

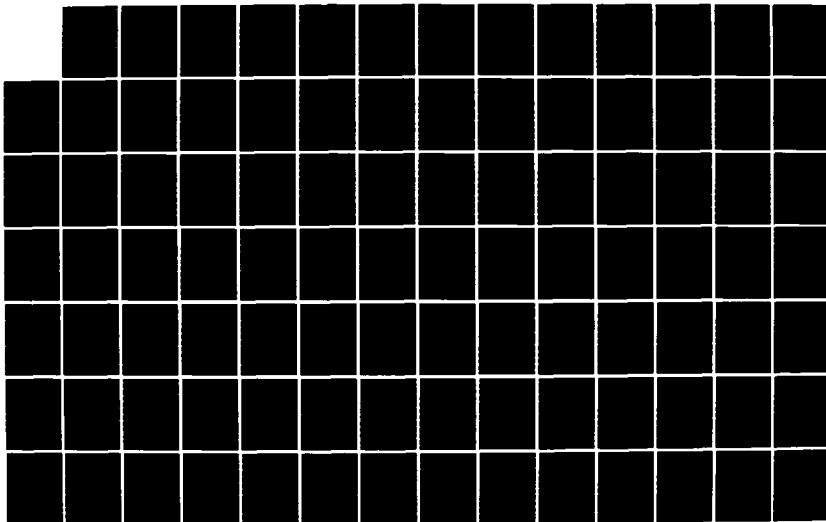
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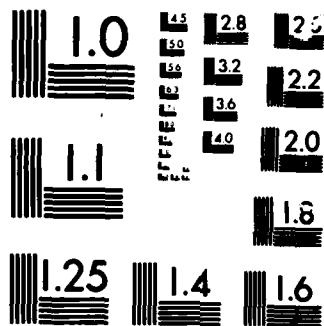
THE USE OF NITRONE CYCLOADDITIONS IN THE SYNTHESIS OF
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FORCE INST OF TECH WRIGHT-PATTERSON AFB OH S W LANDER
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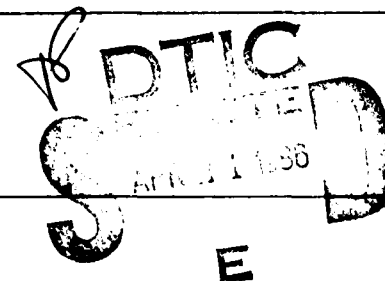
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The Pennsylvania State University

The Graduate School

Department of Chemistry

The Use of Nitrene Cycloadditions in the
Synthesis of β -Amino Aldehydes and
Unsaturated Amines

A Thesis in

Chemistry

by

Stephen W. Lander, Jr.

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

May 1986

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ABSTRACT

Some general parameters have been established for nitronc cycloadditions to 2-substituted vinylsilanes. Nitrones and vinylsilanes react to give isoxazolidines with the TMS group at either the C-5 or C-4 position. While 5-TMS isoxazolidines have been fragmented to α, β -unsaturated aldehydes, these isoxazolidines may also be converted into β -amido aldehydes. β -Amido aldehydes were then elaborated into β -amino acids and β -lactams.

However, 4-TMS isoxazolidines, which are the predominant regioisomers from the cycloaddition, have been converted to allylic amines via a Peterson elimination methodology with stereospecific control of the double bond geometry. These allylic amines were subsequently converted stereoselectively into γ -lactams via a Cu(I) mediated cyclization.

Nitrones and allyltrimethylsilane produced 5-(trimethylsilylmethyl)isoxazolidines exclusively. Using Peterson elimination methodology, these isoxazolidines were subsequently converted into homoallylic amines.

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LIST OF ABBREVIATIONS

DIBAL	diisobutylaluminum hydride
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
THF	tetrahydrofuran
Ac ₂ O	acetic anhydride
pyr	pyridine
M ⁺	molecular ion
Ts	p-toluenesulfonic
Bn	benzyl
Bz	benzoyl
Ac	acetyl
DMAP	4-dimethylaminopyridine
EtOAc	ethyl acetate
PDC	pyridinium dichromate
DMF	dimethylformamide
MeOH	methanol
EtOH	ethanol
Et ₂ O	diethyl ether
TMS	trimethylsilyl
ORTEP	Oak Ridge Thermal Elipsoid Program
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital

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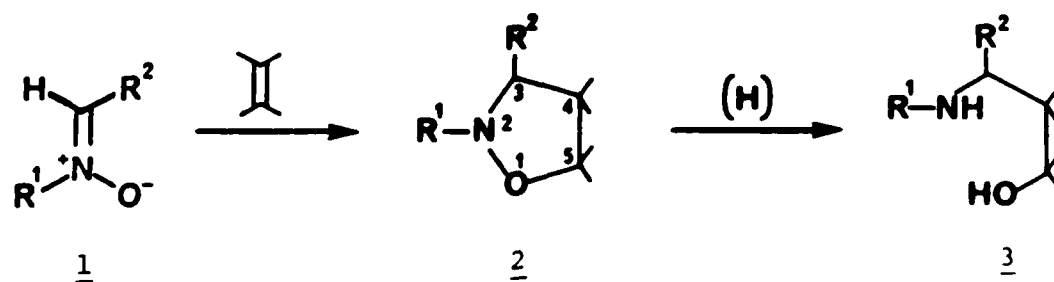
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To Dr. Philip DeShong, I extend my most sincere gratitude for creating an ideal atmosphere for learning. More than a preceptor, his professionalism and friendship will be forever appreciated.

INTRODUCTION

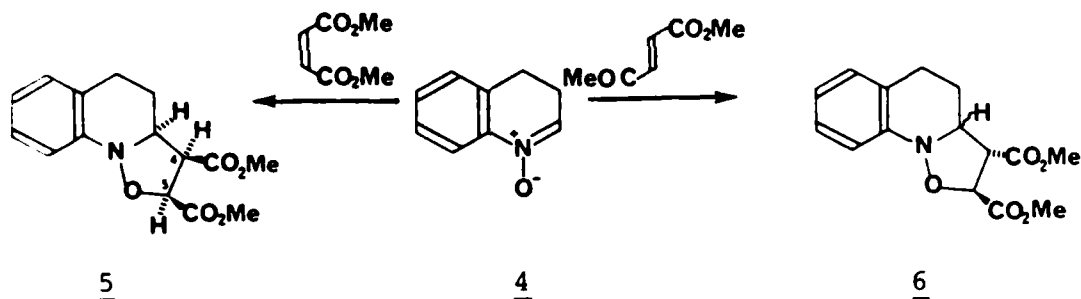
Nitrones (1) are 1,3-dipolar species having 4 π electrons distributed over a skeletal arrangement consisting of three atoms. Nitrones undergo [3+2] cycloadditions with alkenes (dipolarophiles) to produce isoxazolidines (2) in a fashion similar to the [4+2] Diels-Alder reaction.¹ The cycloaddition results in formation of a carbon-carbon bond and introduction of a nitrogen and an oxygen atom which can be converted in subsequent transformations to amine and alcohol functionalities (*i.e.* 3). Because nitrone cycloadditions occur with high regioselectivity the respective sites of introduction can be controlled. Also, the cycloadducts from nitrones retain the stereochemistry of the starting dipolarophile because the cycloaddition occurs in an suprafacial manner. Thus, the stereochemistry of the substituents about the periphery of the isoxazolidine ring can be established.

Scheme 1



Mechanistic studies established that the nitronc cycloaddition was a concerted process in which both electron-rich and electron-deficient alkenes could function as the dipolarophile.² For example, it was demonstrated that dimethyl maleate underwent cycloaddition with cyclic nitronc 4 to give a single isoxazolidine 5 with a syn-C-4,C-5 relationship. On the other hand, dimethyl fumarate yielded a diastereomeric pair of anti-isoxazolidines 6.³ The preservation of dipolarophile geometry observed in these examples was strong evidence for a concerted process.

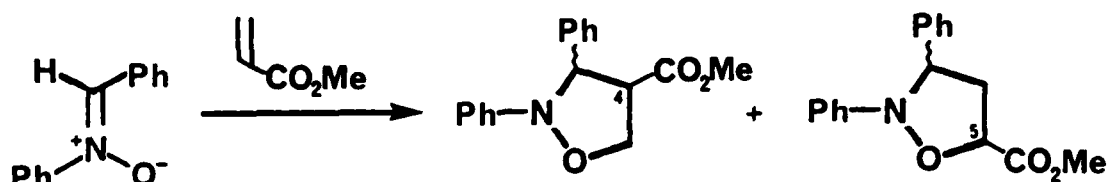
Scheme 2



Nitronc cycloadditions with unsymmetrical dipolarophiles typically display both high regioselectivity and stereoselectivity. With an unsymmetrical dipolarophile, there is the potential to create mixtures of regioisomeric isoxazolidines. For example, C,N-diphenyl-nitronc reacted with methyl acrylate (Scheme 3) to produce a 7:3 mixture of isoxazolidines in which the 5-isomer predominated.⁴ From the results of numerous investigations it has been

established that nitrones react with monosubstituted alkenes to produce the 5-regioisomer preferentially, irrespective of whether the substituent on the alkene is electron-withdrawing or electron-donating.³ Only with nitroethylene, vinyl sulfones and vinyl phosphonates are 4-substituted isoxazolidines formed as the major products in nitrone cycloadditions.⁵

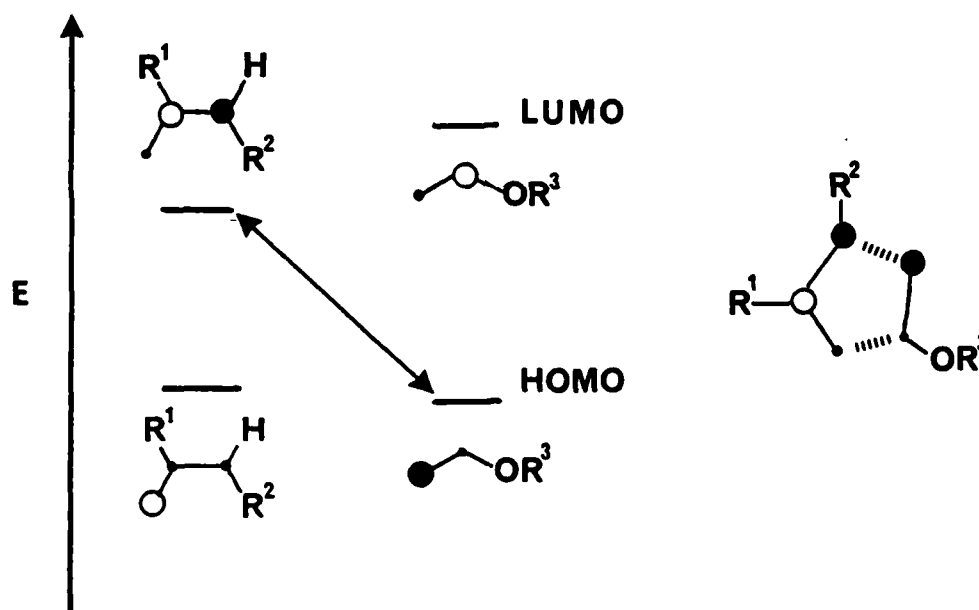
Scheme 3



Frontier molecular orbital (FMO) calculations offer a theoretical explanation for these experimental results.⁶ As qualitatively indicated in Scheme 4 for an electron-rich alkene, the more favorable FMO orbital interaction (smallest energy difference) is between the HOMO of the alkene and the LUMO of the nitrone. The regiochemical outcome of the cycloaddition is determined by the interaction of orbitals on the LUMO and HOMO with the largest coefficients. As shown in Scheme 4, the nitrone carbon, with a large coefficient, bonds preferentially to the unsubstituted carbon of the alkene, resulting in formation of the 5-substituted isoxazolidine regioisomer. With electron-deficient alkenes, the energy of both the

HOMO and LUMO of the alkene are decreased, making the more favorable FMO interaction between the alkene LUMO and nitron HOMO. Orbital coefficients then predict formation of the regioisomeric isoxazolidine. For alkenes bearing substituents which are only weakly directing, the isomer in which the substituent is attached at C-5 is the major product observed; however, the cross-over point depends on subtle changes in the respective nitron or alkene orbital levels.

Scheme 4

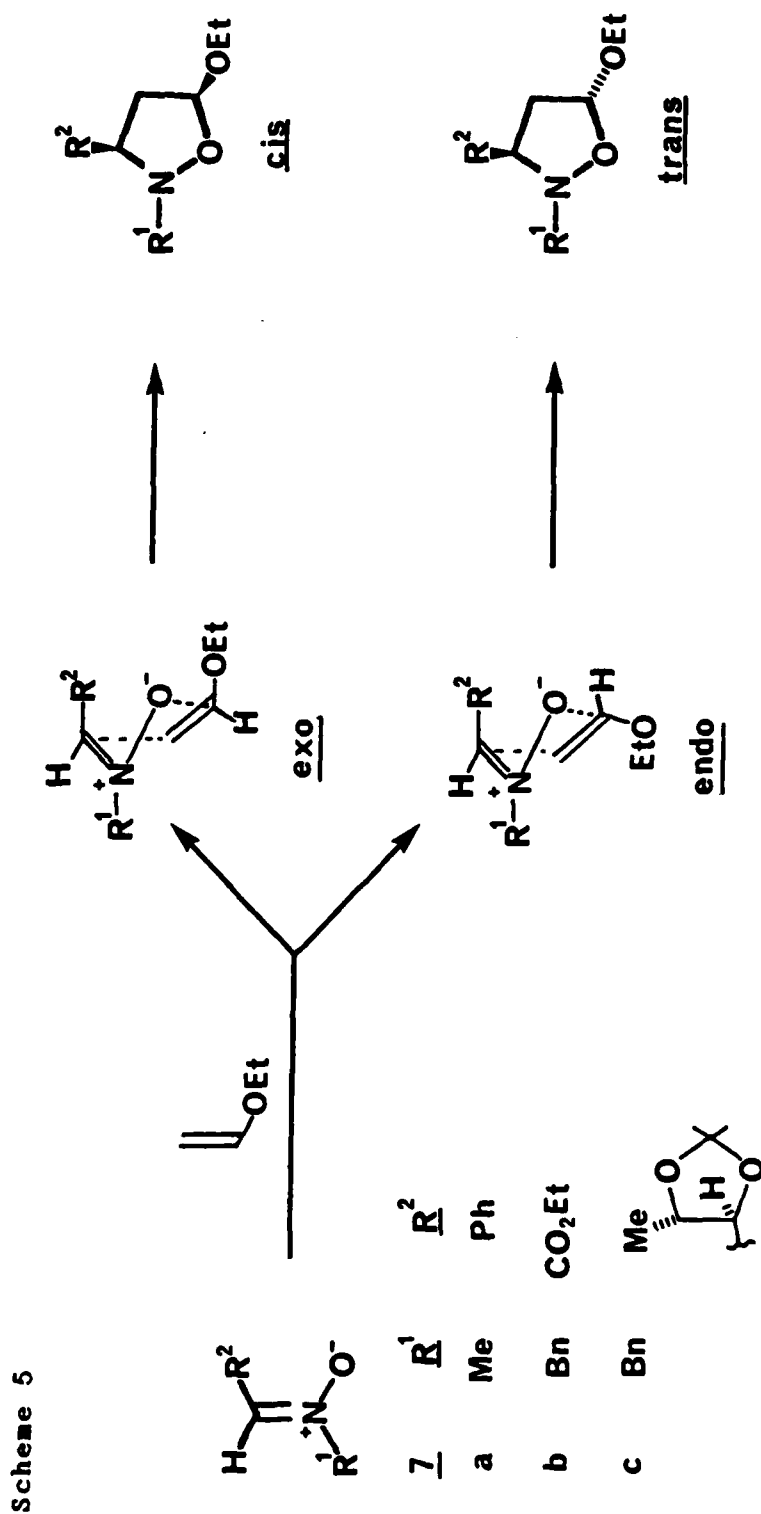


Nitron cycloadditions with unsymmetrical 1,2-disubstituted alkenes also exhibit predictable regioselectivity. As observed experimentally, the respective FMO coefficients of the LUMO and HOMO favor cycloaddition to give an isoxazolidine with the electron-donating substituent at C-5. For example, nitron

cycloadditions with cinnamate esters and β -nitrostyrene produced isoxazolidines where the electron-donating phenyl group occupied the C-5 position exclusively.⁷ If the dipolarophile does not contain a potent directing substituent, there is a loss of regioselectivity in the cycloaddition.

As previously stated, nitron-alkene cycloadditions have the potential to produce stereoisomers. Scheme 5 depicts the reaction of acyclic nitron 7 with ethyl vinyl ether. The nitron is depicted in the thermodynamically more stable Z-geometry, although a few nitrones (i.e., 7b) exist as E,Z-mixtures.⁸

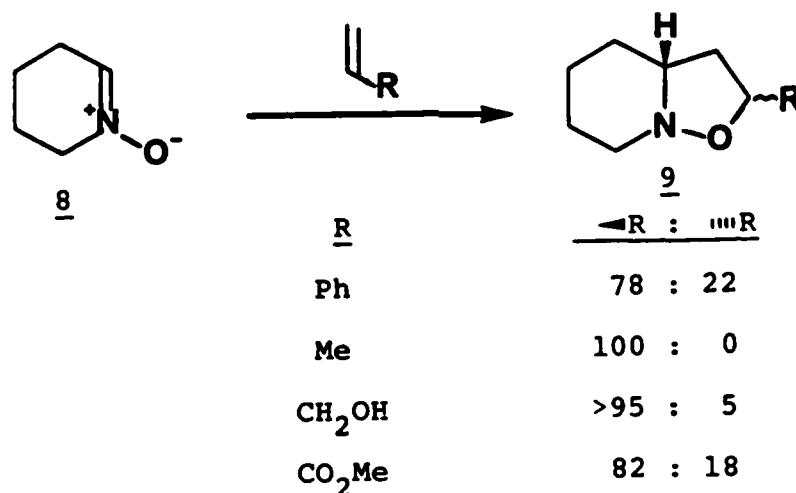
In the transition state of the cycloaddition, the substituent on the dipolarophile could lie under the π system of the nitron (endo) or outside the π cloud of the nitron (exo), resulting in formation of two stereoisomers. Indeed, nitron 7a reacted with ethyl vinyl ether to give a 1:1 mixture of stereoisomers indicating that neither transition state was preferred.⁹ Similarly, the stereoselectivity for nitron 7a in cycloadditions with styrene, methyl acrylate, and cyclohexene was also low.¹⁰ However, both nitrones 7b and 7c underwent cycloaddition with ethyl vinyl ether stereoselectively to produce exclusively the 3,5-trans isoxazolidines.^{9,11} These results suggested that transition state geometry and, thus, cycloaddition stereoselectivity can be controlled by choice of nitron or dipolarophile substituents.



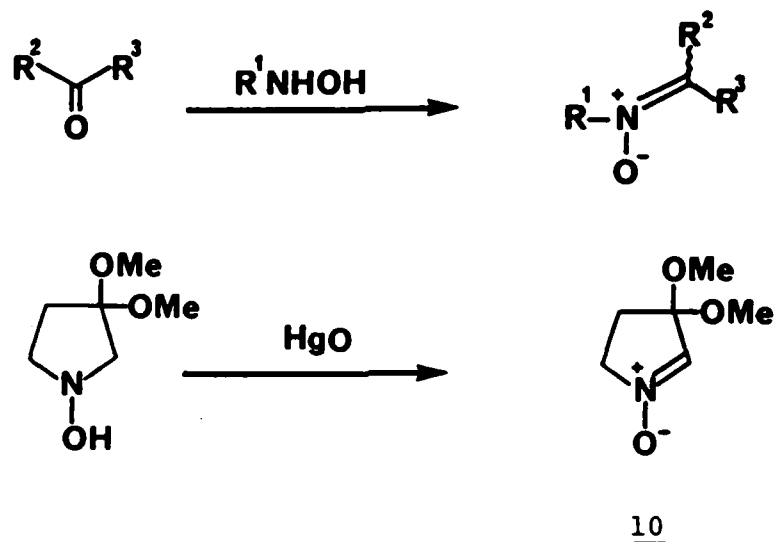
Scheme 5

Tufariello reported that cyclic (E-)nitron 8 underwent cycloaddition with a range of monosubstituted alkenes (see Scheme 6) predominantly through an exo transition state to produce bicyclic isoxazolidine 9.¹⁰ The favored stereoisomer possessed a C-3,C-5 trans stereochemistry.

Scheme 6



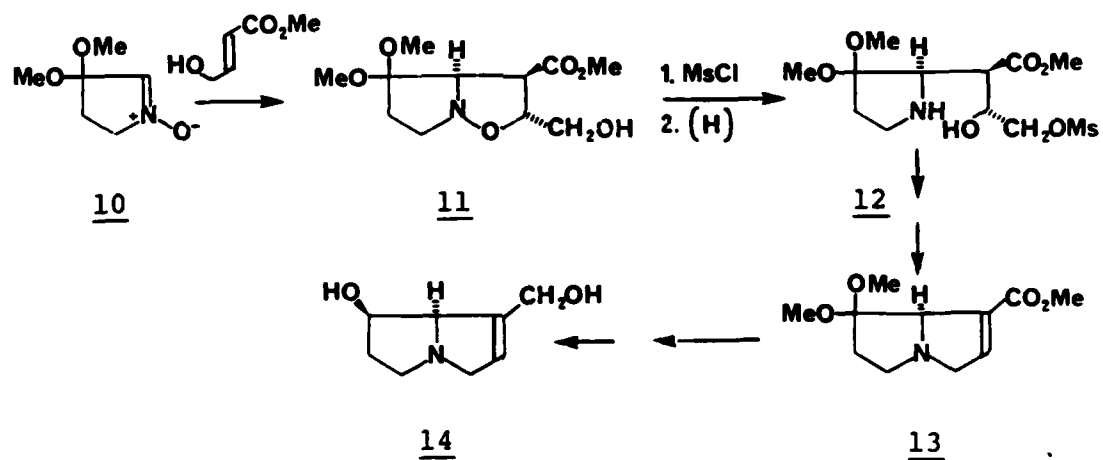
Acyclic nitrones are conveniently synthesized by condensation of an aldehyde or ketone with an N-substituted hydroxylamine (Scheme 7).^{1,12} Alternatively, cyclic N,N-disubstituted hydroxylamines can be oxidized with mercuric (II) oxide to give nitrones (i.e., 10) in good yield, although this reaction is plagued by dimerization of the resulting nitron.^{10,13}

Scheme 7

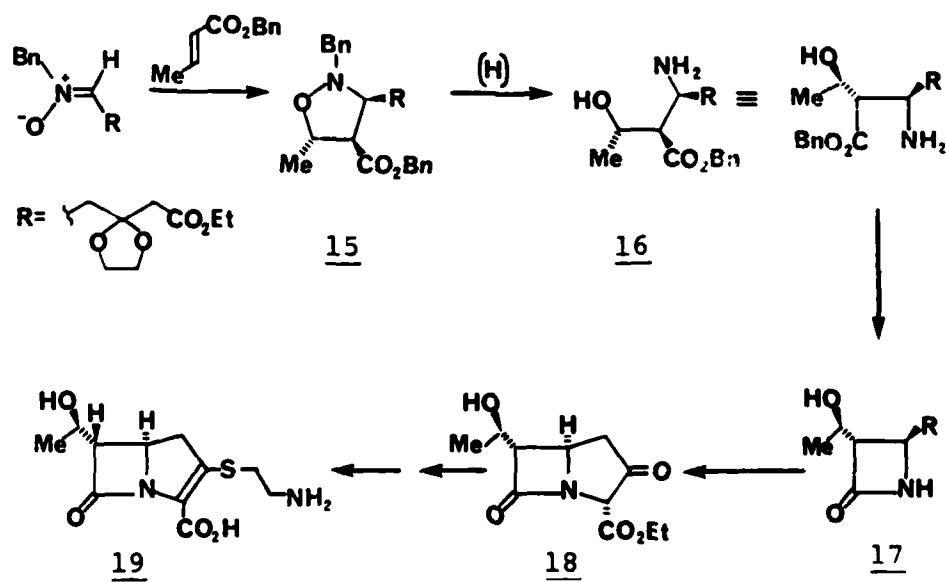
Nitrone cycloaddition strategies have been extensively exploited in the synthesis of natural products. For example, retronecine (14), a pyrrolizidine alkaloid, was synthesized by converting nitron 10 to isoxazolidine 11 (Scheme 8).¹⁰ A single regioisomer was produced in the cycloaddition. Reductive cleavage of the N,O-bond of the corresponding mesylate gave amino alcohol 12 which was cyclized to the pyrrolizidine. Dehydration of the pyrrolizidine gave 13 which was subsequently converted to retronecine.

Thienamycin 19, a member of the carbapenem antibiotics, was recently synthesized employing nitron-alkene cycloaddition reactions.¹⁴ Kametani reported that isoxazolidine 15 was the sole product from the nitron cycloaddition with benzyl crotonate. The cycloaddition sets

Scheme 8



Scheme 9



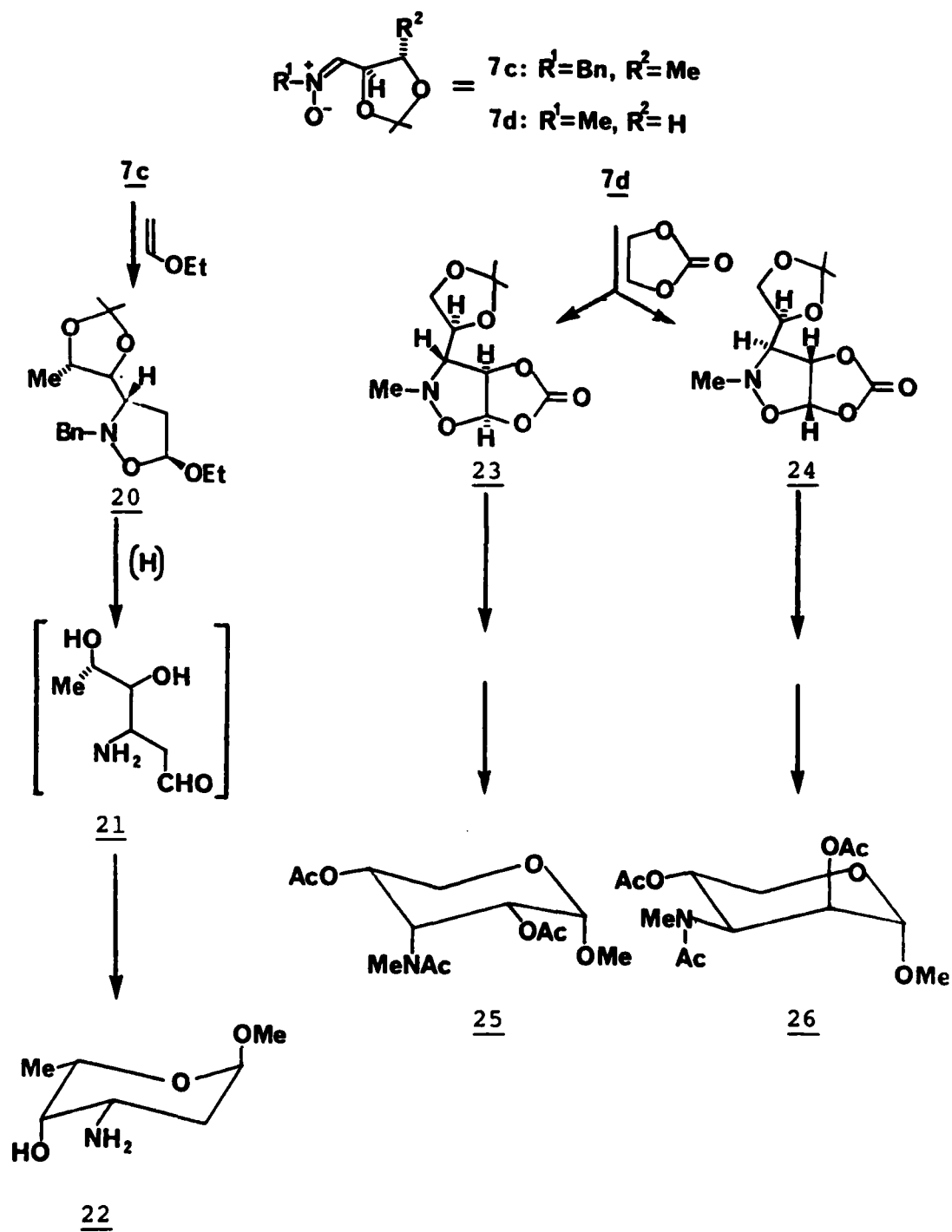
the relative stereochemistry at all of the asymmetric centers in the natural product (Scheme 9). Simultaneous N,O-bond cleavage and debenzylation of 15 gave amino alcohol 16 which was cyclized to β -lactam 17. Subsequently, 17 was converted to thienamycin 19 via ketone 18.

In this laboratory, it was demonstrated that the cycloadducts of nitrones 7c and d (see Scheme 10) with ethyl vinyl ether and vinylene carbonate could be utilized as the basis for short, high yield syntheses of the derivatives of the amino sugars daunosamine (22) and *epi*-gentosamine (25 and 26).¹¹ Nitrone 7c underwent cycloaddition in excess ethyl vinyl ether to give a single isoxazolidine isomer 20. Hydrogenation of 20 in methanolic HCl resulted in reduction of the N,O-bond and removal of the acetonide protecting group to produce the intermediate β -amino aldehyde 21 which cyclized under the acidic conditions to produce the methyl glycosides of daunosamine 22.

With vinylene carbonate nitrone 7d gave two cycloadducts, 23 and 24. Hydrogenation of the individual isoxazolidines under the previous conditions affected N,O-bond cleavage and removal of the carbonate functionality to produce intermediate β -amino aldehydes which were subsequently elaborated into 25 and 26, respectively.

As illustrated above, nitrone cycloaddition utilizing vinyl ester derivatives as the dipolarophile yielded β -amino aldehydes. Traditionally, β -amino aldehydes are

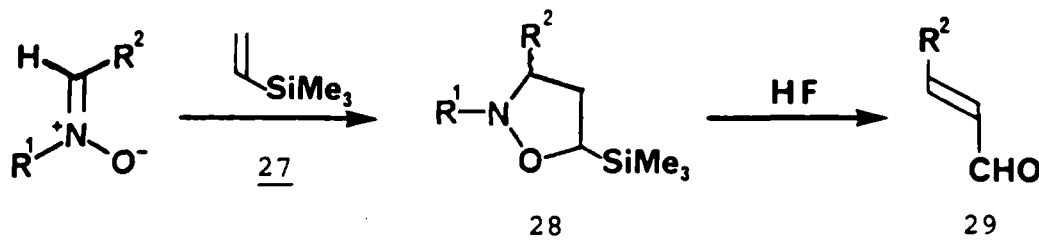
Scheme 10



prepared by the Mannich reaction or one of its modern variants.¹⁵ However, the Mannich reaction is efficient when systems such as 21 are the desired products since under Mannich conditions aldehyde 21 reacts with the starting reagents and produces complex product mixtures. The nitron strategy is clearly advantageous to the Mannich reaction for the preparation of these systems.

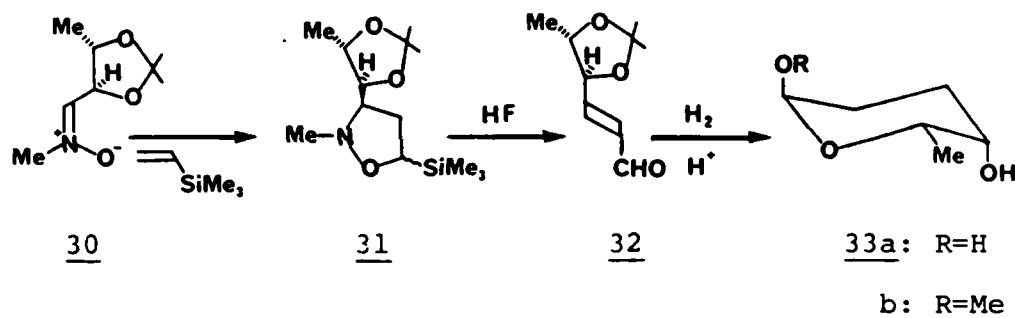
More recent results from DeShong and Leginus have indicated that nitrones undergo cycloaddition with vinyltrimethylsilane 27 with complete regioselectivity to produce 5-trimethylsilylisoxazolidines 28 as a mixture of stereoisomers (Scheme 11).¹⁶ The 5-TMS-isoxazolidine 28 upon treatment with HF was transformed into α,β -unsaturated aldehyde 29. This transformation presumably occurred via a series of steps initiated by fluoride ion attack on silicon to form the β -amino aldehyde, followed by elimination of methylamine. In effect, the overall process served to homologate an aldehyde, the nitron precursor, to an α,β -unsaturated aldehyde with introduction of two carbon atoms.

Scheme 11



This homologation methodology was applied to the synthesis of the rhodinose (33a), the deoxysugar component of the antibiotic streptolydigin.¹⁷ Cycloaddition of nitron 30 with vinyltrimethylsilane proceeded to give isoxazolidine 31, which was fragmented to the α,β -unsaturated aldehyde 32 with dilute HF. Catalytic reduction of the double bond and acetone removal yielded racemic methyl rhodinose 33b as a mixture of anomers in 37% overall yield.

Scheme 12



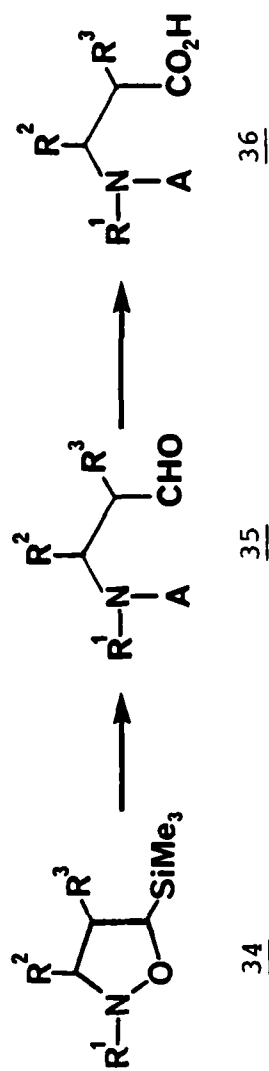
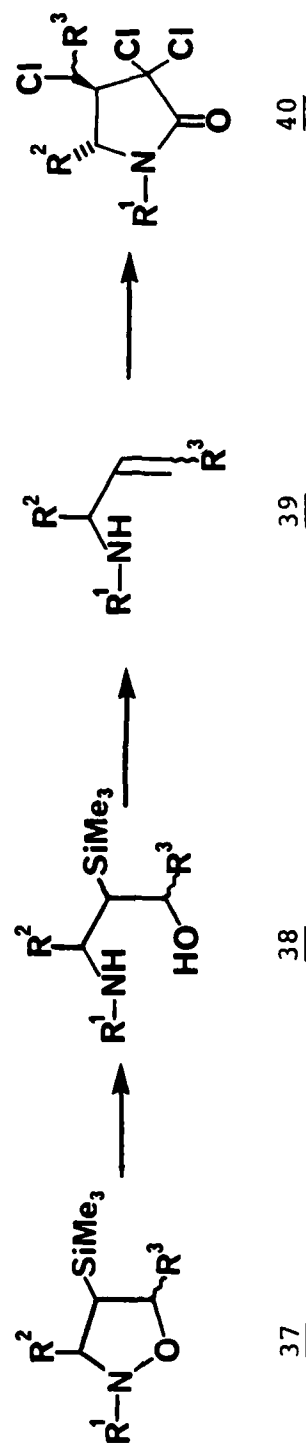
Based upon this report outlining the use of vinylsilanes as dipolarophiles in nitron cycloadditions, further study was initiated to explore the synthetic applicability of this cycloaddition. This thesis describes the study of nitron cycloadditions with 2-substituted vinyltrimethylsilanes and allyltrimethylsilane. The main points of investigation at the outset of this research involved: 1) the reactivity of substituted vinylsilanes and allyltrimethylsilane in nitron cycloadditions, 2) the

regiochemistry of the cycloadditions with these dipolarophiles, and 3) the stereoselectivity displayed in these cycloadditions.

The data will show that unlike vinyltrimethylsilane, 2-substituted vinylsilanes produce isoxazolidines with the TMS-group at either C-5 or C-4, depending upon the directing influence of the other substituent on the alkene. The 5-TMS-isoxazolidines (34) can be fragmented into N-protected- β -amino aldehydes (35, Scheme 13) which retain in that molecule the nitrogen atom from the nitron. These aldehydes were then converted into N-protected- β -amino acids (36).

Isoxazolidines containing the TMS-group at the C-4 position (37) can be transformed into highly substituted allylic amines (39, Scheme 14). The utilization of allylic amines in the preparation of heterocyclic systems such as 40 will be discussed.

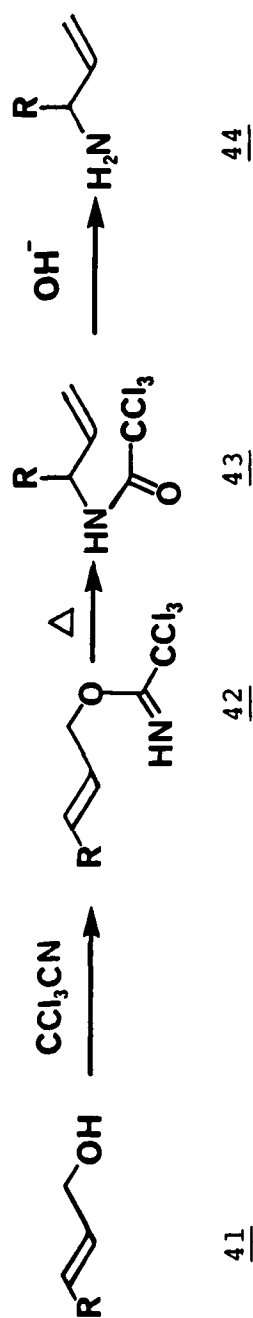
The strategy for synthesis of allylic amines requires, first, reductive cleavage of the N,O-bond of the isoxazolidine to give amino alcohol (38) which is also a 1,2-hydroxysilane. A Peterson elimination of a 1,2-hydroxysilane gives an alkene (i.e., 39).¹⁸ This approach to the synthesis of allylic amines is especially appealing since the geometry of the alkene can be controlled by the choice of reaction conditions for affecting the Peterson elimination. Allylic amines¹⁹ have been prepared previously by the method of Overman, which

Scheme 13Scheme 14

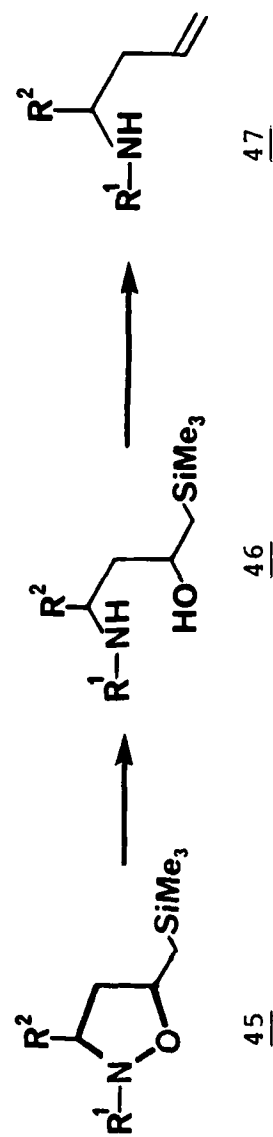
involved the condensation of an allylic alcohol (41, Scheme 15) with trichloroacetonitrile to give a trichloroacetimidate ester (42). Rearrangement of 42 with Hg^{+2} or under thermal conditions produced a trichloroacetamide (43) with a shift of the double bond. Subsequent hydrolysis of 43 gave the allylic amine 44.

Allyltrimethylsilane undergoes nitrene cycloaddition in a fashion similar to other monosubstituted alkenes giving 5-(trimethylsilylmethyl)isoxazolidines (45, Scheme 16). Isoxazolidine 45 is converted to homoallylic amines²⁰ using a strategy similar to the allylic amine synthesis. Reductive cleavage of the N,O-bond of 45 gives amino alcohol 46 which is also a 1,2-hydroxysilane. Peterson elimination of 46 gives homoallylic amine 47.

Scheme 15



Scheme 16



RESULTS AND DISCUSSION

Preparation of Trimethylsilylisoxazolidines.

As described previously (see Scheme 11), a variety of nitrones undergo facile cycloaddition with vinyltrimethylsilane to give exclusively 5-TMS-isoxazolidines. It was a goal of this research to examine the scope of this reaction with 2-substituted vinyltrimethylsilanes and allyltrimethylsilane, determining product regiochemistry and stereochemistry, and tolerance of various functional groups to the reaction conditions. Once these features of the cycloaddition were elucidated, the synthetic utility of these isoxazolidines was to be examined.

Several nitrone-alkene combinations were investigated to identify the synthetic applicability of these cycloadditions and establish trends such that the regiochemical directing ability of the TMS group could be predicted in a generalized nitrone-vinylsilane cycloaddition strategy. The substituted vinyltrimethylsilanes used in this study were prepared by a variety of methods (see Scheme 17). Vinylsilanes 48, 49, and 50 were prepared by DIBAL reduction of the corresponding 1-TMS-acetylene. For example, DIBAL treatment of 1-TMS-2-phenylacetylene in Et₂O followed by acidic protonolysis yielded stereospecifically Z-alkene 49, while DIBAL

Scheme 17

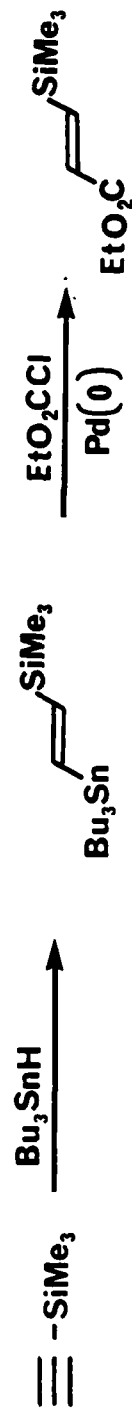


49

48



52



51

reduction in hexane gave E-isomer 48.²¹ REDAL reduction in Et₂O of 3-trimethylsilyl-2-propyn-1-ol cleanly led to E-3-trimethylsilyl-2-propen-1-ol 52.²²

Using the method of Stille, a synthesis of ethyl-3-trimethylsilyl-2(E)-propenoate was developed.²³ When E-1-trimethylsilyl-2-tri-*n*-butylstannyl-ethylene²⁴ and ethyl chloroformate were refluxed in THF containing a catalytic amount of Pd[PPh₃]₄, ester 51 was isolated in 80% yield.

Table I summarized the results obtained in a series of representative nitron-vinylsilane and nitron-allylsilane cycloadditions. From the results, it is clear that the cycloaddition tolerated a variety of functional groups and that the cycloaddition displayed regioselectivity and stereoselectivity. For comparison, data from Leginus's studies is included as entries 1, 11 and 14.²⁵

First, it is evident from Table I (entries 1-11) that the nitron-vinylsilane cycloaddition is tolerant of many functional groups. The nitron can be synthesized from aldehydes substituted with alkyl, aryl, carbethoxy or even the sensitive benzylidene acetal group, and *N*-alkyl or aryl hydroxylamines. Vinylsilanes substituted with either alkyl, aryl, carbethoxy or hydroxymethyl groups underwent cycloaddition with these nitrones in good to excellent yields. These results suggest isoxazolidines could be synthesized with a wide variety of substitution patterns based on the desired application.

Table I. Trimethylsilylloxazolidines.

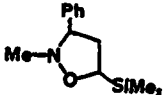
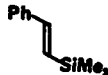
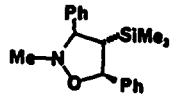
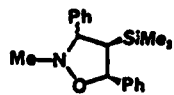
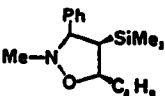
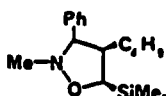
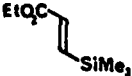
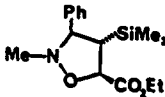
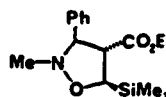
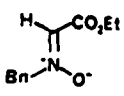
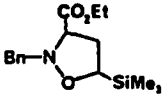
ENTRY	NITRONE	SILANE	ISOXAZOLIDINE ^a	YIELD ^b
1	 <u>7a</u>	 <u>27</u>	 <u>54</u> (1:1)	95
2	<u>7a</u>	 <u>48</u>	 <u>55</u> (6:1)	60
3	<u>7a</u>	 <u>49</u>	 <u>56</u> (12:1)	60
4	<u>7a</u>	 <u>50</u>	 <u>57</u>	75
			 <u>58</u>	
5	<u>7a</u>	 <u>51</u>	 <u>59</u>	70
			 <u>60</u>	
6	 <u>7b</u>	<u>27</u>	 <u>61</u> (3:1)	90

Table I. continued

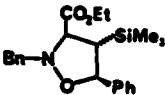
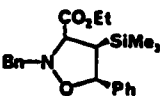
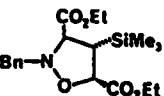
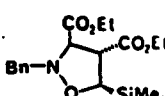
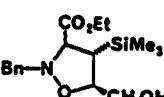
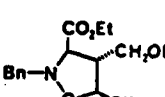
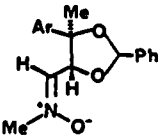
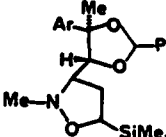
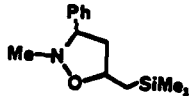
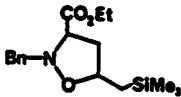
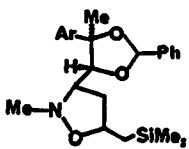
<u>ENTRY</u>	<u>NITRONE</u>	<u>SILANE</u>	<u>ISOXAZOLIDINE</u> ^a	<u>YIELD</u> ^b
7	<u>7b</u>	<u>48</u>	 <u>62</u> (2:1)	70
8	<u>7b</u>	<u>49</u>	 <u>63</u>	65
9	<u>7b</u>	<u>51</u>	 <u>64</u> (2:1)  <u>65</u> (2:1) 1:9 ^c	75
10	<u>7b</u>	<u>52</u>	 <u>66</u> (9:1)  <u>67</u> 9:1 ^c	78
11	 <u>7e</u> 	<u>27</u>	 <u>68</u>	84

Table I. continued

<u>ENTRY</u>	<u>NITRONE</u>	<u>SILANE</u>	<u>ISOXAZOLIDINE</u> ^a	<u>YIELD</u> ^b
12	<u>7a</u>	 <u>53</u>	 <u>69</u> (2:1)	95
13	<u>7b</u>	<u>53</u>	 <u>71</u>	91
14	<u>7e</u>	<u>53</u>		87

^a numbers in parenthesis represent ratios of C-3,C-5 stereoisomers of undetermined stereochemistry

^b percent yield of product mixture after purification by chromatography

^c A mixture of regioisomers. For each regioisomer, if appropriate, a ratio of stereoisomers is given in parenthesis.

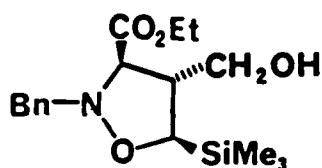
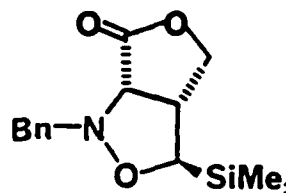
Table I, entries 1, 6, and 11 demonstrate that the TMS group will assume the C-5 position on the isoxazolidine cycloadduct when hydrogens are the other substituents on the parent alkene. This tendency for mono-substituted alkenes to direct C-5 ring substitution was described earlier and explained by a combination of electronic and steric factors.

With 2-substituted vinylsilanes as dipolarophiles, the results demonstrate that it is the substituent at C-2 of the silane and not the TMS group which controls the regiochemistry of the product. Nitronc cycloaddition with alkenes 48 and 49 gave isoxazolidines 55, 56, 62, and 63 with the phenyl group exclusively at the C-5 position. This is the identical regiochemistry obtained from nitronc cycloadditions to styrene,²⁶ β -nitrostyrene and cinnamate esters,⁷ demonstrating that silicon does not alter the strong directing influence of the electron-rich phenyl group.

As the substituent on the vinyltrimethylsilane became less electron-rich, a mixture of regioisomeric isoxazolidines was obtained from the cycloaddition. Mildly electron-rich butyl vinylsilane 50 gave a 7:3 mixture of products with the 5-butylisoxazolidine 57 predominating.

Hydroxymethylvinylsilane 52 showed high regioselectivity giving a 9:1 ratio of regioisomeric isoxazolidines with the 4-TMS isomer predominating. This is a dramatic increase in reactivity over the O-t-butyl-

dimethylsilyl derivative of 52 which failed to react after 24 h in refluxing toluene.²⁷ A trace amount of bicyclic lactone 72 was also isolated from the reaction mixture in addition to adducts 66 and 67. Since the lactone is presumably the 3,4-cis compound, this suggests, but does not prove, that 67 has the 3,4-trans stereochemistry.

6772

Carbethoxyvinylsilane 51 gave a mixture of regioisomeric isoxazolidines with the 5-TMS isomer predominating (Table I, entries 5 and 9). Generally, nitronc cycloadditions to vinyl esters have shown a variety of results since subtle changes greatly influence the orbital picture of the mildly electron-deficient vinyl ester. For instance, with the C,N-diphenyl-nitronc, ethyl acrylate underwent cycloaddition to give the ester functionality exclusively at C-5 of the isoxazolidine.²⁸ However, with no obvious explanation, methyl acrylate reacted with the same nitronc to give a 7:3 ratio of C-5 to C-4 regioisomers.⁴ Crotonate esters add to nitrones to give isoxazolidines with the ester group exclusively at C-4 and the mildly electron-rich methyl group at C-5.²⁹ Thus, vinyl

esters, without the TMS group, do not strongly direct the regiochemistry of isoxazolidines. Rather, the outcome is effected by slight changes in orbitals of both the vinyl ester and nitron.

Table I also summarizes the results obtained in a series of nitron-allylsilane cycloadditions (entries 12, 13, and 14). Allyltrimethylsilane displays total regioselectivity forming 5-(trimethylsilylmethyl)-isoxazolidines in excellent yields. This regioselectivity is characteristic of moderately electron-rich alkenes, as discussed previously.

The regiochemistry of these adducts was determined by ^1H NMR. A single proton multiplet appeared at δ 3.5-4.0 which is a chemical shift characteristic of the C-5 proton in C-5 alkyl isoxazolidines (compare 69 to 57 and 58). Also, the two C-6 protons gave doublet of doublets at δ = 0.9 due to the influence of the α -silicon atom. The other protons on the ring displayed chemical shifts and multiplicities consistent with the structural assignment.

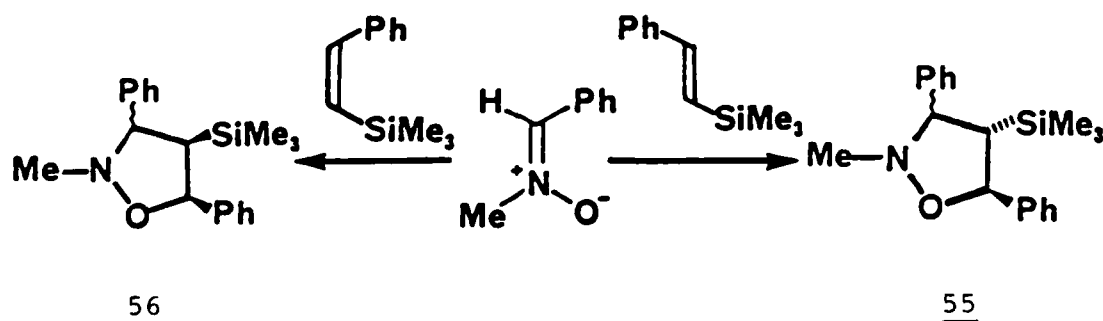
The regiochemical outcome of nitron cycloadditions listed in Table I, entries 1-11, was determined by ^1H NMR. With isoxazolidines 54 and 61 from vinyl trimethylsilane 27, the single C-5 proton was observed at δ 3.6-3.9. Normally a proton on carbon also bonded to oxygen appears at about δ 4.5, but the α -silicon atom causes an upfield shift of almost 1 δ unit. The two C-4 protons in 54 and 61 appeared at δ 2-3.

Isoxazolidines arising from the cycloaddition of 2-substituted vinylsilanes, the regioisomeric pair of adducts could be readily differentiated. For example, 5-TMS-isoxazolidine 58, the C-5 proton doublet appeared at δ 3.9, and C-4 proton multiplet came at δ 2.7. For the 4-TMS-regioisomer 57, the C-5 proton, now a multiplet, appeared at δ 4.3, while a doublet of doublets came at δ 2.1 for the C-4 proton. The chemical shift of the C-5 proton in the other 4-TMS isoxazolidines was dependent upon the influence of the C-5 substituent, but it always appeared at least 0.5 δ units downfield from the C-4 proton signal.

In these cycloadditions, there were also two stereochemical features to consider. First, when a nitron adds to a monosubstituted alkene, two stereoisomeric (3,5-cis or trans) isoxazolidines could be produced. This was exemplified earlier in the discussion of either an exo- or endo-transition state preference during the cycloaddition (see Scheme 5). Mixtures of stereoisomers were formed in most of the cycloadditions shown in Table I. Excellent stereoselectivity was displayed in nitron cycloadditions with Z-alkenes. For example, Z-alkene 49 produced essentially a single stereoisomer in cycloadditions with two different nitrones (Table I, entries 3 and 8). Subsequent transformations of these adducts, however, destroyed the stereochemistry. Therefore, the relative stereochemistry of the stereoisomers was not determined.

The second stereochemical feature of the cycloaddition is more significant for further synthetic considerations. Isoxazolidines derived from cycloadditions of nitrones and 1,2-disubstituted alkenes translated the alkene geometry into the C-4, C-5 substituent relationship. For example, E-alkene 48 yielded a anti C-4,C-5 stereochemistry in 55, while Z-alkene 48 gave an syn relationship between the C-4 and C-5 substituents of isoxazolidine 56. The stereochemistry between C-3 and the fixed C-4,C-5 configurations was not determined since it was destroyed in subsequent transformations. However, the feature that the geometry of the alkene was preserved in 4-TMS-isoxazolidines, was exploited in a stereospecific synthesis of substituted allylic amines (vide infra).

Scheme 18



As previously explained, regioisomeric isoxazolidines have the potential to behave very differently in subsequent transformations. From this point forward, the isoxazolidines listed in Table I will be divided into two classes based on either TMS substitution at C-5, or TMS

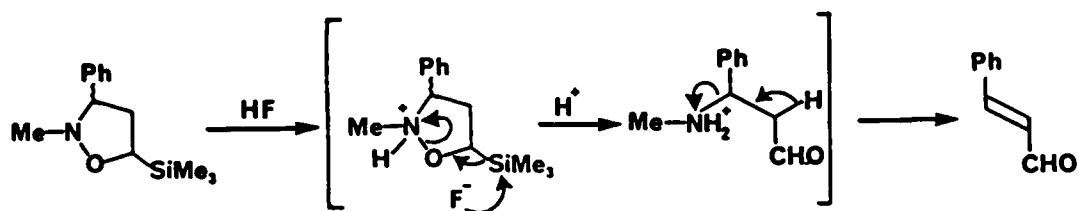
substitution at either C-4 or C-6. This division is appropriate since 5-TMS-isoxazolidines here fragmented into β -amino aldehydes, while unsaturated amines were obtained from 4-TMS-isoxazolidines and 5-(methyltrimethylsilyl) isoxazolidines (see Scheme 13).

Transformation of 5-TMS-Isoxazolidines into N-Protected β -Amino Aldehydes.

As previously discussed, nitrones underwent facile cycloaddition with vinyltrimethylsilane to produce 5-TMS-isoxazolidines. These isoxzaolidines are subsequently transformed to E- α,β -unsaturated aldehydes 28 in good to excellent yields (see Scheme 11).

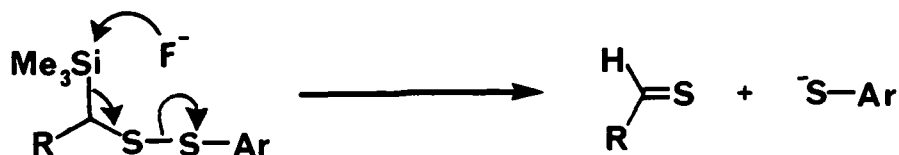
The preceding reaction, which affects a remarkable series of bond fragmentations, was shown to be quite general and occur under several sets of reaction conditions. Aqueous HF in acetonitrile, $\text{Bu}_4\text{N}^+\text{F}^-$ in THF, 20% aqueous HCl or 20% aqueous NaOH smoothly transformed these 5-trimethylsilylisoxazolidines into the corresponding E- α,β -unsaturated aldehydes via the mechanism shown in Scheme 19.

In aqueous HF, 54 underwent protonation on the nitrogen atom. Subsequent attack by fluoride ion on silicon triggered a cascade of bond cleavages, giving the intermediate β -amino aldehyde. Under the acidic conditions, the amine function was eliminated to yield the E- α,β -unsaturated aldehyde.

Scheme 1954

The reaction is a useful method for a two carbon homologation of an aldehyde (a nitron precursor) into an α,β -unsaturated aldehyde. This homologation is affected under extremely mild conditions in which pH sensitive groups like the carbethoxy and benzylidene acetal moieties are tolerated.

In a recent report by Krafft, a similar fluoride triggered reaction was described (Scheme 20).³⁰ In this reaction, fluoride ion attacked the TMS group which was α to a disulfide linkage. Resultant fragmentation of the disulfide bond led to the formation of a thioaldehyde and stable thiophenol anion. This sequence of fragmentations is analogous to the isoxazolidine fragmentation previously described and appears to be a general approach to the preparation of thioaldehydes.

Scheme 20

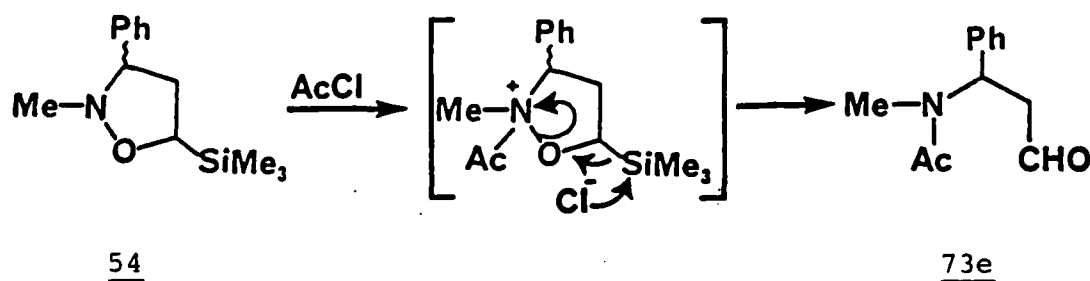
Despite its synthetic efficiency, the fragmentation reaction of 5-TMS-isoxazolidines to yield α,β -unsaturated aldehydes displayed a serious deficiency due to the loss of the amine functionality from the cycloadduct. The loss of the β -amino function negated one of the primary advantages of nitrene cycloadditions. A goal of this research was to develop a repertoire of reagents to trigger N-O bond fragmentation in 5-TMS-isoxazolidines to give β -amino aldehydes and to prevent the subsequent elimination of amine from these molecules. Further transformations could then be selectively performed on the resulting β -amino aldehyde.

The approach which initially proved successful and illustrates the strategy (Scheme 21) involved the use of acetylating agents to trigger N,O-bond fragmentation in the isoxazolidine moiety and to capture the resulting amine prior to elimination. Amides are not basic and are not protonated under the reaction conditions. Thus, they do not readily undergo β -elimination. Indeed, when isoxazolidine

54 was treated with either acetyl chloride in THF, acetic anhydride containing a catalytic amount of H_2SO_4 or acetic anhydride and an equivalent of $\text{Bu}_4\text{N}^+\text{F}^-$, β -amido aldehyde 73e was formed as the sole product in 60% yield. The three different acetylating conditions (acidic, neutral, slightly basic) demonstrated that pH sensitive functional groups could be accommodated.

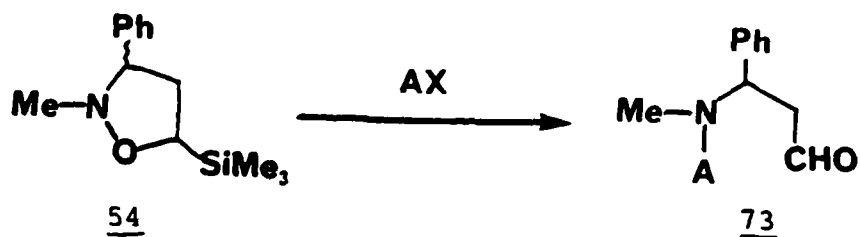
The mechanism shown in Scheme 21 is proposed for this transformation and involves initial electrophilic attack by the acetylating agent on the mildly basic isoxazolidine nitrogen atom. This leads to formation of a quaternary acyl ammonium species, which in turn is attacked at silicon by the counterion to trigger N,O-bond fragmentation, expel the TMS group, and give aldehyde 73e.

Scheme 21



In an attempt to increase the yield of N-protected- β -amino aldehyde obtained, a survey of acylating and sulfonating agents was performed. Isoxazolidine 54 was selected for the survey since it was readily available. As shown by the results in Table II, several reagents were

Table II. 3-[N-Methylamido]-3-Phenylpropanals.

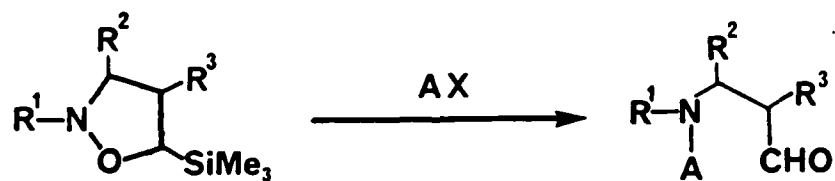


<u>ENTRY</u>	<u>AX</u>	<u>ALDEHYDE 73</u>	<u>YIELD (%)</u>
1	$\text{CCl}_3\text{CH}(\text{Cl})\text{OCOC}\text{Cl}$	a	90
2	$\text{CH}_3\text{CH}(\text{Cl})\text{OCOC}\text{Cl}$	b	90
3	EtOCOCCl	c	70
4	BnOCOCCl	d	68
5	AcCl	e	60
6	$\text{Ac}_2\text{O}/\text{H}^+$		
7	$\text{Ac}_2\text{O}/\text{Bu}_4\text{N}^+\text{F}^-$		
8	$(\text{CCl}_3\text{CO})_2\text{O}$	f	50
9	$\text{TsCl}/\text{pyr}/\text{DMAP}$	g	46

found to induce fragmentation of the isoxazolidine ring to produce the β -amido aldehyde in good to excellent yields. For example, $\text{CCl}_3\text{CH}(\text{Cl})\text{OCOCl}$ (FORCE-Cl) and $\text{CH}_3\text{CH}(\text{Cl})\text{OCOCl}$ (ACE-Cl), two extremely electrophilic acylating agents, initiate β -carbamoyl aldehyde formation in excellent yields. As an amine protecting group, the FORCE moiety is acid stable but can be removed by treatment of the carbamate with $\text{K}_2\text{CO}_3\text{-MeOH}$.³¹ The ACE-Cl reagent was developed by Olofson for the debenzylolation of tertiary amines.³² The ACE-group can be removed by refluxing the carbamate in methanol.

Other electrophilic carbamate-forming reagents (entries 3 and 4, Table II) also work well in the fragmentation sequence. However, attempts at N-sulfonation produced low yields of the β -sulfonamido aldehyde. The sulfonyl group stabilizes a negative charge on nitrogen, making the elimination of sulfonamide to form the unsaturated aldehyde a significant competing reaction.

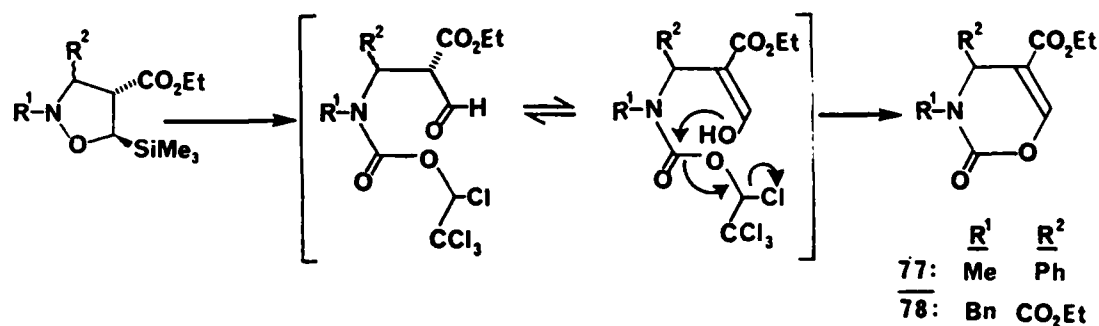
Having ascertained which acylating groups gave the highest yields with isoxazolidine 54, the fragmentation was surveyed with more complex isoxazolidines. As seen by the results summarized in Table III, moderate yields of β -amido aldehydes were obtained. However, treatment of isoxazolidines 60 and 65 (Table III, entries 7 and 8) with FORCE-Cl did not give the expected aldehydes but rather produced heterocyclic compounds 77 and 78 in 50 and 70% yield, respectively (Scheme 22).

Table III. Substituted β -Amido Aldehydes.

<u>ENTRY</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>A</u>	<u>RCHO #</u>	<u>YIELD (%)</u>
1	Me	Ph	C ₄ H ₉	CCl ₃ CH(Cl)OCO	74a	50
2	Me	Ph	C ₄ H ₉	CH ₃ CH(Cl)OCO	74b	40
3	Bn	CO ₂ Et	H	CCl ₃ CH(Cl)OCO	75a	50
4	Bn	CO ₂ Et	H	CH ₃ CH(Cl)OCO	75b	40
5	Bn	CO ₂ Et	H	CH ₃ CO	75c	20
6	Bn	CO ₂ Et	CO ₂ Et	CH ₃ CO	76	70
7	Bn	CO ₂ Et	CO ₂ Et	CCl ₃ CH(Cl)OCO	-	0
8	Me	Ph	CO ₂ Et	CCl ₃ CH(Cl)OCO	-	0

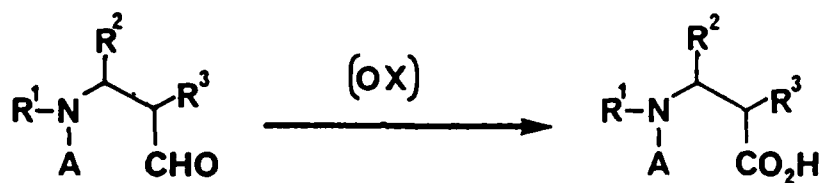
Elevated temperature (refluxing THF) was required for FORCE-Cl to acylate the isoxazolidine nitrogen (see Scheme 22) and trigger N,O-bond fragmentation to give FORCE-aldehyde intermediate. Enolization of the resultant aldehyde followed by attack of the enol on the carbamate with concurrent loss of chloral gave the cyclic enol carbamate.

Scheme 22



The N-protected- β -amino aldehyde derivatives are versatile intermediates for the preparation of β -amino acid derivatives. β -Amino acids are biologically important compounds which can be inserted into protein structures to study enzyme inhibition, and they serve as useful intermediates in the synthesis of β -lactams.³³

Table IV summarizes attempts to oxidize β -amido aldehydes to their respective β -amido acids. The best method (Scheme 23) involved the treatment of the FORCE-protected aldehyde with PDC in DMF to produce the FORCE-protected acid.³⁴ Subsequent removal of the FORCE protecting group gave the β -amino acid 82 which was

Table IV. β -Amido Acids.

ENTRY	R^1	R^2	R^3	A	OX	ACID	YIELD (%)
1	Me	Ph	H	FORCE	PDC ¹	79a	90
2	Me	Ph	H	FORCE	Jones ²		50
3	Me	Ph	H	ACE	PDC	79b	30
4	Me	Ph	H	ACE	Jones		50
5	Me	Ph	H	Ac	Jones	79c	50 ³
6	Me	Ph	C ₄ H ₉	FORCE	PDC	80	68
7	Bn	CO ₂ Et	H	FORCE	PDC	81	50

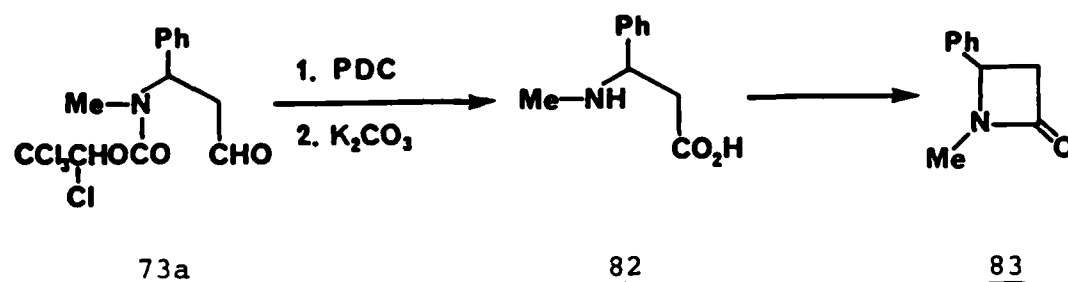
¹ PDC is pyridinium dichromate

² Jones reagent is chromous acid (H₂CrO₄)

³ characterized as the methyl ester.

characterized as the methyl ester. In addition, β -amino acid 82 was cyclized to β -lactam 83, using the phase transfer method of Mukaiyama.³⁵ This routine demonstrates that a nitron strategy can be used to prepare β -amino acids and 4-substituted β -lactams.

Scheme 23



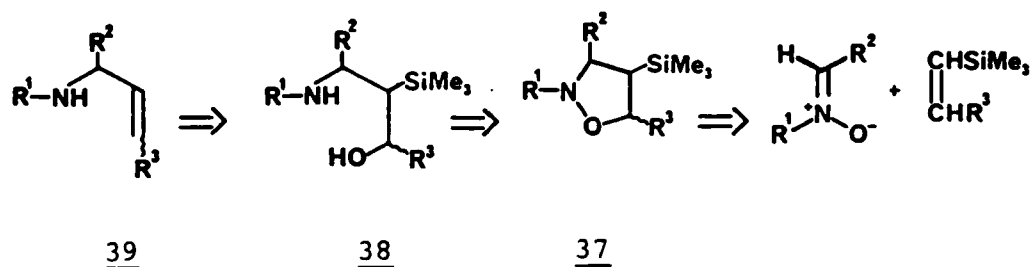
Transformation of 4-Trimethylsilylisoxazolidines into Allylic Amines.

In the previous section, 5-TMS-isoxazolidines were transformed into aldehydes by silicon-induced cleavage of the N,O-bond. However, 4-TMS-isoxazolidines were the predominant products of nitronc cycloadditions with 2-substituted vinyl silanes and these compounds are not susceptible to the fragmentation reaction described in the previous section.

The 4-TMS-isoxazolidines can be transformed into allylic amines, and a retrosynthetic analysis of this process is shown in Scheme 24. Allylic amine 39 could be synthesized from amino hydroxysilane 38 via elimination of the elements of trimethylsilanol. This type of elimination has

been previously documented by Peterson for alkyl 1,2-hydroxysilanes.¹⁸ Furthermore, Peterson reported that the elimination occurred under acidic conditions via an anti-elimination of Me₃SiOH or under basic conditions by syn-elimination. In our scheme, hydroxysilane 38 would be derived from 4-TMS-isoxazolidine 37 by reductive cleavage of the N,O-bond. Since isoxazolidines retain the stereochemistry of the starting dipolarophile and the Peterson elimination allows for control of allylic amine stereochemistry by choice of elimination conditions, the scheme offered flexibility for the stereoselective synthesis of allylic amines.

Scheme 24



As previously mentioned, 4-TMS-isoxazolidines were the predominant product of the cycloaddition of nitrones with 2-substituted vinylsilanes (see Table I). The data shown in Table V indicate that allylic amines can be prepared in excellent yields from 4-TMS-isoxazolidines. For example, isoxazolidine 55 can be transformed into E-allylic amine 84 in 87% yield by treatment with Zn/HCl-THF.³⁶ In this

Table V. Allylic Amines.

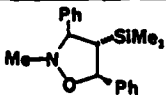
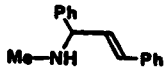
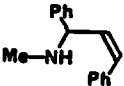
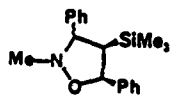
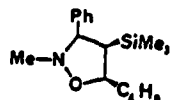
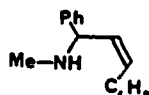
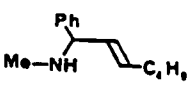
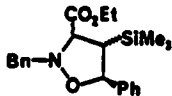
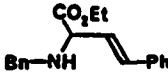
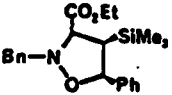
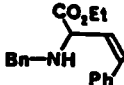
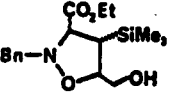
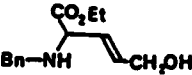
ENTRY	ISOXAZOLIDINE	CONDITIONS	PRODUCT	YIELD ^a
1	 <u>55</u>	A	 <u>84</u>	87
2	<u>55</u>	C, E	<u>84</u>	75
3	<u>55</u>	C, F	 <u>85</u>	84
4	 <u>56</u>	A	<u>85</u>	75
5	<u>56</u>	C, F	<u>85</u>	70
6	<u>56</u>	C, E	<u>84</u>	84
7	 <u>57</u>	A	 <u>86</u>	89
8	<u>57</u>	C, F	 <u>87</u>	81

Table V. continued

<u>ENTRY</u>	<u>ISOXAZOLIDINE</u>	<u>CONDITIONS</u>	<u>PRODUCT</u>	<u>YIELD</u> ^a
9	 <u>62</u>	D	 <u>88</u>	70
10	 <u>63</u>	B	 <u>89</u>	78
11	 <u>66</u>	B or D	 <u>90</u>	30

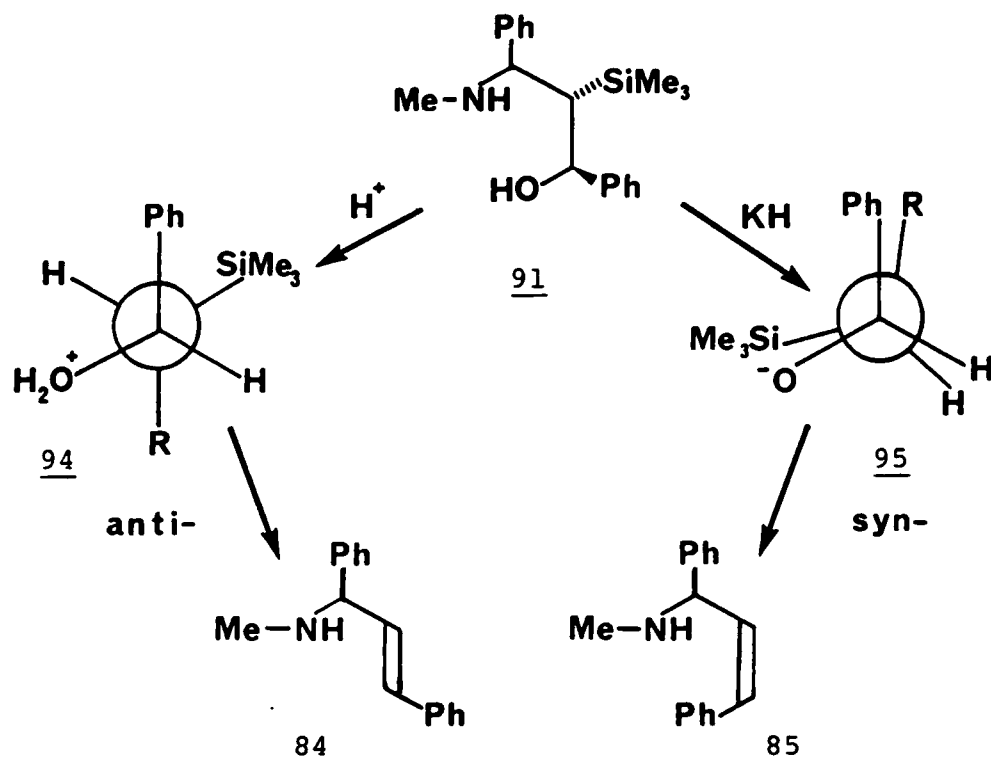
^a percent based on starting isoxazolidine

Reaction Conditions

- A. Zn/10% HCl(aq), THF (1:1), 50°, 1h.
 B. Zn/HCl·EtOH (1M), 50°, 1h.
 C. H₂, Ra-Ni (W-2)/20% NaOH(aq), MeOH (1:10), 12 h.
 D. i) H₂, Ra-Ni (W-2)/EtOH, 12 h; ii) HCl·EtOH (1M), 50°, 4h.
 E. H₂SO₄ (catalytic)/THF, 12 h.
 F. KH/THF, 1h.

reaction, the N,O-bond was cleaved by zinc, and the concurrent anti-elimination of trimethylsilanol occurred under the acidic reaction conditions to produce 84 (Table V, entry 1).

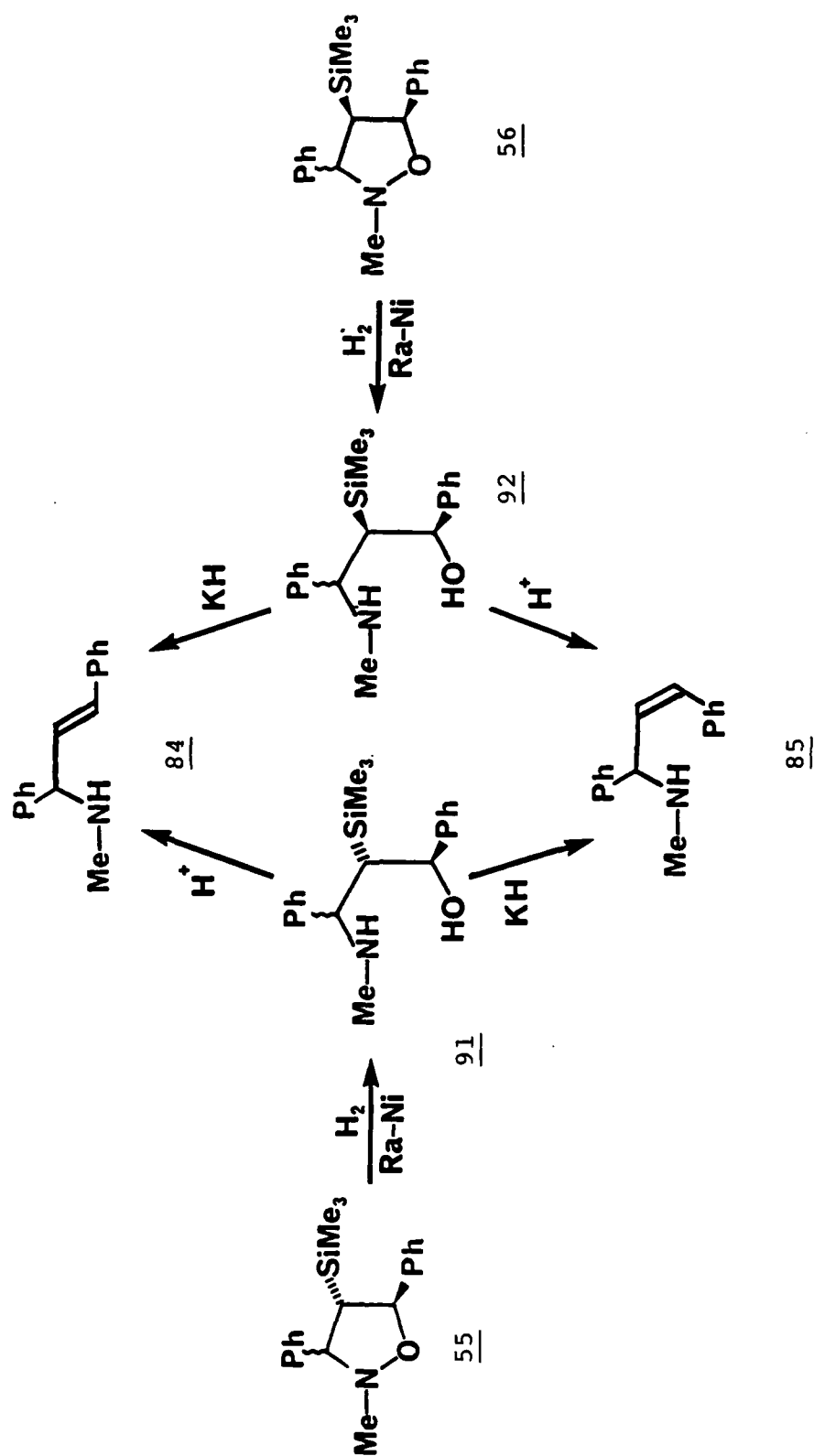
Alternatively, the reduction-elimination steps can be performed by a two-step process in which the N,O-bond of the isoxazolidine is cleaved with hydrogen and Raney-nickel to give an intermediate amino hydroxysilane (i.e. 91, 92, 93). Then, by a choice of acidic or basic elimination conditions, alkene geometry can be controlled. When amino hydroxysilane 91, product of the catalytic hydrogenation of isoxazolidine 55 (4,5-trans), was treated with catalytic H₂SO₄ in THF, only E-allylic amine 84 was formed in 75% yield (Table V, entry 2). Under these conditions, the reactant rotated to the anti conformation 94 (Scheme 25) to eliminate, forming the trans alkene geometry. Conversely, treatment of 91 with KH formed the alkoxide, which eliminated trimethylsilanol from the syn conformation 95 to give Z-alkene 85 in 84% yield (Table V, entry 3). Due to the mechanistic imperative, acid catalyzed elimination always yielded the allylic amine in which the alkene geometry of the amine was identical to the original dipolarophile used in the nitron cycloaddition.

Scheme 25

Scheme 26 demonstrates the flexibility of methodology. Isoxazolidine **55**, prepared from nitronc cycloaddition to the E-dipolarophile, was hydrogenated to give amino alcohol **91** which retained the trans C-4,C-5 stereochemistry. Treatment of **91** with catalytic H₂SO₄ gave E-allylic amine **84**, whereas treatment of **91** with KH yielded Z-allylic amine **85**.

The identical products were obtained by starting from the 4,5-cis isoxazolidine **56**, which arose from the Z-dipolarophile. Hydrogenation of isoxazolidine **56** gave amino hydroxysilane **92**. Treatment of **92** with H₂SO₄ gave Z-allylic amine **85**, while reaction with KH yielded the E-allylic amine **84**. In each case, gas chromatography

Scheme 26

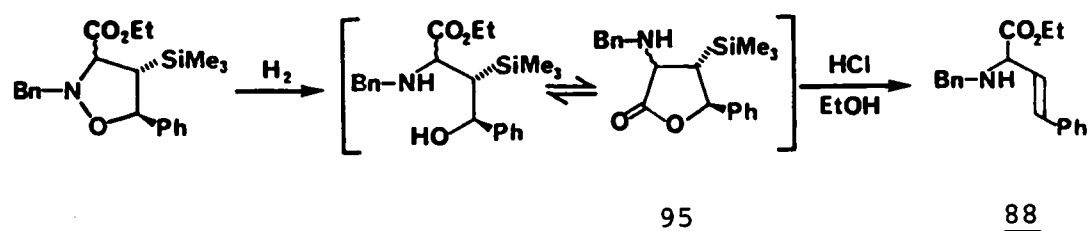


indicated that a single isomer (>99% purity) was formed in the elimination. The method permits the synthesis of a specific allylic amine geometry from either the E or Z dipolarophile by selecting the appropriate reaction conditions. Conversely, both E- and Z-allylic amines can be synthesized from a dipolarophile of a single geometry.

A brief search [Zn/KOH in EtOH, Zn/NaOH in EtOH, NaBH₄, Al(Hg) and Na(Hg)] for a single reagent system to cause simultaneous reduction and syn elimination proved fruitless.

Special attention had to be given during the reduction-elimination process to isoxazolidines 62, 63, and 66, which were prepared from carbethoxy nitrene 7b. Reduction of the N,O-bond in 3-carbethoxy isoxazolidine 62 yielded the intermediate amino alcohol which cyclized under the reaction conditions to produce δ -lactone 96 (Scheme 27). Although Peterson elimination of the lactone was still possible hypothetically, isolation of the unprotected α -amino acid after Peterson elimination proved untenable. However, treatment of the mixture containing 95 with HCl•EtOH (1M) at 60° for 4 hours led to isolation of amino ester 88. Under the reaction conditions, the lactone was converted to the γ -hydroxy ester form, which underwent protonation and anti elimination to form 88.

Scheme 27

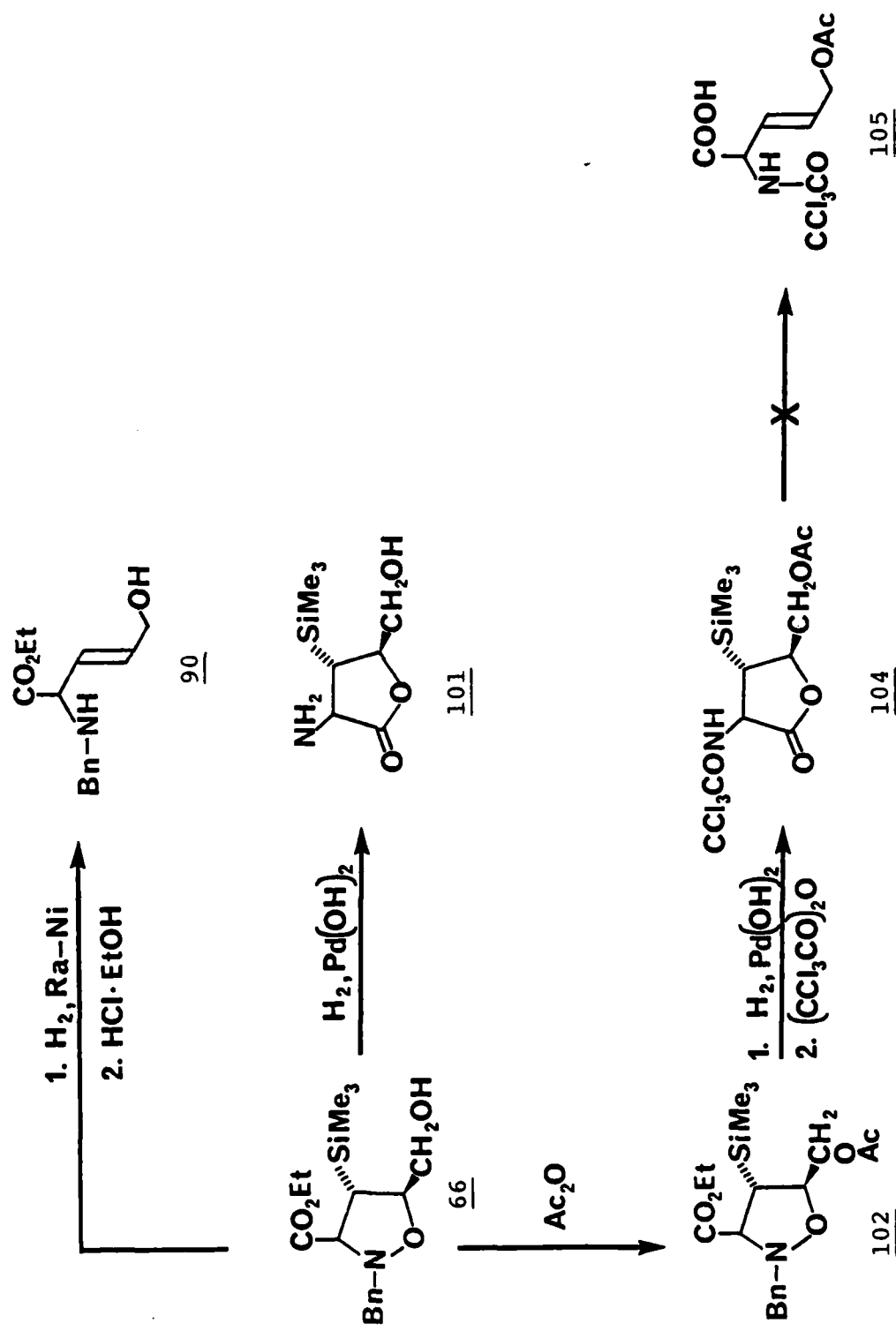


Similarly, treatment of isoxazolidine 63 (Table V, entry 10) with zinc in HCl·EtOH affected concomitant N,O-bond reduction and elimination to give allylic amine 89. Not only was the allylic amine constructed stereospecifically in one step, but the ester was retained, thus simplifying further manipulations. This use of carbethoxy nitrones to form β,γ -unsaturated α -amino acids is complementary to existing literature methods.³⁷

Isoxazolidine 66 underwent conversion to allylic amine 90 in 30% yield when subjected to the reduction-elimination sequence (Table V, entry 11). Catalytic hydrogenation of isoxazolidine 66 resulted in a product mixture in 50% mass balance, suggesting significant competing reactions occurred during the N,O-bond reduction step.

Allylic amine 98 (Scheme 28) was desired as part of a proposed total synthesis of kainic acid.³⁸ Attempted transformation of 5-carbethoxyisoxazolidine 66 into allylic amine 98 proved unsuccessful. Treatment of 66 with either Zn/HCl or H₂/catalyst led to formation of the intermediate

Scheme 29



amino alcohol 97. The more nucleophilic amine attacked the 5-carbethoxy group forming δ -lactam 99. The δ -lactam 99 appeared capable of forming the unsaturated lactam 100 by Peterson elimination, but neither the alcohol nor the corresponding acetate gave unsaturated lactam 100 when subjected to Peterson elimination conditions.

As previously mentioned, an amine similar to 98 was desired as part of a proposed total synthesis of kainic acid. Amine 90 was a precursor to 98, but was prepared in low yield (Table V, entry 11).

Since the total synthesis would require N-benylation at some point, N,O-bond reduction was attempted with Pearlman's catalyst.³⁹ Treatment of 66 with H₂/Pd(OH)₂ in ethanol gave the allylic amine precursor, lactone 101, in 40% yield. In an attempt to increase yield, 66 was acetylated (Ac₂O, pyr, DMAP) to give 102. Reduction of 102 with H₂/Pd(OH)₂ gave a lactone acetate (103, 40% yield) which was protected as the trichloroacetamide 103. However, attempts to induce alkene formation to 104 with BF₃•Et₂O or Bu₄N⁺F⁻ in refluxing THF were unsuccessful.

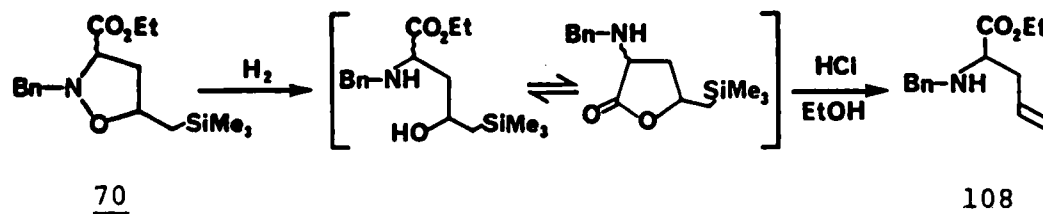
Transformation of 5-(Trimethylsilylmethyl)Isoxazolidines into Homoallylic Amines.

Using the Peterson elimination sequence, isoxazolidine adducts arising from nitrones and allyltrimethylsilane were converted into homoallylic amines.

As noted in Table I, the cycloaddition of allyl trimethylsilane and nitrones occurred with complete regioselectivity to give the 5-(trimethylsilylmethyl)-isoxazolidines as a mixture of diastereomers. Subsequent hydrogenation of isoxazolidine 69 over Raney-nickel catalyst gave the corresponding amino alcohol 106, which was eliminated with catalytic H_2SO_4 to give homoallylic amine 107 (Table VI, entry 1). For unexplained reasons, KH failed to effect the conversion of 106 to 107. Also, one-step reduction-elimination with zinc/ HCl produced 107 and 108 in unusually low yields (30%).

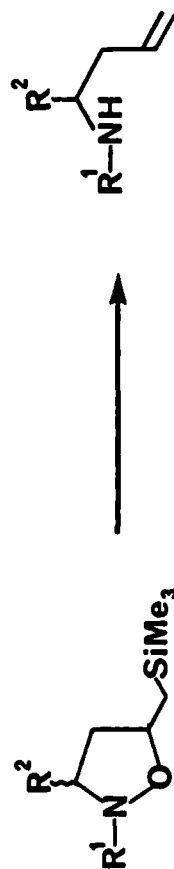
As before, catalytic reduction of carbethoxy-isoxazolidine 70 yielded a γ -hydroxy ester which cyclized to a lactone (see Scheme 30) under the reduction conditions. Treatment of the equilibrium mixture with HCl in ethanol affected both lactone opening and formation of alkene 108.

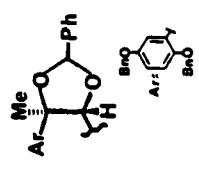
Scheme 30



Another elimination procedure was developed and is illustrated by the conversion of isoxazolidine 71 to amide

Table VI. Homoallylic Amines.

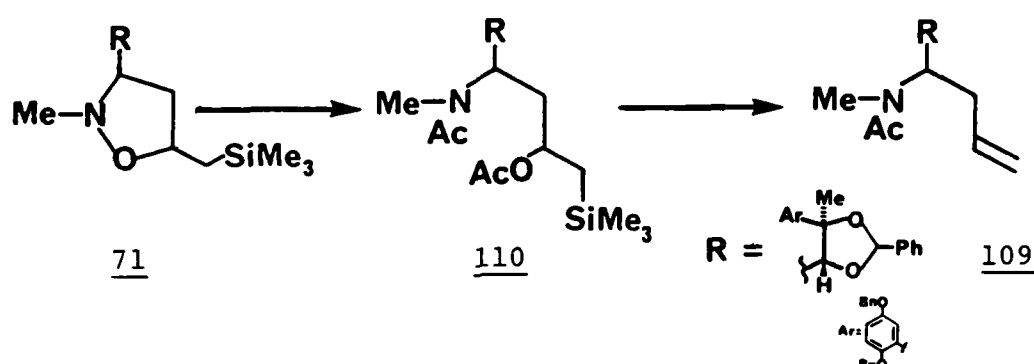


R^1	R^2	AMINE	YIELD (%)
Me	Ph	107	71
Bn	CO ₂ Et	108	78
Me		109	48 ^a

^a Isolated as the amide

109 (Table VI, entry 3).⁴⁰ Isoxazolidine 71 was reduced with zinc in HOAc/H₂O to the corresponding amino alcohol (see Scheme 31). Acetylation (Ac₂O/pyr/DMAP) gave the amide ester 110 which was cleanly eliminated with Bu₄N⁺F⁻ at 70° to give 109.⁴¹ This sequence adds to the repertoire of conditions which affect the Peterson elimination.

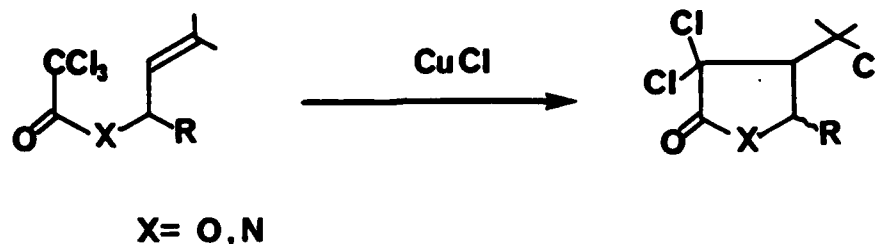
Scheme 31



Transformation of Allylic Trichloroacetamides into δ -Lactams.

With a new method available for the stereoselective synthesis of unsaturated amines, focus was turned to conversion of these amines into heterocyclic compounds. Itoh had reported that trichloroacetyl derivatives of allylic alcohols and allylic amines underwent CuCl initiated cyclization to give the corresponding heterocycles (see Scheme 32).⁴² This report suggested that the allylic amines from Table V could be used as precursors to highly substituted lactams.

Scheme 32

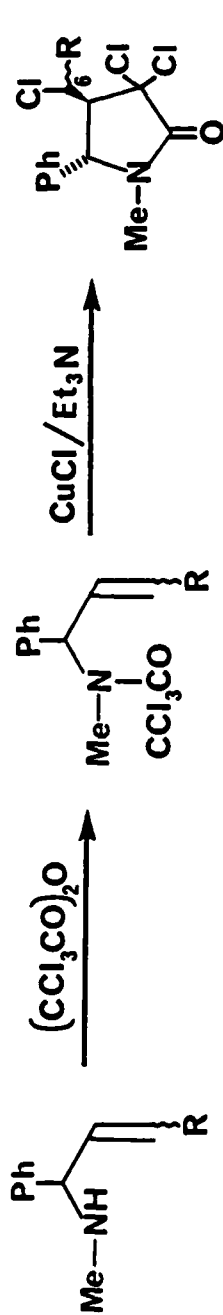


The trichloroacetamide derivatives of amines 84, 85, 86, 87, and 107 were prepared by treatment with trichloroacetic anhydride in pyridine. Initial cyclization attempts with allylic trichloroacetamide 111 using the Itoh conditions (30% mol CuCl in CH₃CN at 160°) proceeded in low yield (30%) to produce lactam 116. Replacement of the insoluble copper catalyst with a CuCl (8%)/Et₃N(15%) system⁴³ resulted in increased yields (at 130°), as reported in Table VII. Attempted cyclization of homoallylic trichloroacetamide 115 by this method gave a complex mixture in low yield.

This cyclization established three contiguous asymmetric centers (C-4, C-5, and C-6) in the lactam, and the trans-stereochemistry at C-4 and C-5 was exclusively obtained irrespective of alkene geometry or substitution. This stereochemical consequence was expected based upon mechanistic considerations (vide infra). The stereochemistry at C-4, C-5 was initially established using ¹H NMR coupling constants. The C-4,C-5 coupling constants

Table VII. γ -Lactams.

ACETAMIDE	$\underline{R}$	LACTAM YIELD (%)	Ratio of epimers at C-6	
			116 : R = Ph	117 : R = n-Bu
111	Ph (E)	75	10 : 1	
112	Ph (Z)	75	10 : 1	
113	n-Bu (E)	65	2 : 1	
114	n-Bu (Z)	85	2 : 1	

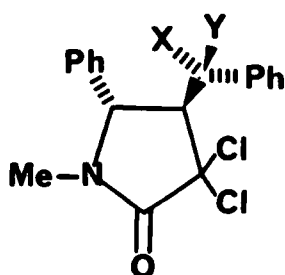


116 : R = Ph

117 : R = n-Bu

for 116 and 117 were between 6.4 and 7.9 Hz, indicative of a trans ring junction, whereas a $J_{cis} = 9-10$.⁴⁴ Itoh observed a cis stereochemistry in several cyclizations, but these were biased by the formation of cis bicyclic systems. An X-ray structure (Figure 1) of 116a unequivocally established the trans assignment and established the stereochemistry at C-6.

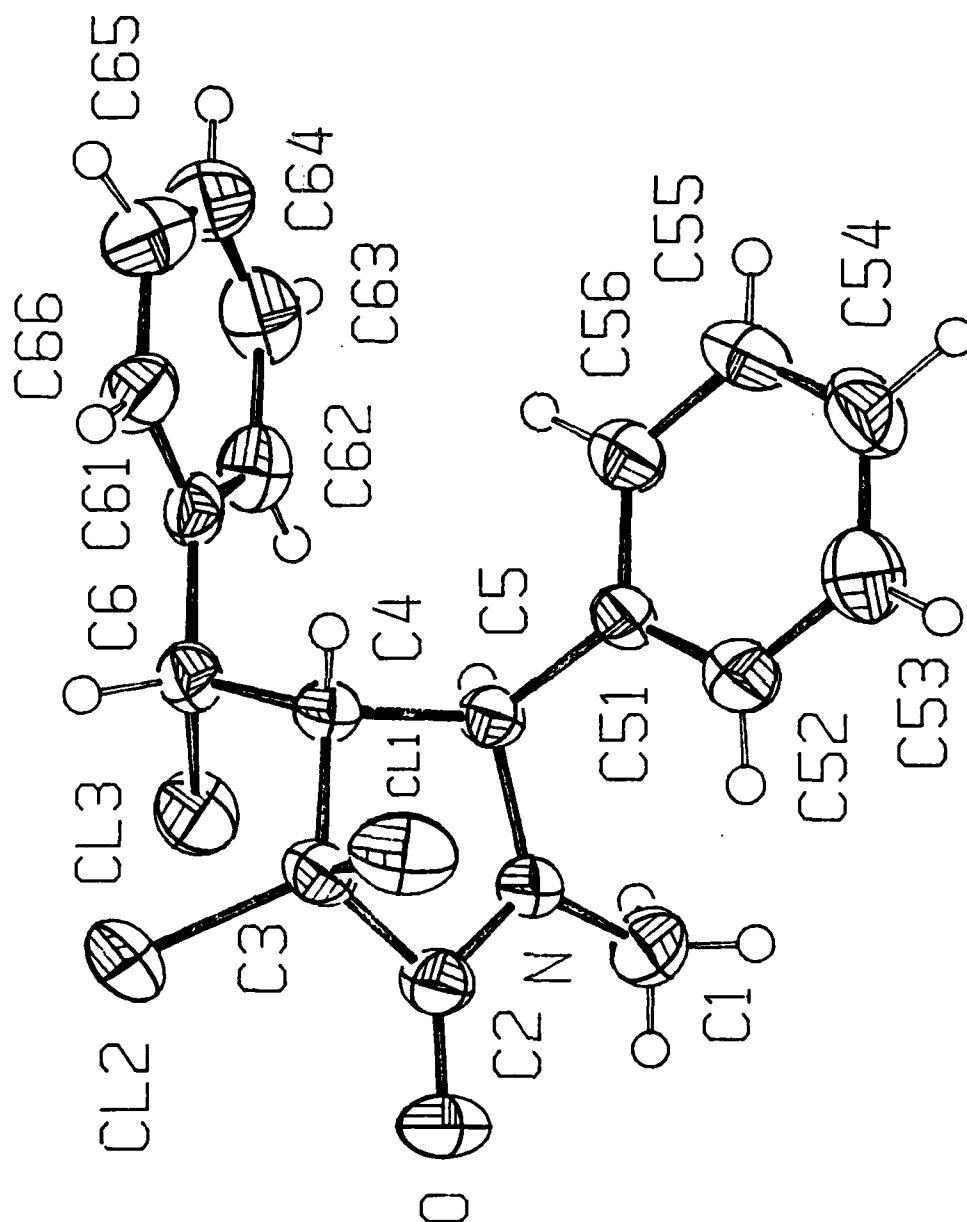
As noted in Table VII, the cyclization also displayed stereoselectivity with regard to the exocyclic asymmetric center at C-6. In the case where R = phenyl, a 10:1 ratio of isomers, diastereomeric only at C-6, was observed (see 116a and 116b). Presumably, copper complexation to the organic intermediate (vide infra) caused stereoselective introduction of chlorine at C-6. The less bulky, non-polarizable n-butyl group demonstrated a reduced stereoselectivity at C-6 (2:1). The relative stereochemistry at C-6 for 117a and b was not determined.



116a: X = Cl, Y = H

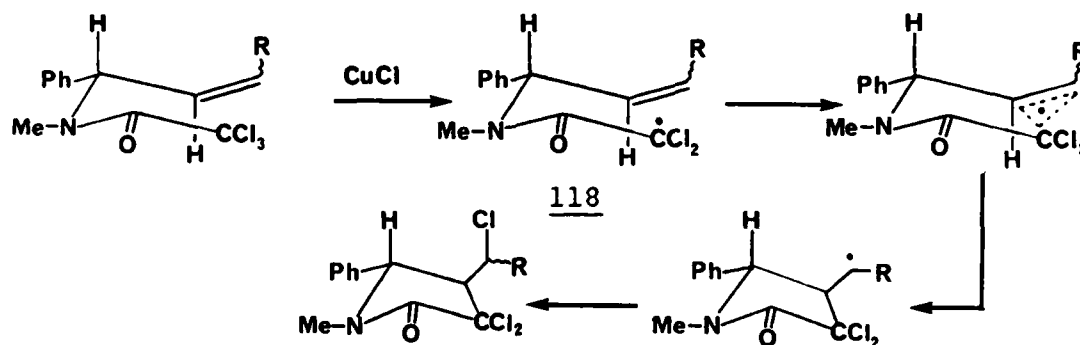
116b: X = H, Y = Cl

Reactions mediated by CuCl are believed to proceed via a free radical mechanism (Scheme 33).^{42, 43} The radical intermediate 118 is postulated to assume the more stable chair-like transition state.⁴⁵ This conformation places the

Figure I - ORTEP of γ -Lactam 116a

bulky substituents in pseudoequatorial positions, setting the trans C-4,C-5 substituent relationship on the product lactam. Complexation by copper ion to the intermediate radical or phenyl group could induce stereoselective introduction of chlorine at C-6. Several reports have established that radical additions to double bonds proceed under kinetic control to preferentially form 5-membered rings.⁴⁶ In addition, the initial E or Z-allylic amine geometry should have no influence on the stereoisomer ratio due to free rotation at C-6 in the resulting cyclized radical. The data in Table VII confirm that alkene geometry makes no difference since the epimeric ratio is the same regardless of starting allylic amine geometry.

Scheme 33



The results of this section prove that highly substituted allylic trichloroacetamides can be converted to δ -lactams in good yields. The cyclization also proceeds stereospecifically to give a trans C-4,C-5 substituent relationship. Finally, a modified catalyst system can be used in this process resulting in improved yields at lower temperatures. The application of this cyclization process to the preparation of complex heterocyclic systems is under investigation.

Summary

Some general parameters have been established for nitronc cycloadditions to 2-substituted vinylsilanes. Nitrones and vinylsilanes react to give isoxazolidines with the TMS group at either the C-5 or C-4 position. While 5-TMS isoxazolidines have been fragmented to α,β -unsaturated aldehydes, these isoxazolidines may also be converted into β -amido aldehydes. β -Amido aldehydes were then elaborated into β -amino acids and β -lactams.

However, 4-TMS isoxazolidines, which are the predominant regioisomers from the cycloaddition, have been converted to allylic amines via a Peterson elimination methodology with stereospecific control of the double bond geometry. These allylic amines were subsequently converted stereoselectively into γ -lactams via a Cu(I) mediated cyclization.

Nitrones and allyltrimethylsilane produced 5-(trimethylsilylmethyl)isoxazolidines exclusively. Using Peterson elimination methodology, these isoxazolidines were subsequently converted into homoallylic amines.

Application of this technology to natural product synthesis is underway.

EXPERIMENTAL

Melting points were taken in Kimax soft-glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406 K) equipped with a calibrated thermometer.

Proton and carbon magnetic resonance spectra (NMR) were recorded on a Varian Associates analytical NMR spectrometer (Model EM-360) or a Bruker WP-200 or WM-360 Super Con spectrometer. Proton chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Coupling constants (J values) are given in hertz (Hz) and spin multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The deuterated NMR solvent contained 99.0-99.8% deuterium in the indicated position. Infrared spectra were recorded on a Perkin-Elmer Model 281B diffraction grating spectrophotometer. Peak positions are given in reciprocal centimeters (cm^{-1}) and are listed as very strong (vs), strong (s), medium (m), or weak (w). Mass spectral data were obtained on a Kratos MS-950 double-focusing high-resolution spectrometer or on a Finnigan 3200 twin EI and CI quadrupole mass spectrometer equipped with a Finnigan 6000 computer. The chemical ionization carrier gas was methane. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

Thin-layer chromatography (TLC) was performed on 0.25 mm Merck silica-coated glass plates with the compounds being identified in one or more of the following ways: UV (254 nm), iodine, sulfuric acid, vanillin and/or ninhydrin charring. Preparative layer chromatography (PLC) was performed on 0.25, 0.50, or 2.0 mm Merck silica-coated glass plates with the compounds identified as above. Column chromatography was performed on 70-230 μ m silica gel 60 (ICN). Flash chromatography was performed by using thick-walled glass columns and "medium pressure" silica (Merck 32-63 μ m) according to the method of Still.⁴⁷ The solvent systems used are reported in each experimental. The conditions for purification via the Chromatotron⁴⁸ (Harrison Research Inc., Palo Alto, CA) are reported as (thickness of silica gel on rotor, eluant). Gas chromatography was performed on a Hewlett-Packard Model 5890A chromatograph equipped with a 0.20 mm x 25 m cross-linked methyl silicone capillary column and flame ionization detector. Nitrogen was the carrier gas.

All solvents were distilled from CaCl_2 unless otherwise noted. Ethyl ether, benzene, and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Acetonitrile was distilled from CaH_2 . Acetyl chloride was distilled from PCl_5 and redistilled from dimethylaniline. Vinyltrimethylsilane, ACE-chloride, FORCE-chloride, ethyl chloroformate and benzoyl chloride were distilled immediately before use. Zinc was activated⁴⁹ before use by

washing for two minutes in 2N HCl in a beaker. The acid was decanted and the zinc was washed with ethanol (95%) and ether and then air dried. Freshly prepared W-2 Raney-nickel⁵⁰ was stored in absolute ethanol at 0°. All reactions were carried out in dried glassware under a blanket of N₂(g), except as noted.

General Method for Sealed Tube Experiments.

The apparatus for sealed tube experiments consisted of a heavy walled glass pressure tube (2 cm dia, 10 cm length) fitted with an 8 or 10 mm vacuum stopcock (ACE model 8194, 90° angle), with the side-arm containing a tapered joint for adaptation to the vacuum pump. To prevent contamination from O-ring decomposition, the stopcock had an O-ring outer seal and dual teflon inner seals.

Reaction mixtures were added to the dried tube through the open barrel and the plug inserted. The tube contents were degassed three times by freezing in liquid nitrogen, application of a vacuum of less than 0.5 mm pressure and thawing to room temperature.

Reaction temperatures were maintained so as not to exceed 10 atmospheres of internal pressure based on the vapor pressure of pure reaction solvent.

Reaction progress was monitored by TLC by occasionally drawing a sample from the cooled tube through the opened stopcock. If starting material remained, the tube was resealed, degassed at least once, and heating resumed.

Workup usually began with the transfer of the tube contents to another flask for further manipulation.

Preparation of Ethyl 3-Trimethylsilyl-E-Propenoate 5l.

To a pressure tube was added 2-E-(tri-n-butyltin)-vinyltrimethylsilane (18.4 mmol), ethylchloroformate (18.0 mmol) and THF (25 mL). After degassing the contents, the tube was transferred to a dry box where $\text{Pd}[\text{PPh}_3]_4$ (0.14 mmol, 0.8%) was added. The tube was removed from the box, degassed again and placed in an oil bath to relax the contents. The solution gradually turned orange over 1 h and the end of reaction was marked in about 24 h by a black Pd precipitate. The tube contents were then partitioned between water and ether (25 mL). The ether layer was washed twice with half-saturated KF (aq) (20 mL) and the white precipitate (Bu_3SnF) filtered off. After drying (MgSO_4), flash chromatography on silica (hexane) yield a yellow oil which was further purified by bulb-to-bulb distillation (90-4°/70 mm) to give **5l** as a clear oil (13.9 mmol, 77%). IR (film) 2950 (m), 1720 (s), 1210 (vs), 940 (m), 820 (s); ^1H NMR 0.1 (s, 9H), 1.3 (t, $J = 7.0$, 3H), 4.2 (q, $J = 7.0$, 2H), 6.2 (d, $J = 19.0$, 1H), 7.1 (d, $J = 19.0$, 1H); mass spectrum, m/z (relative intensity, %) 172 (M^+ , 0.2), 157 ($\text{M}^+ - \text{CH}_3$, 100), 129 (26), 127 (19).

General Method for the Preparation of Isoxazolidines from Vinyl or Allyl Silanes.

A solution of nitron (1 mmol), alkene (1.5 - 2 mmol) and benzene (5 mL) was refluxed in a pressure tube for 7 h-2 days (see separate isoxazolidine entries for specific reaction conditions). The reaction mixture was concentrated in vacuo and flash chromatography (silica, hexane/EtOAc) of the residue provided an isomeric mixture of the isoxazolidines.

N-Methyl-3,5 Diphenyl-4-Trimethylsilylisoxazolidine 55 (from E-alkene 48).

Conditions: 150°, 2d. Yellow oil (60%, 6:1 mixture of stereoisomers). Major isomer: $R_f = 0.35$ in 10:1 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$; IR (CCl_4) 3030 (m), 2960 (m), 1600 (w), 1450 (m), 750 (br, s); ^1H NMR (CDCl_3) -0.1 (s, 9H), 2.2 (dd, $J = 10.9$, 1H), 2.6 (s, 3H), 3.5 (d, $J = 10.9$, 1H), 5.1 (d, $J = 8.5$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 311 (M^+ , 3), 193 (100), 115 (35), 73 (34). Minor isomer: $R_f = 0.23$; IR (CCl_4) 3030 (m), 2960 (m), 1540 (m), 1240 (m), 740 (s); ^1H NMR (CDCl_3) -0.5 (s, 9H), 2.5 (dd, $J = 9.8$, 11.7, 1H), 2.7 (s, 3H), 3.7 (d, $J = 11.7$, 1H), 5.5 (d, $J = 9.8$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 311 (M^+ , 9), 193 (100), 115 (41), 73 (48).

N-Methyl-3,5 Diphenyl-4-Trimethylsilylisoxazolidine 56
(from Z-alkene 49).

Conditions: 150°, 2d. Yellow oil (60%, 12:1 mixture of stereoisomers). Major isomer: $R_f = 0.25$ in CH_2Cl_2 ; IR (CCl_4) 3020 (w), 2950 (s), 1600 (w), 1450 (m); ^1H NMR (CDCl_3) -0.5 (s, 9H) 2.3 (dd, $J = 9.6, 11.0$, 1H), 2.6 (s, 3H), 3.6 (d, $J = 11.0$, 1H), 5.3 (d, $J = 9.6$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 311 (M^+ , 6), 193 (100), 115 (56), 73 (39). Minor isomer: $R_f = 0.35$; IR (CCl_4) 3020 (w), 2950 (m), 1450 (m); ^1H NMR (CDCl_3) -0.1 (s, 9H), 2.3 (dd, $J = 8.2, 10.8$, 1H), 2.6 (s, 3H), 3.5 (d, $J = 10.8$, 1H), 5.0 (d, $J = 8.2$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 311 (M^+ , 1), 296 (2), 193 (100), 115 (43), 73 (41).

N-Methyl-3-Phenyl-5-n-Butyl-4-Trimethylsilylisoxazoline 57
(from Z-alkene 50).

Yellow oil (50%, single stereoisomer). $R_f = 0.16$ in CH_2Cl_2 . IR (CCl_4) 3020 (w), 2960 (s), 2870 (m), 1440 (w). ^1H NMR (CDCl_3) -0.2 (s, 9H), 0.9 (t, $J = 7.0$, 3H), 1.3 (m, 4H), 1.6 (m, 2H), 2.1 (dd, $J = 8.3, 11.0$, 1H), 2.6 (s, 3H), 3.4 (d, $J = 11.0$, 1H), 4.3 (m, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 291 (M^+ , 15), 276 (5), 173 (48), 117 (100).

N-Methyl-3-Phenyl-4-n-Butyl-5-Trimethyl-silylisoxazolidine
58 (from Z-alkene 50).

Conditions = 140°, 2d. Yellow oil (20%, single stereoisomer). R_f = 0.25 in CH_2Cl_2 . IR (CCl_4) 3030 (w), 2960 (s), 2860 (m), 1450 (m); ^1H NMR (CDCl_3) 0.2 (s, 9H), 0.8 (t, J = 7.0, 3H), 1.2 (m, 4H), 1.6 (m, 2H), 2.6 (s, 3H), 2.7 (m, 1H), 3.1 (d, J = 5.7, 1H), 3.9 (d, J = 7.6), 7.4 (m, 5H); mass spectrum, m/z (relative intensity, %) 291 (M^+ , 52), 276 (7), 173 (26), 117 (79), 73 (100).

N-Methyl-3-Phenyl-5-Carbethoxy-4-Trimethylsilyl-
isoxazolidine 59 (from Z-alkene 51).

Clear oil (28%, 3:1 mixture of stereoisomers). Major isomer: R_f = 0.30. IR (CCl_4) 2950 (m), 1755 (s), 1730 (vs), 1200 (s); ^1H NMR 0.0 (s, 9H), 1.3 (t, J = 7.0, 3H), 2.3 (dd, J = 7.0, 10.7, 1H), 2.5 (s, 3H), 3.2 (d, J = 10.7, 1H), 4.3 (dq, J = 1.5, 7.0, 2H), 4.4 (d, J = 7.0, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 307 (M^+ , 13), 262 (14), 234 (8), 144 (100). Minor isomer: R_f = 0.24. IR (CCl_4) 2950 (m), 1740 (s), 1160 (s); ^1H NMR (CDCl_3) -0.3 (s, 9H), 1.3 (t, J = 7.0, 3H), 2.6 (dd, J = 7.7, 9.9, 1H), 2.9 (s, 3H), 4.2 (m, 3H), 4.5 (d, J = 9.9, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 307 (M^+ , 14), 262 (23), 234 (10), 144 (100).

N-Methyl-3-Phenyl-4-Carbethoxy-5-Trimethylsilyl-isoxazolidine 60 (from Z-alkene 51).

Conditions: 100°, 24 h. Clear oil (42%, 3:1 mixture of stereoisomers). Major isomer: R_f = 0.40 in 3:1 hexane/EtOAc. IR (CCl₄) 2950, 1730 (s), 1230 (s); ¹H NMR (CDCl₃) 0.1 (s, 9H), 1.3 (t, J = 7.0, 3H), 2.8 (s, 3H), 3.2 (dd, J = 6.3, 10.5, 1H), 4.1 (d, J = 10.5, 1H), 4.1 (q, J = 7.0, 2H), 4.2 (d, J = 6.3, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 307 (M⁺, 52), 234 (30), 145 (31), 134 (32), 118 (100). Minor isomer: R_f = 0.45, IR (CCl₄) 2950 (m), 1735 (s), 1130 (m); ¹H NMR (CDCl₃) 0.1 (s, 9H), 0.8 (t, J = 7.3, 3H), 2.6 (s, 3H), 3.5 (m, 5H), 4.2 (d, J = 10.3, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 307 (M⁺, 39), 292 (6), 234 (5), 145 (36), 134 (43), 118 (100).

N-Benzyl-3-Carbethoxy-5-Trimethylsilylisoxazolidine 61.

Conditions: 100°, 7 h. Yellow oil (90%, 3:1 mixture of stereoisomers). IR (film) 3040 (m), 2960 (s), 1745 (vs), 1185 (vs); ¹H NMR (CDCl₃) 0.1 (s, 9H), 1.1 (t, 3H), 2.3 (m, 2H), 3.9 (m, 6H), 7.3 (s, 5H).

N-Benzyl-3-Carbethoxy-5-Phenyl-4-Trimethylsilylisoxazoline 62 (from E-alkene 48).

Conditions 130°, 2 d. Yellow oil (75%, 2:1 mixture of stereoisomers. Major isomer: R_f = 0.33 in 5:1 hexane/EtOAc; IR (CCl₄) 3020 (m), 2950 (s), 1740 (vs), 1140 (s); ¹H NMR

(CDCl₃) 0.0 (s, 9H), 1.3 (t, J = 7.2, 3H), 2.3 (t, J = 9.0, 1H), 3.5 (d, J = 9.0, 1H), 4.1 (q, J = 7.2, 2H), 4.1 (s, 2H), 4.8 (d, J = 9.0, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 383 (M⁺, 2), 310 (89), 91 (100).

Minor isomer: R_f = 0.28; IR (CCl₄) 3020 (m), 2940 (m), 1735 (vs), 1160 (s); ¹H NMR (CDCl₃) -0.2 (s, 9H), 1.3 (t, J = 7.0, 3H), 2.1 (dd, J = 8.0, 11.0, 1H), 3.6 (d, J = 8.0, 1H), 4.0 (q, J = 7.0, 2H), 4.1 (s, 2H), 5.2 (d, J = 11.0, 1H), 7.3 (m, 10H).

N-Benzyl-3-Carbethoxy-5-Phenyl-4-Trimethylsilyl-isoxazolidine 63 (from Z-alkene 49).

Conditions 130°, 2d. Yellow oil (65%, single stereoisomer). R_f = 0.13 in 5:1 hexane Et₂O; IR (CCl₄) 3020 (m), 2960 (m), 1730 (s), 680 (s); ¹H NMR (CDCl₃) -0.2 (s, 9H), 1.3 (t, J = 7.0, 3H), 2.5 (t, J = 8.4, 1H), 3.5 (d, J = 8.4, 1H), 4.1 (q, J = 7.0, 2H), 4.2 (s, 2H), 5.3 (d, J = 8.4, 1H), 7.3 (m, 10H).

N-Benzyl-3,5 Dicarbethoxy-4-Trimethylsilylisoxazolidine 64 (from E-alkene 51).

Yellow oil (8%, 1:1 mixture of stereoisomers). More polar isomer: R_f = 0.48 in 10:1 CH₂Cl₂/Et₂O. IR (CCl₄) 2980 (m), 1740 (vs), 1150 (s); ¹H NMR (CDCl₃) 0.1 (s, 9H), 1.3 (2t, J = 7.1, 6H), 2.3 (dd, J = 6.9, 11.0, 1H) 3.9 (d, J = 7.2, 1H), 4.1 (d, J = 7.2, 1H), 4.1 (2q, J = 7.1, 4H), 4.3 (d, J = 6.9, 1H), 4.6 (d, J = 11.0, 1H), 7.3 (m, 5H). Less

polar isomer: $R_f = 0.38$. IR (CCl_4) 2970 (m), 1740 (vs), 1170 (s); ^1H NMR 0.1 (s, 9H), 1.2 (t, $J = 7.2$, 3H), 1.3 (t, $J = 7.2$, 3H), 2.6 (dd, $J = 6.8$, 9.8, 1H), 3.3 (d, $J = 9.8$, 1H), 4.2 (m, 6H), 4.3 (d, $J = 6.8$, 1H), 7.34 (m, 5H).

N-Benzyl-3,4 Dicarbethoxy-5-Trimethylsilylisoxazolidine 65
(from E-alkene 51).

Conditions: 110° , 20 h. Yellow oil (67%, 1:1 mixture of stereoisomers). More polar isomer: $R_f = 0.55$ in 10:1 $\text{CH}_2\text{Cl}/\text{Et}_2\text{O}$. IR (CCl_4) 2980 (m), 1730 (vs), 1160 (s), 1010 (m); ^1H NMR (CDCl_3) 0.1 (s, 9H), 1.2 (t, $J = 7.0$, 3H), 1.3 (t, $J = 7.0$, 3H), 3.7 (dd, $J = 3.9$, 10.3, 1H), 4.1 (m, 8H), 7.4 (m, 5H). Less Polar isomer: $R_f = 0.30$. IR (CCl_4) 2970 (m), 1740 (vs), 1170 (m); ^1H NMR 0.1 (s, 9H), 1.2 (t, $J = 7.0$, 3H), 1.2 (t, $J = 7.0$, 3H), 3.3 (dd, $J = 9.2$, 10.7, 1H), 3.6 (d, $J = 9.2$, 1H), 3.9 (d, $J = 10.7$, 1H), 4.1 (m, 6H), 7.3 (m, 5H).

N-Benzyl-3-Carbethoxy-5-(Hydroxymethyl)-4-Trimethylsilyl isoxazolidine 66 (from E-Alkene 52).

Conditions: 110° , 20 h. Rust oil (70%, 9:1 mixture of stereoisomers). Major isomer: $R_f = 0.10$ in 3:1 hexane/ EtOAc . IR (CCl_4) 3590 (w), 2940 (m), 1740 (s), 1160 (s); ^1H NMR (CDCl_3) 0.1 (s, 9H), 1.2 (t, $J = 7.1$, 3H), 2.1 (dd, $J = 6.9$, 8.8, 1H), 3.3 (d, $J = 6.9$, 1H), 3.7 (m, 1H),

4.0 (d, $J = 2.1$, 2H), 4.1 (q, $J = 7.1$, 2H), 4.1 (m, 2H), 7.3 (m, 5H). Minor isomer: characterized as the acetate derivative (see 101).

N-Benzyl-3-Carbethoxy-4-(Hydroxymethyl)-5-Trimethylsilyl isoxazolidine 67.

Yellow oil (8%). $R_f = 0.2$ IR (CCl_4) 3630 (w), 2950 (m), 1735 (s), 1225 (s); ^1H NMR (CDCl_3) 0.1 (s, 9H), 1.2 (t, $J = 7.0$, 3H), 3.6 (m, 1H), 4.1 (m, 4H), 4.2 (m, 4H), 7.3 (m, 5H).

5-Trimethylsilylisoxazolidine Lactone 72.

Yellow oil (1%). IR (CCl_4) 3020 (w), 2950 (m), 1775 (vs), 1740 (s), 1160 (s); ^1H NMR (CDCl_3) 0.1 (s, 9H), 3.2 (m, 1H), 3.4 (d, $J = 9.7$, 1H), 3.7 (d, $J = 9.2$, 1H), 4.1 (A of ABq, $J = 14.1$, 1H), 4.1 (dd, $J = 3.0$, 9.5, 1H), 4.3 (B of ABq, $J = 14.1$, 1H), 4.4 (dd, $J = 7.2$, 9.5, 1H), 7.3 (m, 5H).

N-Benzyl-3-Carbethoxy-5-Methylacetox-4-Trimethylsilyl isoxazolidine 101.

Isoxazolidine 66 (0.3 mmol) was acetylated by treatment with acetic anhydride (1 mL) and DMAP (20 mg) in pyridine (2 mL) for 20 h. The mixture was concentrated in vacuo, dissolved in CH_2Cl_2 and washed successively with saturated CuSO_4 (aq) and brine. After drying (Na_2SO_4) and concentration, flash chromatography (silica, 5:1

hexane/EtOAc) yielded 101 as a clear oil (0.3 mmol, 100%). Major isomer: R_f = 0.45 in 3:1 hexane/EtOAc; IR (CCl_4) 3020 (w), 2940 (m), 1740 (vs), 1210 (s); ^1H NMR (CDCl_3) 0.0 (s, 9H), 1.1 (t, J = 7.2, 3H), 1.8 (dd, J = 6.6, 9.3, 1H), 2.0 (s, 3H), 3.2 (d, J = 9.3, 1H), 4.0 (m, 2H), 4.1 (m, 2H), 4.1 (q, J = 7.2, 2H), 4.2 (m, 1H), 7.3 (m, 5H). Minor isomer: R_f = 0.5; IR (CCl_4) 3020 (w), 2940 (m), 1740 (vs), 1210 (s); ^1H NMR (CDCl_3) 0.0 (s, 9H), 1.1 (t, J = 7.2, 3H), 2.1 (s, 3H), 2.3 (dd, J = 8.4 10.8, 1H), 3.9 (d, J = 7.3, 1H), 3.9 (m, 2H), 4.0 (q, J = 7.2, 2H), 4.4 (m, 1H), 7.3 (m, 5H).

N-Methyl-3-Phenyl-5-(Trimethylsilylmethyl)isoxazolidine 69.

Conditions: 100°, 16 h. Yellow oil (95%, 1:2 mixture of stereoisomers). Minor isomer: R_f = 0.45 in 30:1 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$; IR (CCl_4) 3020 (w), 2950 (m), 800 (br, s); ^1H NMR (CDCl_3) 0.1 (s, 9H), 0.9 (dd, J = 9.5, 13.9, 1H), 1.1 (dd, J = 5.0, 13.9, 1H), 2.2 (m, 2H), 2.6 (s, 3H), 3.5 (t, J = 8.2, 1H), 4.37 (m, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 249 (M^+ , 13), 208 (75), 203 (25), 73 (100). Major isomer: R_f = 0.40; IR (CCl_4) 3020 (m), 2940 (s), 800 (br, s); ^1H NMR (CDCl_3) 0.0 (s, 9H), 0.9 (dd, J = 8.9, 14.0, 1H), 1.1 (dd, J = 5.8, 14.0, 1H), 1.9 (m, 1H), 2.5 (s, 3H), 2.7 (m, 1H), 3.6 (m, 1H), 4.3 (m, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 249 (M^+ , 5), 208 (32), 203 (12), 73 (100).

N-Benzyl-3-Carbethoxy-5-(Trimethylsilylmethyl)isoxazolidine
70.

Conditions: 120°, 2d. Yellow oil (91%, 2:1 mixture of stereoisomers. Major isomer: R_f = 0.20 in CH_2Cl_2 ; IR (CCl_4) 2940 (m), 1740 (s), 815 (s); ^1H NMR (CDCl_3) 0.1 (s, 9H), 0.8 (dd, J = 8.6, 14.0, 1H), 1.0 (dd, J = 5.9, 14.0, 1H), 1.2 (t, J = 7.1, 3H), 2.0 (m, 1H), 2.5 (m, 1H), 3.5 (dd, J = 5.7, 9.9, 1H), 4.1 (q, J = 7.1, 2H), 4.1 (s, 2H), 4.2 (m, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 321 (M^+ , 4), 280 (5), 248 (22), 91 (100). Minor isomer: R_f = 0.15; IR (CCl_4) 2940 (m), 1740 (s), 815 (s); ^1H NMR (CDCl_3) 0.0 (s, 9H), 0.9 (dd, J = 8.2, 14.2, 1H), 1.1 (dd, J = 6.1, 14.2, 1H), 1.2 (t, J = 7.1, 3H), 2.2 (ddd, J = 6.8, 8.2, 12.2, 1H), 2.6 (ddd, J = 6.4, 8.2, 12.2, 1H), 4.0 (A of ABq, J = 12.9, 1H), 4.1 (q, J = 7.1, 2H), 4.2 (B of ABq, J = 12.9, 1H), 4.4 (dddd, J = 6.1, 6.3, 8.2, 8.2, 1H), 7.4 (m, 5H); mass spectrum, m/z (relative intensity, %) 321 (M^+ , 5), 280 (7), 248 (28), 91 (100).

General Method for the Preparation of N-Protected- β -Amino
Aldehydes.

To a stirred solution of the 5-trimethylsilyl-isoxazolidine (1 mmol) in 25 ml of THF at room temperature was added the fragmentation agent (1.5-2 mmol) via syringe. The reaction was followed by TLC until starting material was consumed. Concentration of the mixture in vacuo

followed by flash chromatography on silica (hexane/EtOAc) of the residue provided the pure N-protected β -amino aldehyde.

3-(N-Methyl-N-[1,2,2,2-Tetrachlorocarbethoxy])amino-3-Phenylpropanal 73a.

Yellow oil (90%), $R_f = 0.3$ in 1:1 hexane/EtOAc. IR (CCl_4) 3020 (w), 2980 (m), 2710 (m), 1735 (vs), 1100 (br, s); ^1H NMR (CDCl_3) 2.7 (m, 3H), 3.1 (m, 2H), 5.9 (m, 1H), 6.8 (m, 1H) 7.3 (m, 5H), 9.8 (m, 1H); mass spectrum, m/z (relative intensity, %) 371 (M^+ , 6), 328 (19), 206 (32), 105 (100).

3-(N-Methyl-N-[1-Chlorocarbethoxy])amino-3-Phenylpropanal 73b.

Yellow oil (90%), $R_f = 0.3$ in 1:1 hexane/EtOAc. IR (CCl_4) 3020 (w), 2920 (m), 2710 (m), 1725 (vs), 1140 (s); ^1H NMR (CDCl_3) 1.8 (d, $J = 5.8$, 3H), 2.7 (m, 3H), 3.1 (m, 2H), 6.0 (m, 1H), 6.6 (m, 1H), 7.4 (m, 5H), 9.8 (br s, 1H).

3-(N-Carbethoxy-N-Methyl)amino-3-Phenylpropanal 73c.

Yellow oil (70%), $R_f = 0.3$ in 1:1 hexane/EtOAc. IR (CCl_4) 2970 (w), 2720 (w), 1725 (s), 1690 (vs), 1310 (s); ^1H NMR (CDCl_3) 1.3 (t, $J = 7.1$, 3H), 2.8 (s, 3H), 4.1 (q, $J = 7.1$, 2H), 6.7 (dd, $J = 7.7$, 16.0, 1H), 7.4 (m, 7H), 9.7 (d, $J = 7.7$, 1H).

3-(N-Carbobenzyloxy-N-Methyl)amino-3-Phenylpropanal 73d.

Yellow oil (68%), $R_f = 0.3$ in 1:1 hexane/EtOAc. IR (CCl_4) 3030 (w), 2720 (w), 1730 (vs), 1700 (vs), 1215 (s); ^1H NMR (CCl_4) 2.7 (s, 3H), 2.8 (dd, $J = 2.5, 8.0, 16, 2\text{H}$), 5.1 (d, $J = 6.5, 2\text{H}$), 5.9 (t, $J = 8.0, 1\text{H}$), 7.3 (m, 10H) 9.7 (t, $J = 2.5, 1\text{H}$).

3-(N-Acetyl-N-Methyl)amino-3-Phenylpropanal 73e.

Yellow oil (60%), $R_f = 0.3$ in 1:1 hexane/EtOAc. IR (CCl_4) 3020 (w), 2720 (w), 1725 (s), 1650 (vs), 1390 (m); ^1H NMR (CDCl_3) 2.1 (s, 3H), 2.7 (s, 3H), 3.0 (m, 2H), 6.5 (m, 1H), 7.3 (m, 5H), 9.8 (m, 1H).

3-(N-Methyl-N-Trifluoroacetyl)amino-3-Phenyl-Propanal 73f.

Yellow oil (50%), $R_f = 0.2$ in 1:1 hexane:EtOAc. IR (CCl_4) 3020 (w), 2710 (m), 1730 (s), 1690 (vs); ^1H NMR (CDCl_3) 1:1 mixture of amide isomers: 2.8 (d, 3H), 3.1 (m, 2H), 6.2 (m, 1H), 7.3 (m, 5H), 9.8 (m, 1H); mass spectrum, m/z (relative intensity, %) 259 (M^+ , 17), 190 (46), 110 (100).

3-(N-Methyl-N-Tosyl)amino-3-Phenylpropanal 73g.

Yellow oil (46%), $R_f = 0.4$ in 1:1 hexane/EtOAc. IR (CCl_4) 3020 (w), 2710 (w), 1730 (vs), 1340 (s), 1140 (vs); ^1H NMR 2.4 (s, 3H), 2.6 (s, 3H), 4.5 (s, 1H) 6.7 (dd, $J = 7.7, 16.0, 1\text{H}$), 7.4 (m, 10H), 9.7 (d, $J = 7.7, 1\text{H}$).

3-[N-Methyl-N-(1,2,2,2 Tetrachlorocarbethoxy)]amino-2-n-Butyl-3-Phenylpropanal 74a.

Clear oil (52%), 1:1 mixture of stereoisomers). More polar isomer: $R_f = 0.3$ in 5:1 hexane/EtOAc. IR (CCl_4) 2940 (m), 2690 (w), 1730 (vs), 1080 (s); ^1H NMR (CDCl_3) 1:1 mixture of amide isomers, 0.8 (m, 3H), 1.2 (m, 4H), 1.6 (m, 2H), 2.7 (2s, 3H), 3.1 (m, 1H), 5.6 (m, 1H), 6.8 (2s, 1H), 7.4 (m, 5H), 9.6 (m, 1H). Less polar isomer: $R_f = 0.2$. IR (CCl_4) 2940 (m), 2690 (w), 1725 (vs), 1080 (s); ^1H NMR (CDCl_3) 1:1 mixture of amide isomers, 0.8 (m, 3H), 1.2 (m, 4H), 1.6 (m, 2H), 2.7 (br s, 3H), 3.2 (m, 1H), 5.7 (m, 1H), 6.9 (m, 1H), 7.4 (m, 5H), 9.5 (d, $J = 5.0$, 1H).

3-(N-Acetyl-N-Methyl)amino-3-Phenyl-2-n-Butyl-Propanal 74b.

Yellow oil (40%). IR (CCl_4) 2920 (s), 2710 (w), 1725 (s), 1645 (vs), 1390 (s); ^1H NMR (CDCl_3) 0.8 (t, $J = 7.0$, 3H), 1.3 (m, 5H), 1.7 (m, 1H), 2.0 (s, 3H), 2.7 (s, 3H), 3.0 (m, 1H), 6.2 (d, $J = 11.9$) 7.3 (m, 5H), 9.5 (d, $J = 5.2$, 1H); mass spectrum, m/z (relative intensity, %) 261 (M^+ , 18), 232 (9), 190 (13), 120 (100).

3-(N-Benzyl-N-[1,2,2,2-Tetrachlorocarbethoxy)]amino-3-Carbethoxypropanal 75a.

Rose-colored oil (50%). $R_f = 0.4$ in 5:1 hexane/EtOAc. IR (CCl_4) 2970 (m), 2710 (w), 1735 (br, vs), 1080 (s); ^1H NMR (CDCl_3) 1.2 (m, 3H), 2.8 (m, 1H), 3.5 (m, 1H), 4.1 (m, 2H), 4.5 (m, 2H), 4.6 (m, 1H), 6.9 (m, 1H), 7.4 (m, 5H),

9.7 (m, 1H); mass spectrum, m/z (relative intensity, %) 459 (M⁺, 0.1), 388 (2), 386 (2), 316 (8), 314 (6), 91 (100).

3-(N-Benzyl-N-[1-Chlorocarbethoxy])amino-3-Carbethoxypropanal 75b.

Yellow oil (40%), R_f = 0.2 in 1:1 hexane/EtOAc. IR (CCl₄) 2980 (w), 2710 (w), 1740 (sh, s), 1725 (vs), 1150 (s); ¹H NMR (CDCl₃) 1.2 (m, 3H), 1.8 (m, 3H), 2.8 (m, 1H), 3.4 (m, 1H), 4.0 (m, 2H), 4.6 (m, 2H), 4.7 (m, 1H), 7.3 (m, 5H), 9.7 (m, 1H).

3-(N-Acetyl-N-Benzyl)amino-3-Carbethoxypropanal 75c.

Yellow oil (20%). IR (CCl₄) 2970 (m), 2710 (w), 1740 (s), 1720 (s), 1655 (s); ¹H NMR (CDCl₃) 1.2 (t, J = 7.2, 3H), 2.2 (s, 3H), 2.8 (dd, J = 5.8, 18.4, 1H), 3.5 (dd, J = 6.3, 18.4, 1H), 4.1 (q, J = 7.2, 2H), 4.5 (dd, J = 5.8, 6.3), 4.6 (s, 2H), 7.3 (m, 5H), 9.7 (s, 1H).

3-(N-Benzyl-N-Acetyl)amino-2,3 Dicarbethoxypropanal 76.

Yellow oil (74%). IR (CCl₄) 2970 (m), 1745 (s), 1635 (vs); ¹H NMR 1:1 mixture of aldehyde and enol forms, aldehyde: 1.2 (t, J = 7.0, 3H), 2.1 (s, 3H), 4.1 (m, 1H), 4.1 (q, J = 7.0, 2H), 4.8 (m, 1H), 4.9 (s, 2H), 7.4 (m, 5H), 10.9 (d, J = 14, 1H), enol: 1.2 (t, J = 7.0, 3H), 2.1 (s, 3H), 4.2 (q, J = 7.0, 2H), 4.9 (s, 2H), 5.5 (s, 1H), 7.4 (m, 5H), 7.9 (d, J = 14.0, 1H).

Preparation of Cyclic Carbamates 77 and 78.

Isoxazolidine (60 or 65, 0.2 mmol) and FORCE-Cl (0.5 mmol) in THF (25 mL) were stirred at RT for 16 h with no reaction by TLC. The mixture was then refluxed for 2 h. After concentration in vacuo, flash chromatography on silica (2:1 hexane/EtOAc) of the residue yielded the cyclic carbamate.

Cyclic Carbamate 77.

White solid (50%); mp 119-120°; R_f = 0.2 in 3:1 hexane/EtOAc; IR (CCl₄) 2970 (m), 1750 (vs), 1720 (vs), 1670 (m), 1280 (s), 1160 (s); ¹H NMR (CDCl₃) 1.2 (t, J = 7.0, 3H), 2.9 (s, 3H), 4.1 (m, 2H), 5.1 (s, 1H), 7.3 (m, 5H), 7.5 (s, 1H); mass spectrum, m/z (relative intensity, %) 261 (M⁺, 29), 204 (30), 158 (58), 130 (100).

Cyclic Carbamate 78.

Clear oil (70%). R_f = 0.25 in 3:1 hexane/EtOAc. IR (CCl₄) 2980 (m), 1750 (vs), 1720 (s), 1670 (m), 1150 (s); ¹H NMR (CDCl₃) 1.2 (t, J = 7.1, 3H), 1.2 (m, 3H), 4.1 (q, J = 7.1, 2H), 4.2 (m, 2H), 4.3 (d, J = 15.0, 1H), 4.7 (s, 1H), 5.1 (d, J = 15.0, 1H), 7.3 (m, 5H), 7.5 (s, 1H); mass spectrum, m/z (relative intensity, %) 333 (M⁺, 2), 260 (37), 91 (100).

Method for the Formation of N-Protected- β -Amino Acids via Jones Oxidation.

To a solution of the aldehyde (1 mmol) in acetone (50 mL) at 0° was added Jones reagent⁵¹ dropwise until an orange color persisted. After 30 minutes, 2-propanol was added to quench unreacted oxidant and the acetone layer decanted. Brine solution was added to the residual chromium salts and this phase was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo. Flash chromatography (silica, 1:2 hexane/EtOAc) yielded the N-protected- β amino acid.

Method for the Formation of N-Protected- β -Amino Acids via PDC Oxidation.

To a solution of aldehyde (1 mmol) in DMF (2 mL) was added PDC (4-5 mmol) and the mixture was stirred for 6 hours. Water (20 mL) was added and the mixture was adjusted to a pH less than 4 with 2N H₂SO₄. Extraction with ether (3 x 25 mL), drying (MgSO₄) and concentration in vacuo led to the crude acid. Further purification could be affected by flash chromatography (silica, 1:2 hexane/EtOAc) giving the N-protected- β -amino acid.

3-(N-Methyl-N-[1,2,2,2-Tetrachlorocarbethoxy])amino-3-Phenylpropanoic acid 79a.

Prepared from 73a via PDC oxidation. White foam (80%); mp 91-95°; IR (CCl₄) 3000 (br, m), 2980 (m), 1735 (vs),

1715 (s), 1090 (s); ^1H NMR (CDCl_3) mixture of amide isomers 2.8 (2s, 3H), 3.1 (br d, 2H), 5.8 (br t, 1H), 6.9 (d, J = 5.8, 1H), 7.3 (m, 5H).

3-N-Methyl-N-[1-Chlorocarbethoxy])amino-3-Phenylpropanoic acid 79b.

Prepared from 73b via Jones oxidation. Clear oil (50%); IR (CCl_4) 3000 (br, m), 2920 (m), 1720 (br, vs), 1070 (s); ^1H NMR (CDCl_3) 1.8 (d, J = 5.8, 3H), 2.7 (s, 3H), 3.0 (d, J = 7.0, 2H), 5.8 (t, J = 7.0, 1H), 6.6 (q, J = 5.8, 1H), 7.3 (m, 5H).

3-(N-Acetyl-N Methyl)amino-3-Phenylpropanoic acid 79c (Methy ester).

Prepared from 73e via Jones oxidation and characterized as the methyl ester (diazomethane, MeOH, 50% from aldehyde); Methyl ester: mp 86.5-87°; IR (CCl_4) 3020 (w), 2940 (m), 1740 (vs), 1650 (vs), 1390 (s); ^1H NMR (CDCl_3) 1.5:1 mixture of amide isomers, major isomer: 2.1 (s, 3H), 2.7 (s, 3H), 2.9 (m, 2H), 3.7 (s, 3H), 6.3 (m, 1H), 7.3 (m, 5H), minor isomer: 2.3 (s, 3H), 2.7 (s, 3H), 3.0 (m, 2H), 3.7 (s, 3H), 5.5 (m, 1H), 7.3 (m, 5H). Anal. Calcd: C, 66.36; H, 7.28. Found: C, 65.31; H, 7.25.

3-(N-Methyl-N-[1,2,2,2-Tetrachlorocarbethoxy])amino-2-n-Butyl-3-Phenylpropanoic Acid 80.

Prepared from 74a (1:1 mixture) via PDC oxidation. Clear oil (68%); $R_f = 0.2$ in 1:2 hexane/EtOAc; IR (CCl_4) 3000 (br, m), 1750 (br, vs), 1710 (s), 1080 (s); ^1H NMR (1:1 mixture of diastereomers) 0.9 (m, 3H), 1.3 (m, 4H), 1.6 (m, 2H), 2.8 (2s, 3H), 3.1 (m, 1H), 5.4 (m, 1H), 6.9 (m, 1H), 7.3 (m, 5H).

3-(N-Benzyl-N-[1,2,2,2-Tetrachlorocarbethoxy])amino-3-Carbethoxypropanoic Acid 81.

Prepared from 75a via PDC oxidation. Yellow oil (50%). $R_f = 0.2$ in 1:2 hexane/EtOAc; IR (CCl_4) 3000 (br, m), 2940 (m), 1730 (br, vs), 1715 (s), 1210 (s), 1085 (s); ^1H NMR (CDCl_3) 1.2 (m, 3H), 2.7 (m, 1H), 3.3 (m, 1H), 4.0 (m, 2H), 4.5 (m, 2H), 4.8 (m, 1H), 6.9 (3s, 1H), 7.4 (m, 5H).

3-(N-Methylamino)-3-Phenylpropanoic Acid Hydrochloride 82.

A solution of acid 73a (0.5 mmol) and K_2CO_3 (6 eq.) in 30% aqueous MeOH (10 ml) was refluxed for 16 hrs. After cooling, the mixture was acidified to pH 2 with 2N HCl (aq), and extracted with ether (3 x 15 mL) The aqueous layer was concentrated in vacuo, the salts titrated with absolute ethanol and the precipitate filtered off. The

ethanol extract was concentrated in vacuo leaving 82 as a viscous yellow oil; ^1H NMR (CD_3OD) 2.3 (s, 3H), 3.0 (m, 2H), 4.4 (t, 1H), 7.3 (m, 5H).

This compound was further characterized through the methyl ester, which was prepared by refluxing the crude acid hydrochloride (0.1 mmol) with thionyl chloride (0.2 mL) and anhydrous MeOH (5 mL) for 16 hrs. The mixture was concentrated in vacuo, treated with 5% NaHCO_3 (10 mL) and extracted with EtOAc (3 x 25 mL). After drying (Na_2CO_3) and evaporation, bulb-to-bulb distillation (110°, 0.6 mm) yielded methyl 3-N-methylamino-3-phenylpropanoate as a clear oil (0.062 mmol, 62%); IR (CCl_4) 3020 (w), 2940 (m), 2780 (m), 1735 (vs), 1150 (m); ^1H NMR 1.9 (s, 1H), 2.3 (s, 3H), 2.7 (ddd, $J = 5.6, 8.3, 15.6$, 2H), 3.7 (s, 3H), 4.0 (dd, $J = 5.6, 8.3$, 1H), 7.3 (m, 5H).

N-Methyl-4 Phenyl-2-Azetidinone 83.

To a solution of acid hydrochloride 82 (0.5 mmol), KHCO_3 (5 eq.) and Bu_4NHSO_4 (15 mol percent) in water (1 mL), was added to a solution of $\text{CH}_3\text{SO}_2\text{Cl}$ (2 eq.) in CHCl_3 (4 mL). The two phases were vigorously stirred for 48 hrs, then partitioned between water and ether. The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo. Bulb-to-bulb distillation (100°, 0.5 mm) yielded the subject β -lactam (0.075 mmol, 15%) as a clear oil; IR (CCl_4) 3020 (w), 2890 (m), 1760 (vs), 1375 (m); ^1H NMR 2.8 (s, 3H), 2.8 (dd, $J = 2.3, 14.6$, 1H), 3.4 (dd, $J = 5.1$,

14.6, 1H), 4.5 (dd, $J = 2.3, 5.1$, 1H), 7.4 (m, 5H); mass spectrum, m/z (relative intensity, %) 161 (M^+ , 11), 118 (23), 104 (100).

General Method for Reductive Cleavage of Isoxazolidine using Hydrogen and Raney-Nickel.

To the isoxazolidine (0.5 mmol) was added W-2 Raney-nickel (approximately 100 mg) in the selected solvent (10 mL). Typically, a MeOH (10mL)/20% aqueous NaOH (1 mL) system was used as the solvent, except that absolute ethanol was used with isoxazolidines containing the carbethoxy group.

The slurry was stirred under an atmosphere of hydrogen for 8-16 h. The catalyst was filtered off on celite and the solvent evaporated leaving the crude product. With the NaOH/MeOH solvent system, this product was partitioned between water and EtOAc, the organic layer dried (Na_2CO_3) and removed in vacuo yielding the 1,3-amino hydroxysilane. When ethanol was used as the hydrogenation solvent, the catalyst was filtered off through celite, the solvent removed in vacuo and the product used without further purification.

Diphenyl-Amino-Hydroxysilane 91 (from 4,5-trans-Isoxazolidine 55).

Yellow oil (99%); $R_f = 0.15$ in 15:1 CH_2Cl_2 /MeOH; IR (film) 3300 (br, m), 3020 (w), 2940 (m), 1230 (s), 810 (s);

^1H NMR (CDCl_3) -0.3 (s, 9H), 1.9 (dd, $J = 6.2, 9.8$, 1H), 2.1 (s, 3H), 3.8 (d, $J = 9.8$, 1H), 5.1 (d, $J = 6.2$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 313 (M^+ , 0.2), 282 (2), 193 (11), 120 (100).

Diphenyl-Amino-Hydroxysilane 92 (from 4,5-cis Isoxazolidine 56).

Yellow oil (95%); $R_f = 0.15$ in 15:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; IR (CCl_4) 3350 (br, m), 3020 (s), 2940 (s), 1445 (s); ^1H NMR (CDCl_3) - 0.3 (s, 9H), 1.7 (dd, $J = 2.7, 7.0$, 1H), 2.3 (s, 3H), 3.9 (d, $J = 7.0$, 1H), 5.1 (d, $J = 2.7$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 313 (M^+ , 0.1), 282 (11), 192 (19), 120 (100).

N-Butyl-Amino-Hydroxysilane 93 (from Isoxazolidine 57).

Yellow oil (98%); $R_f = 0.15$ in 15:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; IR (CCl_4) 3300 (br, m), 2950 (m), 1450 (m); ^1H NMR (CDCl_3) -0.3 (s, 9H), 0.9 (t, $J = 7.0$, 3H), 1.5 (m, 6H), 1.7 (dd, $J = 2.8, 11.2$, 1H), 2.2 (s, 3H), 3.7 (d, $J = 11.2$, 1H), 3.8 (dt, $J = 2.8, 9.9$, 1H), 7.3 (m, 5H).

Trimethylsilyl- γ -Lactam 99 (from Isoxazolidine 64, Major Isomer).

Clear oil (60%); $R_f = 0.4$ in 10:1 $\text{CH}_2\text{Cl}_2/\text{EtO}$; IR (CCl_4) 3300 (br, w), 2950 (m), 1740 (s), 1710 (s), 1180 (s); ^1H NMR (CDCl_3) 0.0 (s, 9H), 1.3 (t, $J = 7.1$, 3H), 1.9

(dd, $J = 2.6, 9.7$, 1H), 3.8 (d, $J = 2.6$, 1H), 4.0 (A of ABq, $J = 14.5$, 1H), 4.1 (q, $J = 7.1$, 2H), 4.8 (d, $J = 9.7$, 1H), 5.0 (B of ABq, $J = 14.5$, 1H), 7.4 (m, 5H).

1-N-Methylamino-2-Phenyl-3-Hydroxy-4-Trimethylsilylbutane
106 (from Isoxazolidine 69).

94%, $R_f = 0.12$ in 15:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$. IR (CCl_4) 3300 (br, w), 2950 (m), 1450 (m), 850 (s); ^1H NMR (CDCl_3) 0.0 (s, 9H); 0.8 (m, 2H), 1.8 (m, 2H), 2.3 (s, 3H), 3.7 (br s, 2H), 3.9 (m, 2H), 7.3 (m, 5H).

General Method for Reductive Cleavage of Isoxazolidines and Debenzylation Using Hydrogen and Palladium Hydroxide.

Isoxazolidine (0.5 mmol), palladium hydroxide (20% on carbon, 100 mg), and absolute ethanol (10 mL) were stirred under atmospheric hydrogen for 4 h. After hydrogen removal, the suspension was warmed in a hot water bath, and the catalyst removed by filtration through paper. Removal of the solvent in vacuo gave the crude product which was further purified by flash chromatography (silica, 3:1 hexane/EtOAc).

Hydroxymethyl γ -Lactone 101 (from Isoxazolidine 66, Major Isomer).

Clear oil (46%). $R_f = 0.5$ in 1:1 hexane/EtOAc; IR (CCl_4) 3400 (w), 2950 (m), 1785 (s), 1750 (s), 1200 (br,

s); ^1H NMR (CDCl_3) 0.2 (s, 9H), 1.6 (dd, $J = 6.0, 9.2$, 1H), 2.2 (s, 3H), 4.1 (d, $J = 9.2$, 1H), 4.2 (m, 2H), 4.7 (m, 1H).

Acetoxymethyl γ -Lactone 103 (from Isoxazolidine 102, Major Isomer)

Clear oil (46%). $R_f = 0.5$ in 1:1 hexane/EtOAc; IR (CCl_4) 3400 (w), 2950 (m), 1785 (s), 1750 (s), 1200 (br, s); ^1H NMR (CDCl_3) 0.2 (s, 9H), 1.6 (dd, $J = 6.0, 9.2$, 1H), 2.2 (s, 3H), 4.1 (d, $J = 9.2$, 1H), 4.2 (m, 2H), 4.7 (m, 1H).

General Method for the Formation of Unsaturated Amines from Amino Hydroxysilanes Under Basic (*Syn*-Elimination) Conditions (Method A).

KH (2 eq, 35% dispersion in mineral oil) was weighed into a flask and washed with hexane (3X), and the hexane replaced with THF (5 mL). The substrate, dissolved in THF (2 mL), was added slowly via syringe and the mixture stirred for 1h. Water (1 mL) was carefully added to quench excess hydride and then the solvent removed in vacuo. To the residue was added 5% Na_2CO_3 solution (10 mL) and extracted with EtOAc (3 x 15 mL). After drying (Na_2CO_3) the organic layer yielded the amine which was further purified by distillation or chromatography (hexane/EtOAc).

General Method for the Formation of Unsaturated Amines from Amino Hydroxysilanes Under Acidic (*Anti*-Elimination) Conditions (Method B).

To the substrate was added solvent and acid. If the substrate contained the γ -lactone and/or carbethoxy functionalities, elimination was carried out in $\text{HCl} \cdot \text{EtOH}$ (1 M, 5 mL) at 60° for 2-4 h. Other substrates were stirred in THF (25 mL) containing catalytic sulfuric acid (5 drops) for 12 h. Upon completion of the reaction, the solvent was removed, 5% Na_2CO_3 solution (10 mL) added and extracted with EtOAc (3 x 15 mL). The extracts were combined, dried (Na_2CO_3) and concentrated in vacuo yielding the crude amine. Further purification was affected by distillation or chromatography (hexane/ EtOAc).

General Method for the Formation of Unsaturated Amines from Trimethylsilylisoxazolidines (Method C).

A slurry of zinc dust and isoxazolidine (0.5 mmol) were stirred in solvent (10 mL) at 60° for 2-4 h. If the substrate contained the carbethoxy group, the reduction/elimination was carried out in $\text{HCl} \cdot \text{EtOH}$ (1M). Otherwise, the reaction was carried out in THF/10% HCl (aq) (1:1). Upon completion, the mixture was cooled and the solvent removed in vacuo. Aqueous Na_2CO_3 (10 mL) and EtOAc (20 mL) were added and the precipitated zinc salts were filtered off. The aqueous layer was extracted twice

more with EtOAc, the organic layer dried over Na_2CO_3 and the solvent removed in vacuo. Distillation or chromatography (hexane/EtOAc) yielded the pure amine.

1-N-Methylamino-1,3-Diphenyl-2-(E)-Propene 84.

Conditions: from 92 (method A, 84%), from 91 (method B, 72%), from 55 (method C, 85%). Clear oil (70-72°, 2 mm). IR (film) 3300 (br, m) 3010 (m), 2940 (m), 1440 (m), 945 (m); ^1H NMR (CDCl_3) 2.4 (s, 3H), 4.3 (d, $J = 7.4$, 1H), 6.3 (dd, $J = 7.4$, 15.8, 1H), 6.6 (d, $J = 15.8$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 223 (M^+ , 100), 193 (18), 146 (43), 120 (24).

1-N-Methylamino-1,3-Diphenyl-2-(Z)-Propene 85.

Conditions: from 91 (method A, 84%), from 92 (method B, 84%), from 56 (method C, 75%). Clear oil (70-72°, 2 mm). IR (film) 3300 (br, m) 3020 (w), 2910 (m), 1440 (m), 670 (s); ^1H NMR (CDCl_3) 2.3 (s, 3H), 4.6 (d, $J = 9.7$, 1H), 5.8 (dd, $J = 9.7$, 11.6, 1H), 6.6 (d, $J = 11.6$, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 223 (M^+ , 74), 193 (39), 146 (41), 120 (100).

1-N-Methylamino-1-Phenyl-2-(Z)-Heptene 86.

Conditions: from 57 (method C, 89%). Clear oil (110°, 1 mm); IR (film) 3030 (m), 2940 (m), 1600 (m), 1450 (m), 675 (m); ^1H NMR (CDCl_3) 0.8 (t, $J = 7.0$, 3H), 1.3 (m, 4H), 2.1

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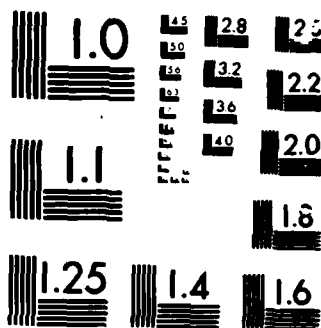
THE USE OF NITRONE CYCLOADDITIONS IN THE SYNTHESIS OF
BETA-AMINO ALDEHYDES AND UNSATURATED AMINES(U) AIR
FORCE INST OF TECH WRIGHT-PATTERSON AFB OH S W LANDER
1986 AFIT/CI/NR-86-41D F/G 7/3

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(m, 2H), 2.3 (s, 3H), 4.3 (d, $J = 6.1$), 5.4 (m, 2H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 203 (M^+ , 3), 202 (16), 172 (100), 120 (19).

1-N-Methylamino-1-Phenyl-2-(E)-Heptene 87.

Conditions: from 93 (method A, 81%). Clear oil (110°, 1.4 mm). IR (film) 3020 (w), 2950 (m), 1450 (m), 950 (m), 675 (m); ^1H NMR ($CDCl_3$) 0.9 (t, $J = 6.8$, 3H), 1.3 (m, 4H), 2.0 (m, 2H), 2.4 (s, 3H), 4.0 (d, $J = 6.8$, 1H), 5.5 (dd, $J = 6.8$, 15.2, 1H), 5.6 (d, t, $J = 6.3$, 15.2, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 203 (M^+ , 5), 202 (26), 172 (96), 120 (100).

Ethyl 2-N-Benzylamino-4-Phenyl-3-(E)-Butenoate 88.

Conditions: from 62 (method B, 83%). Yellow oil. IR (CCl_4) 3020 (m), 2970 (w), 1735 (s), 1160 (s); ^1H NMR ($CDCl_3$) 1.3 (t, $J = 7.1$, 3H), 2.2 (br s, 1H), 3.8 (s, 2H), 4.0 (d, $J = 7.2$, 1H), 4.2 (q, $J = 7.1$, 2H), 6.2 (dd, $J = 7.2$, 15.9, 1H), 6.7 (d, $J = 15.9$, 1H), 7.4 (m, 10H); mass spectrum, m/z (relative intensity, %) 295 (M^+ , 1), 222 (77), 91 (100)

Ethyl 2-N-Benzylamino-4-Phenyl-3-(Z)-Butenoate 89.

Conditions: from 63 (method C, 78%). Yellow oil. IR (CCl_4) 3020 (m), 2970 (m), 1735 (vs), 1170 (s); ^1H NMR ($CDCl_3$) 1.3 (t, $J = 7.1$, 3H), 2.2 (br s, 1H), 3.7 (A of

ABq, $J = 12.9$, 1H), 3.8 (B of ABq, $J = 12.9$, 1H), 4.3 (q, $J = 7.1$, 2H), 4.4 (d, $J = 9.9$, 1H), 5.7 (dd, $J = 9.9, 11.4$, 1H), 6.8 (d, $J = 11.4$, 1H), 7.3 (m, 10H).

Ethyl 2-N-Benzylamino-5-Hydroxy-3-(E)-Pentenoate 90.

Conditions: from 66 (method B or C, 30%). Yellow oil. IR (CCl₄) 3620 (w), 3010 (w), 2970 (m), 1730 (vs), 1160 (s); ¹H NMR (CDCl₃) 1.3 (t, $J = 7.2$, 3H), 3.7 (A of ABq, $J = 13.5$, 1H), 3.8 (B of ABq, $J = 13.5$, 1H), 3.9 (d, $J = 6.6$, 1H), 4.2 (m, 2H), 4.2 (q, $J = 7.2$, 2H), 5.7 (dd, $J = 6.6$, 15.5, 1H), 6.0 (dt, $J = 5.0$, 15.5, 1H), 7.3 (m, 5H).

1-N-Methyamino-1-Phenyl-3-Butene 107.

Conditions: from 106 (method B, 71%), from 69 (method C, 30%). Clear oil (40-2°, 2 mm). IR (film) 3300 (br, w), 3010 (w), 2930 (w), 1640 (m), 680 (s); ¹H NMR (CDCl₃) 2.2 (s, 3H), 2.4 (m, 2H), 3.5 (dd, 1H), 5.0 (m, 2H), 5.7 (m, 1H), 7.3 (m, 5H); mass spectrum (CI), m/z (relative intensity, %) 162 ($M + 1^+$, 62), 160 (45), 131 (100), 120 (100).

Ethyl 2-N-Benzylamino-4-Pentenoate 108.

Conditions: from 70 (method B, 78%; method C, 30%). Yellow oil. IR (CCl₄) 3020 (w), 2970 (m), 1730 (br, s), 1150 (m); ¹H NMR (CDCl₃) 1.3 (t, $J = 7.1$, 3H), 1.9 (br s,

1H), 2.4 (t, J = 6.4, 2H), 3.4 (t, J = 6.4, 1H), 3.7 (A of ABq, J = 17.3, 1H), 5.1 (d, J = 8.9, 1H), 5.8 (m, 1H), 7.3 (m, 5H).

General Method for the Trichloroacetylation of Amines.

To a solution of amine (1 mmol) in pyridine (2 mL) was added trichloroacetic anhydride (1 mL) and stirring continued for 12-16 hrs. The solution was concentrated, dissolved in CH₂Cl₂, washed with CuSO₄ (aq) (2 x 10 mL) and brine, dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (silica, hexane/EtOAc) of the residue yielded the product amide. Gas chromatographic analysis confirmed no double bond isomerization (if applicable) had occurred.

γ -Lactam 104.

Yellow oil (58%). R_f = 0.4 in 1:1 hexane/EtOAc; IR (CCl₄) 2940 (m), 1785 (s), 1750 (s), 1720 (s), 1100 (s); ¹H NMR (CDCl₃) 0.1 (s, 9H), 2.1 (s, 3H), 2.2 (dd, J = 3.4, 10.9, 1H), 4.3 (m, 2H), 4.8 (dd, J = 3.4, 5.0, 1H), 5.0 (dd, J = 6.0, 10.9, 1H).

1-(N-Trichloroacetamido-N-Methyl)-1,3-Diphenyl-2-(E)-Propene 111.

Yellow oil (91%). IR (film) 3030 (m), 2920 (m), 1670 (vs), 955 (m), 645 (m); ¹H NMR (CDCl₃) 3.1 (s, 3H), 6.4 (m,

2H), 6.6 (m, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 367 (M⁺, 7), 332 (70), 296 (54), 250 (54), 115 (100).

1-(N-Trichloroacetamido-N-Methyl)-1,3-Diphenyl-2-(Z)-Propene
112.

Yellow oil (92%). IR (film) 3020 (m), 1670 (s), 1085 (m); ¹H NMR 3.2 (s, 3H), 5.9 (dd, J = 9.3, 11.4, 1H), 6.6 (d, J = 9.3, 1H), 6.9 (d, J = 11.4, 1H), 7.3 (m, 10H); mass spectrum, m/z (relative intensity, %) 367 (M⁺, 3), 332 (53), 296 (42), 115 (100).

1-(N-Trichloroacetamido-N-Methyl)-1-Phenyl-2-(E)-Heptene
113.

Yellow oil (film) 3020 (w), 2940 (m), 1675 (s), 950 (m); ¹H NMR (CDCl₃) 0.9 (t, J = 6.7, 3H), 1.4 (m, 4H), 2.2 (dt, J = 6.3, 6.5, 2H), 3.1 (s, 3H), 5.8 (dt, J = 5.9, 15.5, 1H), 5.9 (dd, J = 6.3, 15.5, 1H), 6.3 (d, J = 5.9, 1H), 7.3 (m, 5H).

1-(N-Trichloroacetamido-N-Methyl)-1-Phenyl-2-(Z)-Heptene
114.

Yellow oil (65%). IR (CCl₄) 3020 (w), 2950 (m), 1675 (s), 1080 (m); ¹H NMR (CDCl₃) 0.8 (m, 3H), 1.3 (m, 4H), 2.1 (m, 2H), 3.1 (s, 3H), 5.8 (m, 2H), 6.6 (d, J = 8.0, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 347 (M⁺, 6), 312 (89), 276 (38), 117 (100).

1-(N-Trichloroacetamido-N-Methyl)-1-Phenyl-3-(Z)-Butene

115.

Yellow oil (92%). IR (CCl₄) 3060 (w), 2950 (w), 1675 (vs), 1390 (m); ¹H NMR (CDCl₃) 2.8 (m, 2H), 3.0 (s, 3H), 5.2 (m, 2H), 5.8 (m, 2H), 7.3 (m, 5H).

General Method for the Formation of γ -Lactams from Allylic Trichloroacetamides.

To a solution of allylic trichloroacetimide (0.5 mmol) and CH₃CN (5 mL) in a pressure tube was added CuCl (8 mol percent) and Et₃N (15 mol percent). The tube contents were heated to 130° for 12-16 h. Initially, the lime green solution rapidly turned yellow and then brown. The product mixture was concentrated and separated via radial chromatography (1 mm, 1:1 hexane/Et₂O) yielding the isomeric γ -lactams.

Diphenyl- γ -Lactam 116.

Conditions: from 111 or 112: Isolated in 75% yield as a 10:1 mixture of epimers. Major isomer (116a): mp 186-7°; R_f 0.25 in 1:1 hexane/Et₂O. IR (CCl₄) 3020 (w), 2910 (m), 1735 (vs), 1390 (m); ¹H NMR (CDCl₃) 2.7 (s, 3H), 3.5 (dd, J = 6.4, 7.3, 1H), 4.7 (d, J = 6.4, 1H), 5.6 (d, J = 7.3, 1H), 7.3 (m, 5H); mass spectrum, m/z (relative intensity, %) 371 (M⁺+4, 8), 369 (M⁺+2, 25), 367 (M⁺, 25), 332 (11), 242 (100); Anal. Calcd: C, 58.64; H, 4.37. Found: C, 58.46; H, 4.37. Minor isomer (116b): R_f = 0.20. IR (CCl₄) 3020

(w), 2910 (m), 1740 (vs); ^1H NMR 2.5 (s, 3H), 3.6 (dd, $J = 7.9$, 10.4, 1H), 4.0 (d, $J = 7.9$, 1H), 5.3 (d, $J = 10.4$, 1H), 7.3 (m, 10H).

X-Ray Crystal Data for 116a (Major Isomer).

Formula: $\text{C}_{18}\text{H}_{16}\text{Cl}_3\text{NO}$, Mr 368.7, triclinic, space group $P\bar{1}$, $a = 10.360(1)$, $b = 10.397(1)$, $c = 10.810(2)$ Å, $Z = 2$, $D_{\text{calc}} = 1.44$ g cm $^{-3}$, $F(000) = 380$, $\text{MoK}\alpha$ radiation $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 5.42$ cm $^{-1}$,

A crystal measuring 0.40 x 0.35 x 0.15 mm was used for data collection with an Enraf-Nonius CAD4 diffractometer. Accurate unit cell data and the crystal orientation matrix were determined from a least-squares refinement of the setting angles of 25 reflections with $10 \leq \theta \leq 15^\circ$. Intensity data were collected in the range $2 \leq \theta \leq 25^\circ$ by the $w/2\theta$ scan method using monochromatic MoK radiation. The intensities of three reflections chosen as standard were monitored every 2 h of exposure time and showed no significant variation. Intensities of 2999 unique reflections were measured of which 2336 had $I \geq 3 \sigma(I)$ and were used in the structure solution and refinement. Data were corrected for Lorentz polarization factors. The linear absorption coefficient was sufficiently small that absorption correction was deemed unnecessary.

The structure was solved by direct methods with MULTAN'82.⁵² The first E-map revealed all the non-hydrogen atoms. Initial full-matrix least-squares refinement

allowing the atoms isotropic vibrations reduced R to 0.133, which dropped to 0.058 after allowing for anisotropic thermal motion in the refinement. A difference map at this stage revealed positions of all 16 protons; these were included in the refinement with isotropic temperature factors. The refinement converged with $R = 0.031$ and $R_w = (\sum w\Delta^2 / \sum wF_o^2) = 0.048$. In the refinement cycles, weights were derived from the counting statistics, $w = 1/(\sigma^2 F + 0.05F^2)$,⁵³ and scattering factors were taken from Cromer and Mann⁵⁴ and Stewart, Davidson and Simpson⁵⁵. A final difference map was free of any significant features. Final fractional coordinates and details of molecular geometry are attached as supplementary data.

n-Butyl-Phenyl- γ -Lactam 117.

Conditions: formed from either 113 (65%) or 114 (85%) as a 2:1 mixture of epimers. Major isomer: yellow oil; $R_f = 0.38$ in 1:1 hexane/Et₂O. IR (CCl₄) 2950 (m), 1735 (vs), 690 (s); ¹H NMR (CDCl₃) 0.9 (t, $J = 7.0$, 3H), 1.3 (m, 4H), 1.7 (m, 1H), 1.9 (m, 1H), 2.7 (s, 3H), 3.1 (dd, $J = 6.1$, 6.7, 1H), 4.4 (m, 1H), 4.6 (d, $J = 6.7$, 1H), 7.4 (m, 5H). Minor isomer (117b): yellow oil; $R_f = 0.25$. IR (CCl₄) 2950 (m), 1735 (vs), 690 (s); ¹H NMR (CDCl₃) 0.8 (t, $J = 7.0$, 3H), 1.3 (m, 4H), 1.6 (m, 1H), 1.8 (m, 1H), 2.7 (s, 3H), 3.2 (t, $J = 7.0$, 1H), 4.3 (m, 1H), 4.5 (d, $J = 7.0$, 1H), 7.4 (m, 5H).

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APPENDIX

Supplementary Data for X-Ray Structure
of γ -Lactam 116a

Table of Bond Distances in Angstroms

Atom1 =====	Atom2 =====	Distance =====	Atom1 =====	Atom2 =====	Distance =====	Atom1 =====	Atom2 =====	Distance =====
C(1)	H(11)	0.91(2)	C(52)	H(52)	0.92(3)	C(63)	H(63)	0.94(3)
C(1)	H(12)	0.95(3)	C(53)	H(53)	0.88(2)	C(64)	H(64)	0.89(3)
C(1)	H(13)	1.00(2)	C(54)	H(54)	1.01(3)	C(65)	H(65)	1.00(3)
C(4)	H(4)	0.90(2)	C(55)	H(55)	0.87(3)	C(66)	H(66)	0.91(3)
C(5)	H(5)	0.88(2)	C(56)	H(56)	0.95(5)			
C(6)	H(6)	1.03(2)	C(62)	H(62)	0.95(2)			

 Numbers in parentheses are estimated standard deviations in the least significant digits.

Table of Bond Distances in Angstroms

Atom1 =====	Atom2 =====	Distance =====	Atom1 =====	Atom2 =====	Distance =====	Atom1 =====	Atom2 =====	Distance =====
CL(1)	C(3)	1.800(2)	C(4)	C(5)	1.552(3)	C(55)	C(56)	1.383(3)
CL(2)	C(3)	1.762(2)	C(4)	C(6)	1.540(2)	C(61)	C(62)	1.385(3)
CL(3)	C(6)	1.801(2)	C(5)	C(51)	1.517(3)	C(61)	C(66)	1.379(3)
O	C(2)	1.211(2)	C(6)	C(61)	1.513(2)	C(62)	C(63)	1.382(3)
N	C(1)	1.441(2)	C(51)	C(52)	1.372(3)	C(63)	C(64)	1.366(3)
N	C(2)	1.340(2)	C(51)	C(56)	1.396(2)	C(64)	C(65)	1.375(3)
N	C(5)	1.464(3)	C(52)	C(53)	1.385(3)	C(65)	C(66)	1.375(3)
C(2)	C(3)	1.531(2)	C(53)	C(54)	1.373(3)			
C(3)	C(4)	1.532(2)	C(54)	C(55)	1.363(3)			

 Numbers in parentheses are estimated standard deviations in the least significant digits.

Table of Bond Angles in Degrees

Atom1 -----	Atom2 -----	Atom3 -----	Angle -----	Atom1 -----	Atom2 -----	Atom3 -----	Angle -----	Atom1 -----	Atom2 -----	Atom3 -----	Angle -----
C(1)	N	C(2)	122.2(1)	C(3)	C(4)	C(6)	115.7(1)	C(53)	C(54)	C(55)	119.4(2)
C(1)	N	C(5)	121.8(1)	C(5)	C(4)	C(6)	112.8(2)	C(54)	C(55)	C(56)	120.9(2)
C(2)	N	C(5)	115.8(1)	N	C(5)	C(4)	103.3(2)	C(51)	C(56)	C(55)	119.9(2)
O	C(2)	N	127.1(2)	N	C(5)	C(51)	113.4(2)	C(6)	C(61)	C(62)	124.1(2)
O	C(2)	C(3)	126.2(2)	C(4)	C(5)	C(51)	115.2(2)	C(6)	C(61)	C(66)	117.1(2)
N	C(2)	C(3)	106.7(1)	CL(3)	C(6)	C(4)	110.6(1)	C(62)	C(61)	C(66)	118.7(2)
CL(1)	C(3)	CL(2)	107.85(9)	CL(3)	C(6)	C(61)	112.3(1)	C(61)	C(62)	C(63)	120.2(2)
CL(1)	C(3)	C(2)	106.0(1)	C(4)	C(6)	C(61)	110.6(1)	C(62)	C(63)	C(64)	120.5(2)
CL(1)	C(3)	C(4)	109.8(1)	C(5)	C(51)	C(52)	122.8(2)	C(63)	C(64)	C(65)	119.6(2)
CL(2)	C(3)	C(2)	111.3(1)	C(5)	C(51)	C(56)	118.4(2)	C(64)	C(65)	C(66)	120.2(2)
CL(2)	C(3)	C(4)	116.1(1)	C(52)	C(51)	C(56)	118.7(2)	C(61)	C(66)	C(65)	120.7(2)
C(2)	C(3)	C(4)	105.4(1)	C(51)	C(52)	C(53)	120.5(2)				
C(3)	C(4)	C(5)	103.6(1)	C(52)	C(53)	C(54)	120.5(2)				

 Numbers in parentheses are estimated standard deviations in the least significant digits.

VITA

Stephen Warren Lander, Jr. was born in Pittsburgh, Pennsylvania, on October 22, 1948, the only child of Stephen Warren and Florence Marie Lenco Lander. He attended South Hills Catholic High School, graduating with honors. He received a Bachelor of Science degree in Chemistry from Duquesne University in May 1970 and was commissioned in the United States Air Force after being an ROTC Distinguished Graduate. During a delay of active duty, he obtained a Master of Science degree in Organic Chemistry at The Pennsylvania State University (1973). He received a Master of Science degree in Business Management from the University of Northern Colorado (1983).

He has served as a scientist and project engineer at the A.F. Armament Laboratory; a program manager at the A.F. Aeronautical Systems Division; and instructor and Head of the Department of Chemistry at the USAF Academy Preparatory School. He was selected for sponsorship for graduate study by the AF Institute of Technology, being readmitted to The Pennsylvania State University for doctoral study under Professor P. R. DeShong in August 1983.

He married the former Linda Rebecca Krumrine (PSU '71) of State College, Pennsylvania, in October 1972 and has three sons: Nathan Reed (b. Oct. '77), Timothy Allen (b. Jul. '78), and Andrew Warren (b. Sept. '80).

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