sylate (11) in 15 mL of anhydrous ($LiAlH_4$) tetrahydrofuran was treated portionwise with 600 mg (15.8 mmol) of lithium aluminum hydride at 0 °C. The reaction mixture was refluxed during 2 h, cooled to 4 °C, acidified with diluted hydrochloric acid, concentrated at room temperature under vacuum, filtered, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (5 g). The fractions eluted with chloroform–ethyl acetate (1:1) gave 20 mg (0.08 mmol, 13%) of **28** as white needles, mp 193–195 °C. Recrystallization from acetone provided the pure substance: mp 198–199 °C; IR (KBr) 3382 cm^{-1} (OH); $[\alpha]_{589}$ −2.8°, $[\alpha]_{578}$ −2.8°, $[\alpha]_{546}$ −3.9°, $[\alpha]_{436}$ −5.7°, $[\alpha]_{365}$ −19.9° (*c* 1.8, ethanol); ^1H NMR (90 MHz, Me_2CO-d_6) δ 5.36 (br s, 1 H, H-2), 4.42 (m, 1 H, H-1), 3.90 (d with further unresolved couplings, 1 H, *J* = 9 Hz, H-7), 3.76 (m, 1 H, H-9), 3.52 (d, 2 H, *J* = 4 Hz, 2 OH), 3.20 (d, 1 H, *J* = 4 Hz, OH), 2.63 (m, 1 H, H-11), 1.73 (t, 3 H, *J* = 1.5 Hz, vinyl Me), 1.51 (s, 1 H, H-5), 1.16, 0.91, and 0.88 (3 s, 3 H each, *gem*-dimethyl and Me at C-10) [the remaining three protons (H-4, H-8, and H-8′) overlap in the δ 2.3–1.8 region]; ^{13}C NMR ($(CD_3)_2CO$), see Table I. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.33; H, 9.44; O, 18.91.

Longipin-2-ene-7β,9α-diol-1-one (14). A solution of 70 mg (0.28 mmol) of longipin-2-ene-1β,7β,9α-triol (**28**) in 2 mL of dioxane was treated with 200 mg (0.88 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone dissolved in 1 mL of dioxane. The reaction mixture was stored at room temperature during 65 h, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (2 g). The fractions eluted with chloroform–ethyl acetate (1:1) were combined and recrystallized from chloroform to yield 7 mg (0.03 mmol, 11%) of **14** as white needles, mp 183–184 C, which was identical in all respects to the sample isolated from *Stevia salicifolia*.

Acknowledgment. We are grateful to Prof. *Jirzy* Rzedowsky (Departamento Botánico, Escuela Nacional de Ciencias Biológicas, IPN, Mexico) for the identification of the plant material, to Dr. J. N. Shoolery and the Varian Associates NMR Applications Laboratory (Palo Alto, CA) for granting the XL-200 instrument time, to A. Posada (CIEA-IPN) for optical rotations, and to CoNaCyT (México) for partial financial support.

Registry No. 1, 80388-43-8; **2**, 80388-57-4; **3**, 80433-25-6; **4**, 80388-60-9; **5**, 97279-98-6; **6**, 97279-99-7; **8**, 97335-20-1; **9**, 97280-00-7; **10**, 97280-01-8; **11**, 97280-02-9; **13**, 97280-03-0; **14**, 97335-21-2; **15**, 97280-04-1; **17**, 97280-05-2; **18**, 97280-06-3; **19**, 97280-07-4; **20**, 97280-08-5; **21**, 97280-09-6; **22**, 97280-10-9; **23**, 97280-11-0; **24**, 97280-12-1; **25**, 97335-22-3; **26**, 97335-23-4; **27**, 97280-13-2; **28**, 97280-14-3; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 84-58-2; longipin-2-ene-7β,8α,9α-triol-1-one 7-tosylate, 97280-15-4.

α-Amino Acids as Chiral Educts for Asymmetric Products. The Synthesis of α′-Amino-α,β-ynones

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Received March 15, 1985

α-Amino acid isoxazolidides have been developed as educts for the preparation of optically pure α′-amino-α,β-ynones. The α-amino acids were first N-protected as their ethoxycarbonyl, *tert*-butoxycarbonyl, or phenylsulfonyl derivatives. The isoxazolidides then were formed by the simple, high yield acylation of isoxazolidine by in situ generated α-amino acid isobutyl carbonic anhydrides. Individual isoxazolidides of L-α-N-substituted alanine, phenylalanine, and methionine, when treated with lithium acetylide, lithium (trimethylsilyl)acetylide, or 1-hexynyllithium, gave high yields of the corresponding optically pure α,β-acetylenic ketones.

Introduction

α,β-Acetylenic ketones are useful synthetic intermediates because of their potential conversion to such compounds as chiral acetylenic alcohols,[1] unsaturated ketones, allylic alcohols, and a variety of Michael addition compounds. Such ynones have thus proven crucial precursors for the total synthesis of some natural products and related analogues such as the marine sesquiterpene (±)-$\Delta^{9(12)}$-capnellene[2] and chiral insect pheromones[3] as well as for the synthesis of a number of heterocyclic compounds.[4]

Of the various methods[5] that have been developed for the synthesis of α,β-acetylenic ketones, besides the oxidation of propargylic alcohols, the acylation of an acetylene derivative by an activated carboxylic acid has been the most common. The choice of reaction conditions and substrates for this general type of acylation are crucial, since the acetylenic ketone product is often of comparable or greater reactivity than the activated carboxylic acid and could conceivably react further to yield side products such as tertiary carbinol and Michael adduct.

One such acylation route is the reaction of (trimethylsilyl)acetylenes with acyl halides and aluminum chloride.[6] Similarly, alkyl carbothioates[7] react with (trimethyl-

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(4) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.

(5) Methods for α,β-ynone synthesis prior to 1969 have been reviewed: Katkevich, R. I.; Vereshchagin, L. I. *Russ. Chem. Rev.* **1969**, *38*, 900.

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0022-3263/85/1950-3972$01.50/0

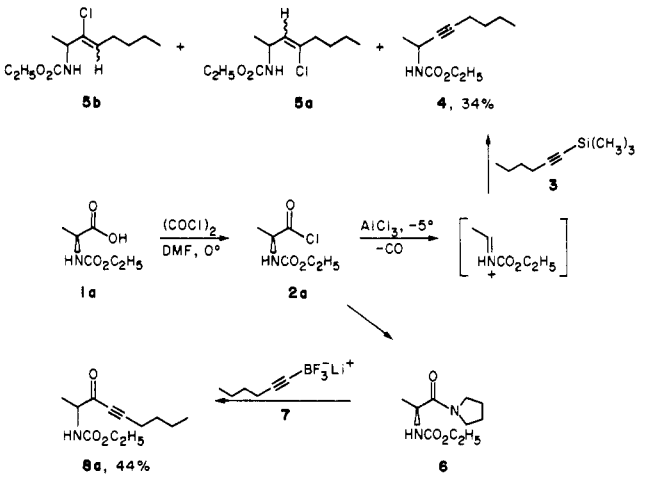
silyl)acetylenes in the presence of silver tetrafluoroborate to yield acetylenic ketones. Acyl halides react with either tin[8] or zinc[9] acetylides under $(PPh_3)_2PdCl_2$ catalysis and with copper acetylides with[10] or without[11] catalyst to produce ynones. Presumably the zinc, tin, and copper acetylides are too unreactive for further reaction with the product ynone and give little tertiary alcohol formation.

A number of methods are described for the conversion of other derivatives of carboxylic acids to α,β-acetylenic ketones. Lithium alkynyltrifluoroborates, which are readily obtained by the addition of $BF_3{\cdot}Et_2O$ to lithium acetylides, react with either carboxylic acid tertiary amides[12] or carboxylic acid anhydrides[13] to provide α,β-acetylenic ketones in high yield. Since no diacetylenic alcohols were reported and since it is known that dialkyl ketones react with alkynyl borates to yield propargylic alcohols,[13] it was assumed that the alkynyl borate and carboxylic acid derivative react to form a quasi-stable intermediate. In a few unique cases and under specialized conditions the more reactive lithium and bromomagnesium acetylides can be acylated. Thus [(trimethylsilyl)-ethynyl]magnesium bromide with dimethylformamide produces an α,β-acetylenic aldehyde.[14] Lactones[15] can be made to react with a lithium acetylide to give the α,β-ynones; the yields are good for δ-lactones but poor with γ- or ε-lactones. In one case[16] the lithium salt of *O*-tetrahydropyranyl-1-butyn-4-ol was made to react with methyl 8-(chloroformyl)octanoate to afford the acetylenic keto ester in 53% yield.

One general approach to the synthesis of ketones from carboxylic acids via an organometallic reagent is to employ as the acylating agent such derivatives as a 2-pyridyl thioate ester,[17] an *N*-acylimidazole,[18] or a *N*-methoxy-*N*-methylamide[19] rather than the usual carboxylic acid halide. Upon reaction with the organometallic reagent these carboxylic acid derivatives are thought to form stabilized tetrahedral intermediates which dissociate to form ketones only after hydrolytic workup. This general approach is now well established in ketone synthesis methodology, but there is only one report[19] of ynones formed in this manner. The reaction of lithium or bromomagnesium phenylacetylide with the *N*-methoxy-*N*-methylamides of benzoic acid and cyclohexanecarboxylic acid led to exclusive ynone formation even in the presence of an excess of organometallic reagent.

Although a variety of acyl compounds has been used in the synthesis of ynones, the successful use of protected α-amino acids as acetylenic ketone precursors has yet to be achieved. Recently the utility of α-amino acids in the synthesis of optically pure, structurally variable α-amino ketones has been established.[20] This ketone synthesis methodology has been the basis for a synthesis of sibirosamine[21] as well as for converting L-serine into various D-amino acids.[22] As an extension of the work employing α-amino acids in the chirospecific synthesis of α-amino ketones, we now report the development of a versatile method which allows the high yield synthesis of optically pure α′-amino-α,β-acetylenic ketones.

Scheme I. Reactions of (Ethoxycarbonyl)alanine Acid Chloride and Pyrrolidide with 1-Hexyne Derivatives



Results and Discussion

As the basis of our investigations we elected to use the simplest optically active α-amino acid, L-alanine. The amino group was protected by the ethoxycarbonyl, *tert*-butoxycarbonyl, or phenylsulfonyl group. Subsequently, our method was extended to similar derivatives of the L-amino acids phenylalanine and methionine. Of the various ynone-forming methods described above, the process that appeared best applicable to α-amino acids was the procedure[6a] employing Friedel–Crafts acylation of a 1-(trimethylsilyl)-1-alkyne. This reaction seemed particularly attractive in light of the recent report[20b] that *N*-(ethoxycarbonyl)-L-alanine acid chloride (**2a**) reacts with benzene in the presence of $AlCl_3$ to afford an optically pure phenyl ketone. Thus, compound **2a** was prepared from *N*-(ethoxycarbonyl)-L-alanine (**1a**) using conditions shown to be nonracemizing.[20b] Reaction of **2a** with 1-(trimethylsilyl)-1-hexyne (**3**) in the presence of aluminum chloride did not lead to the desired α,β-ynone. Instead, the α-aminoalkyne **4** was obtained in 39% yield, along with the double bond isomers of the chloro allylic amines **5a** and **5b** resulting from hydrogen chloride addition to **4** (Scheme I). Evidently silylhexyne **3** is much less reactive than benzene toward Friedel–Crafts acylation. This decreased reactivity allowed the competing decarbonylation to occur forming an acyliminium salt, which then reacted to form **4**. Varying the stoichiometry of **2a**, **3**, and $AlCl_3$, as well as the reaction time, affected the yield and ratio of **4** and **5** but did not lead to the formation of the ynone. When $AlBr_3$ was substituted for $AlCl_3$, the results were essentially the same.

The reaction of disubstituted amides with an acetylide–$BF_3{\cdot}Et_2O$ complex also was investigated as a route to

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(12) Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* **1983**, 35.
(13) Lithium alkynyltrifluoroborates have been chracterized by: Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.* **1984**, *25*, 2411.
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(20) (a) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260. (b) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.
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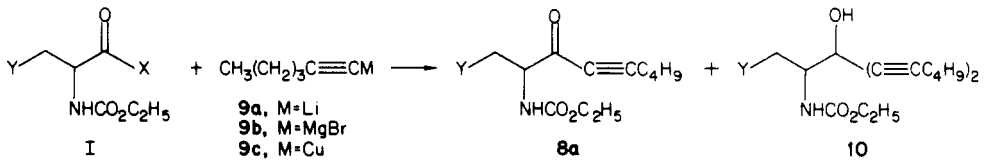
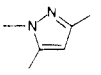
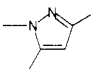
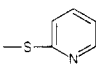
(22) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

Table I. Reaction of Metalloacetylides with Amino Acid Derivatives[a]



I 8a 10

expt	I, alanine substrate	X	9 M, mol %	ratio[b] 8a/10	8a % yield
1	**1a**	OH	Li, 350	no reaction	
2	**2a**	Cl	Li, 210	(100% 10)	(48% 10)
3	**2a**	Cl	Li, 110	1/2	<5
4	**2a**	Cl	MgBr, 230	1/10	<1
5	**2b**		Li, 100	1/10	<1
6	**2b**		MgBr, 400	1/2	<5
7	**2c**		MgBr, 200	1/20	<1
8	**2a**	Cl	Cu, 200	*c*	<5
9	**2d**	$-N(CH_3)OCH_3$	Li, 250	>100/1	84
10	**2e**		Li, 250	>100/1	88
11	**2f**		Li, 250	*c*	74

[a] For Y, see Scheme II. [b] Ratios were determined by NMR analysis. [c] Ratios not determined.

enantiomerically pure α'-amino-α,β-ynones. Originally dimethylamides had been used[13] but after demonstrating that *N*-benzoylpyrrolidine and *N,N*-dimethylbenzamide gave comparable yields, we used the more convenient alanine pyrrolidide (**6**). Compound **6** was obtained from the acid chloride **2a** by the routine acylation of freshly distilled pyrrolidine.

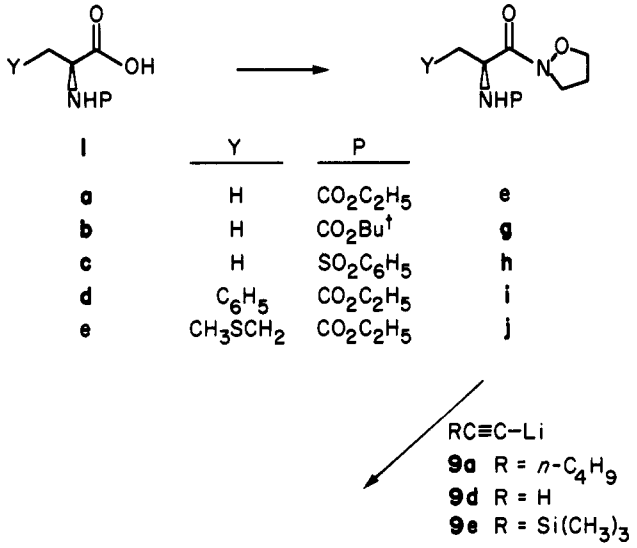
The reaction of pyrrolidide **6** with 1-hexynyltrifluoroborate **7** gave the α,β-acetylenic ketone **8a** in a 44% yield (Scheme I). A comparison of the optical rotation of **8a** produced by this route and **8a** produced by a later racemization-free route (described below) showed the product to be 39% racemized. In attempting to ascertain the cause of this loss of optical purity, we treated product ketone **8a** with $BF_3{\cdot}Et_2O$. Complete recovery of **8a** with no loss of optical activity resulted. Also, from a reaction not carried to completion, we recovered 15% of pyrrolidide **6** and found it to be optically pure. Since neither educt **6** nor product **8a** loses optical integrity under the conditions of the acylation, this loss must occur with some intermediate. Thus partial racemization and low yield made the acylamide route unsuitable.

The reaction of N-protected amino acids with metalated acetylenes was also investigated in our quest for a method of synthesizing optically pure ynones. It is now well established[20-22] that ketones obtained by the reaction of excess organometallic reagents with α-amino acid carboxylates having appropriate N-protecting groups (i.e., ethoxycarbonyl, phenylsulfonyl, etc.) are enantiomerically pure. Therefore, we examined the reactions of the *N*-(ethoxycarbonyl) amino acid **1a** and a variety of its activated forms (**2a–2d**) with a metalated hexyne (**9a–c**). The results are summarized in Table I. The reactions were evaluated on the basis of formation of ketone **8a**, and those reactions which led to substantial formation of tertiary alcohol **10** were not examined further.

The carboxylate of **1a** did not react with the lithium acetylide **9a** even in refluxing THF. Clearly acetylide **9a** was appreciably less nucleophilic than the corresponding alkyl- and alkenyllithium compounds that had reacted quite effectively with carboxylate salts.[20a,22] Reaction of the carboxylic acid derivatives with metalated acetylides was a different story. For example, the alanine acid chloride **2a** reacted readily with either lithio derivative **9a** or Grignard reagent **9b**. However, there was little evidence that a stable intermediate was being formed, based on the appearance of large amounts of **10**. When 210 mol % of **9a** was used, **10** was isolated in 48% yield, and when only 110 mol % of **9a** was added, the carbinol **10** was already being formed.

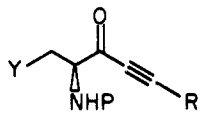
One can circumvent the problem of carbinol formation in two general ways. First one can decrease the reactivity of the acetylide, and it has been shown[11a] that copper acetylides react with acyl chlorides to afford ynones in generally good yields. However, when **2a** was allowed to react with copper acetylide **9c**, generated in situ, ketone **8a** was formed in <5% yield even after 24 h at 20 °C. The second way to avoid alcohol formation is to use a modified form of **1a** which will form a stabilized tetrahedral intermediate[17-19] upon reaction with the organometallic species. Three derivatives were prepared to pursue this idea, viz., the dimethylpyrazolide **2b**, the 2-pyridyl thioate ester **2c**, and the *N*-methoxy-*N*-methylamide **2d**. Compounds **2b**, **2c**, and **2d** were readily made from **2a** by routine acylation of 3,5-dimethylpyrazole, 2-mercaptopyridine, and *N*-methoxy-*N*-methylamine, respectively, in the presence of triethylamine. All three had in common the presence of either a nitrogen or oxygen atom in the expendable portion of the molecule whose lone pair electrons could coordinate with the metal and stabilize the intermediate. The results of these reactions are presented in Table I. Interestingly in the cases of pyrazolide **2b** and thiopyridyl ester **2c** substantial amounts of carbinol **10** were formed. Evidently these derivatives conferred no intermediate stabilization although they reacted readily with both **9a** and **9b**. On the other hand *N*-methoxy-*N*-methylamide **2d** reacted

Scheme II. Formation of α′-Amino-α,β-ynones from Amino Acid Isoxazolides



	Y	P
a	H	$CO_2C_2H_5$
b	H	CO_2Bu^t
c	H	$SO_2C_6H_5$
d	C_6H_5	$CO_2C_2H_5$
e	CH_3SCH_2	$CO_2C_2H_5$

RC≡C–Li
9a R = n-C_4H_9
9d R = H
9e R = $Si(CH_3)_3$



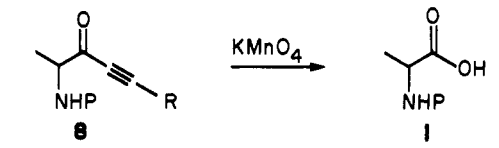
	Y	P	R	Yield, %
a	H	$CO_2C_2H_5$	n-C_4H_9	88
b	H	$CO_2C_2H_5$	H	80
c	H	$CO_2C_2H_5$	$Si(CH_3)_3$	96
d	H	CO_2Bu^t	H	84
e	H	$SO_2C_6H_5$	n-C_4H_9	80
f	H	$SO_2C_6H_5$	H	73
g	C_6H_5	$CO_2C_2H_5$	H	88
h	CH_3SCH_2	$CO_2C_2H_5$	H	87

with excess **9a** and yielded the ynone **8a** exclusively; no carbinol **10** was detected.

Before this reaction was extended to additional amino acids and other lithium acetylides, substitution of O–N-cyclic hydroxylamines for the *O*-methyl-*N*-methylhydroxylamine was pursued. The isoxazolidide **2e** was prepared and found to react with **9a** to form ynone **8a** in an 88% yield (Scheme II). Additionally **2e** is conveniently crystalline, as are the other isoxazolidides, and readily synthesized by the reaction of isoxazolidine[23] and the isobutyloxycarbonic anhydride of **1a** under conditions that have been shown to be nonracemizing in peptide synthesis.[24] The next higher homologue of the isoxazolidide, the tetrahydro-2*H*-1,2-oxazinide **2f** (Table I), was also examined. This cyclic hydroxylamide gave a lower yield of the ynone **8a** and was not investigated further.

The isoxazolidide **2e** was applied in a similar manner with several other lithium acetylides. When a solution of **2e** was added dropwise to a freshly generated solution of lithium acetylide[25] (**9d**) at −78 °C, the ethynyl ketone **8b** was produced. Similarly the reaction involving lithium (trimethylsilyl)acetylide (**9e**) yielded ynone **8c**. Silyl ynone **8c** was unstable to the aqueous isolation conditions, being hydrolyzed readily to **8b**. Treatment of **8c** with silica gel in aqueous methanol desilylated it completely to **8b**.

Scheme III. Determination of Optical Purity of α′-Amino-α,β-ynones



	P	R
a	$CO_2C_2H_5$	n-C_4H_9
b	$CO_2C_2H_5$	H
c	$CO_2C_2H_5$	$Si(CH_3)_3$
e	$SO_2C_6H_5$	n-C_4H_9
f	$SO_2C_6H_5$	H

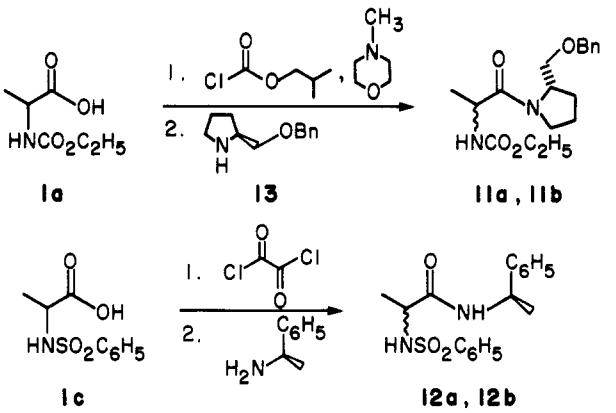


Table II. Optical Purity of Ynones

ynone	diastereomeric ratio[a] crude[b]	purified[b]
8a	>99/1	99/1
8b	>99/1	60/40
8c	98/2	75/25
8e	87/13	
8f	64/36	

[a] Ratio of **11a/11b** for **8a–8c**, and ratio of **12a/12b** for **8e** and **8f**. Diastereomeric amides formed as in Scheme III. [b] Crude is reaction mixture after workup; purified is after chromatography on silica gel using EtOAc/isooctane.

N-(*tert*-Butoxycarbonyl)-L-alanine (**1b**), *N*-(phenylsulfonyl)-L-alanine (**1c**), *N*-(ethoxycarbonyl)-L-phenylalanine (**1d**) and *N*-(ethoxycarbonyl)-L-methionine (**1e**) each afforded its corresponding isoxazolidide **2g–j** under the usual conditions. The yield of **2h** by this procedure was unsatisfactory apparently due to the competitive acylation of the sulfonamide nitrogen by isobutyl chloroformate in the anhydride-forming step. This problem was easily overcome by the quantitative acidolysis of *tert*-butoxycarbonyl isoxazolidide **2g** in neat trifluoroacetic acid followed by sulfonylation in the presence of TEA. The conversion of compounds **2g–j** to ynones using standard conditions proceeded with facility, and, with one exception (**8f**, 73%), the yields were excellent (80–96%).

Optical purity of the ynones was established by the sequence of reactions outlined in Scheme III. Oxidation of ynones by potassium permanganate is known to give an acid retaining the carbonyl.[10b] In this manner, the *N*-(ethoxycarbonyl)alanines **1** were produced from ynones **8a**, **8b**, and **8c** and were coupled to *O*-benzyl-L-prolinol (**13**)[26] to give the diastereomeric amides **11a/11b**. The *N*-(phenylsulfonyl)alanines **1c** from the oxidation of **8e** and **8f**

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(26) *O*-Benzyl-L-prolinol (**13**, $[\alpha]^{23}_D$ +5.73° (*c* 4.7, CH_3OH)) was prepared by the procedure of van den Broek, L. A. G. M.; Porskamp, P. A. T. W.; Haltiwanger, R. C.; Zwanenburg, B. *J. Org. Chem.* **1984**, *49*, 1691.

were coupled to (+)-α-phenylethylamine via the acid chloride of **1c**. This coupling gave the diastereomeric amides **12a/12b**. Both pairs of amides are readily separable by HPLC. The coupling procedures were shown to be nonracemizing.

The optical purities of the ynones were found to be dependent on the nature of the protecting group. When the N-protecting group was ethoxycarbonyl, the crude ynones **8a–8c** were essentially optically pure (Table II). Silica gel chromatography of these ynones leads to racemization of the β-unsubstituted and β-silyl ynones **8b** and **8c**, but not the β-alkyl ynone **8a**. The crude *N*-phenylsulfonyl ynones **8e** and **8f** were shown to be 26% and 72% racemic, respectively. These findings demonstrate that the nitrogen should be protected as an alkyl carbamate rather than phenylsulfonamide to avoid racemization.

Conclusion

The direct addition of alkynyl organometallics to α-N-protected amino acids did not occur, in contrast to the addition of alkyl, alkenyl, and aryl organometallics observed previously.[20-22] The α′-amino-α,β-ynones have been prepared from the isoxazolidides of the α-N-protected amino acids alanine, phenylalanine, and methionine. Our results indicate that this method should be widely applicable to aliphatic, aromatic, and further functionalized amino acids. Use of an alkyl carbamate as a protecting group gives ketones which are essentially optically pure. On the other hand, use of the *N*-phenylsulfonyl protecting group, or of silica gel in the purification, leads to a product which is largely racemized. With these *caveats*, an efficient process has been developed for the high yield synthesis of optically pure α′-amino-α,β-acetylenic ketones. Their use as chiral educts for a number of natural products is under consideration.

Experimental Section

THF was distilled from sodium/benzophenone and methylene chloride (CH_2Cl_2) was distilled from P_2O_5 immediately prior to use; both were transfered by syringe. Acetylene was purified by slow passage through a dry ice/acetone trap, a sulfuric acid trap, and finally a KOH/Drierite drying column. All reactions were carried out under nitrogen. *n*-Butyllithium (*n*-BuLi) was used as a hexane solution. ^1H NMR spectra were recorded at 200 MHz or 250 MHz in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were recorded at 50 MHz or 62.6 MHz in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield from internal tetramethylsilane. Melting points were recorded on a Büchi capillary melting point apparatus and are uncorrected. Chormatographic purifications of reaction products were carried out either by using a Chromatotron or on medium-pressure liquid chromatography (MPLC) columns (30 cm × 3 cm ID or 35 cm × 4 cm ID). HPLC analyses were carried out using a Microsorb 5-μm column (4.6 mm i.d. × 250 mm).

General Procedure for the Preparation of *N*-Acyl-α-amino Acids. To a solution of the amino acid (0.1 mol) and sodium carbonate hydrate (0.3 mol) in water (100–150 mL) was added phenylsulfonyl chloride or ethyl chloroformate (0.12 mol). The mixture was stirred at 20 °C for 12 h, then washed with ether (2×10 mL), acidified with concentrated HCl to pH 1.5, saturated with NaCl, and extracted with either ethyl acetate or CH_2Cl_2 (5 × 20 mL). Rotary evaporation of the solvents afforded the N-protected amino acid which was crystallized as needed.

***N*-(Ethoxycarbonyl)-L-alanine (1a)** was obtained as a colorless oil in 64% yield: (lit.[27] oil); ^1H NMR δ 1.26 (t, 3 H), 1.47 (d, 3 H), 4.13 (q, 2 H), 4.40 (m, 1 H), 5.30 (br d, 1 H), 9.30 (br s, 1 H).

***N*-(Phenylsulfonyl)-L-alanine (1c)** was obtained in 84% yield: mp 126–127 °C (lit.[20b] mp 124–126 °C); ^1H NMR δ 1.32 (d, 3 H, *J* = 7.2 Hz), 3.86 (m, 1 H), 4.0 (br s, 2 H), 7.54 (m, 3 H), 7.86 (m, 2 H).

***N*-(Ethoxycarbonyl)-L-phenylalanine (1d)**: 95% yield; mp 83–85 °C (lit.[28] mp 85 °C); ^1H NMR δ 1.22 (t, 3 H, *J* = 7.1 Hz), 3.15 (m, 2 H, 7 lines), 4.11 (q, 2 H, *J* = 7.1 Hz), 4.67 (q, 1 H, *J* = 7.0 Hz), 5.12 (br d, 1 H), 7.27 (m, 5 H), 9.12 (br s, 1 H).

***N*-(Ethoxycarbonyl)-L-methionine (1e)** was obtained as a colorless syrup in 86% yield (lit.[27] oil): ^1H NMR δ 1.22 (t, 3 H), 2.00 (m, 2 H), 2.07 (s, 3 H), 2.55 (t, 2 H), 4.11 (q, 2 H), 4.49 (m, 1 H), 5.45 (br d, 0.7 H), 6.70 (br s, 0.3 H), 8.70 (br s, 1 H).

***N*-(Phenylsulfonyl)-L-proline**: 96% yield; mp 84–86 °C (lit.[22] mp 84–86 °C); ^1H NMR: δ 1.79 (m, 1 H), 1.96 (m, 2 H), 2.18 (m, 1 H), 3.30 (m, 1 H, 6 lines), 3.55 (m, 1 H, 7 lines), 4.32 (dd, 1 H, *J* = 3.5, 8.2 Hz), 7.60 (m, 1 H), 7.88 (m, 2 H).

***N*-(*tert*-Butoxycarbonyl)-L-alanine (1b)** was prepared in 85% yield as described.[20b]

Reaction of *N*-(Ethoxycarbonyl)-L-alanine Acid Chloride (2a) with 1-(Trimethylsilyl)-1-hexyne (3). A solution of *N*-(ethoxycarbonyl)-L-alanine (**1a**, 0.49 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C under nitrogen, then treated with oxalyl chloride (0.42 g, 0.29 mL, 3.3 mmol) and DMF (5 μL, dried previously over 4Å sieves), allowed to warm to 20 °C, and stirred for 1.5 h. The solution was then evaporated, and the oily acid chloride was dissolved in CH_2Cl_2 (2 mL), combined with 1-(trimethylsilyl)-1-hexyne[29] (**3**, 0.48 g, 3.1 mmol), and added dropwise over 30 min to a stirred mixture of $AlCl_3$ (1.21 g, 9.1 mmol) in CH_2Cl_2 (10 mL) at −5° to −10 °C. The slowly darkening mixture was stirred for an additional 30 min and then poured slowly onto a mixture of 10% H_3PO_4 (100 mL), ice, and ethyl acetate (100 mL). The organic layer was separated, washed with a saturated solution of $NaHCO_3$ (2×20 mL) and a saturated solution of NaCl (1×20 mL), and finally dried. Filtration and evaporation yielded a crude oil (0.50 g) which was chromatographed (MPLC), eluting with a mixture of isooctane/ethyl acetate, 7/1. Three pooled fractions were collected.

4: 0.23 g; (39%) clear liquid, R_f 0.40 (isooctane/ethyl acetate, 5/1); GC (Dexsil 300–5% Anachrom Q, 190 °C) t_R 4 min (small peak at 6 min for **5a** and **5b**); IR 3310 cm^{-1}, 2240, 1700; MS (CI): 198 ($M^+ + 1$); ^{13}C NMR δ 155.08 (NCO_2Et), 81.71 ($C{\equiv}CCH_2$), 78.16 ($C{\equiv}CCH_2$), 60.09 ($NCO_2CH_2CH_3$), 58.44 (−*C*HNH), 30.22 ($CH_2CH_2CH_2CH_3$), 22.45 ($CH_2CH_2CH_2CH_3$), 21.31 ($CH_2CH_2CH_2CH_3$), 17.68 (H_3CHNH–), 14.02 ($CO_2CH_2CH_3$), 12.98 ($CH_2CH_2CH_2CH_3$); ^1H NMR δ 0.90 (t, 3 H, *J* = 7.1 Hz), 1.24 (t, 3 H, *J* = 7.2 Hz), 1.37 (d, 3 H, *J* = 6.8 Hz), 1.45 (m, 4 H), 2.15 (t, 1 H, C≡CC*H*a, *J* = 6.9 Hz), 2.16 (t, 1 H, C≡CCHb, *J* = 6.9 Hz), 4.12 (q, 2 H, *J* = 7.1 Hz), 4.50 (m, 1 H), 4.80 (br s, 1 H). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1. Found: C, 66.7; H, 9.8; N, 7.3.

5a: 0.04 g, 5.6%, clear liquid; R_f 0.35 (isooctane/ethyl acetate, 5/1); GC (Dexsil 300–5% Anachrom Q, 190 °C) t_R 6 min; IR 3310, 1690 cm^{-1}; MS (EI), 234 (M^+), 218 ($M^+ - 16$), 198 ($M^+ - HCl$); ^1H NMR δ 0.93 (t, 3 H, *J* = 7.2 Hz), 1.24 (m, 6 H), 1.35 (m, 4 H), 2.47 (m, 2 H, 10 line pattern), 4.10 (q, 2 H, *J* = 7.0 Hz), 4.42 (m, 1 H), 4.6 (s, 1 H, NH), 5.48 and 5.44 (2 s, 1 H).

5b: 0.02 g (2.8%) pale yellow liquid, R_f 0.30 (isooctane/ethyl acetate, 5/1); GC (Dexil 300–5% Anachrom Q, 190 °C) t_R 6 min; IR 3310 cm^{-1} 1690; MS (EI), 234 (M^+), 218 ($M^+ - 16$), 198 ($M^+ - HCl$); ^1H NMR δ 0.91 (t, 3 H, *J* = 7.2 Hz), 1.24 (m, 8 H), 1.52 (m, 2 H), 2.30 (pseudo triplet, 2 H, *J* = 7.3 Hz), 4.11 (q, 2 H, *J* = 7.0 Hz), 4.58 (q, 1 H, *J* = 7.0 Hz), 4.7 (br s, 1 H), 5.42, 5.39 (2 s, 1 H).

***N*-(Ethoxycarbonyl)-L-alanine Pyrrolidide (6).** To a solution of *N*-(ethoxycarbonyl)-L-alanine (**1a**, 3.61 g, 22 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was added oxalyl chloride (3.41 g, 27 mmol) and then DMF (50 μL). The resulting solution was stirred under N_2 for 3 h at 20 °C and then evaporated to a residue of **2a**. This was dissolved in dry THF (15 mL) and added dropwise to a solution of TEA (2.73 g, 27 mmol), pyrrolidine (1.92 g, 27 mmol), and THF (30 mL) at 10 °C, resulting in a suspension, which was stirred at 20 °C for 30 min. This mixture was then poured into 10% phosphoric acid (3 mL), the aqueous layer was separated and washed with EtOAc (3×50 mL), and the combined

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organic layers were extracted sequentially with 10% phosphoric acid (1 × 10 mL), saturated $NaHCO_3$ (3 × 25 mL), and saturated NaCl (1 × 25 mL) and then dried. Filtration and evaporation followed by crystallization from EtOAc/isooctane gave **7** (3.29 g, 69%): mp 71–72 °C; ^1H NMR δ 1.24 (t, 3 H, J = 7.1 Hz), 1.33 (d, 3 H, J = 6.8 Hz), 1.97 (m, 4 H, 7 line pattern), 3.50 (m, 4 H), 4.10 (q, 2 H, 7.1), 4.48 (m, 1 H), 5.62 (br s, 1 H). Anal. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.1; H, 8.5; N, 13.1. Found: C, 56.0; H, 8.4; N, 13.1.

2-[(Ethoxycarbonyl)amino]-3-oxo-4-nonyne (8a). A solution of 1-hexyne (0.246 g, 3 mmol) in dry THF (5 mL) under N_2 at −78 °C was treated with 1.53 M n-BuLi in hexane (1.96 mL, 3 mmol) and stirred for 30 min. The solution was then treated with $BF_3{\cdot}Et_2O$ (0.4 mL, 3.2 mmol) and stirred for an additional 30 min. A solution of pyrrolidide **6** (0.214 g, 1.0 mmol) in dry THF (2 mL) was then added to this boron acetylide solution via syringe. After 30 min the reaction was poured onto saturated ammonium chloride (30 mL) and stirred vigorously for 60 min. The aqueous layer was washed with EtOAc (1 × 10 mL), and the combined organic layers were washed with saturated NH_4Cl solution and finally dried. Filtration and evaporation yielded an oil which was chromatographed under medium pressure on SiO_2 (Michelle–Miller, 30 cm × 3 cm ID), eluting with isooctane/EtOAc, 4/1, to yield **8a** (0.10 g, 44%) as a colorless oil: ^{13}C NMR δ 186.52 (C-3), 155.66 (NCO_2Et), 98.23 (C-4), 78.53 (C-5), 60.84 (OCH_2CH_3), 57.03 (C-2), 29.40 (C-7), 21.75 (C-8), 18.58 (C-6), 17.64 (C-1), 14.36 (OCH_2CH_3), 13.27 (C-9); ^1H NMR δ 0.94 (t, 3 H, J = 7.2 Hz), 1.25 (t, 3 H, J = 7.1 Hz), 1.45 (d, 3 H, J = 7.3 Hz), 1.50 (m, 4 H), 2.41 (t, 2 H, J = 6.9 Hz), 4.12 (q, 2 H, J = 7.1 Hz), 4.44 (m, 1 H), 5.38 (br s, 1 H); IR 2200 cm^{-1} (s, C≡C); UV λ_{max} CH_3OH 220 nm; MS (EI) 225 (M^+); MS (CI) 226 (M^+ + 1), 180, 154, 116; $[\alpha]^{23}_D$ −15.7° (c 0.8, CH_3OH).

***N*-(Ethoxycarbonyl)-L-alanyl-3,5-dimethylpyrazole (2b).** To a cooled (0 °C) solution of **1a** (1.05 g, 6.5 mmol) was added oxalyl chloride (1.24 g, 9.8 mmol) and DMF (2 drops). The ice bath was removed, the solution was allowed to stir for 1 h, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (25 mL). 3,5-Dimethylpyrazole (680 mg, 7.2 mmol) was added with cooling (0 °C) followed by the slow addition of pyridine (605 mg, 7.65 mmol). The solution was stirred for 1 h, washed with H_2O (3 × 20 mL), and then dried. Filtration and evaporation afforded a residue which was recrystallized from EtOAc/isooctane: yield of **2b**, 0.930 g, 60%; mp 72–73 °C; ^1H NMR δ 1.23 (t, 3 H, J = 6.5 Hz), 1.5 (d, 3 H, J = 6.0 Hz), 2.23 (s, 3 H), 2.51 (s, 3 H), 4.13 (q, 2 H, J = 6.5 Hz), 5.46 (m, 2 H), 5.96 (s, 1 H). Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.2; H, 7.2; N, 17.6. Found: C, 55.2; H, 7.2; N, 17.5.

***N*-(Ethoxycarbonyl)-L-alanine 2-Pyridylthio Ester (2c).** A solution of **1a** (0.35 g, 2.2 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, treated with oxalyl chloride (0.21 mL, 2.5 mmol) and DMF (5 μL), and then stirred for 1 h at 20 °C. Evaporation left **2a** as a residue which was immediately dissolved again in CH_2Cl_2 (1 mL) and added dropwise to a solution of 2-mercaptopyridine (0.20 g, 1.8 mmol) and TEA (0.61 g, 6.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The resulting solution was stirred for 60 min at 20 °C and evaporated, and the residue was partitioned between ethyl acetate (50 mL) and water (10 mL). The organic layer was washed with water (3 × 10 mL) and then saturated $NaHCO_3$ solution (3×10 mL) and finally dried. Filtration and evaporation afforded crude **2c** (0.35 g, 62%) as a yellow syrup: ^1H NMR δ 1.27 (t, 3 H, J = 7.1 Hz), 1.46 (d, 3 H, J = 7.3 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 4.58 (quin, 1 H, J = 7.5 Hz), 5.93 (d, 1 H, J = 8.0 Hz), 7.31 (m, 1 H, 7 lines), 7.61 (d, 1 H, J = 7.8 Hz), 7.75 (dt, 1 H, J = 1.9, 7.7 Hz), 8.63 (dd, 1 H, J = 1.0, 4.9 Hz).

***N*-(Ethoxycarbonyl)-L-alanine *N*-Methoxy-*N*-methylamide (2d).** To a cooled (0 °C) solution of **1a** (5.28 g, 32.8 mmol) in CH_2Cl_2 (100 mL) was added oxalyl chloride (6.23 g, 49.1 mmol) and DMF (2 drops). The ice bath was removed and the solution was allowed to stir for 1 hour. The solvent was evaporated affording acid chloride **2a** which was dissolved in CH_2Cl_2 (125 mL), and *N,O*-dimethylhydroxylamine hydrochloride (3.51 g, 36 mmol) was added. With cooling (0 °C) pyridine (5.71 g, 72 mmol) was added dropwise, the solution was stirred for 1 h, the solvent was evaporated, and the residue was dissolved in Et_2O/CH_2Cl_2 (1/1, 100 mL). This solution was washed with HCl (1M, 3 × 20 mL) and then saturated $NaHCO_3$ (1 × 20 mL) and dried. The solvent was evaporated, and the residue was sublimed (60 °C/1 mm) to give **2d** (3.98 g, 60%): ^1H NMR δ 1.21 (t, 3 H, J = 7.0 Hz), 1.31 (d, 3 H, J = 7.0 Hz), 3.19 (s, 3 H), 3.7 (s, 3 H), 4.07 (q, 2 H, J = 7 Hz), 4.67 (quin, 1 H, J = 7.5 Hz), 5.33 (s, 1 H). Anal. Calcd for $C_8H_{16}N_2O_3$: C, 47.0; H, 7.9; N, 13.7. Found: C, 47.3; H, 7.6; N, 13.5.

General Procedure for Preparation of Amino Acid Isoxazolidides. A solution of the N-protected amino acid in THF (0.5 M) was cooled to −15 °C and treated with one portion of *N*-methylmorpholine (100 mol%) and then with one portion of isobutyl chloroformate (100 mol %). The resulting suspension was stirred for 60 s and then treated with a 1.0 M mixture of isoxazolidine hydrochloride (100 mol %) and triethylamine (110 mol %) in DMF. The suspension which resulted with stirred for 30 min and then warmed to 20 °C, the solvents were evaporated, and the resulting residue was partitioned between ethyl acetate/10% H_3PO_4 (20 mL/10 mL). The organic layer was washed with 10% H_3PO_4 (2×10 mL) and then saturated $NaHCO_3$ (3×10 mL) and dried. Filtration and evaporation afforded a residue which was chromatographed on silica gel on a Chromatotron, eluting with a suitable mixture of isooctane/ethyl acetate. The product was then crystallized from ethyl acetate/isooctane.

***N*-(Ethoxycarbonyl)-L-alanine isoxazolidide (2e)**: 65% yield; mp 95–96 °C; ^1H NMR δ 1.24 (t, 3 H, J = 7.1 Hz), 1.37 (d, 3 H, J = 7.0 Hz), 2.35 (quin, 2 H, J = 7 Hz), 3.55 (m, 1 H), 4.00 (m, 5 H, 15 lines), 4.73 (quin, 1 H), 5.6 (br d, 1 H); $[\alpha]^{23}_D$ −36.0° (c 0.3, CH_3OH). Anal. Calcd for $C_9H_{16}N_2O_4$: C, 50.0; H, 7.5; N, 12.9. Found: C, 50.2; H, 7.6; N, 12.8.

***N*-(Ethoxycarbonyl)-L-alanine tetrahydro-2*H*-1,2-oxazinide (2f)** was prepared as outlined above for **2e** from **1a** (2.15 g, 13.3 mmol) and tetrahydro-2*H*-1,2-oxazine hydrochloride[23] (1.65 g, 13.3 mmol). The product was isolated as a clear, colorless oil: 1.90 g, 62% yield: ^1H NMR δ 1.25 (t, 3 H, J = 7.1 Hz), 1.32 (d, 3 H, J = 6.9 Hz), 1.76 (m, 4 H), 3.45 (m, 2 H), 4.06 (m, 4 H), 4.78 (pseudo-quin, 1 H, J = 7.6 Hz), 5.50 (br d, 1 H, J = 7.6 Hz). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.9; N, 12.2. Found: C, 52.1; H, 8.0; N, 12.1.

***N*-(*tert*-Butoxycarbonyl)-L-alanine isoxazolidide (2g)**: 70% yield; mp 38–40 °C; ^1H NMR δ 1.35 (d, 3 H, J = 6.9 Hz), 1.44 (s, 9 H), 2.34 (quin, 2 H, J = 6.9 Hz), 3.55 (br m, 1 H), 4.0 (m, 3 H, 14 lines), 4.69 (br quin, 1 H), 5.30 (br d, 1 H); $[\alpha]^{23}_D$ −30.0° (c 1.3, CH_3OH). Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.1; H, 8.2; N, 11.5. Found: C, 54.1; H, 8.1; N, 11.4.

***N*-(Ethoxycarbonyl)-L-phenylalanine isoxazolidide (2i)**: 91% yield; mp 73–74 °C; $[\alpha]^{23}_D$ +38.4 (c 1.1, CH_3OH); ^1H NMR δ 1.20 (t, 3 H, J = 7.1 Hz), 2.25 (m, 2 H), 2.97 (dd, 1 H, J = 6.7, 13.4 Hz), 3.09 (dd, 1 H, J = 6.4, 13.4 Hz), 3.55 (m, 1 H), 3.71 (m, 1 H), 3.86 (m, 2 H), 4.07 (q, 2 H, J = 7.1 Hz), 5.01 (br m, 1 H), 5.29 (br d, 1 H), 7.2 (m, 5 H). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.6; H, 6.9; N, 9.6. Found: C, 61.8; H, 7.0; N, 9.7.

***N*-(Ethoxycarbonyl)-L-methionine isoxazolidide (2j)**: 80% yield; mp 63–64 °C; $[\alpha]^{23}_D$ −38.8° (c 1.8, CH_3OH); ^1H NMR δ 1.24 (t, 3 H, J = 7.1 Hz), 1.90 (m, 1 H, 7 line°, 2.10 (s, 3 H), 2.12 (m, 1 H, 7 lines), 2.35 (m, 2 H, 5 lines), 2.57 (t, 2 H, J = 7.8 Hz), 3.53 (br m, 1 H), 3.94 (m, 2 H, 8 lines), 4.09 (m, 1 H), 4.10 (q, 2 H, J = 7.1 Hz), 4.83 (br m, 1 H), 5.46 (d, 1 H). Anal. Calcd for $C_{11}H_{20}N_2O_4S$: C, 47.8; H, 7.3; N, 10.1. Found: C, 48.0; H, 7.1; N, 10.0.

***N*-(Phenylsulfonyl)-L-alanine Isoxazolidide (2h).** To **2g** (2.05 g, 8.4 mmol) was added trifluoroacetic acid (6 mL). The resulting solution was stirred at 20 °C for 1 h and then evaporated. The residue was then reevaporated with THF (2 × 10 mL) and treated with solution of phenylsulfonic acid hydrate (1.63 g, 9.2 mmol) in THF (10 mL). Evaporation followed by reevaporation with THF (2 × 10 mL) gave a white residue which was dried, suspended in CH_2Cl_2 (20 mL), and treated with TEA (1.70 g, 17 mmol) and DMAP (0.1 g). The solution was cooled to 0 °C, and treated dropwise with phenylsulfonyl chloride (1.63 g, 9.2 mmol), and then stirred at 20 °C for 16 h. Evaporation afforded a residue which was treated with ether (50 mL) and aqueous HCl (1 M, 20 mL) and stirred for 1 h. The organic layer was washed with 10% H_3PO_4 (1 × 10 mL) and saturated $NaHCO_3$ (3 × 10 mL) and dried. Evaporation and recrystallization from hexane/ethyl acetate yielded **2h**: 0.72 g, 30%; mp 111–113 °C; ^1H NMR δ 1.34 (d, 3 H, J = 7.0 Hz), 2.10 (m, 2 H), 3.26 (m, 2 H, 12 lines), 3.67 (q, 1 H, J = 7.5 Hz), 3.98 (dt, 1 H, J = 7.6, 5.4 Hz), 4.34 (m, 1

H, 6 lines, J = 9.1, 7.0 Hz), 5.6 (br d, 1 H, J = 9.1 Hz), 7.52 (m, 3 H), 7.85 (m, 2 H); $[\alpha]^{23}_D$ −14.4° (c 0.8, CH_3OH). Anal. Calcd for $C_{12}H_{16}N_2O_4S$: C, 50.7; H, 5.7; N, 9.9. Found: C, 50.6; H, 5.7; N, 9.8.

2-(*S*)-[(Ethoxycarbonyl)amino]-3-oxo-4-nonyne (8a). A solution of 1-hexyne (0.21 g, 2.5 mmol) in THF (4 mL) at −78 °C was treated dropwise with 1.63 mL of *n*-BuLi in hexane (1.53 M, 2.5 mmol) over 5 min. The solution was allowed to warm to 20 °C, then added over 1 h via syringe to a solution of **2e** (0.22 g, 1.0 mmol) in THF (3 mL) at 0 °C. The resulting solution was stirred for 2 h at 0 °C and then poured into 10% H_3PO_4/ether (20 mL/40 mL). The aqueous layer was separated and extracted with ether (1 × 20 mL), and the combined ether layers were washed with 10% H_3PO_4 (2 × 10 mL) and saturated NaCl solution (3 × 10 mL) and then dried. Filtration and evaporation afforded a residue which was chromatographed on silica gel on a Chromatotron (2 mm plate), eluting with isooctane/ethyl acetate (4/1). Evaporation of the eluent afforded **8a** as a colorless oil (0.197 g, 88%); $[\alpha]^{23}_D$ − 27.2° (c 1.52, CH_3OH); ^1H NMR identical with that reported above for **8a** synthesized from **6**. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 64.0; H, 8.5; N, 6.2. Found: C, 64.1; H, 8.7; N, 6.2.

2-(Phenylsulfonamido)-3-oxo-4-nonyne (8e). A solution of 1-hexyne (0.21 g, 2.5 mmoles) in THF (5 mL) at −78 °C was treated dropwise with *n*-BuLi in hexane (1.53 M, 2.5 mmol) over 5 min. The solution was allowed to warm to room temperature and then added via syringe to a solution of **2h** (0.28 g, 1.0 mmol) in THF (5 mL) at −10 °C over 30 min. After 30 min the solution was poured into a mixture of ice and 10% H_3PO_4/ether (20 mL/40 mL). The aqueous layer was separated and extracted with ether (1 × 20 mL), the combined ether layers were washed with 10% H_3PO_4 (2 × 10 mL) and then saturated NaCl solution (2 × 10 mL) and dried. Filtration and evaporation afforded a residue which was chromatographed on silica gel (MPLC), eluting with isooctane/EtOAc (3/1) and yielding **8e** as an oil (0.233 g, 80%): ^1H NMR δ 0.92 (t, 3 H, J = 7.2 Hz), 1.46 (d, 3 H, J = 7.3 Hz), 1.5 (m, 4 H), 2.37 (t, 2 H, J = 7.0 Hz), 4.05 (m, 1 H, 5 lines), 5.52 (d, 1 H), 7.50 (m, 3 H), 7.85 (m, 2 H); IR 2200 cm^{-1} (s). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.6; H, 6.6; N, 4.7.

Reaction of Lithium (Trimethylsilyl)acetylide (9e) with 2e and Conversion of the Product Mixture to Ynone 8b. Lithium (trimethylsilyl)acetylide (250 mol %) was prepared from (trimethylsilyl)acetylene[30] and *n*-BuLi in hexane at −78 °C, and this was added to **2e** (0.613 g, 3.0 mmol) in THF according to the procedure used to prepare ynone **8a**. The usual isolation afforded a residue (0.69 g, 96% crude) which contained a 10/1 mixture of the trimethylsilyl ynone **8c** and ynone **8b**: ^{1}NMR δ 0.23 (s, 9 H), 1.22 (t, 3 H, J = 7.2 Hz), 1.43 (d, 3 H, J = 7.3 Hz), 4.10 (q, 2 H, J = 7.2 Hz), 4.44 (quin, 1 H), 5.28 (br s, 1 H), 3.36 (s, 0.1 H, C≡CH from **8b**); IR 2160 cm^{-1} (w).

Chromatography on silica gel with ethyl acetate/isooctane, 1/4, gave a 39% yield of **8c** and a 24% yield of **8b**. **8c**. Anal. Calcd for $C_{11}H_{19}NO_3Si$: C, 54.5; H, 7.9; N, 5.8. Found: C, 54.7; H, 8.0; N, 5.8.

A portion of this **8c**/**8b** mixture (0.40 g) was dissolved in methanol (5 mL), treated with SiO_2 (0.5 g) and stirred at 20 °C under N_2 for 16 h. Filtration and evaporation of the filtrate gave a brown syrup which was chromatographed on SiO_2 (Chromatotron, 1 mm plate, eluting with isooctane/ethyl acetate, 5/1) to give **8b** (0.20 g, 71% based on **2d**) as a colorless oil.

General Procedure for the Ynone Reaction with Lithium Acetylide (9c). Lithium acetylide (250 mol %) was generated by the dropwise addition of *n*-BuLi (1.53 M in hexanes) to a THF solution containing excess acetylene which had been bubbled in at −78 °C for 30 min.[25] To assure complete conversion a gentle stream of acetylene was bubbled in for an additional 15 min.

A solution of N-protected amino acid isoxazolidide or *N*-methoxy-*N*-methylamide (100 mol%) in THF (0.1 M) was cooled to −78 °C and then added under N_2 via canula to the above stirred lithium acetylide solution at −78 °C. After the addition was complete, the resulting mixture was allowed to warm to 0 °C over 30 min and then was poured into a vigorously stirred, cold (0 °C) mixture of ether, excess 1 M NaH_2PO_4, and ice. The aqueous layer was separated and extracted once with ether, and the combined ether layers were washed cold with 1 M NaH_2PO_4 (2×) and with saturated NaCl (3×) and then dried. Filtration and evaporation afforded an oil which was immediately chromatographed on silica gel, eluting with isooctane/ethyl acetate. The ynone product was stored in the dark under N_2 at 0 °C.

4-(*S*)-[(*tert*-Butoxycarbonyl)amino]-1-pentyn-3-one (8d) was prepared as described from **2g** in 84% yield: mp 65–66.5 °C after sublimation at 55 °C (0.05 mm Hg); ^1H NMR δ 1.45 (m, 12 H), 3.36 (s, 1 H), 4.42 (br quin, 1 H), 5.12 (br s, 1 H); $[\alpha]^{23}_D$ −22.4° (c 1.2, CH_3OH). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.7; N, 7.1. Found: C, 60.7; H, 7.7; N, 7.5.

4-(*S*)-[(Ethoxycarbonyl)amino]-1-pentyn-3-one (8b): 80% yield; ^1H NMR δ 1.23 (t, 3 H, J = 7.1 Hz), 1.44 (d, 3 H, J = 7.3 Hz), 3.37 (s, 1 H), 4.11 (q, 2 H, J = 7.1 Hz), 4.46 (br quin, 1 H), 5.28 (br s, 1 H); IR 2100 cm^{-1} (s). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.7; H, 6.7; N, 8.3.

4-(Phenylsulfonamido)-1-pentyn-3-one (8f): 73% yield; mp 81–89 °C; ^1H NMR δ 1.47 (d, 3 H, J = 7.3 Hz), 3.39 (s, 1 H), 4.14 (quin, 1 H, J = 7.3 Hz), 5.40 (br d, 1 H, J = 7.0 Hz), 7.51 (m, 3 H), 7.84 (m, 2 H). Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7; N, 5.9. Found: C, 55.5; H, 4.6; N, 5.9.

4-(*S*)-[(Ethoxycarbonyl)amino]-5-phenyl-1-pentyn-3-one (8g): 88% yield; $[\alpha]^{23}_D$ 4.3° (c 2.0, CH_3OH); IR 2130 cm^{-1} (s); ^1H NMR δ 1.23 (t, 3 H, J = 7.1 Hz), 3.26 (m, 2 H, 7 lines), 3.45 (s, 1 H), 4.12 (q, 2 H, J = 7.11 Hz), 4.76 (m, 1 H, 4 lines), 5.12 (br d, 1 H), 7.25 (m, 5 H). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.4; H, 6.2; N, 5.6.

4-(*S*)-[(Ethoxycarbonyl)amino]-6-(methylthio)-1-hexyn-3-one (8h): 87% yield; $[\alpha]^{23}_D$ −15.2° (c 1.8, CH_3OH); IR 2130 cm^{-1} (s); ^1H NMR δ 1.26 (t, 3 H, J = 7.1 Hz), 2.02 (m, 1 H, 6–7 lines), 2.11 (s, 3 H), 2.34 (m, 1 H), 2.57 (t, 2 H, J = 7.2 Hz), 3.43 (s, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 4.60 (m, 1 H), 5.37 (br d, 1 H). Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.4; H, 6.6; N, 6.1. Found: C, 52.5; H, 6.6; N, 6.3.

Preparation of Isoxazolidine Hydrochloride. The following is a modification of the procedure of King.[23] To a solution of KOH (26.71 g, 0.48 mol) and hydroxyurethane (50.0 g, 0.48 mol) in ethanol (210 mL, commercial absolute) was added 1,3-dibromopropane (24.0 mL, 0.23 mol). The resulting suspension was heated at reflux for 1 h. After the mixture had cooled, an additional portion of KOH (13.35 g, 0.24 mol) and of dibromopropane (12.0 mL, 0.12 mol) was added. This mixture was then refluxed for 1 h, cooled to 20 °C, and evaporated. The residue was suspended in boiling ether and filtered. The white salts were digested a second time in hot ether and filtered. The combined filtrates were dried over sodium sulfate, filtered, and evaporated, and the residue was fractionally distilled. The main fraction (bp 107–111 °C, 10 mmHg) gave 43.14 g (85% based on 1,3-dibromopropane) of *N*-(ethoxycarbonyl)isoxazolidine: ^1H NMR δ 1.30 (t, 3 H, J = 7.0 Hz), 2.26 (quin, 2 H, J = 6.8 Hz), 3.65 (dd, 2 H, J = 6.8, 7.2 Hz), 3.92 (t, 2 H, J = 7.0 Hz), 4.20 (q, 2 H, J = 7.0 Hz).

A portion of of this *N*-(ethoxycarbonyl)isoxazolidine (17.48 g, 0.12 mol) was dissolved in aqueous HCl (5.2 M, 93 mL, 0.48 mol) and heated at reflux for 2 h. After being cooled to 20 °C, this solution was washed with ether (3×40 mL) and then evaporated affording crude isoxazolidine hydrochloride which was recrystallized from ethanol/ether yielding 6.25 g (47%, mp 123–125 °C, lit.[23] mp 124–125 °C): ^1H NMR (Me_2SO-d_6) δ 2.40 (quin, 2 H, J = 7 Hz), 3.49 (t, 2 H, J = 7.0 Hz), 4.19 (t, 2 H, J = 7.0 Hz), 4.40 (br s, 2 H).

General Procedure for the Determination of Optical Purity of α,β-Ynones 8. The ketone was dissolved in acetone (10 mL/mmol) at 0 °C and then treated dropwise with an aqueous solution of $KMnO_4$ (300 mol%) in 15 mL of 1 M phosphate buffer, pH 6.0. The dark mixture was stirred at 20 °C for 20 h and then filtered through a Celite pad which was subsequently washed with aqueous NaOH (1 M). The combined filtrate and washes were washed once with ether, acidified with 20% H_2SO_4, saturated with NaCl, and extracted with CH_2Cl_2 (3×), and the extracts were dried. Filtration and removal of solvent by rotary evaporator gave the amino acid **1a** or **1c** which was dried overnight prior to coupling.

The ethoxycarbonyl-protected amino acid **1a** was coupled to **13**[26] with use of the procedure described above for the preparation of amino acid isoxazolidides. The crude amides were taken up in ether and analyzed by HPLC, eluting with Et_2O/isooctane, 1/1.

The phenylsulfonyl-protected amino acid **1c** was converted to its acid chloride by the procedure described above for the prep-

aration of 3. The solvents were evaporated and the acid chloride resuspended in dry THF. To this was added 300 mol % of (+)-α-(phenylethyl)amine in dry THF, and the solution was stirred at 0° for 2 h. Isolation as described above for the amino acid isoxazolidides gave the crude amides which were taken up in EtOAc and analyzed by HPLC, eluting with EtOAc/hexanes, 35/65.

Acknowledgment. We thank Gregory A. Anderson for his assistance in the preparation of several of the starting materials used in this investigation and Saul Rosenberg for the preparation of **13**. This work was supported in part by NIH Postdoctoral Fellowship 5F32 GM08752 to T.L.C.

Registry No. **1a**, 16639-86-4; **1b**, 15761-38-3; **1c**, 29268-18-6; **1d**, 19887-32-2; **1e**, 5700-77-6; **2a**, 79821-79-7; **2b**, 97973-80-3; **2c**, 97973-81-4; **2d**, 89312-80-1; **2e**, 97973-82-5; **2f**, 97973-83-6; **2g**, 97973-84-7; **2h**, 97973-85-8; **2i**, 97973-86-9; **2j**, 97973-87-0; **3**, 3844-94-8; **4**, 97973-88-1; **5a**, 97973-89-2; **5b**, 97973-90-5; **6**, 97973-91-6; **7**, 97973-79-0; **8a**, 97973-92-7; **8b**, 97973-93-8; **8c**, 97973-94-9; **8d**, 97973-95-0; **8e**, 97973-96-1; **8f**, 97973-97-2; **8g**, 97973-98-3; **8h**, 97973-99-4; **9a**, 17689-03-1; **9b**, 1119-64-8; **9c**, 33589-44-5; **9d**, 1111-64-4; **9e**, 54655-07-1; **10**, 97974-00-0; L-alanine, 56-41-7; L-phenylalanine, 63-91-2; L-methionine, 63-68-3; L-proline, 147-85-3; phenylsulfonyl chloride, 98-09-9; ethyl chloroformate, 541-41-3; pyrrolidine, 123-75-1; 1-hexyne, 693-02-7; 3,5-dimethylpyrazole, 67-51-6; 2-mercaptopyridine, 2637-34-5; dimethylhydroxylamine hydrochloride, 16645-06-0; isoxazolidine hydrochloride, 39657-45-9; tetrahydro-2*H*-1,2-oxazine hydrochloride, 54722-74-6; phenylsulfonic acid, 98-11-3; (trimethylsilyl)acetylene, 1066-54-2; 1,3-dibromopropane, 109-64-8; hydroxyurethane, 589-41-3; *N*-(ethoxycarbonyl)isoxazolidine, 54020-55-2; *N*-(phenylsulfonyl)-L-proline, 88425-46-1.

Intramolecular Michael Reactions. Addition to the α-Carbon of Ynamides

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Received January 29, 1985

A number of substituted cinnamamides were synthesized to determine the feasibility of preparing 4-arylnipecotate derivatives via an intramolecular Michael reaction. With these substrates, β-elimination of the cinnamamide residue was the dominant reaction. 3-Phenylpropynamide substrates, however, underwent an unusual "anti-Michael" addition to the α-carbon of the acetylene to produce pyrrolidinones, whose structures were confirmed by independent synthesis.

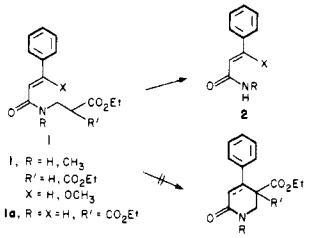
For some time we have been interested in the synthesis of 4-arylpiperidines as precursors to a variety of natural products.[1] As a route to such compounds, we envisioned employing an intramolecular Michael reaction of a suitably functionalized cinnamamide in a convergent synthesis of the piperidine ring.

Results and Discussion

A variety of cinnamamide substrates of the general structure **1** were subjected to ring-closure conditions (NaOEt/EtOH, LDA/THF, *t*-BuOK/DMF or Me_2SO). In all cases only elimination of acrylate occurred providing cinnamamides **2**. Even when the basicity of the enolate was less than that of the cinnamamide anion, as in compound **1a**, elimination was the only reaction observed (Scheme I).

If elimination could not be suppressed relative to ring closure then perhaps a more active Michael acceptor would increase the rate of addition relative to that of elimination. The doubly activated α-cyanocinnamamide residue was examined first. α-Cyanocinnamamide **3** was prepared from α-cyanocinnamoyl chloride[2] and subjected to a variety of ring-closure conditions (Scheme II). No piperidone or elimination products were observed, with only unidentified polar products predominating. It is possible that 1,2-addition to the nitrile was occurring since reaction of α-methoxy carbonyl derivative **4**, in which the amide carbonyl is not present, results in Dieckmann cyclization product **5** rather than Michael condensation.[3]

Scheme I. Attempted Ring Closure of Cinnamamides



Scheme II

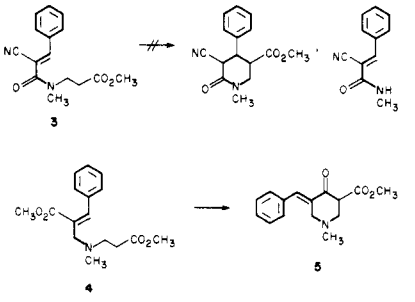


Table I. Effect of the Nitrogen Substituent on the Ratio of Ring Closure to Elimination for Acetylenic Amido Esters

substrate	R	9[a]	11[a]
6a	CH_3	48	39
6b	$CH(C_6H_5)_2$	31	52
6c	$C(CH_3)_3$	89	5

[a] Isolated yield after chromatography.

These results were encouraging in that they proved that reaction, albeit not the desired reaction, is possible without elimination of methyl acrylate provided a sufficiently reactive electrophilic center is present. An acetylenic Mi-

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(2) Dietz, G.; Fielder, W.; Faust, G. *Chem. Ber.* **1969**, *102*, 522.

(3) Experiment performed by M. Peled, this laboratory.

0022-3263/85/1950-3979$01.50/0