstow[13] have alluded to the difficulty of removing the benzoyl group from α-substituted N-benzoyl amino acids using various acid and base catalysts as well as Meerwein's reagent. Steglich found that even propargyl groups are hydrated to give ketones under the conditions required to hydrolyze benzamides in acid.[14]

Scheme 1



a R_1 = $PhCH_2$, R_2 = H, R_3 = H

b " R_2 = H, R_3 = CH_3

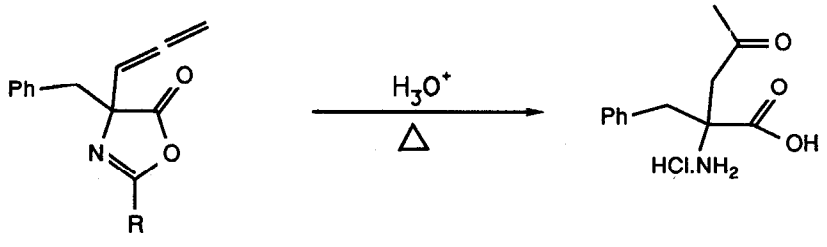
c " R_2 = CH_3, R_3 = H

a, $HOCH_2C{\equiv}CR_3$, DCC or EDCI, DMAP, CH_2Cl_2; b, Ph_3P, CCl_4, NEt_3, CH_3CN; c, MeOH/NEt_3; d, $Et_3O^+BF_4^-$, CH_2Cl_2; e, 10% HOAc; f, 1.0M NaOH/MeOH

In our hands, the only general procedure for the conversion of α-allenyl-α-benzamido esters 5 to amino acids 8 that proved to be successful for a wide range of substrates involved imidate formation using freshly prepared Meerwein's reagent[15] for five days (Scheme 1). Following hydrolysis with 10% aqueous acetic acid, workup provided amine 7 in 60 - 70% yield. This procedure can be adapted to a wide variety of amino acids containing acidic, basic, and neutral side chains and thus provides the hitherto inaccessible α-allenyl-α-amino acids.[6] Initially, we had hoped to circumvent the harsh conditions required for benzamide hydrolysis by using N-protecting groups in starting material that could be carried through the rearrangement, and which were subject to facile hydrolysis in the protected allenic ester corresponding to 5. With phenylalanine propargyl ester, N-protected by either a Boc, trifluoroacetyl, formyl, or Cbz group, no allenic product could be detected spectroscopically upon treatment with triphenylphosphine, triethylamine, and carbon tetrachloride in acetonitrile at room temperature. (These conditions are normally employed to induce the rearrangement.) With N-acetyl protection, the 2-methyl-oxazolone 9 was obtained in 27% yield. Higher yields are associated with the rearrangement of the benzamido esters and may reflect the known stabilizing effect of a 2-phenyl group on the oxazolone framework.

As expected, acid hydrolysis of 4a or 9 with 50% HCl at reflux leads to rapid hydration of the allene with the formation of the known α-acetonyl phenylalanine hydrochloride 10.[14] Attempts at converting the amido ester 5a to the amino ester 7a using PCl_5/CH_3OH[16] or hydrazinolysis[17] (of the corresponding acid) were also unsuccessful. Ionic reductions of 4a were attempted using trichloroacetic acid - triethylsilane[18] and $NaBH_3CN/TsOH$[19] in dry DMF. Even after raising the temperature of the reaction mixture to 70°C (the stability limit of 4a) no loss of the imine could be observed. In aqueous media hydrolysis of 4a occurred before reduction of the imine could be affected by $NaBH_3CN/MeOH/H_2O$/pH 5.

A few attempts were made to transform the amide functionality of 5a to the more nucleophilic thioamide group, which was expected to undergo facile conversion to the thioimidate with Meerwein's reagent.[15] Treatment of 5a with Lawesson's reagent[20] in refluxing benzene (containing anhydrous K_2CO_3 to neutralize acidic byproducts) for 16 h resulted in considerable loss of the allene signals in the IR and NMR spectrum of the reaction mixture. Extensive chromatography of this mixture on silica gel yielded approximately 30% of the starting material, 10% of the desired allenic thioamide, 20% of two olefin containing substances which appear by ^1H NMR to be adducts of the thioamide to the allene, plus 10% of an unidentified allene-containing product devoid of the methyl ester group.



4a, R = Ph

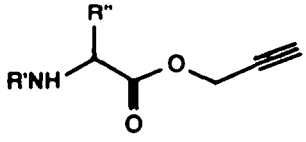
9 R = CH_3

10

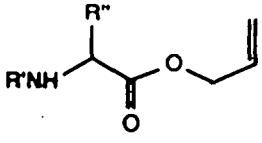
α-Allenyl-α-Amino Acids: Ireland-Claisen Route

Allenyl glycinates are not available by the oxazolone route above and an alternate approach was required. We failed to isolate oxazolone 4 (R_1, R_2, R_3 = H, scheme 1) upon rearrangement of 2 (R_1, R_2, R_3 = H), although 5-10% of an allenic product was present in the early stages of the reaction as judged by monitoring the infrared band at 1960 cm^{-1}.

At the outset of this project, the Ireland-Claisen rearrangement[21] applied to N-protected propargyl esters of α-amino acids 11 (R' = N-protecting group; R'' = α-amino acid side chain) represented an attractive means of translocating a three carbon residue from the ester oxygen to the α-position with concomitant conversion of propargyl to allenyl functionality.



11 a, R'' = H; b, R'' = CH_3; c, R'' = $PhCH_2$



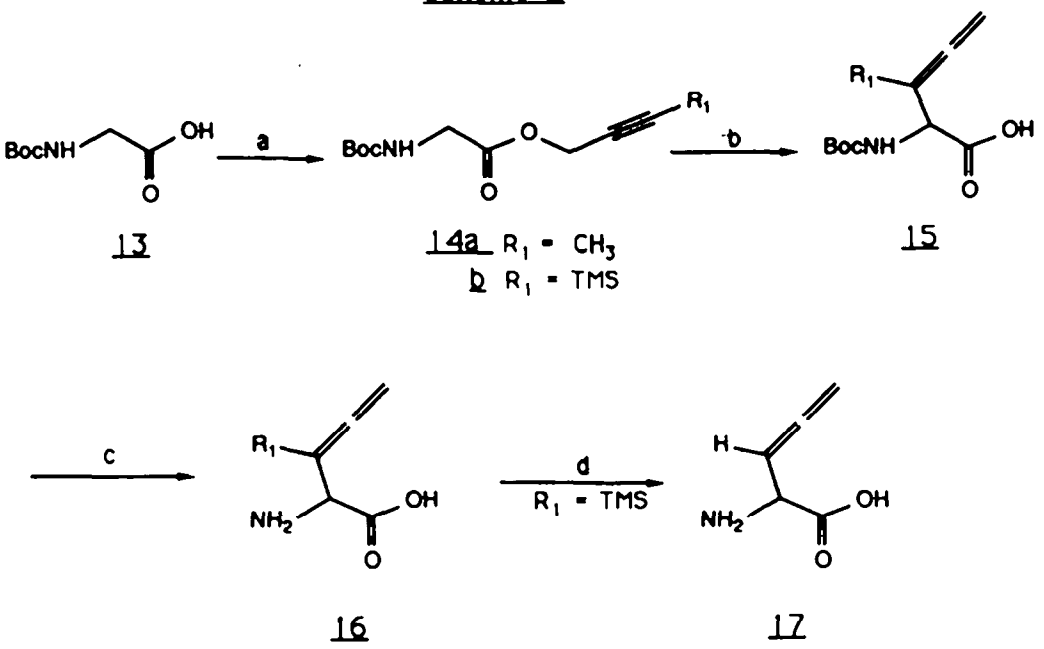
12 a, R'' = H; b, R'' = CH_3

Bartlett and Barstow[13] have since commented on their attempts to optimize yields of the rearrangement of the analogous allylic esters 12 by systematically varying the reaction conditions. The standard conditions employed by these investigators involving silylation with TMSCl of an N-Boc protected amino acid dianion, preformed with LDA/THF at -75°C, and then warming to reflux for 1 h, proved to be optimal. This aspect of their report conforms with our experience involving the propargyl ester, although they achieved much better, reproducible yields with the more docile allylic system. Using the standard procedure, N-Boc but-2-ynylglycinate, 14a, (Scheme 2) was converted to 15 (R_1 = CH_3) in 20% yield. Yields obtained from the rearrangement of the corresponding propargyl ester 14b were erratic and never exceeded 15%. With benzoyl and benzylidene protecting groups and Stabase adducts of alanine 11b, no allenic product could be detected by monitoring the reaction mixture with IR or NMR spectroscopy. Only limited success was achieved using phthaloyl as an N-protecting group of ester 14b or the alanine and phenylalanine esters 11b and 11c, respectively. In a few instances, using 2.5 equivalents of LDA/TMSCl with N-phthaloyl alanine propargyl ester 11b followed by warming to room temperature, 5-10% of product was observed but yields were not generally reproducible. With the N-phthaloyl alanine propargyl and but-2-ynyl esters, changing the base from LDA to LICA or $KN(SiMe_3)_2$, or using $ClSi(Me_2)$-t-Bu to trap the enolate, did not result in detectable allene absorption of the reaction mixture which consisted of over 80% of starting material.

α-Substituted Glycinates

A number of α-ethynyl-α-amino acids that are fully substituted on the α-carbon are accessible via the sequential alkylation and acylation of anions derived from protected forms of propargylamine.[2b] However, the parent ethynylglycine 18b and higher homologs have not been reported.[22] α-Vinyl-α-amino acids that are fully substituted on the α-carbon can be

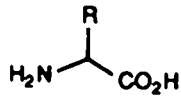
scheme 2

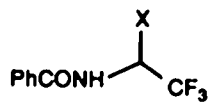


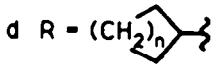
a, $HOCH_2C{\equiv}CR_1$/DCC or EDCI/DMAP, b, R_1 = CH_3 (20%), R_1 = TMS (5-10%), (i) 2.1 equiv LDA or LICA/ -78°, (ii) TMS-Cl, (iii) MeOH/RT, c, H^+/EtOAc, d, OH^-

conveniently prepared by the method of Greenlee,[23] which involves quenching the anion obtained from a dehydroamino acid synthon with the requisite alkylating agents. Until recently,[24] no general method for the preparation of β,γ-unsaturated glycinates 18 had been demonstrated, although a considerable number of useful and interesting syntheses applicable to a narrow range of substrates had been documented.[25] The methods of Rapoport[25a] and that of Hanessian[25b] provide optically active 18a by the degradation of methionine and glutamic acid, respectively. A number of β,γ-olefinic amino acids can be obtained from the corresponding unsaturated aldehydes by use of Strecker condensations.[26] Recently, Fitzner et al.[25c] reported that the oxidative rearrangement of γ-phenylseleno-α,β-unsaturated esters affords in some cases good yields of protected β,γ-unsaturated-α-amino acids. Enolate based strategies which utilize ethynyl phenyl sulfone and trans-2-chlorovinyl sulfone as vinyl cation equivalents in the synthesis of vinyl glycine have been developed by Steglich[27] and Metcalf,[28] respectively.

We sought a simple and direct synthesis of α-substituted glycinates that would allow considerable variation of the α-substituent, and embrace olefinic, acetylenic, small ring, and higher alkyl group functionalities that were not readily accessible via enolate based strategies. An efficient route to these types of amino acids could be envisaged through the agency of known organometallic reagents and a cationic amino acid synthon. Steglich[10] provided an early precedent for this umpolung strategy by demonstrating the feasibility of condensing organometallics with reactive imine intermediates that are conveniently derived by base-promoted elimination of HX from halide and sulfone precursors 19.



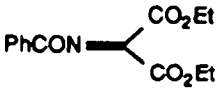


18 a R = H_2C=CH-
b R = HC≡C-
c R = alkyl, alkenyl
d R = 

19

X = Cl, Br, $EtSO_2$-

Ben-Ishai[29] successfully utilized hydroxyhippuric acid in a Friedel Crafts type of amidoalkylation of benzyl chloride, as a route to para-substituted D,L-phenylglycines. Subsequently, various substitution reactions of α-bromoacylaminomalonic esters have been effected by the addition of organometallic compounds and other C-nucleophiles to the intermediate acyliminomalonic ester 20.[30] Although a wide range of reagents including aryl, heteroaryl, alkenyl, and alkynyl moieties can be introduced into benzoylaminomalonic esters by this procedure, access to β,γ-unsaturated amino acids is, in principle, complicated by the demands of the decarboxylation step.[9] Very recently, O'Donnell[31] has called attention to the utility of cationic amino acid synthons, and has developed routes to α-aryl amino acids and difficultly accessible heteroatom-substituted amino esters in Schiff base form that exploit the cationic glycine synthon 21. The appeal of these approaches, involving reagents with electron demands opposite to those employed in enolate based strategies, has been further enhanced by recent high enantio- and diastereo-selective syntheses of α-amino acids using electrophilic glycinates[32,33] and α-iminoesters[34] as substrates.



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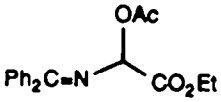

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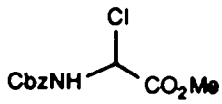
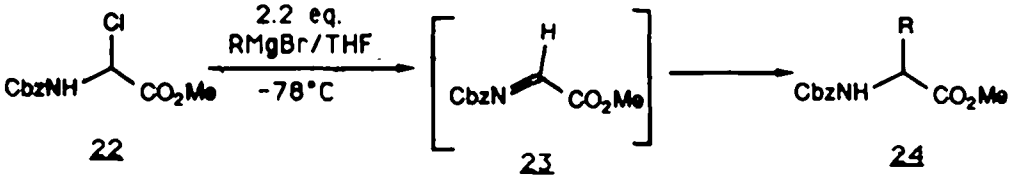


22

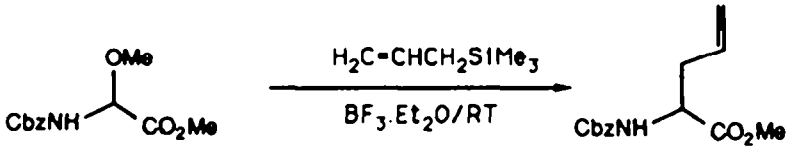
Our approach to β,γ-unsaturated-α-amino acids draws on the Steglich[10,31] precedents with organomagnesium reagents, but utilizes N-carbobenzyloxy-α-chloroglycine methyl ester 22 as a versatile glycine cation equivalent. β,γ-Unsaturated amino acids in the protected form 24 can be obtained in good to excellent yields by adding 2.2 eq. of a vinylic Grignard reagent in THF to a solution of 22 in THF at -78°C. After two hours, the reaction is quenched with 1.0 N citric acid or 5% aqueous HCl, worked-up, and then purified by chromatography. Attack by Grignard reagents at the ester or carbamate is not observed. In this procedure, one equivalent of the Grignard reagent serves as a base, eliminating the elements of HCl to provide the reactive imine intermediate 23. Steglich[24b] has demonstrated in analogous cases that Et_3N or Hunig's base can be used for such a purpose, rather than consuming the organometallic reagent if it is limiting.

Attempted reaction of a more stable version of a cationic-glycine synthon, α-methoxy N-Cbz-GlyOMe 25 with vinyl magnesium bromide does not



22 23 24

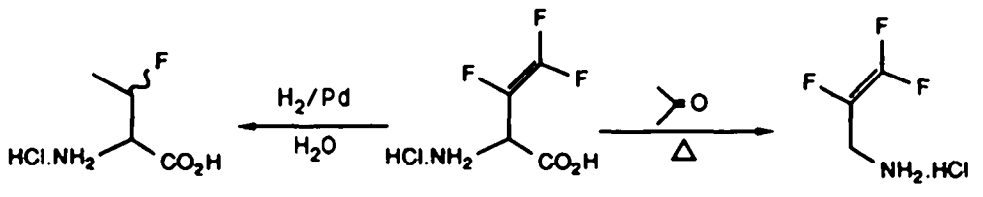
produce 24. Maintaining the reaction mixture at -10°C for 1 h results in the recovery of only 50% of the material balance, which consists primarily of starting material. However, this synthon is potentially useful as we have found that under Lewis acid conditions, 25 reacts with allyltrimethylsilane in the presence of $BF_3.Et_2O$ at room temperature to give 26 in near quantitative yield.



25 26

Harada[35] has developed a sterically controlled synthesis of aspartic acid whose key step is the addition of dialkyl malonates to N-carbobenzyloxy-L-alanyl-2-chloroglycine methyl ester. The more bulky alkyl malonates lead to aspartic acid with higher optical purity. The reaction of a simple Grignard reagent such as vinyl magnesium bromide with N-benzyloxycarbonyl--L-phenylalanine-2-chloroglycine methyl ester does not result in asymmetric induction, but leads to a 1:1 ratio of diastereomeric esters 30 (table 1). Despite this limitation, the method described herein for functionalizing glycine at the α-position through cation equivalents is quite general and leads to diverse amino acid precursors.

An interesting example involves the preparation of the trifluorovinyl ester 33. This compound is obtained in excellent yield from condensation of the Grignard reagent $F_2C{=}CFMgBr$ with 22, and is potentially a useful intermediate. Hydrolysis (50% HCl/reflux/1 h) gives the corresponding trifluorovinyl glycine hydrochloride 43 which readily exchanges an α-H in D_2O ($t_{1/2}$ at 65°C ~ 75 min). Upon heating the amino acid hydrochloride 43 to reflux in acetone for ~ 30 min, decarboxylation generates the novel trifluorovinyl amine 44 (probably via an adduct of 43 with acetone).



45 43 44

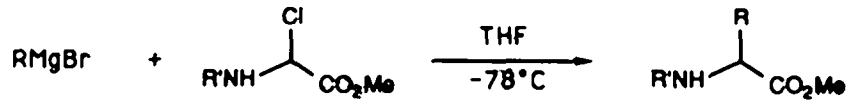
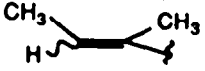
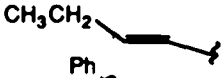
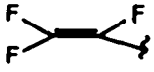
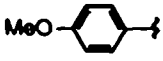
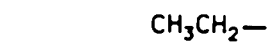
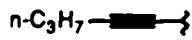
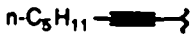
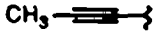
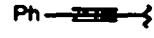


Table 1

R	R'	Product	Yield[a,b]
	Cbz	27[25a,b]	65%
	-	28[25e]	56%
	-	29[25e,26]	60%
	Cbz-L-Phe	30[25e]	60%
	Cbz	31[26]	60%
	-	32[24a]	65%
	-	33[24b]	85%
	-	34	10%
	-	35	46%
	-	36[24b]	63%
	-	37[42]	35%
	-	38[43]	60%
	-	39	69%
	-	40	63%
	-	41	31%
	-	42	33%

a. Refers to isolated (non-optimized) yields of chromatographically pure products.
b. About 10-20% of N-Cbz-α-hydroxy-Gly-OMe is usually recovered

We have also found that the hydrogenation of 43 in water under one atmosphere of hydrogen with 10% Pd/C or 1% Pd/Al_2O_3 at room temperature provides access to monofluorides: an 86:14 ratio of 2-amino-3-fluorobutanoic acid hydrochloride, 45,[34] (≈ 9:1 ratio of diastereomers) and α-ethyl glycine hydrochloride is obtained. The catalytic hydrogenation of fluoro-olefins has few precedents.[37]

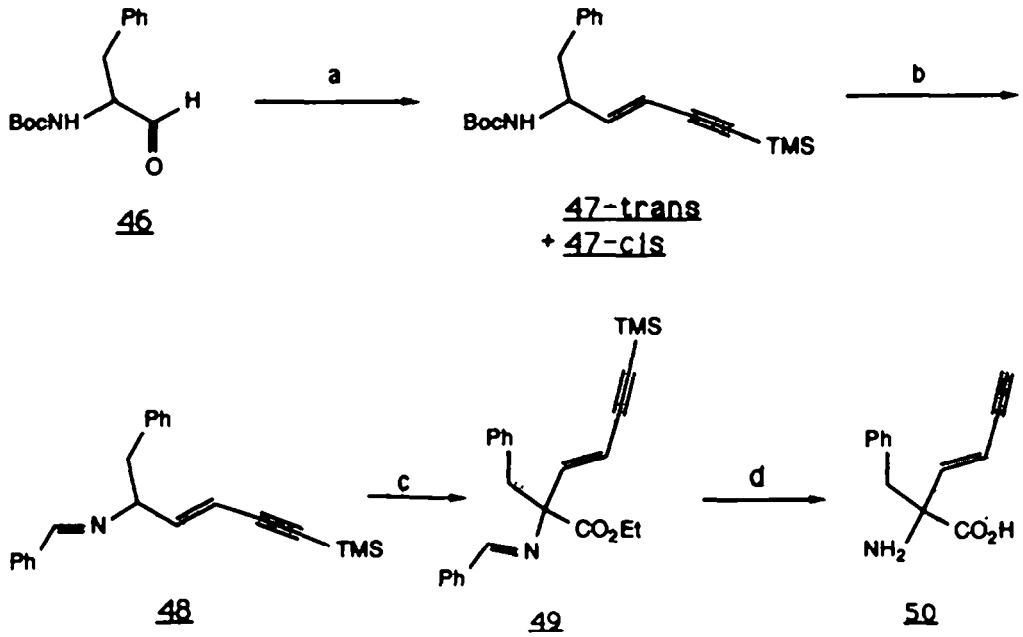
α-Alkynyl-α-amino acids even in protected form have not been readily accessible.[22] We have discovered that alkynyl magnesium reagents add to 22, providing α-acetylenic amido esters 39 - 40 free from allenic products in good yield.

It is worth noting, in light of the apparent difficulty of controlling

carboxylation of synthetic equivalents of propargyl amine carbanions,[22] that treatment of the anion generated from the benzylidene enyne 48 with ethyl chloroformate gives the trans-enyne 49 (a 2:3 mixture of benzylidenes 49 and 48 was obtained). After overnight treatment of this mixture with 10% aqueous HCl/THF followed by basic hydrolysis and ion-exchange chromatography, the novel trans-α-enyne phenylalanine 50 was obtained in 20% overall yield from trans-enyne 47 (Scheme 3).

In summary, we have demonstrated that methodologies based on the concept of cationic glycine equivalents can draw on the extraordinary diversity of Grignard reagents and provide access to new and unusual amino acids. α-Allenyl-α-amino acids are available by the route outlined in Scheme 1. Use of Meerwein's reagent, to facilitate the hydrolysis of the benzamide 5, is critical to the success of the sequence which is applicable to a variety of amino acids.[30]

Scheme 3



46 47-trans + 47-cis 48 49 50

a, $Ph_3P{=}CHC{\equiv}CTMS$/THF, 80%, 5:1 (E,Z); b, HCO_2H; PHCHO/NEt_3/CH_2Cl_2;
c, LDA/THF/-78°; $ClCO_2Et$; d, H_3O^+, HO^-

Acknowledgement: We are grateful to Valerie Robinson for assistance with NMR spectroscopy and to Dr. John Moffatt (Syntex, Palo Alto) for helpful discussions.

Experimental Section

General Procedures: Melting points were determined on a Buchi 510 capillary melting point apparatus, in open capillary tubes, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 136 spectrometer. Spectra were recorded for as KBr pellets and for liquid samples neat between

NaCl plates. Proton, carbon, and fluorine nuclear magnetic resonance spectra (^1H, ^{13}C, and ^{19}F NMR) were measured on a Bruker WP-80 spectrometer, at 20.13 and 75 MHz for ^{13}C and ^{19}F respectively) in $CDCl_3$ and D_2O solutions. Chemical shifts are reported in ppm relative to tetramethylsilane or 3-(trimethylsilyl)propionic acid-2,2,3,3-d_4 sodium salt, and are followed by multiplicity, integral, spin-spin coupling constant, and assignment. UV spectra were obtained on a Perkin-Elmer 559A UV-VIS spectrophotometer. Mass spectra were recorded on an Atlas CH-4 or CH-7 instrument. HPLC was conducted with Whatman Magnum 20 Partisil and Magnum 20 ODS-3 semi-preparative columns.

General Procedure for Propargyl Ester Formation: N-benzoyl α-amino acids were obtained commercially or prepared from the appropriate α-amino acid with benzoyl chloride.[39] Acetylenic esters **2**, **11**, and **14** were prepared in a straightforward manner by coupling the appropriate N-protected α-amino acid and acetylenic alcohol using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).[40] Thus a solution of **1** or **13** (10 mmol), DCC (11 mmol), acetylenic alcohol (11 mmol) and DMAP (1.1 mmol) in 30 ml of CH_2Cl_2 was stirred overnight at room temperature under argon. The reaction mixture was filtered and the filtrate washed with 2 x 15 ml portions of 5% HOAc, and then 20 ml each of H_2O, 5% $NaHCO_3$, and brine. Drying of the organic portion over anh. $MgSO_4$ and then concentrating gave **2**a-c and **14**a,b in 65-90% yields.

2a: IR: ν_{max} 3300 (br NH, C≡C-H), 2105 (C≡C), 1735 (CO_2C), 1640-1650 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 2.5 (t, 1H, J = 2.4 Hz, C≡CH), 3.3 (app d, 2H, $PhCH_2$), 4.8 (m, 2H, OCH_2), 5.2 (m, 1H, CHN), 6.5 (br d, 1H, NH), 7.0-8.0 (m, 10H, Ph).

2b: IR: ν_{max} 3300 (br NH), 2235 (C≡C), 1745 (CO_2C), 1635 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 1.85 (m, 3H, CH_3), 3.3 (d, 2H, $PhCH_2$), 4.75 (m, 2H, CH_2O), 5.0-5.25 (m, 1H, CHN), 6.55 (br d, 1H, J = 8 Hz, NH), 7.1-7.8 (m, 10H, Ph).

2c (mix. of isomers): IR: ν_{max} 3100-3600 (NH, C≡C-H), 2110 (C≡C), 1740 (CO_2C), 1640 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 1.5 (2d, 2H, J 6.0 Hz, CH_3), 2.5 (2d, 1H, J = 2.4 Hz, C≡C-H), 3.3 (m, 2H, $PhCH_2$), 5.0-5.5 (m, 1H, CHN), 5.3-5.65 (m, 1H, CHO), 6.6 (br app d, 1H, NH), 7.1-7.8 (m, 10H, Ph).

14a: IR ν_{max} 3370 (br s, NH), 2240 (C≡C), 1760 (CO_2C), 1700 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H, Boc), 1.87 (t, 3H, J = 2.5 Hz, CH_3), 3.95 (d, 2H, J = 6.9 Hz, CH_2N), 4.73 (q, 2H, J = 2.5 Hz, CH_2O), 4.8-5.1 (br s, NH).

14b: IR ν_{max} 3400 (br s, NH), 2170 (C≡C), 1740-1750 (CO_2C), 1700 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 0.18 (s, 9H, $SiMe_3$), 1.45 (s, 9H, Boc), 3.95 (d, 2H, J = 5.7 Hz, CH_2N), 4.75 (s, 2H, CH_2O), 4.8-5.2 (br s, 1H, NH).

Rearrangement via Oxazolone Route/General Procedure: To a solution of **2** (2.1 mmol) in 10 ml of CH_3CN were added successively NEt_3 (5.8 mmol), CCl_4 (4.9 mmol), and Ph_3P (4.3 mmol) at room temperature under argon. The reaction mixture was left stirring overnight after which it was concentrated and applied to a silica gel column (hydrolysis of **4** on silica gel was observed in some cases), and eluted with 10% EtOAc/hexane. Methanolysis of **4** in HCl/MeOH for 15 min at room temperature gave **5** quantitatively. Alternatively, addition of 0.1 ml NEt_3 and 1 ml of MeOH after the rearrangement generates **5**

directly in 90-100% yield.

5a: IR ν_{max} 1960 (C=C=C), 1740 (CO_2Me), 1635 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 3.65 (AB, 2H, J = 14 Hz), $PhCH_2$), 3.85 (s, 3H, OMe), 4.95 (app dd, 2H, H_2C=C=C), 5.65 (app t, 1H, HC=C=C), 6.85 (s, 1H, NH), 7.0-7.8 (m, 10H, Ph).

5b: IR ν_{max} 3400 (br NH), 1958 (C=C=C), 1730 (CO_2Me), 1650 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 1.77 (br t, 3H, J = 3.8 Hz, CH_3), 3.7 (AB, 2H, J = 14.8 Hz, $PhCH_2$), 3.85 (s, 3H, OMe), 4.7-5.5 (m, 2H, H_2C=C=C), 6.9 (br s, 1H, NH), 6.95-7.8 (m, 10H, Ph).

5c: (mix. of isomers): ν_{max} 3100-3000 (br NH), 1962 (C=C=C), 1730 (CO_2Me), 1650 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 1.6-1.85 (2 app d, 3H, CH_3CH=C=C), 3.65 (AB, J = 13.6 Hz, $PhCH_2$), 3.83 (s, 3H, OMe), 5.2-5.65 (m, 2H, HC=C=CH), 6.75 (br s, 1H, NH), 7.1-7.8 (m, 10H, Ph).

Hydrolysis of 5; General Procedure: Benzamides **5** (1.6 mmol) were treated with a 1.54 M $Et_3O^+BF_4^-$ solution in CH_2Cl_2 for 5 days under argon. Analysis of an aliquot indicated approximately 80% conversion of starting material by ^1H NMR. The reaction mixture was concentrated and then stirred overnight with 10 ml of 10% HOAc/THF (1:1). Dilution with 30 ml of ether and extraction with 2x10 ml of 5% HCl gave an aqueous fraction which was basified with 1.0 N NaOH to pH 8. The aqueous fraction was extracted with 3x20 ml of CH_2Cl_2, and the combined organic extract was washed with 20 ml of brine, dried over anh. $MgSO_4$ and then concentrated to give **6** in ~ 70% yield (not based on recovered starting material). The oil was stirred in 15 ml THF/0.1 N NaOH (2:1) at room temperature under argon for 24 hr. The hydrolysate was then partitioned between ether and water. Acidification of the aqueous portion to pH 3 with 10% HCl followed by ion-exchange chromatography (Bio-Rad Ag 50W-X8 column eluting with 20% aqueous pyridine), provided the α-allenic-α-amino acids **8**.

8a: mp 210 - 220°C (dec); IR (KBr): ν_{max} 1962 cm^{-1} (C=C=C); UV (H_2O): λ_{max} 245 (ε 107), 250 (ε 129), 257 (ε 148), 263 (ε 115); ^1H NMR (D_2O): δ 3.15 (AB, 2H, $PhCH_2$), 5.0 (app d, 2H, H_2C=C=C), 5.55 (app t, 1H, CH=C=C), 7.4 (m, 5H, Ph); ^{13}C NMR (D_2O): δ 44.6, 65.8, 83.9, 94.1, 130.8, 131.7, 133.0, 136.6, 176.5, 208.6; MS (CI): 204 (MH^+), 186 (MH^+-H_2O), 158 (MH^+-CO_2H).

8b: mp 213 - 214°C (dec); IR (KBr): ν_{max} 1955 cm^{-1} (C=C=C); ^1H NMR (D_2O): δ 1.75 (app t , 3H, CH_3), 3.17 (AB, 2H, $PhCH_2$), 4.92 (app q, 2H, H_2C=C=C), 7.4 (m, 5H, Ph); ^{13}C NMR (D_2O): δ 17.1, 42.4, 68.5, 82.3, 100.7, 130.8, 131.9, 133.0, 136.9, 176.1, 208.7; MS(EI): m/z 217 (M^+); (CI) 218 (MH^+).

8c: (more polar isomer): mp 220°C (dec); IR (KBr): ν_{max} 1962 cm^{-1} (C=C=C); ^1H NMR (D_2O): δ 1.7 (dd, 3H, CH_3), 3.27 (AB, 2H, J = 14.3 Hz, $PhCH_2$) (m, 2H, HC=C=CH), 7.4 (m, 5H, Ph); ^{13}C NMR (D_2O): δ 15.9, 44.5, 66.0, 93.6, 96.2, 130.8, 131.8, 133.1, 136.2, 176.1, 205.2.

8c: (less polar isomer): mp 195°C (dec); IR (KBr): ν_{max} 1960 cm^{-1} (C=C=C); ^1H NMR (D_2O): δ 1.65 (dd, 3H, CH_3), 3.27 (AB, 2H, J = 14.3 Hz, $PhCH_2$), 5.6 (m, 2H, HC=C=CH), 7.4 (m, 5H, Ph); ^{13}C NMR (D_2O): δ 15.7, 44.2, 65.0, 92.2, 97.5, 131.1, 131.8, 133.2, 135.2, 174.3, 205.2.

2-Amino-3-methyl-3,4-pentadienoic acid, 16 (R_1 = CH_3): To a solution containing LDA (75.6 mmol prepared from diisopropylamine and 1.55 M n-butyl lithium at -78°C) in 100 ml of dry THF was added dropwise 36 mmol of but-2-ynyl N-Boc glycinate, **14a**, in 20 ml of THF. After 1 h, 9.6 ml of

chlorotrimethylsilane were added and the reaction mixture was slowly brought to room temperature and then heated to reflux for 1 h. On cooling to room temperature, 20 ml of methanol were added and after another hour, the reaction mixture was concentrated. The resulting residue was dissolved in ethyl acetate and extracted repeatedly with 5% $NaHCO_3$. The aqueous portion was acidified in a two phase system containing CH_2Cl_2 to pH 3 with 20% HCl. The CH_2Cl_2 portion was separated and the aqueous phase repeatedly extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, and then brine, and dried over anh. $MgSO_4$. On concentration, 1.3 g of a showing an allene band at 1960 cm^{-1} was obtained. This material was dissolved in 50 ml of an ethyl acetate solution saturated with HCl at room temperature, whereupon a yellow precipitate formed. After 1 h, the mixture was concentrated and the resulting residue dissolved in water and washed with CH_2Cl_2. The aqueous portion was then applied to an ion-exchange column (H^+) (Bio-Rad, Ag 50W-X8) and eluted with 20% pyridine-water. The eluant containing product was concentrated, partially purified by reverse phase chromatography and upon crystallization from acetone-water, the desired product 16 was obtained. mp 195 - 200°C (dec); IR (KBr): ν_{max} 1960 cm^{-1} (C=C=C); ^1H NMR (D_2O): δ 1.82 (t, 3H, J = 3.2 Hz, CH_3), 4.2 (t, 1H, J = 1.7 Hz, CHN), 5.0 (m, 2H, H_2C=C=C).

2-Amino-3,4-pentadienoic acid, 17: Proceeding in essentially the same manner as above, 2-amino-3,4-pentadienoic acid was obtained from 14b. After the [3,3] rearrangement of ester 14b, the trimethylsilyl group was hydrolyzed by treatment with 0.1 N NaOH/MeOH for 2 h at room temperature. After removal of the Boc group with HCl/EtOAc, purification by ion-exchange chromatography (eluting with 20% pyridine-water) and HPLC reverse phase chromatography (eluting with water) gave the desired product. ^1H NMR (D_2O): δ 4.25 (m, 1H, CHN), 5.15 (m, 2H, H_2C=C=C), 5.5 (app t, 1H, J = 6.7 Hz, HC=C=C); 17.TFA salt: MS(CI): 245 (MNH_4^+), 228 (MH^+), 227 ($MNH_4^+-H_2O$).

Preparation of 47:[41] A dry THF solution (30 ml) of [Ph_3P^+-CH_2C≡CSiMe$_3$] Br^- (4.5 mmol) stirred at -78°C under argon was treated with 1.6 M n-BuLi (4.81 mmol). The reaction mixture was then brought to -40°C within 10-15 min, and after 30 min was cooled to -78°C. A solution of aldehyde 46 (3.0 mmol in 10 ml dry THF) was added dropwise, after which the reaction mixture was warmed to 0°C over 20 min and maintained at this temperature for 1 h. Ether (200 ml) was added, the resulting precipitate was filtered off, and the filtrate was concentrated to a residue. Purification by flash chromatography eluting with 10% EtOAc/hexane gave two fractions: Fraction #1 contained 630 mg of trans-enyne 47 and fraction #2 contained 140 mg of cis-enyne 47 (75% yield). trans-Enyne 47 has: IR ν_{max} 3200-3600 (br NH), 2138 (C≡C), 1700 cm^{-1} (CONH); ^1H NMR ($CDCl_3$): δ 0.17 (s, 9H, $SiMe_3$), 1.37 (s, 9H, Boc), 2.83 (m, 2H, $PhCH_2$), 4.47 (br m, 2H, NH, CHN), 5.57 (d, 1H, J = 15.5 Hz, HC≡C), 6.25 (ddm, J = 4.78, 15.5 Hz, C≡C<u>H</u>CHN), 7.25 (m, 5H, Ph).

Preparation of 50: trans-Enyne 47 (400 mg) was dissolved in 10 ml of formic acid at room temperature. After 1.5 h, the reaction mixture was concentrated to give a pinkish solid residue. Trituration with ether gave a white precipitate. mp 134-136°C (dec); IR (KBr): ν_{max} 2300-3200 (br, OH, NH), 2120, 2160, 2220 (br, C≡C), 1560 cm^{-1} (CO_2^-); ^1H NMR (D_2O): δ 0.17 (s, 9H, $SiMe_3$),

3.05 (app d, 2H, J = 7.0 Hz, CH_2), 4.15 (q, 1H, J = 7.0 Hz, CHN), 5.7 (d, 1H, J = 15.5 Hz, HC=C), 6.2 (dd, 1H, J = 7.2, 15.5 Hz, C=C<u>H</u>CHN), 7.35 (m, 5H, Ph), 8.43 (br s, HCO_2). The above salt (160 mg) was treated with benzaldehyde (60 μl), NEt_3 (1 ml), and anh. $MgSO_4$ (2 g) in 40 ml of CH_2Cl_2 stirring at room temperature overnight. Filtration <u>in-vacuo</u> followed by concentration gave an oily residue which was dissolved in 50 ml of ether, washed with 20 ml of brine, dried over anh. $MgSO_4$ and concentrated to give <u>48</u> as a yellow oil (190 mg). ^{1}H NMR ($CDCl_3$): δ 0.18 (s, 9H, $SiMe_3$), 3.0 (br d, J = 7.0 Hz, $PhCH_2$), 4.0 (br q, 1H, J = 7.0 Hz, HCN), 5.78 (dd, 1H, J = 1.2, 15.5 Hz, HC=C), 6.45 (dd, 1H, J = 6.0, 15.5 Hz, C=C<u>H</u>CHN), 7.1~7.8 (m, 10H, Ph), 7.9 (s, 1H, HC=N). Benzylidene <u>48</u> (190 mg) in 2 ml of dry THF was added dropwise to 1.1 equiv. of an LDA solution (made from diisopropylamine (0.1 ml) and 1.5 M n-BuLi (0.43 ml) at 0°C in 4 ml of dry THF) at -78°C with stirring under argon. After 15 min, ethyl chloroformate (60 μl) was added in one portion resulting in a purple coloured solution which subsequently turned orange-red and finally light orange. After 40 min, the mixture was slowly warmed to -40°C and treated with a saturated solution of $NH_4^+Cl^-$ (2 ml). Dilution with 50 ml of ether was followed by rapid washing with cold brine (20 ml), drying over anh. $MgSO_4$, and concentration to an oil. ^{1}H NMR analysis indicated a 2:3 ratio of product and starting material (benzylidene protons resonate at δ 8.13 and 7.9 for the product and starting material respectively). The mixture was next treated with 2% HCl (10 ml) and THF (20 ml) and stirred overnight at room temperature. Concentration gave a residue which was dissolved in 2 N NaOH/THF (30 ml, 1:2) for two days at room temperature. The THF was then removed and the resulting residue diluted with 50 ml of water and washed with CH_2Cl_2 (2x10 ml). Acidification of the aqueous extracts to pH 2 was followed by washing once with CH_2Cl_2 (10 ml) and ion-exchange chromatography (Bio-Rad Ag 50W-X8 column) eluting with 20% aqueous pyridine. Concentration of the ninhydrin positive eluant gave <u>50</u> (10 mg). In D_2O, the acetylenic proton exchanged with deuterium on preparing an NMR sample. IR (KBr): ν_{max} 2575 (C≡C-D), 2099 (C≡C), 1590 cm^{-1} (CO_2^-); ^{1}H NMR (D_2O): δ 3.05 (AB, 2H, J = 13.2 Hz, $PhCH_2$), 5.65 (d m, 1H, J = 16.2 Hz, HC=C), 6.65 (d, 1H, J = 16.2 Hz, HC=C), 7.35 (m, 5H, Ph). Acidification with 10% HCl and concentration gave <u>50</u>.HCl. mp 160-162°C (dec); UV (H_2O, c = 2.78×10^{-5} M): λ_{max} 230 nm (ε 14300); ^{1}H NMR (D_2O): δ 3.45 (AB, 2H, J = 14.3 Hz, $PhCH_2$), 3.65 (dd, 1H, J = 2.4 Hz, C≡C-H), 5.95 (dd, 1H, J = 2.4, 16.2 Hz, HC=C), 6.67 (dd, 1H, J = 16.2 Hz, C=CHCN), 7.45 (m, 5H, Ph).

<u>N-Carbobenzyloxy Allylglycine Methyl Ester 26:</u> α-Methoxy-N-carbobenzyloxy glycine methyl ester <u>25</u> (0.5 g), dissolved in 30 ml of dry CH_2Cl_2, was treated with 1 ml of allyltrimethylsilane and 0.8 ml of $BF_3.Et_2O$ with stirring at 0°C. The reaction mixture was brought to room temperature, left for 24 h, and treated with 50 ml of brine. The organic phase was separated and further washed with 20 ml of brine, dried over anh. $MgSO_4$, filtered, and concentrated to give an oil (0.56 g). TLC (30% EtOAc/Hexane, R_f = 0.4) and ^{1}H NMR analysis of the reaction product indicated ~ 80% conversion of starting material to product. ^{1}H NMR ($CDCl_3$): δ 2.55 (b t, 2H, CH_2), 3.73 (s, 3H, OMe), 4.3-4.6 (m, 1H, CHN), 5.12 (s, 2H, $PhCH_2$), 5.0-6.0 (m, 4H,

H_2C=CH, NH), 7.35 (s, 5H, Ph).

N-Carbobenzyloxy Cyclopropyl Glycine Methyl Ester 37:[42] Cyclopropyl magnesium bromide was prepared in 6 ml of dry THF from cyclopropyl bromide, 0.56 g, and magnesium, 170 mg. The Grignard solution was then added via syringe to N-carbobenzyloxy-α-chloro-glycine methyl ester 22, 0.54 g, in 10 ml of dry THF at -78°C. Two hours after the addition, the reaction mixture was quenched with 10 ml of 1.0 N citric acid. Ether (100 ml) was added and the organic portion was washed with 2 x 20 ml of water, 20 ml brine, dried over anh. $MgSO_4$, and concentrated to a light oil. Purification by flash chromatography, eluting with 30% EtOAc/hexane, gave 165 mg of product 37 as a light oil. IR: ν_{max} 3200-3500 (CONH), 1700-1750 cm^{-1} (CO_2Me, CON); ^1H NMR ($CDCl_3$): δ 1.35-1.7 (m, 4H, $-CH_2CH_2-$), 1.85-2.3 (m, 1H, CH), 3.77 (s, 3H, OMe), 3.7-4.0 (m, 1H, CHN), 5.1 (s, 2H, $PhCH_2O$), 5.4 (br d, 1H, NH), 7.35 (s, 5H, Ph).

Proceeding in the same manner, the compounds reported in Table 1 were isolated. The Grignard precursors to the alkynes 39 to 40 were prepared at room temperature for 1 h from the requisite alkyne and EtMgBr.

39: IR: ν_{max} 3200-3500 (NH), 2227 (C≡C), 1752 (CO_2Me), 1680-1720 cm^{-1} (CON); ^1H NMR ($CDCl_3$): δ 0.96 (t, 3H, J = 7.4 Hz, CH_3), 1.3 - 1.75 (m, 2H, CH_2), 2.16 (dt, 2H, J = 2.2, 6.7 Hz, CH_2C≡C), 3.8 (s, 3H, OMe), 5.0-5.2 (br m, 1H, CHN), 5.14 (s, 2H, $PhCH_2O$), 5.5 (br d, 1H, NH), 7.35 (s, Ph). MS, m/z 289.1324 (289.1314 calcd for $C_{14}H_{19}NO_4$).

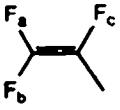
40: IR: ν_{max} 3200-3500 (NH), 2230 (C≡C), 1752 (CO_2Me), 1720 cm^{-1} (CON); ^1H NMR ($CDCl_3$): δ 0.9 (br t, 3H, CH_3), 1.1-1.7 (m, 6H, CH_2), 2.05-2.3 (br dt, 2H, CH_2C≡C), 3.81 (s, 3H, OMe), 5.0-5.2 (m, 1H, CHN), 5.14 (s, 2H, $PhCH_2O$), 5.3 (br d, 1H, NH), 7.37 (s, 5H, Ph). MS, m/z 317.1619 (317.1627 calcd for $C_{18}H_{23}NO_4$).

41: IR: ν_{max} 3200-3450 (NH), 2237 (C≡C). 1755 (CO_2Me), 1690-1745 cm^{-1} (CON); ^1H NMR ($CDCl_3$): δ 1.82 (d, 3H, J = 2.4 Hz, CH_3), 3.80 (s, 3H, OMe), 4.95-5.2 (br m, 1H, CHN), 5.13 (s, 2H, $PhCH_2O$), 5.42 (br d, 1H, NH). 7.35 (s, 5H, Ph). MS, m/z 261.10096 (261.10011 calcd for $C_{14}H_{15}NO_4$).

42: IR: ν_{max} 3220-3460 (NH), 2222 (C≡C), 1751 (CO_2Me), 1690-1745 cm^{-1} (CON); ^1H NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 5.16 (s, 2H, $PhCH_2O$), 5.37 (br d, 1H, CHN), 5.65 (br d, 1H, NH), 7.35 (s, 10H, Ph). MS, m/z 323.1161 (323.11576 calcd for $C_{19}H_{17}NO_4$).

1,1,2-Trifluoro allyl amine hydrochloride, 44: Compound 33,[24a] 7.0 g, was refluxed in 50 ml of 50% HCl for 1 h. After cooling, the aqueous solution was washed with 20 ml of CH_2Cl_2 and concentrated to a residue. Trituration with ether gave 4.0 gm of trifluorovinyl glycine hydrochloride, 43. mp 165-166°C. ^1H NMR (D_2O): δ 5.0 (d m, J = 29.8 Hz, CHN); ^{19}F NMR (D_2O): δ -95.6 (dd, F_a, J_{ab}^{gem} = 64.6 Hz; J_{ac}^{cis} = 34.2 Hz), -114.3 (ddd, F_b, J_{ba}^{gem} = 64 Hz, J_{bc}^{trans} = 115 Hz, $J_{b\text{-}H}$ = 2.3 Hz, CHN), -184.5 (ddd, F_c, J_{ca}^{cis} = 34.1 Hz, J_{cb}^{trans} = 115.6 Hz, $J_{c\text{-}H}$ = 29.5 Hz). Trifluorovinyl glycine hydrochloride, 43 (500 mg), was taken up in 20 ml of acetone and heated on a steam bath for ~ 30 min. Concentration gave the amine hydrochloride 44 (350 mg). mp 205 - 215°C (dec.). IR: ν_{max} 2600-3600 (NH), 1800 cm^{-1} (F_2C=CF); ^1H NMR (D_2O): δ 4.05 (d m, J ~ 21 Hz, CH_2N); ^{13}C NMR: δ 37.0, 37.2, 37.3, 38.2, 38.3, 38.4 (d t, $\underline{C}H_2N$), 118.4, 119.4, 121.0, 122.0, 130.0, 131.0,

132.6, 133.6 (ddd, CF), 141.3, 143.4, 169.6, 171.7, 155.2, 155.7, 157.4, 157.8 (ddd, CF). ^{19}F NMR (D_2O): δ -97.6 (b ddt, F_a, J_{ab}^{gem} = 68.4 Hz, J_{ac}^{cis} = 32.3 Hz, J_{a-H} ~ 2.1 Hz), -115.6 (ddt, F_b, J_{ba}^{gem} = 68.3 Hz, J_{bc}^{trans} = 114.8 Hz, J_{b-H} = 3.4 Hz), -179.6 (ddt, F_c, J_{ca}^{cis} = 33.3 Hz, J_{cb}^{trans} = 114.9 Hz, J_{c-H} = 21.0 Hz).



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