A STUDY OF THE REARRANGEMENT OF THE bis-SILYLATED DIANION OF SUBSTITUTED ALLYL N-PHENYLACETYLGLYCINATES

by

MRINAL SHARMA

A Thesis Submitted to the Faculty of Graduate Studies and Research of McGill University in Partial Fulfillment of the Requirements for the Degree of Master of Science

Department of Chemistry
McGill University
Montreal, Quebec, Canada
© October 1984
Dedicated to my mother: my greatest teacher

and

My brother-in-law: a constant source of inspiration
Chemistry

M.Sc.

A STUDY OF THE REARRANGEMENT OF THE \( \text{bisilylated dianion} \)
OF SUBSTITUTED ALLYL N-PHENYLACETYLGLYCINATES

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ABSTRACT

The stereochemical outcome of the ester enolate Claisen rearrangement of 3'-substituted allyl N-phenylacetylglycinates was investigated\(^1\). E-Crotyl N-phenylacetylglycinate gave a 9:1 threo to erythro diastereomeric mixture, which was reversed in the case of its Z counterpart. Substitution of trimethylsilyl for methyl, in the case of the E isomer, resulted in an appreciable loss of stereoselectivity. The rearrangement of E-3'-chloroallyl N-phenylacetylglycinate gave an inseparable mixture of the expected product and the product of elimination.
Chimie M.Sc.

ETUDE DU REARRANGEMENT DES ANIONS DOUBLES bia-SILYLES DE N-PHENYLACETYLE GLYCINATES D'ALLYLE SUBSTITUES.

par

Mrinal Sharma

RESUME

La stéréochimie du réarrangement de Claisen des énolates d'ester a été étudiée pour des glycinates d'allyle substitués. Un mélange diastéréomérique avec un rapport thréo à érythro de 9:1 a été obtenu pour le glycinate de E-crotyl N-phénylacétyle. Ce rapport était inversé dans le cas de l'isomère "Z". En substituant un groupe -Si(CH₃)₃ au méthyle, de l'isomère "E", la stéréosélectivité du réarrangement est passablement diminuée. Le réarrangement du E-chloroallyl-3' N-phénylacétylglycinate a donné un mélange inséparable du produit attendu et du produit d'élimination.
ACKNOWLEDGEMENTS

I would especially like to express my gratitude to Dr. George Just, without whose understanding, patience, guidance and encouragement, this work would not have been possible.

I also wish to thank:
- The Chemistry Department of McGill University for financial support in the form of teaching assistantships and scholarships;
- Natural Sciences and Engineering Research Council of Canada for a NSERC Scholarship 1983-1984;
- Dr. A.O. Mamer and associates for recording mass spectra;
- Dr. Françoise Sauriol, and Brian O'Connor for recording 300/200 MHz nmr spectra;
- Dr. Matthias Kamber for HPLC separation;
- Ms. Joan Boivin for translating the abstract into French;
- Mrs. A. Cerrone-Mancini for efficient typing;
- and to all my co-workers, especially Dr. A. Padmapriya and G. Sacripante who, with their sustained friendship, helpful discussions both in research and courses, have made my stay worthwhile and enjoyable.
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# Glossary of Abbreviations

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<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>br.</td>
<td>Broad</td>
</tr>
<tr>
<td>br.d</td>
<td>Broad doublet</td>
</tr>
<tr>
<td>br.s</td>
<td>Broad singlet</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet</td>
</tr>
<tr>
<td>2dd</td>
<td>Two doublet of doublets</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>DCC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>EA</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>eq</td>
<td>Equivalents</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>2m</td>
<td>Two multiplets</td>
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<td>Methyl</td>
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<tr>
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<td>mL</td>
<td>Milliliter</td>
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<td>mmol</td>
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<tr>
<td>ms</td>
<td>Mass spectrum</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear overhauser effect</td>
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<tr>
<td>PMR</td>
<td>Proton magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluene sulphonate</td>
</tr>
<tr>
<td>PE</td>
<td>Petroleum ether</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>2s</td>
<td>Two singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
<tr>
<td>TMSCL</td>
<td>Trimethylsilyl chloride</td>
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Introduction

Since the discovery of penicillin, a great deal of research effort has been focused on the synthesis of related penams. Medicinal chemists have made many structural modifications on the penicillins in their search for materials with better therapeutic properties for the treatment of bacterial infections.

It has been shown that penicillins interfere in the terminal step of bacterial cell wall biosynthesis. They do this by acylation (via the β-lactam carbonyl) of membrane associated enzymes (e.g. trans peptidases) which affect the cross-linking of linear peptidoglycan, thereby preventing the formation of the peptide bridges which give structural strength to the cell wall.

Recently, Keith et al. have proposed a mechanism which attempts to elucidate the mode of action, as far as penicillin G is concerned. They have proposed, as shown in Figure 1, that hydration of the amide side chain of the antibiotic leads to an intermediate in which a newly generated nucleophilic function is ideally located for intramolecular attack on the β-lactam carbonyl function. Further transformation of 2 to a highly reactive oxazolone sets the stage for the irreversible acylation of the penicillin sensitive enzyme (e.g. trans peptidase), as in 4.
Figure 1

It is shown that steric strain of the β-lactam (ν ≥ 1765 cm⁻¹) is responsible for the chemical reactivity and hence the biological activity of β-lactam antibiotics. But this
Steric strain can be replaced by strain generated by electron withdrawing groups attached to the nitrogen atom of the β-lactam moiety as in the case of monobactams \(^5\) and mono-phospham \(^6\).

\[
\begin{align*}
\text{CH}_3\text{CONH} & \text{H} \\
\text{O} & \text{N} \\
\text{SO}_3^- & \\
5
\end{align*}
\]

Also, it is known that an increase in ring strain of the β-lactam, as exhibited by an increase in the IR stretching frequency of the β-lactam carbonyl band, leads to an increase in its activity \(^7\). Therefore, it can be envisioned that an activated β-lactam function \(\nu \geq 1765 \text{ cm}^{-1}\), which is postulated to act as an acylating agent (Figure 1), could be replaced by a saturated \((\nu \geq 1780 \text{ cm}^{-1})\) or \(\beta,\gamma\)-unsaturated lactone \((\nu \geq 1800 \text{ cm}^{-1})\) \(^8\), which should have similar acylating properties. Synthesis of the former was carried out by Dr. Kamber of our laboratories following the scheme outlined in Figure 2 \(^9\).

We decided to explore this approach for the synthesis of \(\beta,\gamma\)-unsaturated lactones of type A, which would have mono-alkyl phosphono ester at the γ-position, rendering it
Figure 2

structurally similar to monophospham 6, and hence allowing it to mimic similar antibiotic properties.

A plausible route to A is depicted in Figure 3.

As shown in Figure 3, synthesis of A is possible through two routes. In the shorter of these two, elimination of chlorine is shown to give α,β and β,γ-unsaturated lactones. β,γ- Unsaturated lactone 11 is then converted to A.
Figure 3
However, the other route, where $X = \text{SPh, SePh and Si(CH}_3\text{)}_3$, involves an additional step of oxidation.

Compounds of type 7 (Figure 3, page 5) can be obtained, in principle, by ester enolate Claisen rearrangement of 3'-substituted allyl N-phenylacetylglycinate. However, the stereochemical course of the rearrangement for various 3'-substituted allyl N-phenylacetylglycinates has not been explored yet. With this objective in mind, we decided to synthesize various stereochemically pure 3'-substituted allyl N-phenylacetylglycinates. It was believed that their rearrangement would offer an insight into the stereoselectivity of ester enolate Claisen rearrangements, and also a way to the synthesis of $\beta,\gamma$-unsaturated lactone A. In the first chapter of this thesis, we will deal with the synthesis of 3'-substituted allyl N-phenylacetylglycinates, and in the second chapter we will look at the rearrangement reactions and their stereoselectivity.

To avoid, at times, a confusing nomenclature because of priority changes when going from CH$_3$ to Si(CH$_3$)$_3$ to Cl, we will be using a threo and erythro notation, as exemplified below, in which the carbomethoxy group will be equivalent to the vinyl group.
Synthesis of E-crotyl N-phenylacetylglucinate (17)

In our first attempt to synthesize the E-crotyl ester, glycine was allowed to react with an excess crotyl alcohol and three equivalents of chlorotrimethylsilane according to the method of Brook and Chan10. Whereas this method was successful for making the allyl esters of glycine9, it failed in this case because of the low solubility of glycine in crotyl alcohol. We therefore decided to first acylate glycine with phenylacetyl chloride in aqueous bicarbonate. This reaction also failed, and only phenylacetic acid was recovered.

Clearly, a new approach was warranted, namely formation of glycine methyl ester hydrochloride, acylation and then transesterification, using the alcohol of choice, to provide 3'-substituted allyl N-phenylacetylglucinates. This approach is outlined in Figure 4 (page 8), also shown is the approach which involves a DCC mediated coupling between N-phenylacetylglucine and the alcohol of choice to effect the synthesis of desired esters1.

Using the method of Brook and Chan10, methyl glycinate hydrochloride 13 was obtained in quantitative yield. Then a methylene chloride solution of methyl glycinate hydrochloride was treated with triethylamine and phenylacetyl chloride to provide methyl N-phenylacetylglucinate in close to quantitative yield. The methyl ester 14, was then directly
Synthesis of 3'-substituted allyl N-phenylacetylglycinates

\[
\text{NH}_2\text{CH}_2\text{COOH} + \text{Cl}^-\text{NH}_3^+\text{CH}_2\text{COOMe} \rightarrow \text{PhCH}_2\text{CONHCH}_2\text{COOMe}
\]

26 PhCH\text{CONHCH}_2\text{COOH}

\[\text{DCC coupling}\]

15 \(Y=\text{Cl}, X=\text{H}\)

16 \(Y=\text{Si(CH}_3)_3, X=\text{H}\)

17 \(X=\text{H}, Y=\text{CH}_3\)

18 \(X=\text{CH}_3, Y=\text{H}\)

19 \(X=\text{CH}_3, Y=\text{CH}_3\)

20 \(X=\text{H}, Y=\text{Si(CH}_3)_3\)

21 \(X=\text{H}, Y=\text{Cl}\)

\text{Figure 4}
transformed to crotyl ester 17, by an adaptation of Brook and Chan's method, in which a crotyl alcohol solution of the methyl ester containing TMSCl was stirred overnight at room temperature. Crystallization then gave E-crotyl N-phenylacetylglycinate (17) in 76% yield. PMR data of 17 gave a coupling constant of 15.3 Hz for the olefinic protons, hence indicating a E geometry of the double bond. The synthesis of dimethylallyl N-phenylacetylglycinate 19 was effected in a similar manner. Transesterification proceeded with a yield of 56% to give 19.

Synthesis of Z-crotyl N-phenylacetylglycinate (18)

Synthesis of 18 was realized by hydrogenation of 2-butynyl N-phenylacetylglycinate 22, which is easily synthesized by a transesterification reaction as shown below (Figure 5).

\[
\begin{align*}
\text{PhCH}_2\text{CONH}_2\text{COO} & \text{Me} & \xrightarrow{\text{TMSCl}} & \text{PhCH}_2\text{CONHCH}_2\text{COOCH}_2\text{C}=\text{CCH}_3 \\
\text{2-butyn-1-ol} & & \text{Ni boride} & \\
\text{CH}_3\text{C}=\text{CCH}_2\text{OH} & & \text{H}_2 & \\
\text{PhCH}_2\text{CONHCH}_2\text{COOCH}_2\text{C}=\text{CCH}_3 & \xrightarrow{\text{H}_2} & \text{PhCH}_2\text{CONHCH}_2\text{COOCH}_2\text{C}=\text{CCH}_3
\end{align*}
\]

Figure 5
Compound 18 was obtained in an overall 67% yield. A coupling constant of 10 Hz, between alkene protons indicated the formation of the cis isomer exclusively. The mass spectral data of 18 indicated that some over reduction did take place, since a peak was observed at 249, indicating reduction of the double bond. However, the PMR spectrum appeared quite clean, indicating that the over reduction product was probably less than 3%. Compound 18 was subjected to rearrangement without any further purification, since the saturated ester would not undergo a rearrangement, and therefore would not interfere in the interpretation of the results.

**Synthesis of E-3'-trimethylsilylallyl N-phenylacetylglucinate (20)**

Synthesis of 20 involves coupling between E-3'-trimethylsilylallyl alcohol 16 (Figure 6, page 11) and N-phenylacetylglucine. In this field, Marcel Banasinski of our laboratories had already done some preliminary work. He had developed an efficient synthesis of E and Z 3'-trimethylsilylallyl alcohol, and studied the rearrangement of their corresponding N-carbobenzyloxyglucine esters. In that study, he showed that the E ester rearranged in about 5% yield, and that the Z ester did not rearrange at all. Since it seemed important to confirm these results, we decided to repeat the reaction of the E-ester on the analogous N-phenylacetylglucine ester.
This required an efficient synthesis of 16, which was done using the scheme below (Figure 6).

\[
\text{HC} = \text{CHCH}_2\text{OH} \rightarrow \text{HC} = \text{CHCH}_2\text{OC(CH}_3)_2\text{OMe} \rightarrow \text{Si(CH}_3)_3\text{C} = \text{CHCH}_2\text{OC(CH}_3)_2\text{OMe}
\]

\[
\text{PhCH}_2\text{CONHCH}_2\text{COH \rightarrow PhCH}_2\text{CONHCH}_2\text{COOMe}
\]

\[
\text{Si(CH}_3)_3\text{C} = \text{CHCH}_2\text{OH} \rightarrow \text{HCCOCH}_2\text{COOH \rightarrow PhCH}_2\text{CONHCH}_2\text{COOMe}
\]

**Figure 6**

Starting with readily available propargyl alcohol, the hydroxyl group was protected to obtain methoxyisopropylidene propargyl alcohol 23 in 65% yield. Formation of the acetylenic anion by n-butyllithium at -78°C in dry THF, followed by silylation with chlorotrimethylsilane, gave 3'-trimethylsilyl-O-(methoxyisopropylidene)propargyl alcohol 24 in 83% yield. The removal of the protecting group
using a catalytic amount of pyridinium tosylate in methanol gave 25 in 84% yield\(^{13}\).

Reduction of 25 was effected by refluxing it with lithium aluminum hydride (1 eq) in dry THF for a duration of 15 h\(^{14}\). Thus, E-3'-trimethylsilyl alcohol 16 was obtained in 59% yield. The PMR spectrum of 16 (200 MHz, CDCl\(_3\)) confirmed the E stereochemistry of the compound since the AB coupling constant of vinyl protons was 18.9 Hz. The mass spectrum showed a strong peak at 73 (intensity = 71%), indicating the presence of the $\text{Si}(\text{CH}_3)_3$ fragment. Hydrolysis of methyl N-phenylacetylglutamic acid 14, using LiOH (1 eq) as a base, gave N-phenylacetylglutamine 26 in 80% yield. Esterification of this with E-3'-trimethylsilylallyl alcohol, using DCC as a coupling reagent and 4-dimethylaminopyridine as catalyst, gave 20 in 83% yield. PMR (300 MHz, CDCl\(_3\)) confirmed the trans-geometry of 20, since the AB coupling constant of the vinyl protons was 18.6 Hz.

**Synthesis of E-3'-chloroallyl N-phenylacetylglutamic acid (21)**

Synthesis of 21 was effected by esterification of E-3'-chloroallyl alcohol with N-phenylacetylglutamic acid 26. The former is readily obtained by stereospecific ring opening of epichlorohydrin with n-butyllithium as shown in Figure 7a. This procedure developed by Hoeg et al.\(^{15}\) provided E-3'-chloroallyl alcohol 15 in 70% yield. The PMR (200 MHz,
CDCl$_3$) data were in agreement with those reported in the literature. They showed the presence of one isomer only, having AB coupling constant of 13.3 Hz for the vinyl protons. Esterification of this alcohol with N-phenylacetylglucose 26, using DCC as coupling reagent and 4-dimethylaminopyridine as catalyst gave 21 in 93% yield. The PMR spectrum of 21 showed the presence of one isomer, having an AB coupling constant of 13.2 Hz for vinyl protons.
General spectroscopic data of 3'-substituted allyl N-phenylacetylglycinates

![Diagram](image)

**Figure 7b**

17 $X = H$, $Y = CH_3$

18 $X = CH_3$, $Y = H$

19 $X = CH_3$, $Y = CH_3$

20 $X = H$, $Y = Si(CH_3)_3$

21 $X = H$, $Y = Cl$

A general description of the spectroscopic data of compounds 17-21 is given below.

The PhCH$_2$ protons appear as singlet ($\delta$: 3.40-3.61). Immediately downfield to this appears the doublet arising from NHCH$_2$ protons ($\delta$: 3.90-4.00, $J = 4.76-8.0$ Hz). More downfield to this doublet, appears the signal arising from the OCH$_2$ protons ($\delta$: 4.53-4.60). The olefinic protons appear as multiplets ($\delta$: 5.34-6.32). In the case of E-crotyl N-phenylacetylglycinate 17, the terminal vinyl proton appears more downfield ($\delta$: 5.63-5.87), compared to the non-terminal olefinic proton $H_A$ (see Figure 7b), and on decoupling of the CH$_3$ signal it appears as a doublet ($J = 15.3$ Hz). The olefinic proton $H_A$ appears more upfield ($\delta$: 5.43-5.63) and on decoupling of allylic protons (OCH$_2$), it appears as a doublet ($J = 15.3$ Hz). The same type of pattern is observed for the olefinic protons in Z-crotyl N-phenylacetylglycinate 18.
In the case of E-3'-chloroallyl N-phenylacetylglycinate 21, the terminal vinyl proton appears as a triplet of doublets (δ: 6.27-6.37) due to long range coupling with OCH₂ (J = 1.5 Hz). The olefinic proton Hₐ appears as a triplet of doublets (δ: 5.93-6.02) as well, however in this case a higher J value (6.9 Hz) is observed.

In the case of E-3'-trimethylsilylallyl N-phenylacetyl­
glycinate 20, the terminal vinyl proton appears as a doublet (δ: 5.92, J = 18.6 Hz). The Hₐ proton appears as a triplet of doublets (δ: 5.94-6.07) due to its coupling with the -OCH₂ protons (J = 4.5 Hz).

The PMR spectra of compounds 20 and 21 are shown in Figures 8 and 9.

Compounds 17-21 all gave molecular ion peaks in their mass spectra, and all underwent McLafferty rearrangements to give peaks at 193 (PhCH₂CONHCH₂COOH).

\[
\text{PhCH₂CNHCH₂C} \xrightarrow{Y} \text{PhCH₂CNHCH₂COOH + CH₂C=C} \\
\]

X = H, CH₃, CH₃, H, H, respectively for 17-21
Y = CH₃, H, CH₃, Si(CH₃)₃, Cl, respectively for 17-21
Figure 8: 300 MHz PMR spectrum of compound 20.
Figure 9: 300 MHz PMR spectrum of compound 21.
The rearrangement of all the esters (17-21) was effected using a procedure developed by Bartlett and Barstow. This procedure involves formation of the dianions of substituted allyl esters at -78°C in THF. The dianions are then silylated, and the reaction mixture is heated to 50-60°C for 1 h. After hydrolysis of the thus formed silyl ester, the free acid is separated from unreacted esters by extraction into water of its sodium salt. Reacidification then gives free acid. This sequence of events is depicted in Figure 10 for the case of E-crotyl N-carbobenzyloxyglycinate: an ester the rearrangement of which has been studied by Bartlett and Barstow.

They report that the rearrangement of this E-crotyl glycinate proceeds in 65% yield to give a 9:1 diastereomeric mixture.

They proved the stereochemistry of the rearranged product by hydrogenating the double bond and deprotecting the amine functionality to get isoleucine diastereomers. $^{13}$C NMR comparison with authentic material showed that the minor diastereomer corresponded to the natural isomer of isoleucine, which had the erythro configuration (for the threo and erythro nomenclature used throughout the thesis, see page 6). Thus the major isomer was the threo isomer.

From this result they concluded, given a proclivity for the chairlike transition state for Claisen rearrangements,
that the geometry of the dianion must have been $E$ (which, because of change in priority rules becomes $Z$ on silylation of the dianion) to give a threo product preferentially. The
formation of 10% of erythro isomer was not explained.

In our study involving the rearrangement of E-2-crotyl N-phenylacetylglucinate, PMR of the rearranged products showed a 9:1 diastereomeric mixture. We decided to prove the stereochemistry of the products by formation of a γ lactone.

This approach turned out to be successful in our case. However, in the case of E-2-crotyl carbobenzyloxyglucinate, Bartlett et al. reported, that whilst attempting the sequence to be described below, they were unable to ozonolize the double bond.

**Formation of 2-phenylacetamidp-3-methylbutyrolactone (29a)**

A short synthetic sequence was explored, which is shown below (Figure 11).

![Figure 11](image)

**Figure 11**
It was envisioned that ozonolysis of a mixture of 27, followed by sodium borohydride reduction and lactonization, will give lactone 29a,b in the same isomeric ratio as the starting material, hence would delineate if the major isomer is 29a (i.e. threo) or 29b (i.e. erythro).

Ozonolysis of the isomeric mixture of olefins 27a,b, in MeOH at -78°C, followed by reduction with dimethylsulphide, gave the aldehyde 28a,b in 90% yield. The PMR data showed two singlets at 9.57 and 9.61 ppm respectively, arising due to the aldehyde protons. They were present in 9:1 ratio respectively. Hence the 9:1 diastereomeric ratio was maintained during this reaction.

NaBH₄ reduction of aldehyde 28a,b, after workup, gave 3 spots on TLC, all of them less polar than aldehyde 28, thus indicating that lactonization had occurred. However, only one of these 3 spots reacted with ninhydrin, thus indicating the presence of an amide bond. Separation of this spot by HPLC, gave 5 mg of threo lactone 29a (14% yield from aldehyde 28a,b).

The structure of 29a was confirmed by nuclear Overhauser effect.
On irradiation of the methyl signal, we observed: (i) enhancement of the \( H_4 \) and \( H_2 \) signals, (ii) no effect on NH signal. This implied: (i) \textit{cis} relationship between \( CH_3 \) and \( H_4 \) proton, (ii) \textit{cis} relationship between \( CH_3 \) and \( H_2 \) proton.

On irradiation of the \( H_3 \) signal, we observed: (i) enhancement of the \( H_4 \) signal, (ii) no effect on the \( H_2 \) signal.

This implied: (i) \textit{cis} relationship between \( H_3 \) and \( H_4 \) protons and (ii) \textit{trans} relationship between \( H_2 \) and \( H_3 \) protons.

Through decoupling experiments we found: \( J_{H_2-H_3} = 11.6 \) Hz, \( J_{H_3-H_4} = 10.7 \) Hz and \( J_{H_2-H_4} = 8.0 \) Hz, these \( J \) values further confirm that structure 29a had a \textit{trans} relationship of the \( H_2 \) and \( H_3 \) protons. The PMR spectrum and nuclear Overhauser results of 29a are shown in Figures 12-14.

**Rearrangement of Z-crotyl N-phenylacetylglycinate (18)**

Having established the stereochemistry, in the case of Z-crotyl N-phenylacetylglycinate, we decided to investigate the stereoselectivity of the rearrangement of its Z counterpart. The rearrangement proceeded in \( \sim 40\% \) yield, and its PMR spectrum indicated a 9:1 diastereomeric mixture.

On correlating the PMR data of 18, with those of its E counterpart, it was concluded that the major isomer was erythro and the minor isomer was threo. Thus the rearrangement
Figure 12: 200 MHz PMR spectrum of lactone 29a.
Figure 13 (NOE results): Irradiation of the methyl group signal in 29a enhances the $H_4'$ and $H_2$ signals.
Figure 14 (NOE results): Irradiation of the H₃ signal in 29a enhances the H₄ signal.
was shown to proceed stereoselectively (Figure 15).

\[ \text{trans crotyl glycinate 17} \quad \text{cis crotyl glycinate 18} \]

Figure 15

Rearrangement of dimethylallyl N-phenylacetylglucinate (19)

The rearrangement of 19 gave an acid, which upon methylation gave the ester 30 in 37% overall yield from 19.
The PMR spectrum of 30 showed that the methyl groups adjacent to the olefin appear as two singlets (δ: 0.96, 1.01). The NHCH proton appears as a doublet (δ: 4.39). The terminal vinyl protons appear as two doublet of doublet (δ: 4.66-4.84, 4.84-4.98).

Rearrangement of E-3'-trimethylsilylallyl N-phenylacetyl-glycinate (20)

Rearrangement of 20 gave acid 31, as an isomeric mixture, in 32% yield.

The PMR data of 31 showed that the H4 proton appears as a doublet of doublet. We observed two doublet of doublets in a 7:3 ratio, indicating a 7:3 diastereomeric mixture.

Though all the other acids obtained after rearrangement were soluble in methanol, acid 31 was found to be insoluble in methanol or ethyl ether at room temperature. Therefore, methylation was carried out at 40-50°C using Brook and Chan's procedure.10

At the end of the esterification, two products were
isolated: one was the expected methyl ester 32, which was isolated in only 12% yield. The PMR spectrum of 32 showed that two OMe signals were present in a 7:3 ratio, indicating that the 7:3 diastereomeric mixture was maintained.

The other product was assigned the following structure 33, on the basis of its PMR and mass spectral data, which are explained below.

The CH₃ group appears as doublet of doublets (δ: 1.60-1.84), two doublet of doublets were observed in 7:3 ratio, indicating an isomeric mixture. The terminal vinyl proton appears as a multiplet (δ: 5.55-5.80); more upfield, the non-terminal olefinic proton appears as a multiplet (δ: 5.30-5.50). PhCH₂ appears as a singlet (δ: 3.60); the NHCH proton appears
as doublet of doublets (\(\delta: 5.0-5.1\)). A singlet is observed for OMe protons (\(\delta: 3.70\)) and a broad NH proton peak is seen at 6.80 ppm.

The mass spectral data showed a molecular ion peak at 247. The peaks corresponding to loss of OMe and COOMe groups were seen at 216 and 188 respectively.

The formation of the elimination product is a classical example of protodesilylation, as depicted below.

![Diagram](image)

The stereochemistry of the isomeric mixture of the unrearranged ester of 31 was not proven in a rigorous way. However, correlation of the PMR spectrum of the mixture, as detailed below, with those of olefins 17 and 18 seems to indicate that the major isomer had the threo configuration and the minor, the erythro configuration.

Following observations are made from the threo and erythro isomers of the rearranged product of 17 and 18.
1) $H_2$ proton is more downfield for the threo isomer.
2) $H_3$ proton is more upfield for the threo isomer.
3) PhCH$_2$ signal is more upfield for the threo isomer.
4) OMe signal is more upfield for the threo isomer.
5) NH signal is more downfield for the threo isomer.

All of the above hold true for threo and erythro isomers of ester 32, with an exception for the first point, where the reverse holds true. This difference is rationalized by looking at the conformations of the most stable rotomers of the threo and erythro isomers of 32 (Figures 16a,b).
H₂ proton is upfield in the case of threo isomer of 31 due to anisotropic shielding by benzene; however, the bulky -Si(Me)₃ group in the case of erythro prevents this from happening. Another simple argument is that the antiperiplanar relationship between H₂ proton and -Si(Me)₃ group, in the case of the threo isomer, results in effective shielding of H₂ by -Si(Me)₃, and hence shifts it more upfield compared to the erythro isomer.

Having concluded that the erythro isomer is present as 30% of the diastereomeric mixture, the next question is why is there a loss of stereoselectivity observed as the size of the group increases from CH₃ to SiMe₃. To approach this, let us first look at the ways in which the erythro isomer can be obtained. It can be obtained in the following ways, either
1) the silyl enolate has the same Z geometry as is postulated for the rearrangement of the major isomer and the rearrangement proceeds through a boat, or 2) the silyl enolate of the starting material consists of a 7:3 mixture of Z and E enolates and both rearrangements proceed through a chairlike transition state, 3) a combination of both pathways described above. This is detailed in Figure 17.

In the Z chairlike transition state there exists a severe equatorial-equatorial gauche interaction between SiMe₃.
and the silylated amide functionality. In the boat form we see this interaction changes to axial-equatorial gauche interaction; however, at the same time a very severe 1,3-diaxial interaction between SiMe$_3$ and OSiMe$_3$ (which is apparent in even twist boat form) would tend to make the boatlike transition state less favourable for the erythro isomer formation. In the case of E chairlike form, there are two interactions: (1) 1,3-diaxial interaction between H and OSiMe$_3$ and (2) axial-equatorial gauche interaction between SiMe$_3$ and silylated amide functionality. Given the stability of the chair form over boat form, and also the lack of severe 1,3-diauxial interactions between SiMe$_3$ and OSiMe$_3$, would seem to favour E chairlike transition state for the erythro isomer formation. Evidently, as the size of the group increases from CH$_3$ to SiMe$_3$, it appears that equatorial-equatorial gauche interactions, in a Z chairlike transition state, become very severe, and hence the competition from E chairlike transition state becomes more and more pronounced.

Though logical, this argument is not conclusive. Since we do not know if the transition state is similar to the product or starting material, no firm conclusion may be derived.

**Rearrangement of E-3'-chloroallyl N-phenylacetylglucinate 21**

In the rearrangement of 21 a mixture of eliminated and non-eliminated products was obtained. This mixture was
inseparable on TLC.

The PMR spectrum of this mixture showed two doublet of doublets. These correspond to H\textsubscript{3} and H\textsubscript{2} protons in 34. On decoupling of H\textsubscript{3} proton, H\textsubscript{2} proton appears as a doublet, and vice versa. A similar phenomenon had been observed for all the other rearranged products. The doublet of doublets for H\textsubscript{3} proton was quite downfield compared to the doublet of doublets observed in the case of other rearranged products. This was expected, due to better deshielding ability of the chlorine atom.

Two different OMe, and two different PhCH\textsubscript{2} signals were observed indicating the presence of the expected product, and the product of elimination. GC mass spectra showed the following features.

For the product of elimination 35, the mass spectrum showed a strong M\textsuperscript{+} peak at 245. Also peaks corresponding to the loss of COOMe (at 186) and H\textsubscript{2}C=C=CH\textsubscript{2} fragment (at 206) were quite intense.

For the expected chloromethyl ester 34, M\textsuperscript{+} was observed
at 281 and 283 in an ~ 3:1 ratio, as expected from natural isotope abundance of $^{35}\text{Cl}$ and $^{37}\text{Cl}$ isotopes. Further peaks were observed at 222,224 (indicating loss of OMe), at 250,252 (indicating loss of COOMe), and a base peak at 245 pointed to the loss of HCl.

**General spectroscopic data of rearrangement products**

![Chemical structure](image)

The $H_4$ proton appears as a doublet of doublets, when $X=\text{Cl}$, or $-\text{Si(CH}_3)_3$. In the case when $X=\text{Cl}$, it appears in the 4.60-4.75 ppm range. In the case when $X=\text{Si(CH}_3)_3$, it appears in the 1.88-2.08 ppm range for the major isomer. In the case when $X=\text{CH}_3$, it appears as multiplet in the 2.45-2.60 ppm range. The $H_3$ proton appears as doublet of doublet. In the case when $X=\text{CH}_3$ it appears in 4.56-4.68 range; however, when $X=\text{Cl}$, $\text{Si(CH}_3)_3$, the range of 4.90-5.00 and 4.62-4.70 (for major isomer) ppm was observed respectively. A singlet is observed for PhCH$_2$ protons ($\delta$: ~ 3.62-3.75). Also, OMe appears as a singlet ($\delta$: ~ 3.68-3.77). The NH proton appears.
as a broad peak (δ: ~ 5.79-6.05). The H₅ proton appears as a multiplet (δ: ~ 5.27-5.62), immediately downfield to the multiplet of H₆ and H₇ protons (δ: ~ 4.72-5.00). The PMR spectra of some of the rearranged products are shown in Figures 18-21.

All of the rearranged esters give molecular ion peaks, and most of them give peaks at 207, indicating McLafferty rearrangement.

\[
\begin{align*}
17a \quad & X = \text{CH}_3, \ Y = \text{H} \\
19a \quad & X = \text{CH}_3, \ Y = \text{CH}_3 \\
20a \quad & X = \text{SiMe}_3, \ Y = \text{H} \\
21a \quad & X = \text{H}, \ Y = \text{Cl}
\end{align*}
\]
Figure 18: 300 MHz PMR spectrum of the rearrangement products, 27a,b of compound 18.
Figure 19: 200 MHz PMR spectrum of the rearrangement product, 30 of compound 19.
Figure 20: 200 MHz PMR spectrum of the rearrangement products 32a,b of compound 20.
Figure 21: 200 MHz PMR spectrum of the mixture of compounds 34 and 35.
Contributions to Knowledge

1. An efficient synthetic method for the synthesis of 3-substituted allyl N-phenylacetylglycinates is described.

2. Stereoelectivity of ester enolate Claisen rearrangement of 3'-substituted allyl N-phenylacetylglycinates was shown to be compromised on substitution of $-\text{Si(CH}_3)_3$ for CH$_3$ in E-crotyl N-phenylacetylglycinate.

3. Initial studies were done to explore the potential of the synthetic scheme devised to effect an efficient synthesis of $\beta,\gamma$-unsaturated lactones, potential antibiotics, of type A.

![Chemical Structure](image_url)
General Experimental

Mass spectra (ms) were obtained on a HP 5984 or LKB 9000 mass spectrometer at 70 eV unless otherwise specified. Proton magnetic resonance spectra were recorded on a Varian T-60, XL-200 or XL-300 spectrometer, using tetramethyl silane (TMS) as an internal standard, unless otherwise indicated. Chemical shifts are given on the δ scale in parts per million. In the spectra containing cis and trans isomeric mixture, where possible, the interpretation is done for the major isomer, otherwise the value for the mixture is reported without a differential assignment of peaks. Doublets (d), triplets (t), and quartets (q) were recorded at the centre of peaks. For multiplets (m) and doublet of doublets (dd) absorption range is recorded. Infrared (ir) spectra were obtained on a Perkin-Elmer 297 spectrophotometer.

The HPLC separation was performed on a Beckman 110A instrument, using Ultrasphere SI 5μm (4, 6 x 250 mm) column and UV detector at 254 nm. Silica gel (0.05-0.20 mm) was used for flash chromatograph. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60F254 aluminum-backed plates, and was visualized either under UV, and/or by dipping into a solution of 2.5 g ammonium molybdate and 1 g ceric sulphate in 10 mL conc. H2SO4/90 mL H2O and heating on a hot plate.
All evaporations were carried out under reduced pressure (water aspirator) with a bath of 35-45°C unless otherwise indicated. Solvents were reagent grade unless otherwise specified.
**Methylglycinate hydrochloride (13)**

To a stirred solution of glycine (4 g, 54 mmol) in methanol (150 mL) chlorotrimethylsilane (17 mL, 134 mmol) was added dropwise over a period of 10 min. The solution was stirred at room temperature for 18 h. Evaporation of solvent gave 4.33 g of the product 13, in 98% yield. IR (film) \( \text{max: } 1740, 1300, 1050 \text{ (COOMe); 3000 (NH}_3\cdot\text{HCl) cm}^{-1}. \) PMR (60 MHz, CD\(_3\)OD) \( \delta: \) 3.40 (s, 3H, OMe); 4.32 (s, 2H, CH\(_2\)).
**Methyl N-phenylacetylglycinate (14)**

To a stirred solution of glycine methyl ester hydrochloride 13 (5 g, 39.6 mmol) in CH₂Cl₂ (160 mL) at 0°C, triethylamine (12.3 mL, 88.3 mmol) was added dropwise over a period of 8 min. After 10 min, phenylacetyl chloride (5.8 mL, 44 mmol) was added dropwise over a period of 20 min, and the reaction mixture was allowed to stir at room temperature for 24 h. At this point, TLC (70% PE : 30% EA) showed complete disappearance of the starting material and appearance of a less polar spot. To the reaction mixture ice was added (50 g) and stirring was continued for 30 min at 0°C. The organic layer was washed with 5% NaHCO₃ (2 x 20 mL), 2N HCl (2 x 20 mL), H₂O (2 x 20 mL) and dried over MgSO₄, filtered and solvent was evaporated to give 7.82 g of methyl N-phenylacetyl- glycinate (14) in 95% yield. IR (film) ν_max: 3260, 3080 (N-H); 1700 (CONH); 1750 (COOME) cm⁻¹. PMR (60 MHz, CDCl₃) δ:

- 3.60 (s, 2H, PhCH₂);
- 3.72 (s, 3H, OMe);
- 3.96 (d, 2H, NHCH₂, J = 6.88 Hz);
- 6.48 (br.s, 1H, NH);
- 7.19-7.40 (m, 5H, Ph).
**E-Crotyl N-phenylacetylglucinate (17)**

To a solution of trans-crotyl alcohol (10.3 g, 120 mmol) methyl N-phenylacetylglucinate (14)(1.0 g, 4.8 mmol) was added at room temperature. To this reaction mixture chlorotrimethylsilane (1.9 mL, 14.4 mmol) was added dropwise over a period of 2 min. The reaction was stirred at room temperature for 24 h, at which point TLC (50% PE : 50% EA) showed the disappearance of the starting material and appearance of a less polar spot. Excess of crotyl alcohol was pumped off at 50°C. The brown oil thus obtained was washed with hexane (5 x 5 mL) and crystallized (hexane/ether) to give 900 mg of 17, m.p. 40°C (76% yield). PMR (200 MHz, CDCl₃) δ: 1.65-1.78 (m, 3H, =CHCH₃); 3.61 (s, 2H, φCH₂); 3.99 (d, 2H, NHCH₂, J = 5.22 Hz); 4.53-4.66 (m, 2H, OCH₂); 5.34-5.63 (m, 1H, CH₃CH=CH); after decoupling of allylic protons, CH=CH appeared as AB system, J = 15.3 Hz); 5.63-5.87 (m, 1H, CH₃CH=CH); 5.92 (br.s, 1H, NH); 7.29-7.39 (m, 5H, Ph). Ms m/e: 247 (M⁺), 193 (M⁺ - CH₃CH=C=CH₂), 119 ( φCH₂CO⁺).
Dimethylallyl N-phenylacetylglycinate (19)

To a solution of 3-methyl-2-buten-1-ol (20 mL, 196 mmol), containing methyl N-phenylacetylglycinate (14) (2.0 g, 9.6 mmol) was added chlorotrimethylsilane (3.7 mL, 29 mmol) over a period of 2 min. The reaction mixture was left to stir for 18 h. TLC (60% PE : 40% EA) showed appearance of a less polar spot. The reaction mixture was washed with hexane (5 x 8.0 mL) and pumped for 1 h at 50°C to give 1.4 g of 19 as a yellow oil (56%). PMR (60 MHz, CDCl₃) δ: 1.66, 1.76 (2s, 6H, CH₃CH₂C=C-); 3.56 (s, 2H, PhCH₂); 3.90 (d, 2H, NHCH₂, J = 8.0 Hz); 4.60 (d, 2H, -OCH₂CH=CH₂, J = 8.4 Hz); 5.05-5.22 (t, 1H, CH₃CH=CH-CH₂); 6.2 (br.s, 1H, NH); 7.19-7.38 (m, 5H, Ph). MS m/e: 261 (M⁺), 193 (M⁺ - (CH₃)₂C=CH₂), 119 (PhCH₂CO⁺).
2-Butynyl N-phenylacetylglucinate (22)

To a stirred solution of 2-butyn-1-ol (10 mL, 133 mmol) containing methyl N-phenylacetylglucinate 14 (1.0 g, 4.8 mmol), chlorotrimethylsilane (2.0 mL, 15.7 mmol) was added dropwise over a period of 2 min. After 18 h, TLC (70% PE : 30% EA) showed the appearance of a less polar spot accompanied by the disappearance of starting material. The excess of 2-butynol was removed by washing with hexane (8 x 5.0 mL). The thick oil thus obtained was dissolved in ethyl ether, and passed through a silica gel pad and evaporated to give 780 mg of the product 22 (66%). PMR (60 MHz, CDCl₃) δ: 1.85 (t, 3H, CH₃); 3.51 (s, 2H, PhCH₂), 3.86 (d, 2H, NHCH₂, J = 6.88 Hz); 4.45 (q, 2H, O-CH₂-C≡C-CH₃); 6.0-6.2 (br.s, 1H, NH), 7.18 (s, 5H, Ph). Ms m/e: 245 (M⁺), 154 (CH₃C≡CCH₂OCOCH₂NHCO⁺), 118 (M⁺ - H⁺ - CH₃C≡CCH₂OCOCH₂NH⁺).
Z-Crotyl N-phenylacetylglycinate (18)

To nickel acetate (312 mg, 1.25 mmol) in a two-necked flask equipped with a septum was added absolute ethanol (2.0 mL). The reaction flask was connected to a hydrogenation apparatus and was flushed several times with hydrogen. The catalyst was produced by inserting through the septum 2.5 mL of 0.5 M NaBH₄ (50 mg, 1.32 mmol), and the reaction vessel was again flushed with hydrogen. Ethylenediamine (0.17 mL, 2.57 mmol) was then added. Hydrogenation was initiated by introducing 2-butylnyl N-phenylacetylglycinate (22), (245 mg, 1.0 mmol) in absolute ethanol (1.25 mL). The hydrogen uptake was quantitative and was complete in about 40 min. The reaction mixture was filtered through Celite. The ethanol was removed under reduced pressure and the residue was extracted with ethyl ether (3 x 75 mL), washed with H₂O (3 x 5 mL). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure to yield 235 mg of 18 as a brown oil (95% yield). PMR (200 MHz, CDCl₃) δ: 1.61-1.72 (m, 3H, CH₃); 3.60 (s, 2H, PhCH₂); 4.00 (d, 2H, NHCH₂, J = 6.34 Hz); 4.66 (d, 2H, -OCH₂-CH=C-, J = 7.93 Hz), 5.35-5.60 (m, 1H, CH₃CH=CH-, after decoupling of allylic protons, HC=CH appeared as AB system, J = 10 Hz); 5.60-5.85 (m, 1H, CH₃CH=CH-, J = 10.0 Hz); 5.95 (br.s, 1H, NH), 7.19-7.34 (m, 5H, Ph). MS m/e: 247 (M⁺), 193 (M⁺ - CH₂HC=C=CH₂), 148 (ΦCH₂CONHCH₂⁺), 119 (ΦCH₂CO⁺).
Methoxyisopropylidene propargyl alcohol (23)

To a solution of propargyl alcohol (4.35 mL, 75 mmol) in dry CH₂Cl₂ (225 mL) at 5°C under N₂ was added methoxypropene (8 mL, 83 mmol) and pyridinium tosylate (1.88 g, 7.5 mmol). The reaction mixture was stirred at 5°C for 4 h, washed with 5% aqueous NaHCO₃ (5 x 20 mL) and water (2 x 20 mL). The organic layer was dried over MgSO₄, filtered. The distillation (65°C at 43 torr) gave 6.2 g of the product (64.6%). PMR (60 MHz, CCl₄) δ: 1.27 (s, 6H, 2CH₃); 2.13 (t, 1H, J = 2 Hz, H-C≡C); 3.07 (s, 3H, OCH₃); 3.96 (d, 2H, J = 2 Hz, CH₂).
3-Trimethylsilyl O-(methoxyisopropylidene)propargyl alcohol (24):

To a stirred solution of protected propargyl alcohol 23 (1 g, 7.8 mmol) in 20 mL of dry THF under N₂ at -78°C was added n-butyllithium (5.5 mL of 1.55 M, 7.8 mmol). After 20 min chlorotrimethylsilane (1.1 mL, 8.6 mmol) was added dropwise over a period of 2 min. After 6 h, TLC (70% PE : 30% EA) showed complete disappearance of starting material and appearance of a new less polar spot. Evaporation gave a residue which was dissolved in water (15 mL) and extracted with ethyl ether (2 x 100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to yield 1.3 g of 24 as a yellow oil (83% yield). PMR (60 MHz, CDCl₃) δ: 0.20 (s, 9H, -Si(CH₃)₃); 1.36 (s, 6H, 2CH₃), 3.22 (s, 3H, OCH₃); 4.1 (s, 2H, -CH₂).
3-Trimethylsilyl propargyl alcohol (25)

To a solution of 24 (1.3 g, 6.5 mmol) in methanol (100 mL) was added pyridinium tosylate (65 mg) and the reaction mixture was stirred for 3 h. Methanol was evaporated and the residue was extracted in CH₂Cl₂ (150 mL), washed with 5% NaHCO₃ (4 x 10 mL) and dried over MgSO₄, filtered and evaporated to give 700 mg of the product 25 as a yellow oil (84% yield). PMR (60 MHz, CDCl₃) δ: 0.20 (s, 9H, -Si(CH₃)₃); 2.83 (s, 1H, OH), 4.26 (s, 2H, -CH₂).
E-3-Trimethylsilyl allyl alcohol (16)

To a solution of 3-trimethylsilyl propargyl alcohol (25) (700 mg, 5.47 mmol) in dry THF (30 mL) under N₂ atmosphere at room temperature was added LiAlH₄ (208 mg, 5.47 mmol). The reaction mixture was stirred at room temperature for 10 min and then refluxed for 15 h. The reaction was cooled and the excess LiAlH₄ was destroyed by addition of 0.2 mL of H₂O, followed by 0.2 mL 15% NaOH and then followed by 0.6 mL of H₂O¹⁷. The precipitate was filtered off and most of the THF was evaporated under reduced pressure. The residue was diluted with ethyl ether (50 mL) and was washed with water (3 x 8 mL). The ether layer was dried over MgSO₄, filtered, and evaporated to yield 420 mg of 16 (59%). PMR (200 MHz, CDCl₃) δ: 0.08 (s, 9H, -Si(CH₃)₃); 1.80 (s, 1H, OH), 4.10-4.24 (m, 2H, -CH₂O); 6.00-6.20 (m, 1H, Si(CH₃)₃HC=CH, after decoupling of allylic protons, HC=CH appeared as AB system, J = 18.9 Hz); 5.70-5.95 (m, 1H, Si(CH₃)₃HC=CH-CH₂, J = 18.9 Hz). Ms m/e: 115 (M⁺ - CH₃), 73 ((CH₃)₃Si⁺).
N-Phenylacetylglycine (26)

To a solution of methyl N-phenylacetylglycinate (14) (200 mg, .96 mmol) in THF (1.5 mL) and H₂O (0.25 mL), LiOH (46 mg, 1.09 mmol) was added. Reaction mixture was allowed to stir for 40 min. At this point a thick yellowish precipitate formed. TLC (70% PE : 30% EA) showed disappearance of starting material and appearance of a new polar spot. The reaction mixture was evaporated and the residue was dissolved in 2N HCl (5 mL) and extracted with CH₂Cl₂ (3 x 30 mL), dried over MgSO₄, filtered and evaporated at reduced pressure to give 160 mg of the product 26 (80% yield). PMR (60 MHz, CD₃OD) δ: 3.35 (s, 2H, CH₂); 3.70 (s, 2H, NHCH₂), 6.82-7.10 (m, 5H, Ph). IR (film) ν_max: 3380 (N-H); -2600-3000 (OH); 1720 (COOH), 1600 (CONH) cm⁻¹.
**E-3'-Trimethylsilylallyl N-phenylacetylglycinate (20)**

To a solution of E-3'-trimethylsilylallyl alcohol 16 (400 mg, 3.08 mmol), N-phenylacetylglycine (26) (594 mg, 3.08 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (591 mg, 3.08 mmol) in dry THF (8.0 mL) was added a catalytic amount of 4-(dimethylamino)pyridine (5 mg) and the mixture was stirred at 22°C for 18 h. The reaction mixture was evaporated under reduced pressure, extracted with CH₂Cl₂ (300 mL) and washed with 2N HCl (2 x 20 mL), aqueous NaHCO₃ (2 x 20 mL) and H₂O (2 x 20 mL). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure to give 780 mg of 20 as a yellow oil in 83% yield. PMR (300 MHz, CDCl₃) δ: 0.67 (s, 9H, Si(CH₃)₃); 3.63 (s, 2H, PhCH₂), 4.07 (d, 2H, NHCH₂, J = 4.76 Hz); 4.63 (d, 2H, OCH₂-CH=C-, J = 3.17), 5.92 (d, 1H, Si(CH₃)₃CH=CH, J = 18.6 Hz); 5.98-6.07 (m, 1H, Si(CH₃)₃CH=CH), 5.98 (br.s, 1H, NH); 7.26-7.40 (m, 5H, Ph). Ms m/e: 305 (M⁺), 290 (M⁺ - CH₃), 193 (M⁺ - Si(CH₃)₃CH=C=CH₂), 176 (M⁺ - Si(CH₃)₃CH=CHCH₂O), 134 (PhCH₂CONH⁺), 119 (PhCH₂CO⁺).
E-3'-Chloroallyl alcohol (13)

To a solution of epichlorohydrin (3.91 mL, 50 mmol) in dry THF (100 mL), under N₂, n-butyllithium (32.25 mL, 50 mmol) in hexane was added over a period of 10 min. The reaction mixture was allowed to stir for 3 h at -78°C, and, after warming to 20°, poured into water (200 mL). The upper organic phase was separated. The aqueous phase was made slightly acidic and extracted with ethyl ether (2 x 200 mL). The organic phases were combined, dried over MgSO₄ and the solvent was removed by vacuum stripping. The residue was distilled (b.p.155 120°C) to yield 3.23 g of 13 (70% yield).

PMR (200 MHz, CDCl₃) δ: 1.87 (br.s, 1H, OH); 4.08-4.18 (m, 2H, ClCH-CHCH₂OH); 6.00-6.15 (m, 1H, ClCH=CH, on decoupling allylic protons, HC=CH appeared as AB system, J = 13.3 Hz), 6.20-6.35 (m, 1H, ClCH=CH, J = 13.3 Hz).
E-3'-Chloroallyl N-phenylacetylglycinate (21)

To a solution of chloroallyl alcohol \( \text{13} \) (221 mg, 2.4 mmol), N-phenylacetylglycine (465 mg, 2.4 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (461 mg, 2.4 mmol) in dry THF (5.0 mL) was added a catalytic amount of 4-(dimethyl-amino)pyridine (5 mg) and the mixture was stirred at 22°C for 18 h. The reaction mixture was evaporated under reduced pressure and residue was extracted with \( \text{CH}_2\text{Cl}_2 \) (200 mL) and washed with 2N HCl (2 x 15 mL), aqueous 5% NaHCO\(_3\) (2 x 15 mL) and H\(_2\)O (2 x 20 mL). The organic layer was dried over MgSO\(_4\), filtered and evaporated under reduced pressure to give 600 mg of pale yellow oil, 21 (93% yield). PMR (300 MHz, CDCl\(_3\)) \( \delta \):

3.57 (s, 2H, PhCH\(_2\)); 3.94 (d, 2H, NHCH\(_2\), \( J = 4.76 \) Hz); 4.53-4.55 (dd, 2H, O-CH\(_2\)-CH=CHCl); 5.93-6.02 (m, 1H, ClCH=CH, on decoupling allylic protons, HC=CH appeared as AB system, \( J = 13.2 \) Hz), 6.27-6.32 (m, 1H, ClCH=CH, \( J = 13.2 \) Hz), 7.22-7.42 (m, 5H, Ph). MS m/e: 267 (M\(^+\)), 232 (M\(^+\) - Cl), 193 (M\(^+\) - CH\(_2\)=C=CHCl), 176 (M\(^+\) - OCH\(_2\)CH=CHCl), 118 (M\(^+\) - NH\(_2\)CH\(_2\)COOCH\(_2\)CH=CHCl).
Compounds 17-21 were all rearranged using general procedure, which is outlined below for the case of E-crotyl N-phenylacetylglycinate 17.
Ester enolate Claisen rearrangement of E-crotyl N-phenylacetyl-glycinate (17) to give olefins (27a,b)

To a solution of hexamethyldisilazane (0.5 mL, 2.2 mmol) in dry THF (6.2 mL) at 0°C was added n-butyllithium in hexane (1.5 mL of 1.55 M, 2.32 mmol). After 20 min, the solution was cooled to -78°C and 17 (247 mg, 1 mmol) in THF (1.0 mL) was added over a period of 2 min. After stirring for 45 min a yellowish precipitate was observed, at this point chlorotrimethylsilane (0.3 mL, 2.2 mmol) was added over a period of 1 min. The reaction mixture was allowed to warm up to room temperature over a period of 30 min. The mixture was then heated at reflux for 1 h, cooled, diluted with methanol (5.0 mL) and allowed to stand for 15 min. The solution was diluted with ether (50 mL) and extracted 3 times with 5% ice cold NaOH (4 x 10 mL). To the combined aqueous layer ice was added (40 g) and it was acidified to pH = 1, extracted with CH₂Cl₂ (4 x 40 mL). The organic layer was dried over MgSO₄, filtered and evaporated at reduced pressure to yield 150 mg of yellow oil, which appeared on TLC (60% PE : 40% EA) as a non-moving polar spot. This oil was dissolved in methanol (4.5 mL) and to this solution chlorotrimethylsilane (0.5 mL, 3.6 mmol) was added dropwise over a period of 1 min. The reaction mixture was allowed to stir at room temperature for 18 h, washed with H₂O (2 x 4.0 mL) extracted with CH₂Cl₂ (150 mL), dried over MgSO₄, filtered and evaporated at
Reduced pressure to give 158 mg of 27a,b in 61% overall yield from 17 in a 1:9 erythro to threo isomeric ratio. PMR (200 MHz, for trans isomer, CDCl₃): 0.95 (d, 3H, \(-\text{CHCH}_3\), J = 7.00 Hz), 2.45-2.60 (m, 1H, \(-\text{CHCH}_3\)); 3.59 (s, 2H, \(\text{PhCH}_2\)); 3.68 (s, 3H, \(\text{OCH}_3\)), 4.56-4.68 (dd, 1H, NHCH); 4.80-5.00 (m, 2H, \(\text{CH}_2=\text{C}\)); 5.54-5.59 (m, 1H, \(\text{CH}_2=\text{CH}\)); 5.86 (br. d, 1H, NH); 7.24-7.40 (m, 5H, pH). MS m/e: 261 (M⁺), 230 (M⁺ - OMe), 207 (M⁺ - \(\text{CH}_2=\text{C}=\text{CHCH}_3\)), 202 (M⁺ - COOMe), 91 (\(\Phi\text{CH}_2\)^+).
Aldehyde 28a,b from olefin 27a,b

To a solution of olefin 27a,b (100 mg, 0.38 mmol) in methanol (3 mL) at -78°C, O₃ was bubbled until the solution became faint blue. Dimethylsulphide (2.5 mL) was then added to the reaction mixture and it was allowed to warm up to room temperature and stirred for 18 h. Complete disappearance of starting material accompanied with appearance of a more polar spot on TLC (70% PE, 30% EA) was observed. Evaporation gave 90 mg of 28a,b, slightly contaminated with DMSO, as a 9:1 threo to erythro mixture in 90% yield. PMR (60 MHz, CDCl₃) δ: 0.90, 1.18 (2d, 3H, CH₃, J = 7.00, 7.99 Hz, respectively); 2.62-3.20 (m, 1H, CH₃); 3.60, 3.63 (2s, 2H, CH₂); 3.70, 3.73 (2s, 3H, OMe); 4.82-5.20 (dd, 1H, NHCH₂), 6.20 (br.d, 1H, NHCH₂, J = 7.9 Hz); 7.3 (s, 5H, Ph); 9.57, 9.61 (2s, 1H, COH). MS m/e: 207 (M⁺ - CH₂CO), 204 (M⁺ - COOMe), 175 (PhCH₂CONHCH=CHCH₃⁺), 91 (PhCH₂⁺).
To a solution of 28a,b (40 mg, 0.152 mmol) in ethanol (2.0 mL) NaBH₄ (6 mg, 0.158 mmol) was added. After 20 min, TLC (70% PE : 30% EA) showed disappearance of starting material and appearance of a more polar spot. The ethanol was evaporated and residue was washed with H₂O (2 x 2 mL) and extracted with CH₂Cl₂ (2 x 20 mL), dried over MgSO₄, filtered and evaporated to give 20 mg of yellow oil. This yellow oil showed 3 spots on TLC (15% CH₃CN : 85% CH₂Cl₂), all less polar than starting aldehyde; however, only second most non-polar spot burned on treatment with ninhydrin, indicating the presence of an amide bond. HPLC separation of this oil (15% CH₃CN : 85% CH₂Cl₂ eluent) gave 5 mg of 29a in 14% overall yield from 28a,b. PMR (200 MHz, CDCl₃):

1.17 (d, 3H, CH₃, J = 6.34 Hz); 2.28-2.47 (m, 1H, CH₃CH), 3.65 (s, 2H, -NH₂); 3.69-3.87 (dd, 1H, H₄, decoupling at H₃ gave J₄₋₄₃ = 9.0 Hz, decoupling at H₄ gave J₃₋₄₃ = 10.7 Hz); 4.25-4.38 (dd, 1H, H₂, decoupling at H₃ gave J₇₋₇₂ = 7.8 Hz, decoupling at NH gave J₂₋₃ = 11.6 Hz); 4.34-4.46 (dd, 1H, H₄, decoupling at H₄ gave J₃₋₄₃ = 8.0 Hz); 5.69 (br.d, 1H, NHCH, J = 7.8 Hz); 7.25-7.39 (m, 5H, Ph). IR (CHCl₃) max: 1780 (CO), 1670 (CONH) cm⁻¹. MS m/e: 233 (M⁺), 188 (M⁺ - H⁺ - CO₂), 142 (M⁺ - CH₂), 119 (CH₃CO⁺), 134 (CH₃CONH⁺).
Ester enolate Claisen rearrangement of Z-3'-methylallyl
N-phenylacetylglutamate 18 to give olefins 27a,b

Using the general procedure, 16 (90 mg, 0.364 mmol) was
rearranged to give 39 mg of 27a,b as a 1:9 to threo to
erthro mixture (40.3% yield). PMR for cis isomer (300 MHz,
CDCl₃) δ: 0.97 (d, 3H, CH₃-H, J = 5.71 Hz); 2.66-2.73
(m, 1H, CHCH₃); 3.70 (s, 3H, OMe); 3.72 (s, 2H, PhCH₂);
4.50-4.62 (dd, 1H, NHCH); 4.90-5.00 (m, 2H, H₂C=C-); 5.45-5.62
(m, 1H, CH₂=CH-); 5.77 (br.d, 1H, NHCH, J = 8.1 Hz); 7.21-7.45
(m, 5H, Ph). Ms m/e: 261 (M⁺), 230 (M⁺ - OMe), 207 (M⁺ -
CH₃CH=C=CH₂), 202 (M⁺ - COOMe).
Ester enolate Claisen rearrangement of dimethylallyl N-phenylacetylglutamate 19 to give (30)

Using the general procedure 19 (280 mg, 1.07 mmol) was rearranged to give 110 mg of the product in 37.2% yield.

PMR (200 MHz, CDCl₃) δ: 0.96, 1.01 (2s, 6H, 2CH₃); 3.58 (s, 2H, PhCH₂); 3.68 (s, 3H, OMe); 4.39 (d, 1H, NH, J = 6.34 Hz); 4.66-4.84, 4.84-4.98 (2dd, 2H, CH₂=C=CH₂); 5.57-5.76 (dd, 1H, CH₂=CH₂); 5.79 (br.d, 1H, NH); 7.17-7.46 (m, 5H, Ph).

Ms m/e: 275 (M⁺), 216 (M⁺ - COOMe), 207 (M⁺ - CH₃CH₃C=CH₂), 119 (PhCH₂CO⁺).
Ester enolate Claisen rearrangement of E-3-trimethylsilyl N-phenylacetylglycinate 20 to give 31

Using the general procedure 20 (295 mg, 0.92 mmol) was rearranged to give 90 mg of 31 (7:3 erythro isomorphic mixture) as a white crystalline solid, m.p. 82-86°C (32% yield).

PMR (200 MHz, CDCl₃) δ: 0.08 (s, 9H, Si(CH₃)₃); 1.72-1.90, 1.90-2.14 (2dd, 1H, CH₂Si(CH₃)₃); 3.56, 3.60 (s, 2H, PhCH₂); 4.57-4.68 (dd, 1H, NHCH₂COOH); 4.72-5.00 (m, 2H, H₂C=CH-); 5.30-5.66 (m, 1H, H₂C=CH); 5.80, 6.21 (2br.d, 1H, NH, J = 8.25 and 7.56 Hz, respectively); 7.22-7.50 (m, 5H, Ph); 8.81 (br.s, 1H, COOH). Ms m/e: 305 (M⁺), 289 (M⁺ - OH), 260 (M⁺ - COOH), 232 (M⁺ - Si(CH₃)₃), 186 (M⁺ - \textPhi\textsubscript{2}CH₂CO), 170 (M⁺ - H⁺ - \textPhi\textsubscript{2}CH₂CONH).
From acid 31 to ester 32

To a suspension of isomeric mixture of 31 (90 mg, 0.29 mmol) in methanol (3.5 mL) was added chlorotrimethylsilane (0.12 mL, 0.94 mmol) dropwise at room temperature while stirring. The reaction mixture was heated at reflux for 5 h. At this point an aliquot from reaction mixture showed the disappearance of the peak at : 8.81 in NMR (i.e. the acid peak). The solvent was removed by evaporation and the residue was extracted with CH₂Cl₂ (200 mL), washed with H₂O (2 x 20 mL) to give 90 mg of yellow oil. TLC (70% petroleum ether : 30% ethyl acetate) of this oil showed two spots, which were separated using flash chromatography (70% PE : 30% EA as eluent) to obtain 35 mg (overall 12% yield from 20) of less polar, non-eliminated product 32, as a 7:3 threo : erythro mixture. PMR (200 MHz, CDCl₃) δ: 0.07 (s, 9H, Si(CH₃)₃); 1.73-1.88, 1.88-2.08 (2dd, CHSi(CH₃)₃); 3.64-3.77 (2s, 3H, OMe); 3.67, 3.75 (2s, 2H, PhCH₂); 4.62-4.70 4.69-4.75 (2dd, 1H, NHCH₂); 4.72-5.00 (m, 2H, CH₂=); 5.27-5.60 (m, 1H, CH₂=); 5.80, 6.05 (br.d, 1H, NH, J = 8.42, 7.36 Hz respectively); 7.22-7.52 (m, 5H, Ph). Ms m/e: 319 (M⁺), 288 (M⁺ - OMe), 260 (M⁺ - COOMe), 246 (M⁺ - Si(CH₃)₃), 207 (M⁺ - CH₂=CHSi(CH₃)₃), 200 (M⁺ - PhCH₂CO), 185 (M⁺ - PhCH₂CONH).
Rearrangement of E-3-chloroallyl N-phenylacetylglycinate 21 to give non-eliminated product 34 and eliminated product 35

Using general procedure, 21 (270 mg, 1.067 mmol) was rearranged to give 120 mg of yellow oil which appeared as 3 spots on TLC (50% PE : 50% EA). The second most polar spot turned out to be UV active, and visible after treatment with dip solution. This spot was separated using flash chromatography (50% PE : 50% EA as eluent) to give 70 mg of an inseparable mixture of 34 and 35 in a 14% yield from 21. PMR and mass spectral data confirmed the presence of 34 and 35, but a complete assignment of signals to different protons could not be rendered due to mixing of signals from 34 and 35.


