

**SYNTHETIC STUDIES OF AMINOKETENES AND
ISOCYANATOKETENES AND NUCLEOPHILIC REACTIONS
OF 2,3-BIS(TRIMETHYLSILYL)-1,3-DIENE-1,4-DIONE**

by

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A thesis submitted in conformity with the requirements

for the degree of Master of Science

Graduate Department of Chemistry

University of Toronto

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Reactions of 2,3-Bis(trimethylsilyl)buta-1,3-diene-1,4-dione

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Master of Science, 1997, Graduate Department of Chemistry, University of Toronto

Abstract

The synthesis of *N,N*-dimethylamino-*tert*-butyl ketene was pursued via E1cB type reaction, as it is a potentially stable and persistent aminoketene. The bases used included DBU, potassium hydride and triethylamine while the leaving group used was pentafluorophenoxide. Failure of the synthesis of this aminoketene and the stable phthalimido-*tert*-butylketene using these and other similar conditions indicates that they may not be suitable in the generation of aminoketenes.

The synthesis of the unknown cumulene substituted ketene, *tert*-butylisocyanatoketene, was attempted by reacting *tert*-leucine with triphosgene to give an isocyanato acid chloride as a ketene precursor. The acid chloride could not be made this way, but rather *tert*-leucine-*N*-carboxyanhydride was synthesized very efficiently.

The synthesis of medium sized lactones using the *n*-BuLi catalyzed reaction between 2,3-bis(trimethylsilyl)buta-1,3-diene-1,4-dione (bisketene) and diols was attempted. Dimeric tetralactones were obtained in low yields as the only isolable products. The uncatalyzed reaction between the same bisketene and a variety of amines was attempted. Conversion to the corresponding succinamides using primary amines was fast and high yielding with little or no competition from desilylation reactions. It was also discovered that succinimides could be generated in this fashion.

I would like to take this opportunity to thank a few of the people who contributed not only to the completion of this thesis but also throughout the duration of my studies at the University of Toronto. First and foremost I would like to thank Professor Thomas T. Tidwell for his input over the past two years and especially over the last couple of months. Prof. Tidwell was able to guide while allowing me to work and think independently. I am especially grateful for this as I believe it is valuable commodity that will serve well in the future.

I would also like to thank all the members of the Tidwell group, past and present, that I have had the pleasure of working with over the duration of my studies. A finer group of colleagues I will be hard pressed to find. In this regard, I would like to recognize Adel Rafai Far for his unselfish sharing of ideas and time (could you run a quick carbon on the 400 for me, Adel?). My thanks are also extended to the entire staff of the chemistry department who contributed to the completion of this work, especially Dan Mathers, Dr. Alex Young and Tim Burrows.

See you on the outside,

Patrick A. Moore

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Ac	acetate
Bu	butyl
calc	calculated
CI+MS	positive ionization chemical ionization mass spectrometry (low resolution)
cm ⁻¹	wavenumber (inverse centimeters)
°C	degrees centigrade
Δ	thermal energy
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DMF	dimethylformamide
d	doublet
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EIMS	electron impact mass spectrometry (low resolution)
ESR	electron spin resonance
Et	ethyl
FT-IR	Fourier transform infrared
g	grams
hν	ultraviolet radiation
HRMS	high resolution mass spectrometry (electron impact)

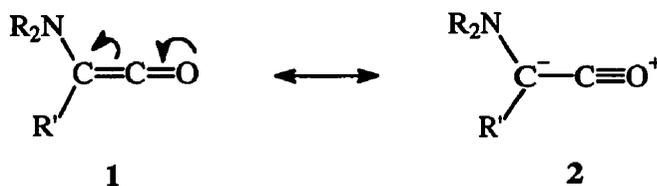
IR	infrared
J	coupling constant
kcal	kilocalories
λ_{\max}	wavelength of maximum absorbance
M	molarity
m	multiplet in NMR spectroscopy; medium intensity transmission in IR
M ⁺	molecular ion
Me	methyl
MHz	megaHertz
mg	milligrams
min	minutes
mL	millilitres
mmol	millimoles
mol	mole (Avogadro's)
m.p.	melting point
<i>m/z</i>	mass to charge ratio
n-	normal
nm	nanometres
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million

RT	room temperature
s	singlet in NMR spectroscopy; strong intensity absorption in IR
t	triplet
t-	tertiary
TBAF	tetra- <i>n</i> -butylammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
μL	microlitres
UV	ultraviolet
w	weak absorption in IR

Aminoketenes and Isocyanatoketenes

Aminoketenes are molecules containing a ketene functional group with an amine group on the β -carbon of the ketene. Ketenes substituted with electronegative substituents such as amines are predicted to be unstable relative to ketenes with more electropositive substituents such as alkyl groups.¹ Destabilization of aminoketenes can be attributed to three different effects. The β -carbon of ketenes carries a substantial negative charge, best represented by resonance structure **2** (Figure 1.1). Thus a π -repulsion exists between the lone pair on nitrogen and the electron rich $C_\beta p$ orbital.

Figure 1.1

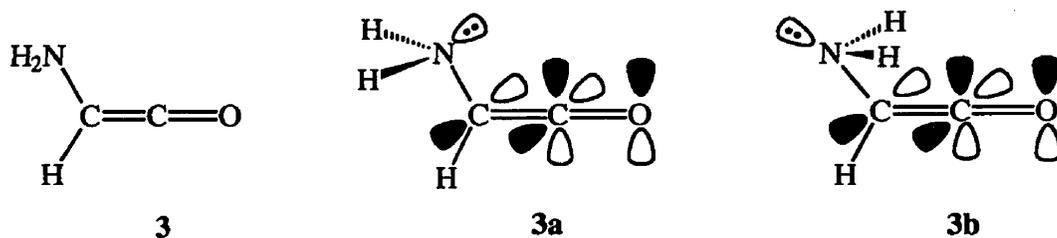


A dipolar repulsion also exists between the electronegative ketenyl oxygen and the electronegative nitrogen. Lastly, because electropositive substituents stabilize ketenes through π -donation to C_α , an electronegative substituent such as amine may destabilize the ketene by comparison.

Figure 1.2 shows the simplest aminoketene **3** whose preferred geometry is calculated to be that of **3a** with the lone pair of electrons from nitrogen in the ketene plane.¹ This conformation puts the lone pair of nitrogen perpendicular to the electron rich p orbital of C_β

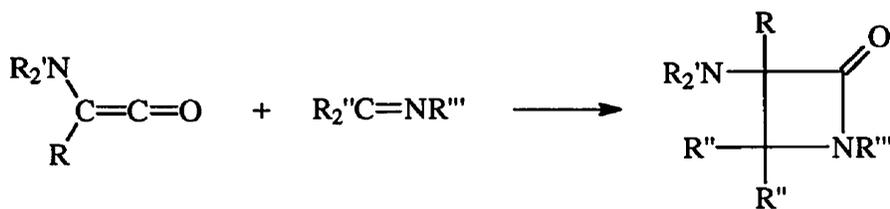
existence of such a repulsion. These same calculations have shown **3b** to be only slightly higher in energy than **3a** which rules out a bonding interaction between the lone pair on nitrogen and the electron deficient C_α of the ketene.

Figure 1.2



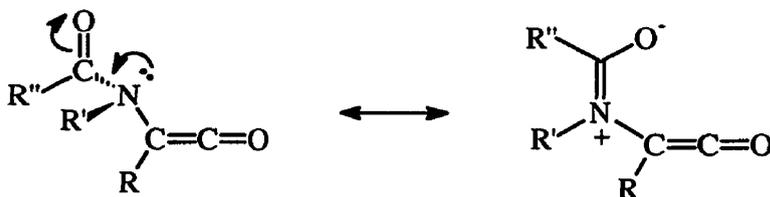
Synthetically, aminoketenes have found application in the preparation of amino-substituted β -lactams, whose utility in the formation of penicillins have led to extensive investigations into the generation of nitrogen substituted ketenes.² Scheme 1.1 shows the 2 + 2 cycloaddition reaction of aminoketenes with imines (also known as the Staudinger reaction) to form β -lactams.

Scheme 1.1



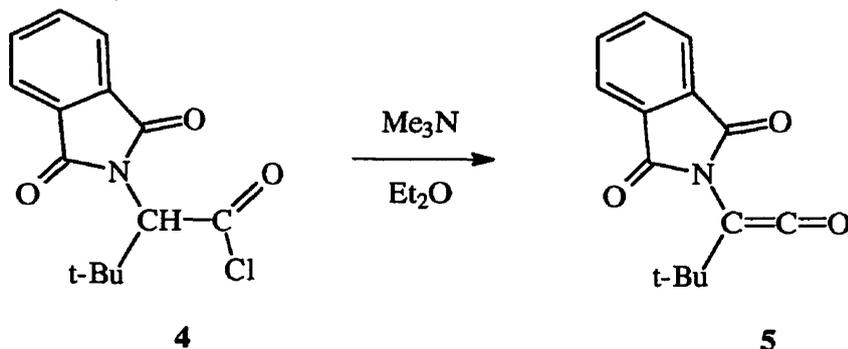
dehydrohalogenation of an acyl chloride or by elimination of tosylate from a mixed carboxylate-tosylate anhydride.^{2c,2j} Both methods employ tertiary amines as the base. Another general feature of the aminoketenes used is that they are usually *N*-acylated.³ The acyl group withdraws negative charge from nitrogen thus stabilizing the aminoketene by reducing repulsion between nitrogen and the ketenyl carbon (Figure 1.3).

Figure 1.3



To date, the only stable and persistent aminoketene known is phthalimido-*tert*-butylketene **4** (Scheme 1.2), synthesized in 1966 by Winter and Pracejus and obtained as a crystalline solid.⁴

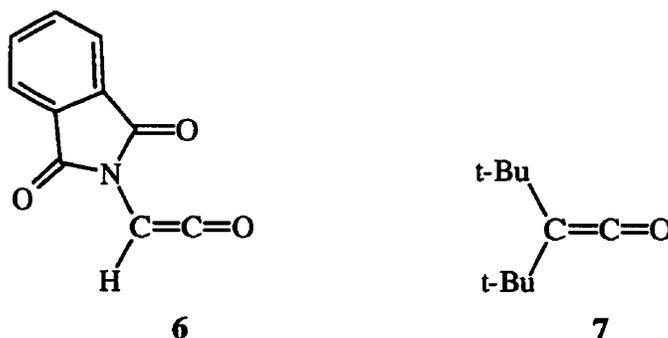
Scheme 1.2



responsible for the stability of aminoketene **5**. It is important to note, however, that phthalimidoketene **6** (Figure 1.4) has not been isolated. It has been generated *in situ* for synthesis of squaric acid derivatives via 2 + 2 cycloaddition.⁶ Thus it is unlikely that the phthaloyl group is solely responsible for the stability of **5**.

It is also well known that di-*tert*-butylketene **7** (Figure 1.4) is a stable and persistent alkylketene that is resistant to dimerization and to nucleophilic reactions.⁷

Figure 1.4

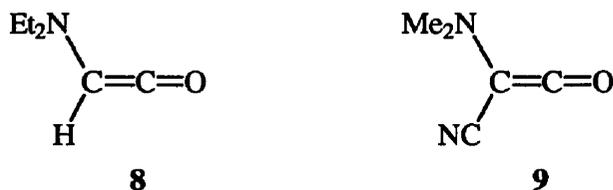


Alkyl substituents have been calculated to slightly destabilize ketenes relative to hydrogen.¹ However, it is well known that ketenes substituted with two bulky groups are much less reactive than ketenes that are less crowded. This has been evidenced in part by the fact that *tert*-butylketene is much more reactive than di-*tert*-butylketene **7**.⁸ Therefore it would appear that the stability of phthalimido-*tert*-butylketene **5** is mostly a function of steric bulk of the substituents with some contribution from the electronically stabilizing phthaloyl group.

Only a few alkylaminoketenes have been reported in the literature. These ketenes would be expected to be less stable than the parent aminoketenes due to an increase in

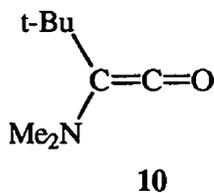
(Figure 1.5) has been generated by Wolff rearrangement and trapped with methanol in 12% yield.⁹ Cyanodimethylaminoketene **9** (Figure 1.5) has been generated by thermolysis and trapped by 2 + 2 cycloaddition with imines in yields as high as 89%.¹⁰

Figure 1.5



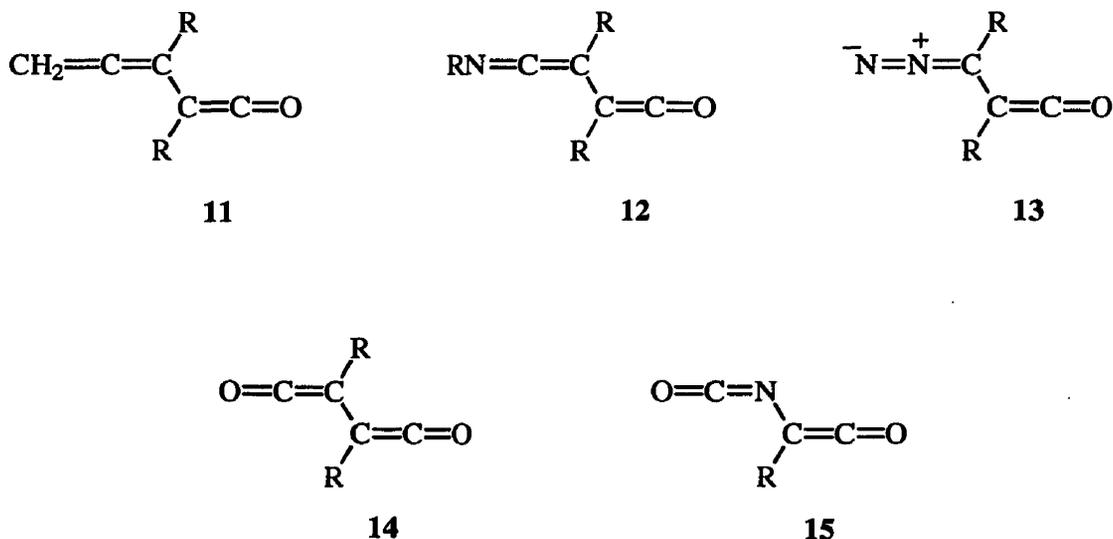
Despite the lack of thermodynamic stability of alkylaminoketenes, a degree of kinetic stability may be imparted by crowding the ketene group with bulky substituents. By replacing the cyano group of **9** with the bulkier *t*-butyl group, the amino analogue (**10**) of di-*tert*-butylketene **7** is formed (see Figure 1.6). The stability of di-*tert*-butylketene **7** has allowed its synthesis to be accomplished in a number of ways, including dehydrochlorination of the acid chloride,^{7a} dehydration of the acid with DCC,^{7c} and dehalogenation of *t*-Bu₂CClCOBr with Zn.^{7d} It is the synthesis of dimethylamino-*tert*-butylketene **10** (Figure 1.6) as a potentially stable alkylaminoketene that is the focus of a large part of this chapter.

Figure 1.6



of molecules known as cumulene substituted ketenes. These include allenylketenes (**11**), keteniminyketenes (**12**), diazomethylketenes (**13**), ketenylketenes (**14**) as well as isocyanatoketenes (**15**).

Figure 1.7

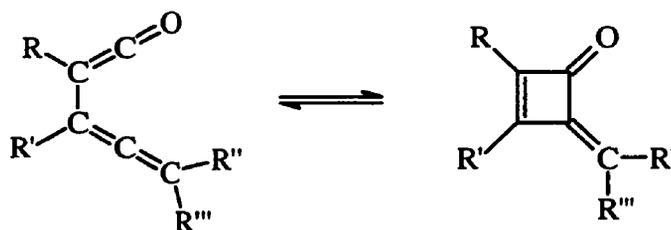


Stable and persistent forms of **11** and **14** have been synthesized in our laboratory and their stability, reactivity and geometry have been studied extensively.¹¹⁻¹³ The substituents on **14** and **11** play an important role in the stability of these molecules with respect to their ring closure products **16** and **17** (Scheme 1.3). Both **11** and **14** are drawn in their syn conformations for clarity in Scheme 1.3, however it should be noted that calculations support the anti conformation as the lowest energy planar structure for cumulene substituted ketenes.



14

16

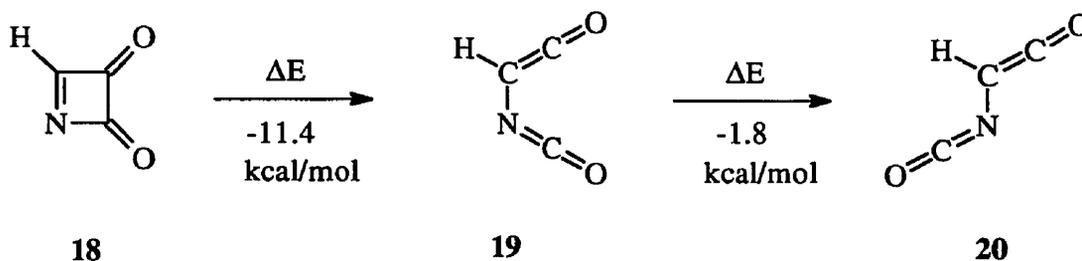


11

17

The stabilities of the syn, anti and cyclized structures of isocyanatoketene have been calculated¹⁴ (Figure 1.8). The results indicate that for the planar forms of isocyanatoketene, the anti isomer **20** is slightly more stable than the syn isomer **19**. Both of these isomers are calculated to be significantly more stable than the ring closed product **18** indicating that isocyanatoketene **20** should be relatively stable towards ring closure.

Figure 1.8



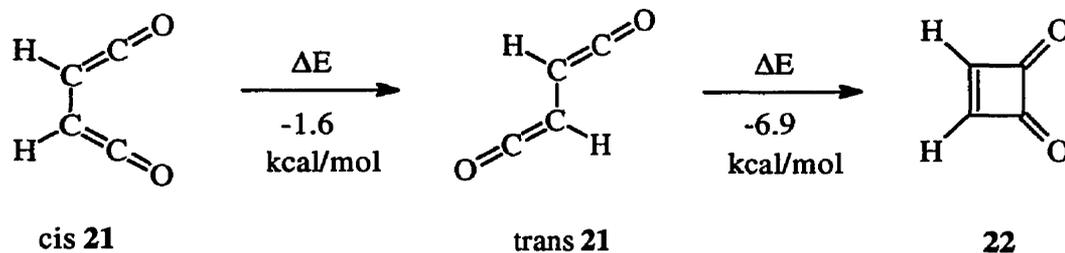
18

19

20

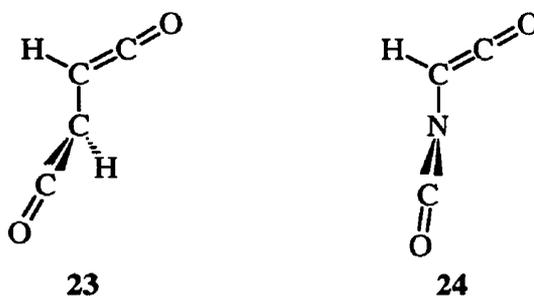
calculations¹ indicate that the ring closed product **22** is 8.5 kcal/mol more stable than cis **21** and 6.9 kcal/mol more stable than trans **21**.

Figure 1.9



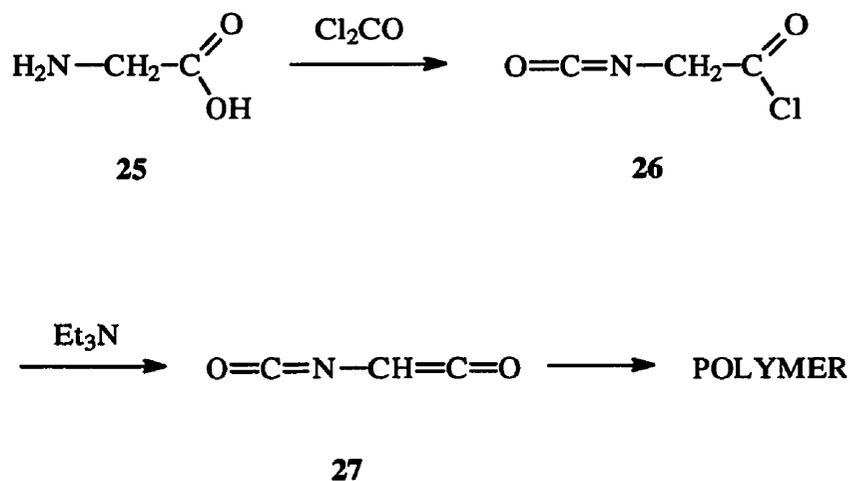
Further calculations¹⁵ have revealed that the twisted conformation **23** is only 2.9 kcal/mol less stable than **22**. The molecule twists in order that the *p* orbitals of the two ketenyl groups can minimize interaction by achieving a conformation that has the orbitals closer to an orthogonal position than overlapping. While no calculations have been done on non-planar conformations of isocyanatoketenes this same twisting could be predicted to occur, albeit to a lesser extent due to a destabilizing interaction between the *p* orbital of the ketene and the lone pair of electrons on the isocyanato nitrogen, giving **24**.

Figure 1.10



a myriad of reactions. The high functionality of isocyanatokenes and the interesting chemistry of both ketenes and isocyanates make isocyanatokenes synthetically attractive molecules. While there has been some success in the synthesis of other cumulene substituted ketenes, to date there is only one report¹⁶ of the existence of isocyanatokene. The synthetic strategy used is shown in Scheme 1.4.

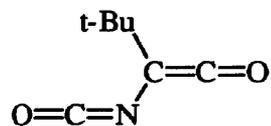
Scheme 1.4



While the authors saw no direct evidence of isocyanatokene **27**, they hypothesized that the oligomeric products they obtained were the result of formation of **27**. They did have success with this strategy in making isocyanatokenes where the isocyanate group and the ketene group were separated by four or more carbons. The products obtained were a result of the intermolecular 2 + 2 cycloaddition of two ketene groups.

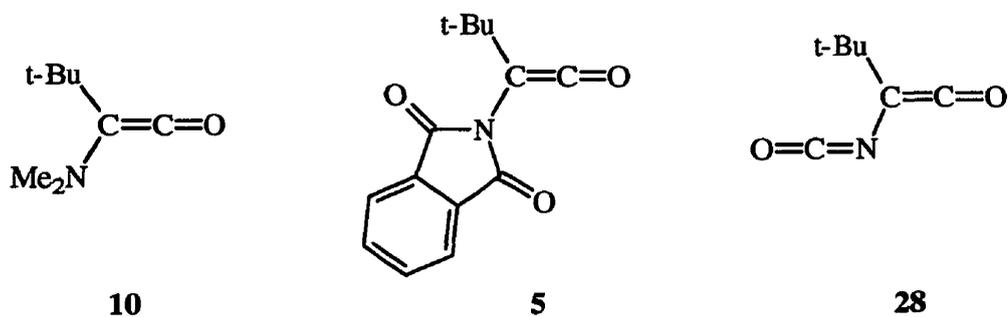
ability to stabilize ketenes. With this in mind, the potential exists that isocyanatoketene **28** (Figure 1.11) may be obtained as an observable species.

Figure 1.11

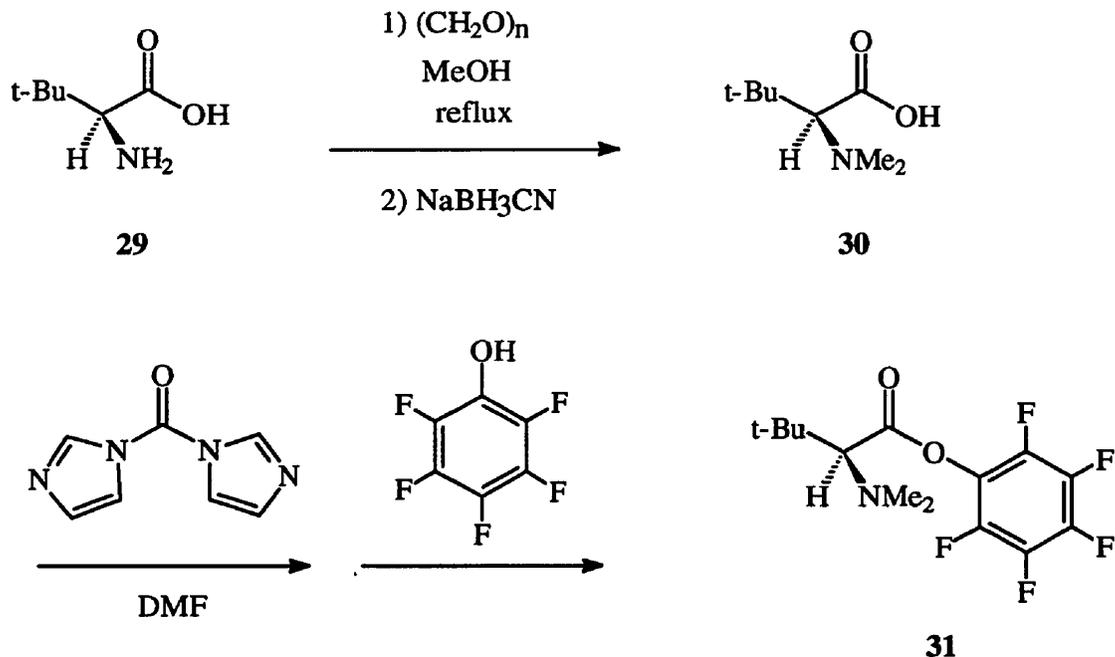


28

Figure 1.12



Details of the attempted synthesis of aminoketene **10**, aminoketene **5**, and isocyanatoketene **28** will be discussed. Scheme 1.5 shows the synthetic route taken to a possible aminoketene **10** precursor, pentafluorophenyl ester **31**. Pentafluorophenyl esters have been shown to be highly reactive in peptide synthesis.¹⁷ Pentafluorophenoxide is a good leaving group and therefore might be a good candidate for ketene synthesis via E1cB type reaction - a well documented route to ester hydrolysis involving a ketene intermediate.



The method used to prepare N,N-dimethyl-*tert*-leucine **30** from *tert*-leucine **29** was a variation of the procedure used by Borch and Hassid¹⁸ for methylating amines. This method has been reported to be successful in the N-methylation of amino acids.¹⁹ The variation is simply the use of methanol solvent rather than acetonitrile, an important consideration for decreasing the likelihood of monomethylating the amine, according to Charles and coworkers.²⁰ A suspension of **29**, paraformaldehyde and methanol was refluxed for 45 minutes affording a bis(methoxymethyl)amine²⁰ intermediate which is subsequently reduced to the dimethylamine using sodium cyanoborohydride, a mild and selective reducing agent. Following work-up, **30** is obtained in excellent yield (93%), identified by comparison with the reported²¹ ¹H NMR (D₂O) chemical shifts of N,N-dimethylvaline, the reported²² ¹H NMR (*d*-DMSO) chemical shifts of **30** and by signal integration. Compound **30** was the only water

form. There were no proton signals attributable to the monomethylated amine group and the only impurity appeared to be some unreacted paraformaldehyde. The product **30** was used in subsequent reactions with no further purification.

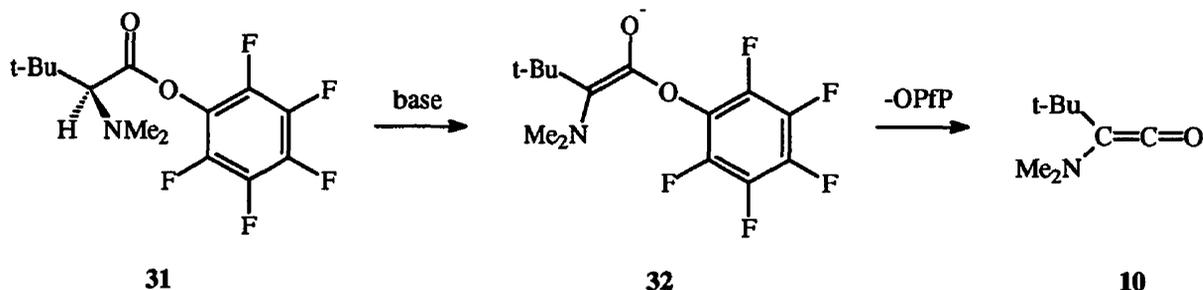
Attempts at synthesizing pentafluorophenyl ester **31** using carbodiimides as the coupling reagent were unsuccessful. Using 1,3-dicyclohexylcarbodiimide (DCC), a product thought to be **31** was made, however attempts to remove the resulting dicyclohexylurea from the product mixture were unsuccessful. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was used instead of DCC since the resulting urea is water soluble and therefore easily removed with extraction. Analysis by ¹H NMR of the product revealed that **31** had not formed. It appears that carbodiimides could not be used as coupling reagents under acidic conditions (dimethylamino acid **30** was stored as an acidic aqueous solution and only the water was removed prior to use).

Pentafluorophenyl ester **31** was successfully synthesized using N,N'-carbonyldiimidazole as the coupling reagent. This reagent has been used in the preparation of a variety of protected amino acid *p*-nitrophenyl esters.²³ N,N'-Carbonyldiimidazole was added to a suspension of dimethylamino acid **30** in DMF. The product of the reaction is a highly reactive acylimidazole. While acylimidazoles are generally crystalline and therefore isolable and easy to handle, isolation is most often unnecessary.²⁴ Thus, pentafluorophenol was added to the reaction mixture with no isolation of the intermediate acylimidazole. After the reaction mixture was stirred overnight the product mixture was purified by radial chromatography, and

yield of pure product.

Scheme 1.6 shows the planned synthetic step from pentafluorophenyl ester **31** to aminoketene **10**.

Scheme 1.6

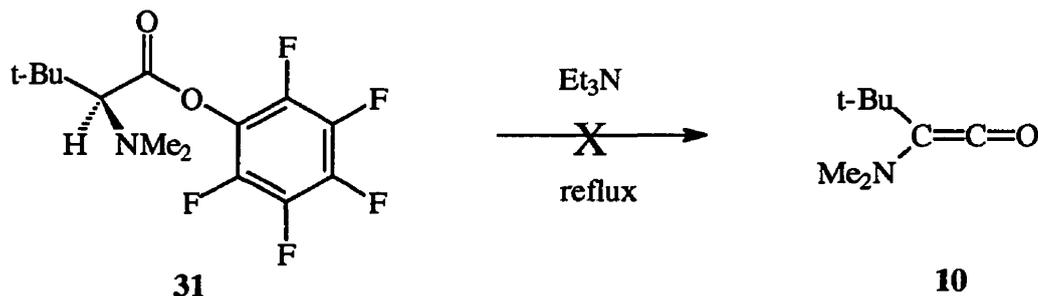


Scheme 1.6 is representative of a reaction that could occur via an E1cB mechanism. This is a well-documented route for ester hydrolysis and in fact a large number of ketenes have been synthesized using this method. Two important criteria must be met in order for such a reaction to occur to give ketene as a product. The proton adjacent to the carbonyl group must be somewhat acidic and a good leaving group must be present as part of the ester. Knowing that pentafluorophenyl esters meet the second of these criteria, the issue seemed to be whether the α -proton of ester **31** could be readily removed.

The non-nucleophilic organic bases that seemed best suited for this reaction were triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Triethylamine has been used extensively in dehydrochlorination reactions to give a wide variety of product ketenes³

reaction of pentafluorophenyl ester **31** with triethylamine is shown in Scheme 1.7.

Scheme 1.7

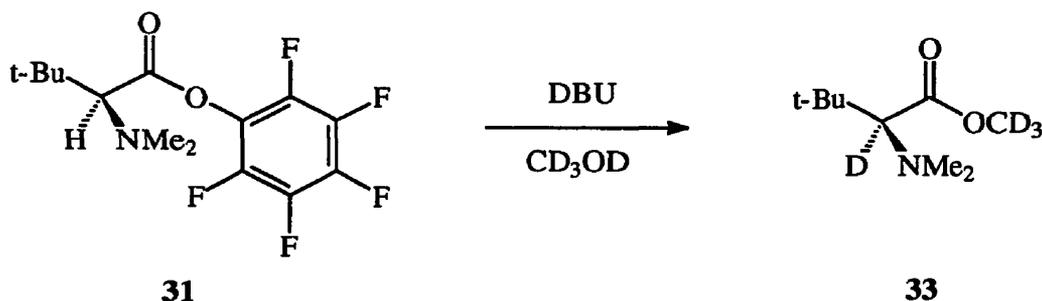


A solution of ester **31** in triethylamine was allowed to reflux under argon for 48 hours with aliquots taken out of the reaction flask periodically. The infrared spectra of these aliquots were recorded immediately as triethylamine solutions, however no ketene stretch was ever observed. Initially it was assumed that aminoketene **10** was unstable and would decompose before an infrared spectrum could be recorded. On closer inspection of the starting materials, it seems more likely that aminoketene **10** had not formed at all. The pK_a 's of triethylamine and the dimethylamino group of **31** would be quite similar. If pentafluorophenyl ester **31** exists as a stable compound, then certainly a base of similar pK_a to that of **31** itself could not deprotonate **31** in the first step of an E1cB mechanism.

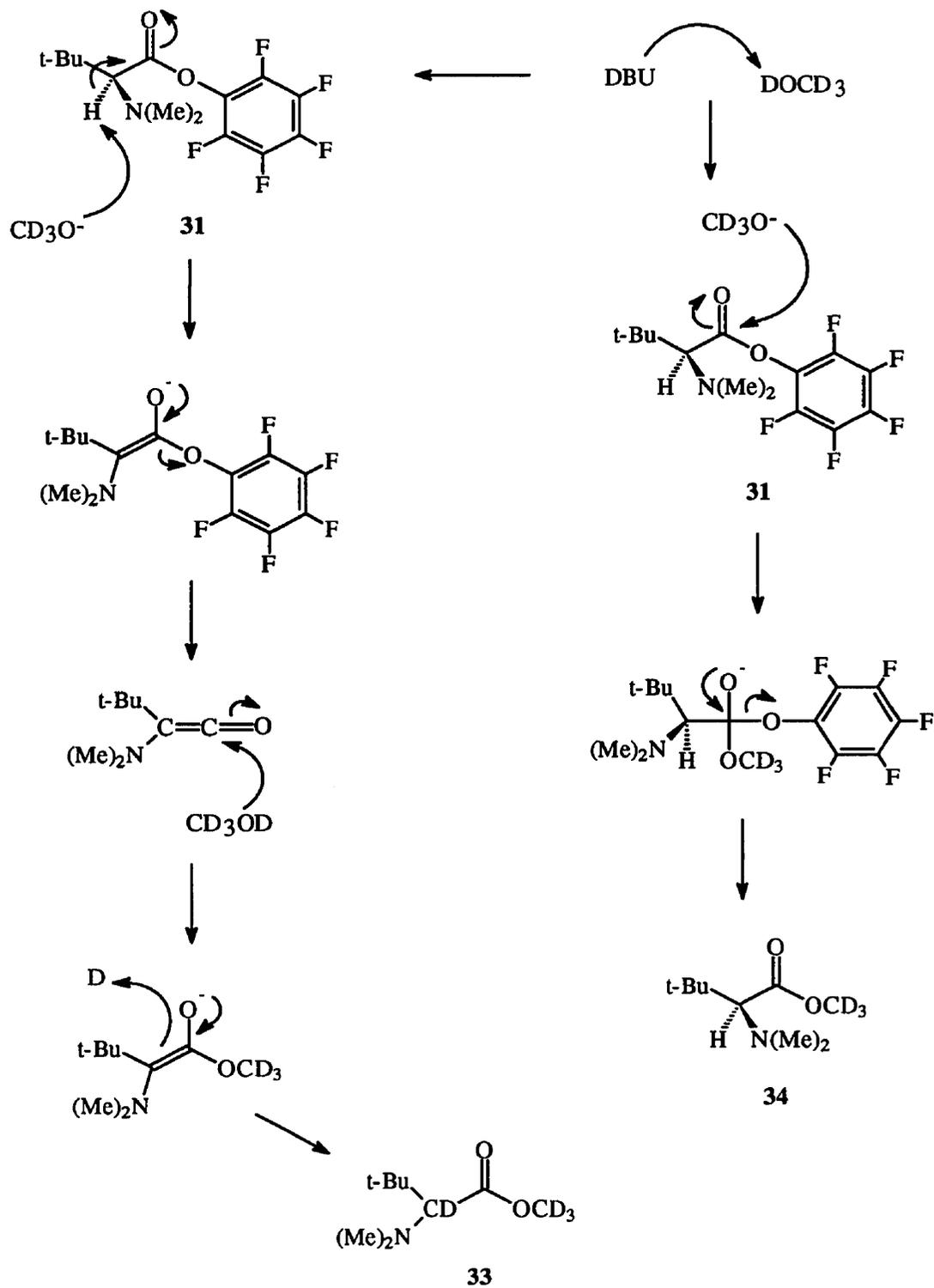
Two synthetic adjustments were made in an attempt to overcome the problems of the previous reaction. First, DBU was used as the base in place of triethylamine. DBU has a higher pK_a than that of triethylamine and it is also quite bulky thereby giving it non-nucleophilic character. Secondly, if aminoketene **10** forms but is too unstable to observe

identification of the resulting ester and provide evidence of ketene formation. Scheme 1.8 shows the intended reaction of pentafluorophenyl ester **31** with DBU and deuterated methanol.

Scheme 1.8



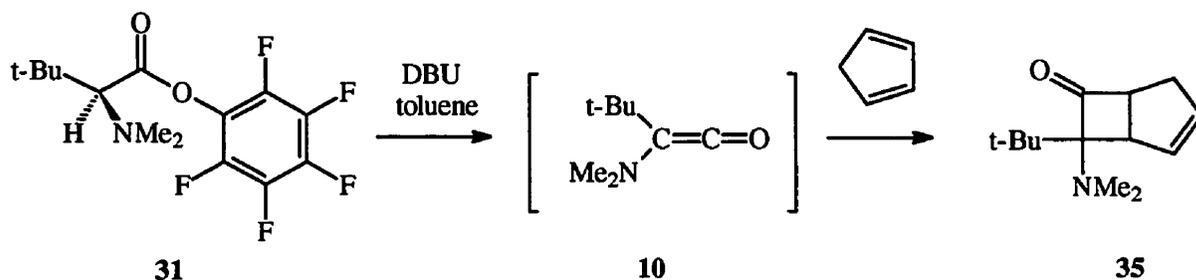
The reaction was carried out in a sealed NMR tube and thus could be monitored by ¹H NMR for the disappearance of the proton adjacent to the carbonyl. As both time and reaction temperature increased, the marked disappearance of signals from **31** was accompanied by the appearance of a second set of *t*-butyl and dimethylamino signals. Unfortunately, the α -proton signal was covered by signals from excess DBU. However the steady increase in intensity of a singlet at δ 4.8 indicated that CD₃OH was forming and that the reaction was proceeding as proposed. After extraction of DBU with water, the ¹H NMR was re-recorded in CDCl₃ which revealed the presence of a proton adjacent to the carbonyl group. While the integration of this signal was not exactly proportional to that of the dimethylamino and *t*-butyl signals, it appeared that the deuteromethyl ester **34** (see Scheme 1.9) was the major product with no or little formation of ester **33**. Scheme 1.9 shows the likely reaction pathways accounting for the favoured formation of ester **34**.



deuterated before deprotonating ester **31**. However, the low integration value of the α -proton in the ^1H NMR may be evidence that deprotonation of ester **31** is occurring with methoxide, be it a much less favored process than methoxide attack at a reactive carbonyl center. Unfortunately, all products were lost during purification and therefore mass spectrometry could not be employed to confirm the presence of both products.

With the possibility that aminoketene **10** was indeed forming, deprotonation with DBU was attempted once again, with cyclopentadiene as the trapping reagent. Because ketenes undergo characteristic 2 + 2 cycloadditions,³ the presence of a 2 + 2 product would unambiguously provide evidence of the formation of aminoketene **10**. Scheme 1.10 shows the attempted reaction to obtain 2 + 2 cycloaddition product **35**.

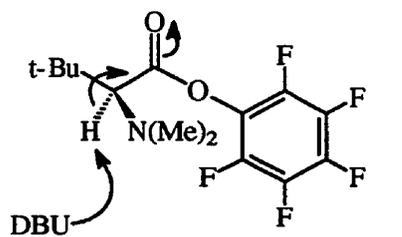
Scheme 1.10



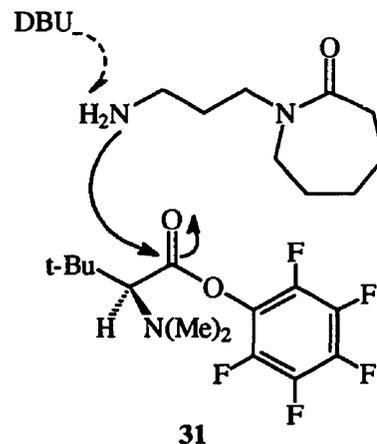
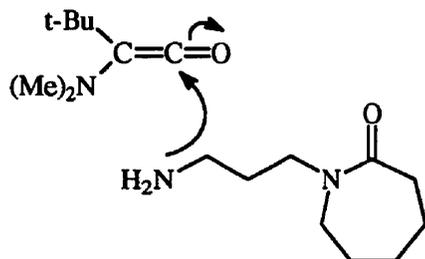
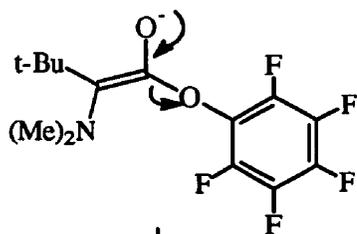
Freshly distilled cyclopentadiene was added to a stirring solution of pentafluorophenyl ester **31** and DBU in toluene. After refluxing for 2 hours, the heat was removed and the reaction was allowed to stir under argon overnight. The toluene was removed under reduced pressure, the product dissolved in diethyl ether and the ether layer was washed with water to remove DBU. ^1H NMR analysis of the organic layer revealed the presence of both *t*-butyl and

DBU and other impurities. Purification of the product was done using flash column chromatography on silica gel with 10% ethyl acetate in hexanes. The only UV visible fraction to elute with this solvent was unreacted ester **31**. Washing the column with methanol produced a small amount of UV visible product whose ^1H NMR was inconsistent with cycloaddition product **35**. Further analysis of the product by IR and mass spectroscopy indicate that the product is likely the result of N-(3-aminopropyl)- ϵ -caprolactam (a hydrolysis product of DBU²⁴) attacking ester **31** in a base catalyzed amidation reaction. This result, however, does not rule out the possibility of aminoketene **10** reacting with the caprolactam. Scheme 1.11 (see page 20) shows the possible reaction pathways.

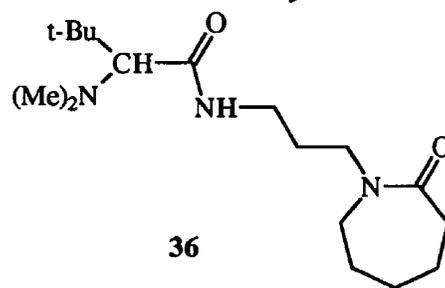
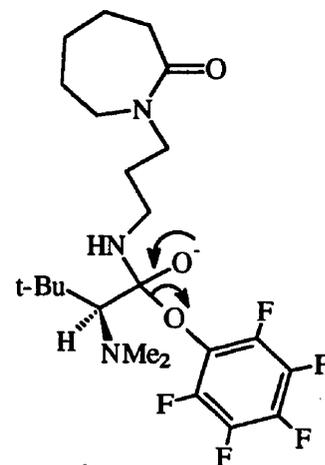
The first of the reaction pathways goes through aminoketene **10**. The likelihood of this pathway occurring is minimal when one considers that N-(3-aminopropyl)- ϵ -caprolactam is only present in small quantities while cyclopentadiene is present in excess, yet amide **36** and unreacted starting material are the only identifiable compounds in the product mixture. The lack of any cycloaddition product seems evidence enough of the lack of aminoketene **10** using DBU as a base.



31



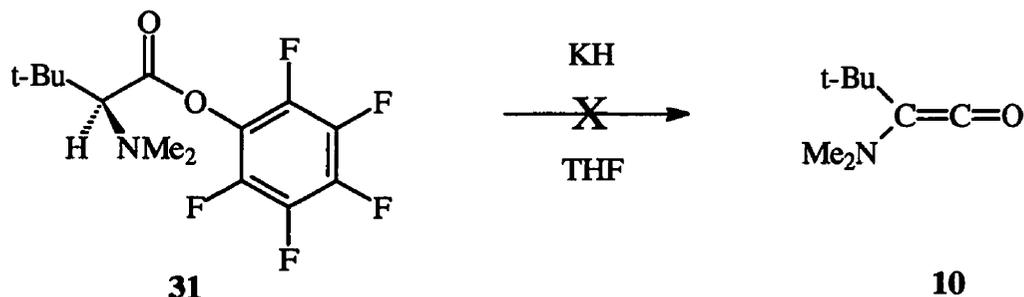
31



36

sterically demanding *t*-butyl and dimethylamino groups next to the proton adjacent to the carbonyl group of pentafluorophenyl ester **31**. A strong, small non-nucleophilic base such as hydride may then be useful in generating aminoketene **10**. Scheme 1.12 shows the attempted synthesis of aminoketene **10** using potassium hydride as a base.

Scheme 1.12

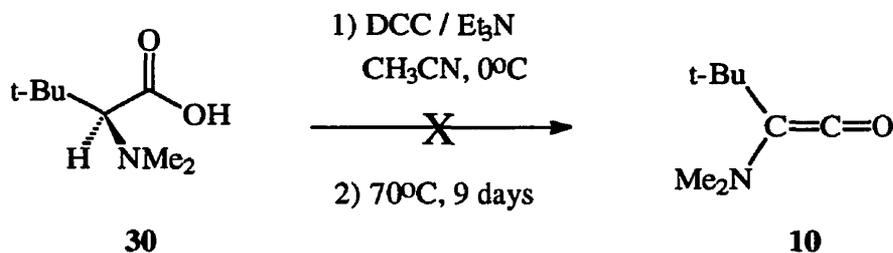


Ester **31** was added as a solution in THF to a stirring suspension of KH in THF under argon. After 2 hours of stirring, an aliquot of the supernatant liquid was removed from the reaction flask and the IR spectrum recorded as solution in THF. No ketene absorption was observed. A strong carbonyl stretch at 1778 cm^{-1} was observed; a band attributable to the starting material, ester **31**. Either aminoketene **10** did not form at all, or at equilibrium was only present in small amounts. Adding TMSCl to the reaction mixture could have protected pentafluorophenoxide to prevent attack on the ketene or it could have trapped the resulting enolate. The presence of such an enolate would have been evidence of deprotonation of ester **31** and proven the effectiveness of KH as a base in this synthetic strategy.

synthesis of ketenes, most notably in the synthesis of di-*tert*-butylketene.^{7a} Attempts at synthesizing the acid chloride of dimethylaminoacid **30** using standard procedures with each of oxalyl chloride, thionyl chloride and triphosgene were unsuccessful. Unreacted starting material was recovered in high yields in all cases.

Dehydration of di-*tert*-butylacetic acid with DCC has been used successfully in the synthesis of di-*tert*-butylketene.^{7c} Dehydration of dimethylaminoacid **30** using DCC was attempted (Scheme 1.13).

Scheme 1.13



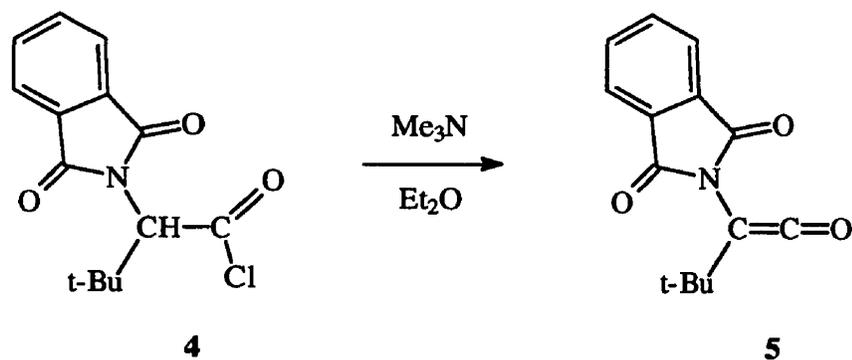
After the removal of acetonitrile under reduced pressure, vacuum distillation of the product afforded a clear colourless liquid. IR and ¹H NMR analysis revealed the presence of acetonitrile and DCC as the main components of the mixture as well as an unidentified component with *t*-butyl and dimethylamino signals. The lack of ketene absorption in the IR spectrum led to the abandonment of this method.

The attempted synthesis of aminoketene **10** failed on a number of counts. Unsure of whether failure was a result of the instability of aminoketene **10**, insufficient base strength, or using pentafluorophenoxide as a leaving group, the feasibility of using pentafluorophenyl ester

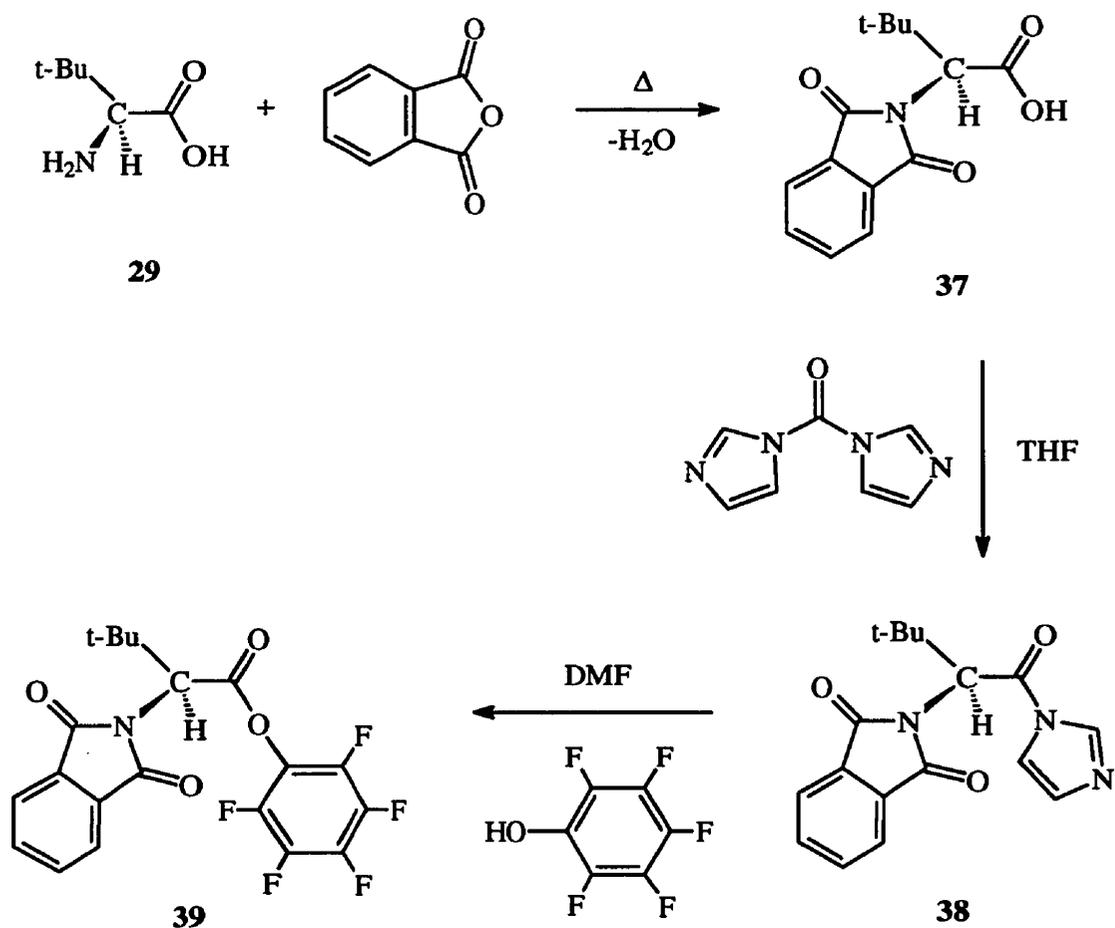
investigated.

Scheme 1.14 shows the synthetic route taken by Winter and Pracejus⁴ in making the persistent and crystalline aminoketene, phthalimido-*tert*-butylketene **5**.

Scheme 1.14



The resulting aminoketene **5** is persistent and trimethylamine has a sufficiently high pK_a to remove the proton adjacent to the carbonyl. Therefore changing the leaving group from chloride to pentafluorophenoxide and using similar conditions otherwise, should provide insight into whether pentafluorophenyl esters are good candidates for E1cB type generation of aminoketenes in general. Scheme 1.15 shows the synthetic route taken to obtain pentafluorophenyl ester **39**.



tert-Leucine **29** was converted to its *N*-phthaloyl derivative **37** using a facile procedure described by Sheehan and coworkers.²⁵ *N*-Phthaloyl *tert*-leucine was obtained as a white solid in 80% pure yield and was identified by its ¹H NMR spectrum.

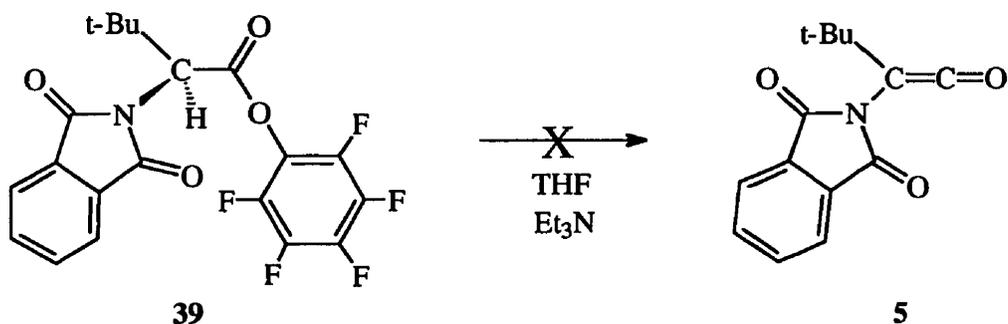
Attempts to synthesize pentafluorophenyl ester **39** in a one pot procedure as previously described gave low yields of product and considerable quantities of unreacted starting materials. As a result, acylimidazole **38** was synthesized first by refluxing a solution of **37** and carbonyldiimidazole in THF for two hours. Acylimidazole **38** was easily isolated by extracting

38 as a pure white solid in 76% yield. Acylimidazole **38** was fully characterizable and did not decompose appreciably over the following few days that it was used.

Pentafluorophenyl ester **39** was successfully made by dissolving acylimidazole **38** in an 80:20 DMF:ethyl acetate solvent mixture followed by the addition of excess pentafluorophenol. After one hour of stirring at room temperature, pentafluorophenyl ester **39** was isolated by extraction techniques and purified by radial chromatography. Pentafluorophenyl ester **39** was obtained pure as an oil in a reasonable 44% yield. The success of this reaction seems entirely dependent on the polarity of the solvent system. A one-pot procedure from N-phthaloyl-*tert*-leucine **37** to pentafluorophenyl ester **39** should be possible as long as acylimidazole **38** will form in the more polar medium.

Scheme 1.16 shows the reaction attempted to synthesize aminoketene **5** by an E1cB type reaction using triethylamine as the base.

Scheme 1.16

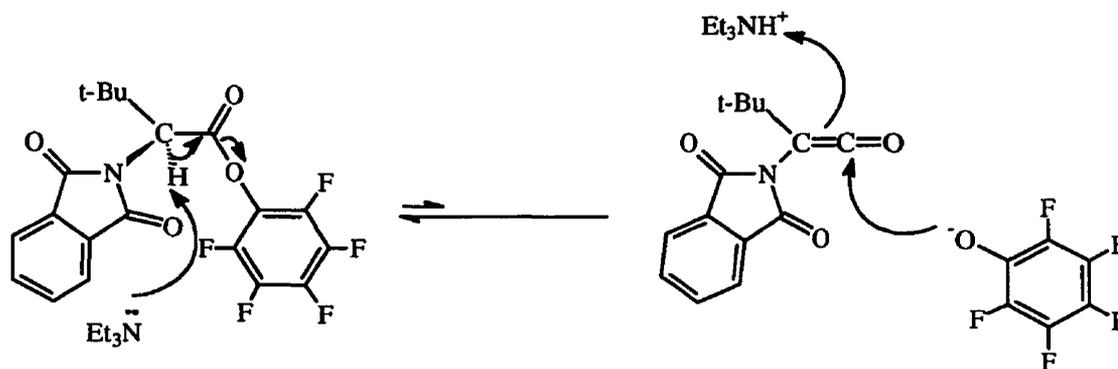


A solution of triethylamine, THF, and pentafluorophenyl ester **39** was refluxed for 20 hours. A 1 mL aliquot was taken out of the reaction flask and the solvents removed under reduced pressure. If aminoketene **5** had formed, a solid should be left in the flask. Instead, a

Carbonyl stretches at 1728 cm^{-1} and 1803 cm^{-1} were observed and are both characteristic of the starting ester **39**.

The lack of formation of aminoketene **5** under conditions similar to those used by Winter and Pracejus can be explained by at least two reasons. First, if triethylamine was successful in deprotonating ester **39** to start the E1cB reaction, then pentafluorophenoxide leaving is the next step. As soon as this phenoxide (a reasonable nucleophile in ketene additions) leaves, it would attack the resulting ketene immediately if it is not removed from the reaction as it forms. Imagining the formation of aminoketene **5** as an equilibrium process then, the equilibrium would lie heavily to the left, as shown in Figure 1.13.

Figure 1.13

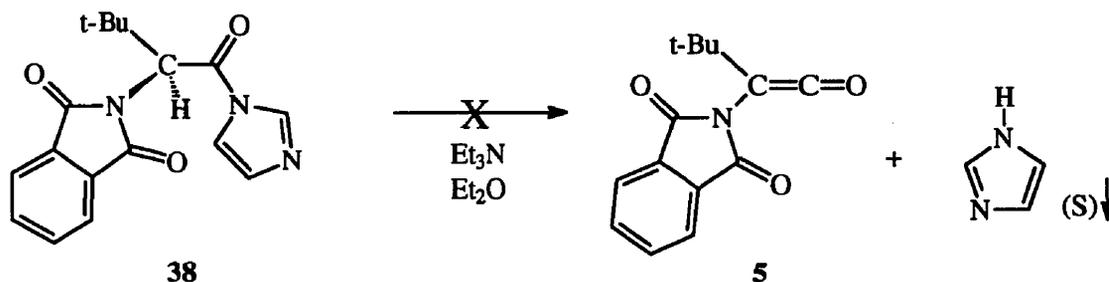


The second possibility for the lack of success is the extra steric demand of the pentafluorophenyl group relative to the acyl chloride used by Winter and Pracejus. This may account for lack of any deprotonation by triethylamine, or any other base for that matter, if it can't get close enough to the labile proton of ester **39**.

successful at least partly as a result of the insolubility of the resulting triethylammonium chloride. Precipitation of this salt as the chloride ion leaves removes it from the reaction and makes the dehydrochlorination reaction irreversible.

Imidazole has a very low solubility in many organic solvents including diethyl ether. Acylimidazole **38** has been synthesized and isolated in fairly high yield as described earlier. Imidazolide is known to be a good leaving group so if the imidazolide can precipitate out of the reaction mixture as imidazole, then ketenes may be able to form in an analogous manner to dehydrochlorination reactions. Scheme 1.17 shows the attempted 'deimidazolation' of acylimidazole to give aminoketene **5**.

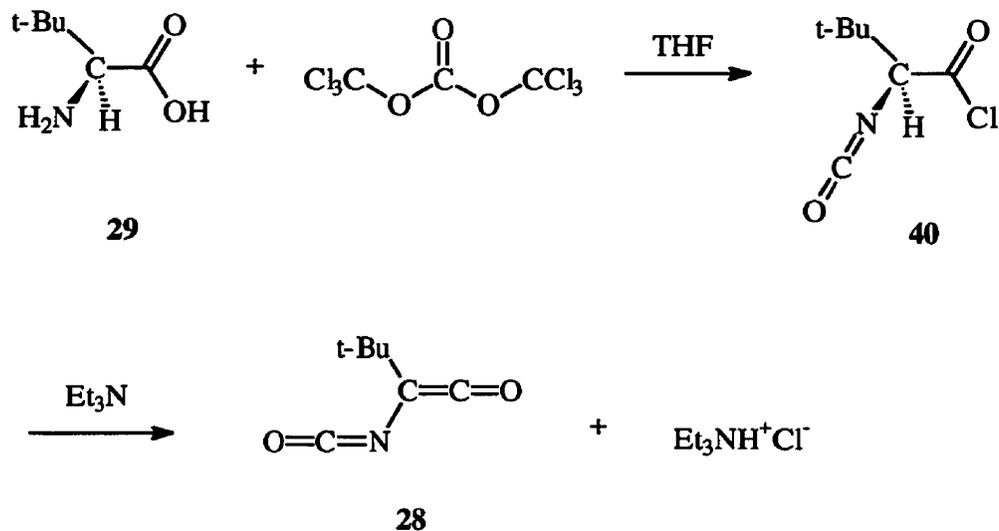
Scheme 1.17



The reaction was allowed to stir at room temperature for 48 hours during which time no precipitate was observed. Analysis of the solution by IR spectroscopy showed carbonyl absorptions at 1724 cm⁻¹ and 1753 cm⁻¹, characteristic of the starting material acylimidazole **38**. The reaction was repeated using DBU, a stronger base, and similar results were obtained. The acylimidazole may present steric problems similar to those hypothesized for pentafluorophenyl ester.

ketene, was made. A number of isocyanatoketenes have been prepared by Mormann and coworkers¹⁶ and isolated as the 2 + 2 cycloaddition dimers. Their synthetic strategy was employed, with the minor variation of triphosgene being used in place of phosgene. Triphosgene (bis(trichloromethyl) carbonate) is a less toxic phosgene surrogate and is said to react as 3 moles of phosgene gas.²⁴ The synthetic strategy to isocyanatoketene **28** is shown in Scheme 1.18 below.

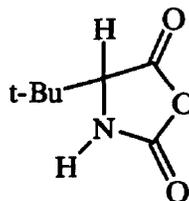
Scheme 1.18



The first step of the sequence involved adding triphosgene as solution in THF to a stirring suspension of *tert*-leucine **29** and refluxing the mixture under argon. In fifteen minutes from the time of triphosgene addition, a clear colourless solution resulted. After 3 hours of reflux an aliquot was taken from the flask, the THF removed under reduced pressure and an IR spectrum of the resulting white solid was recorded. Two carbonyl absorptions were seen at

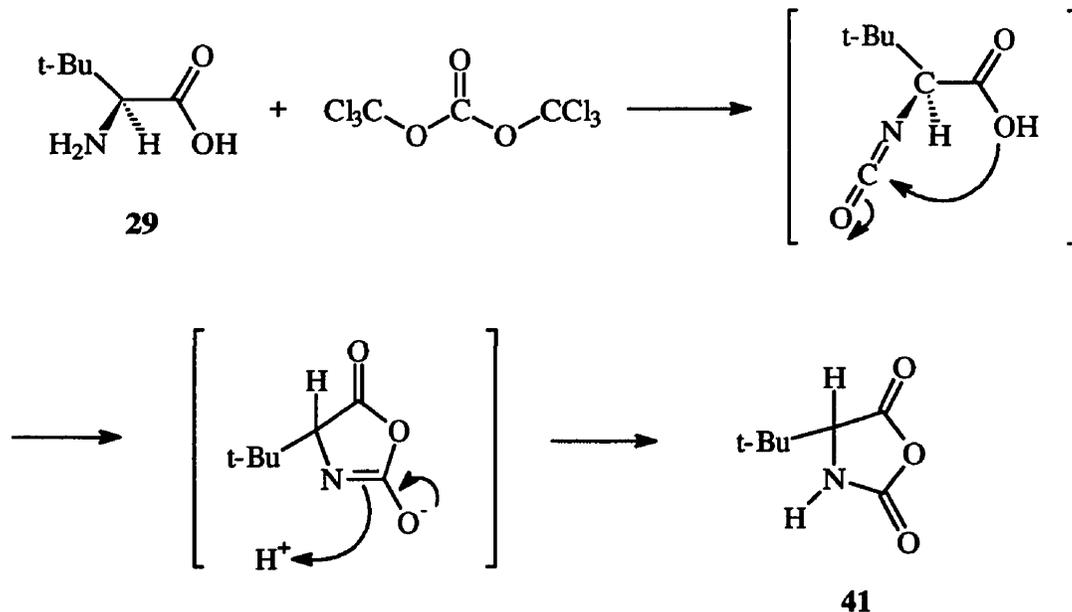
2200 cm^{-1} . ^1H NMR analysis revealed a very pure product with a *t*-butyl signal at $\delta 1.1$, an α -CH signal at $\delta 4.0$ and an NH signal at $\delta 6.95$ in a 9:1:1 integration ratio respectively. These spectra taken in conjunction with a mass spectrum identified the compound as *L*-*tert*-leucine-N-carboxyanhydride **41**, pictured in Figure 1.14.

Figure 1.14



41

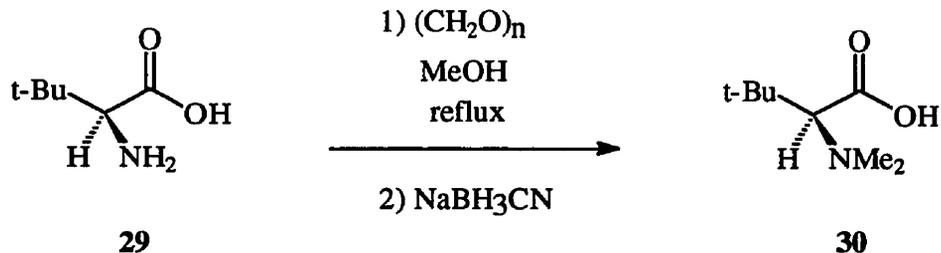
If the isocyanate forms before the acid chloride, then the isocyanato group is open to intramolecular attack from the acid OH group forming a stable five membered ring. This process must be of considerably lower energy than formation of the acyl chloride as **41** was obtained very pure in high yield. A partial mechanism is shown in Scheme 1.19.



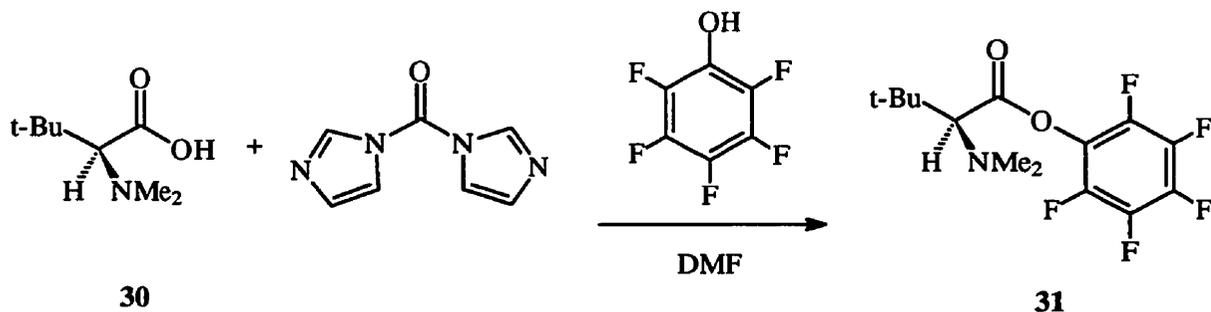
In fact, treatment of α -amino acids with phosgene in this manner has been used to make α -aminoacid-N-carboxyanhydrides (NCA's) since 1951²⁶ and indeed **41** has been made using this procedure.²⁷ The chemistry of NCA's has been of interest in peptide synthesis for some time.²⁸ Given these results, the synthesis of isocyanatoketene in this manner was abandoned.

General:

All glassware was oven-dried (115 °C) overnight while all plastic equipment was blown dry with air and stored in a desiccator prior to use. All reactions were carried out under an atmosphere of argon. Tetrahydrofuran was distilled from Na/benzophenone just prior to use. Triethylamine was distilled from CaH₂ and stored under argon in a sealed flask from which it was taken as needed. The L-isomer of *tert*-leucine was used with no regard to the resulting stereochemistry of any reaction. All other solvents and reagents were used as provided by commercial sources. Flash column chromatography was performed on 230-400 mesh Aldrich silica gel. Radial chromatography was performed on a Harrison Research Chromatotron, model 7924, with plates made from Merck TLC grade 7749 silica gel containing gypsum binder and fluorescent indicator. Thin layer chromatography was performed on TLC grade silica. Bands were detected using portable UV lamp. ¹H NMR spectra were obtained at 200 MHz on a Varian Gemini spectrometer, 400 MHz or 500 MHz on a Varian Unity spectrometer. ¹³C NMR spectra were obtained at 100 MHz or 125 MHz on a Varian Unity spectrometer. ¹⁹F NMR spectra were obtained at 400 MHz on a Varian Unity spectrometer. IR spectra were obtained on either a Nicolet DX FT-IR spectrometer, a Perkin Elmer FT-IR Spectrum 1000 spectrometer, or a Bohem Hartmann and Braun MB Series spectrometer. Ultraviolet spectra were obtained on a Perkin Elmer UV/Vis Spectrometer Lambda 12.



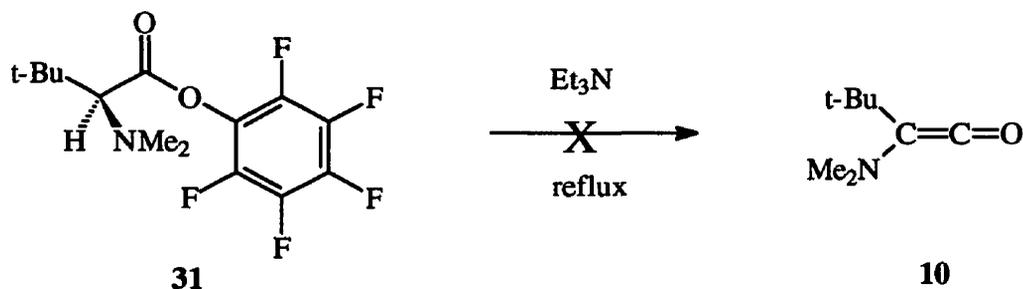
A suspension of *tert*-leucine (**29**, 493 mg, 3.76 mmol) and paraformaldehyde (675 mg, 22.5 mmol) in methanol (25 mL) was refluxed under argon for one hour. The heat source was removed and the reaction was allowed to cool to room temperature at which time NaBH₃CN (570 mg, 9.07 mmol) was added and stirring continued under argon. After two hours, 5 mL of water was added to the reaction and the methanol was removed under reduced pressure. The mixture was diluted with water (25 mL) and the solution made acidic with 1M HCl (vigorous bubbling). After sitting for 16 hours to facilitate complete H₂ (g) evolution, the aqueous solution was added to a separatory funnel and washed with diethyl ether (2 X 40 mL) and CHCl₃ (2 X 30 mL). The aqueous layer was collected and the water removed under reduced pressure leaving **30** as a white solid (579 mg), identified by comparison of its reported^{21,22} ¹H NMR values. A small amount of paraformaldehyde impurity is also seen in the spectrum. The yield of **30** was 93%, determined by internal standard ¹H NMR (D₂O) using sodium acetate.



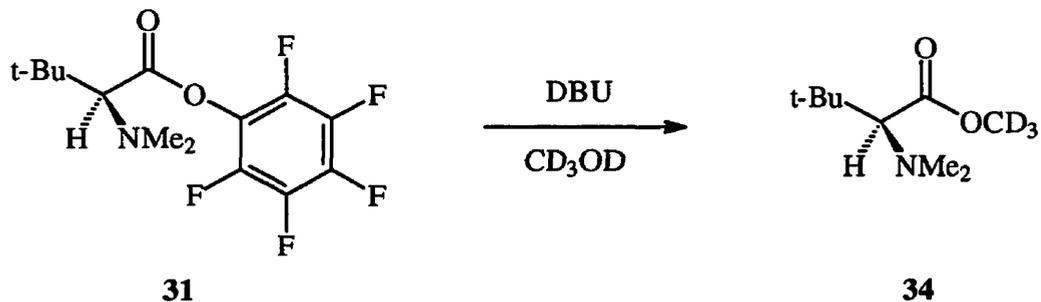
To a stirring suspension of **30** (143 mg, 0.90 mmol) in DMF (10 mL) cooled to 0 °C in an ice bath, was added carbonyldiimidazole (382 mg, 2.36 mmol). The reaction was placed under argon and allowed to stir at 0 °C for one hour. The ice bath was then removed and pentafluorophenol (331 mg, 1.80 mmol) was added to the reaction flask. After 18 hours of stirring under argon, the reaction mixture was added to 20 mL of diethyl ether in a separatory funnel and washed with H₂O (3 X 20 mL). Vigorous CO₂ (g) evolution was seen during the first water wash. The organic layer was collected, dried over anhydrous MgSO₄ and filtered. Removal of the solvents under reduced pressure gave a yellowish liquid with white solid suspended in it. ¹H NMR analysis revealed the major product to be **31** with imidazole impurity. TLC analysis using 10% ethyl acetate in hexanes showed three spots under UV light: R_f 0.51, R_f 0.18, and a baseline spot. Purification of **31** was achieved by first running the products through a short column of silica gel with 10% ethyl acetate in hexanes. Fractions showing spots at R_f 0.5 after TLC analysis (90:10 hexanes:ethyl acetate) were combined and further purified by radial chromatography on silica gel with 6% ethyl acetate in hexanes. **31** was obtained as a clear colourless liquid in 48% pure yield (141 mg). ¹H NMR (CDCl₃)

δ 27.2 (t-butyl), δ 35.0 (CMe₃), δ 44.4 (N(CH₃)₃), δ 75.5 (α -CH), δ 136, δ 138, δ 139, δ 140, δ 141, δ 142 (6 multiplets, OC₆F₅), δ 166.2 (CO); ¹⁹F NMR (CDCl₃) δ -162.63 (m, 2F), δ -158.32 (t, 1F, J = 22 Hz), δ -151.34 (m, 2F); IR (CCl₄) 1785 cm⁻¹; UV (isooctane) λ_{max} = 255 nm; EIMS *m/z* 325 (M⁺, 3), 310 (M⁺-CH₃), 268 (M⁺-C₄H₉, 100), 240 (9), 114 (M⁺-C₇H₁₆N, 72), 99 (21), 86 (24), 85 (44), 57 (C₄H₉⁺, 41).

N,N-Dimethylamino-*tert*-butyl ketene (10):



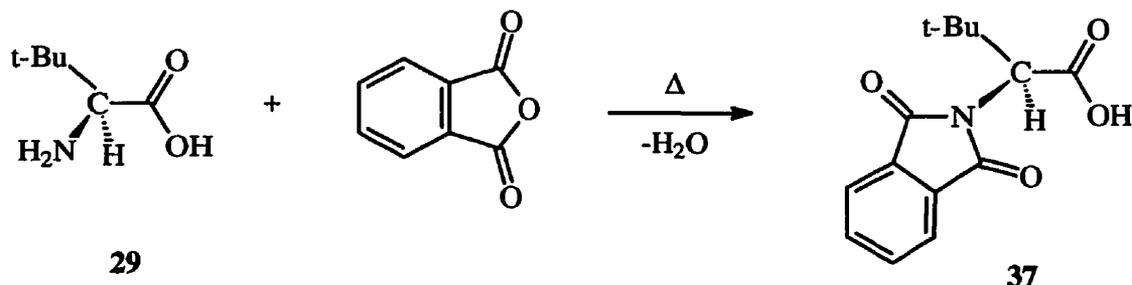
To a sample of ester **31** (39.6 mg, 0.122 mmol) under argon in a 2-necked round bottomed flask equipped with a water condenser was added dry triethylamine (6 mL) by syringe. This clear colourless solution refluxed for 48 hours. A 1 mL aliquot of the resulting pale yellow solution was subsequently removed from the flask and a solution IR spectrum immediately recorded. No ketenyl stretch was observed in the 2100 cm⁻¹ region. A strong absorption at 1785 cm⁻¹ was observed and was identified as the carbonyl stretch of ester **31**. ¹H NMR (CDCl₃) analysis of the aliquot confirmed that the major component of the aliquot was ester **31**.



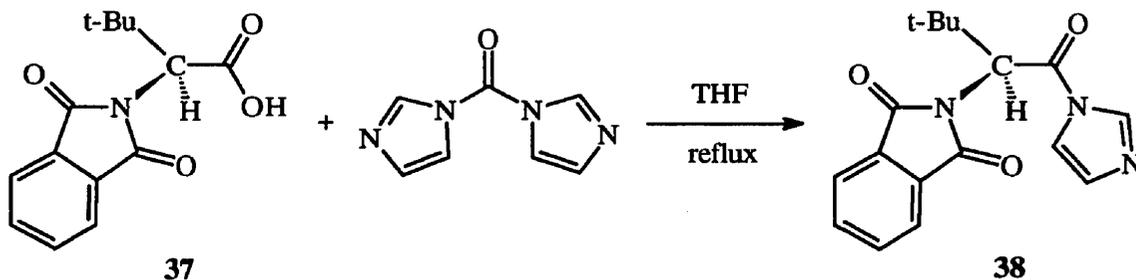
To a solution of **31** (23.7 mg, 0.0729 mmol) in CD₃OD (1 mL) in an NMR tube was added 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU, (30 μL, 0.20 mmol) by syringe. The tube was cooled to -78 °C and flushed with argon for 15 minutes. The glass tube was then flame sealed and allowed to warm to room temperature. After 20 minutes the ¹H NMR spectrum revealed signal attributable to ester **31** and DBU as well as a small signal at δ4.8, assigned to CD₃OH. The tube was warmed to 55 °C in an oil bath for one hour and the ¹H NMR spectrum recorded. The signal at δ4.8 had become relatively larger and a second set of t-butyl and dimethylamino signals were observed slightly upfield from those of ester **31**. The tube was then warmed to 85 °C in an oil bath for 3 hours and the ¹H NMR re-recorded. The signal at δ4.8 was larger than previously while the signals for ester **31** had become relatively small compared to those of the new product. The tube was warmed at 85 °C for 17 hours more. The contents of the tube were dissolved in diethyl ether (10 mL) and added to a separatory funnel. The ether layer was washed with water (2 X 10 mL), dried over anhydrous MgSO₄ and filtered. Removal of solvents by reduced pressure yielded a small amount of clear yellow liquid. The ¹H NMR (CDCl₃) spectrum revealed one t-butyl singlet at δ0.98, one

Purification of ester **34** was attempted using radial chromatography on silica gel with 10% ethyl acetate in hexanes. The ^1H NMR (CDCl_3) spectra of all fractions collected were recorded but none showed evidence of a *t*-butyl or dimethylamino signal.

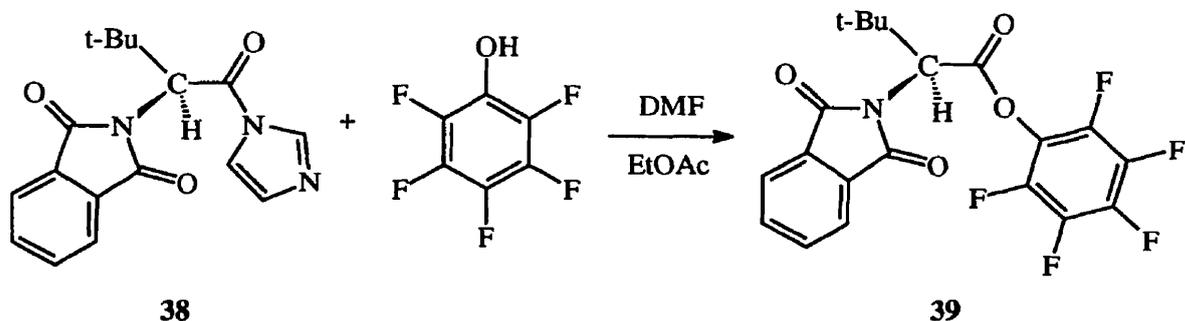
N,N-Phthaloyl-*tert*-leucine²⁵ (37):



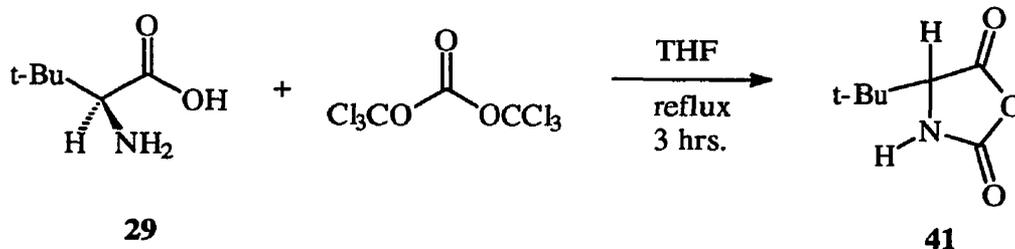
tert-Leucine (**29**, 509 mg, 3.88 mmol) and phthalic anhydride (564 mg, 3.81 mmol) were added to a 25 mL round bottom flask as solids. The flask was fitted with a condenser, the mixture stirred, and the apparatus flushed with argon. The mixture of solids was heated to 170°C and stirred as a liquid mixture for 2.5 hours. After cooling to room temperature overnight, a yellowish syrup-like product was obtained. Recrystallization of the product from methanol/water afforded pure **37** as a fine white solid in 80% yield (796 mg). **37** was identified by ^1H NMR and IR spectroscopy. ^1H NMR (CDCl_3) δ 1.2 (s, 9H, *t*-butyl), δ 4.6 (s, 1H, α -CH), δ 7.8 (m, 4H, *N*-phthaloyl), δ 10-11 (broad, 1H, COOH); IR (CDCl_3) 2500-3500 cm^{-1} (m, very broad), 1775 cm^{-1} (m), 1720 cm^{-1} (s).



To a stirring solution of **37** (432 mg, 1.66 mmol) in dry THF (10 mL) was added carbonyldiimidazole (313 mg, 1.93 mmol) as a solid. The solution was heated to reflux under argon. After two hours of reflux, the product was allowed to cool to room temperature and the THF was removed by reduced pressure leaving an oily residue. Diethyl ether (20 mL) was added to the residue to precipitate imidazole, which was then filtered off through a cotton plug. The ether solution was then washed with water (2 X 20 mL) in a separatory funnel. The ether layer was dried over anhydrous MgSO_4 and filtered. Evaporation of the ether under reduced pressure gave pure **38** as a white solid in 76% yield (392 mg). ^1H NMR (CDCl_3) δ 1.198 (s, 9H, $\text{C}(\text{CH}_3)_3$), δ 4.994 (s, 1H, α -CH), δ 6.919, δ 7.240, δ 7.972 (3s, 3H, acylimidazole); δ 7.784 (m, 4H, N-Phthaloyl); ^{13}C NMR (CDCl_3) δ 27.4 (CH_3), δ 37.0 ($\text{C}(\text{CH}_3)_3$), δ 59.1 (α -CH), δ 115.9, δ 136.0 (acylimidazole), δ 124.0, δ 130.9, δ 134.8 (N-phthaloyl), δ 163.5 (CO, acylimidazole), δ 167.4 (CO, N-phthaloyl); IR (CDCl_3) 1754 cm^{-1} (m), 1723 cm^{-1} (s); EIMS m/z 312 (7, MH^+), 244 (41, $\text{MH}^+ - \text{C}_3\text{H}_4\text{N}_2$), 216 (100, $244 - \text{CO}$), 160 (49), 148 (57), 130 (40), 104 (39), 69 (33), 57 (18, Me_3C^+); HRMS m/z calc. for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_3$ 312.1348 found 312.1340.



To a stirring solution of **38** (304 mg, 0.978 mmol) in DMF/ethyl acetate (80/20, 15 mL) under argon was added pentafluorophenol (500 mg, 2.7 mmol). After three hours of stirring, the reaction mixture was diluted with 20 mL diethyl ether and added to a separatory funnel. The solution was washed with water (3 X 40 mL), aqueous K_2CO_3 (2 X 50 mL), dried over anhydrous $MgSO_4$ and filtered. Removal of the solvent by reduced pressure yielded an oily residue determined to be slightly impure **39** by 1H NMR analysis. Purification of **39** was accomplished using flash column chromatography on silica gel (4% ethyl acetate in hexanes). Ester **39** (44% isolated yield, 185 mg, white oil) 1H NMR ($CDCl_3$) δ 1.208 (s, 9H, $C(CH_3)_3$), δ 4.939 (s, 1H, α -CH), δ 7.842 (m, 4H, N-Phthaloyl); ^{13}C NMR ($CDCl_3$) δ 27.5 (CH_3), δ 36.2 ($C(CH_3)_3$), δ 59.1 (α -CH), δ 123.8, δ 131.5, δ 134.4 (N-phthaloyl), δ 136, δ 138, δ 139, δ 140, δ 141, δ 142 (6 small multiplets, $COOC_6F_5$), δ 163.4 (CO, pentafluorophenyl), δ 167.4 (CO, N-phthaloyl); IR ($CDCl_3$) 1801 cm^{-1} (m), 1724 cm^{-1} (s) 1521 cm^{-1} (s); EIMS m/z 428 (1, MH^+), 371 (6, MH^+ -t-Bu), 244 (20, MH^+ - OC_6F_5), 216 (100, 244-CO), 160 (52), 148 (62), 130 (36), 104 (37), 69 (30), 57 (33, Me_3C^+); HRMS m/z calc for $C_{20}H_{15}NO_4F_5$ 428.0921 found 428.0911.



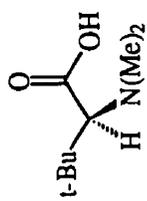
A 50 mL 2-necked round bottom flask containing **29** (52.7 mg, 0.402 mmol) was fitted with a reflux condenser and the apparatus was flushed with argon. Dry THF (6 mL) was added by syringe and to the resulting heterogeneous mixture was added triphosgene (130 mg, 0.44 mmol) as a solution in THF (6 mL) by syringe. The mixture was heated with an oil bath at 65 °C and after fifteen minutes, the heterogeneous reaction mixture became a clear colourless solution. After three hours of stirring at 65 °C, a 3 mL aliquot was removed from the flask and the solvent was evaporated under reduced pressure leaving **41** as a powdery white solid in very high purity by ¹H NMR analysis. ¹H NMR (CDCl₃) δ 1.1 (s, 9H, t-butyl), δ 4.0 (s, 1H, α-CH), δ 6.9, (broad s, 1H, NH); IR (CDCl₃) 1848 cm⁻¹, 1778 cm⁻¹; EIMS *m/z* 158 (MH⁺, 11), 130 (MH⁺-CO, 35), 101 (MH⁺-C₄H₉, 48), 83 (16), 70 (31), 57 (C₄H₉⁺, 100).

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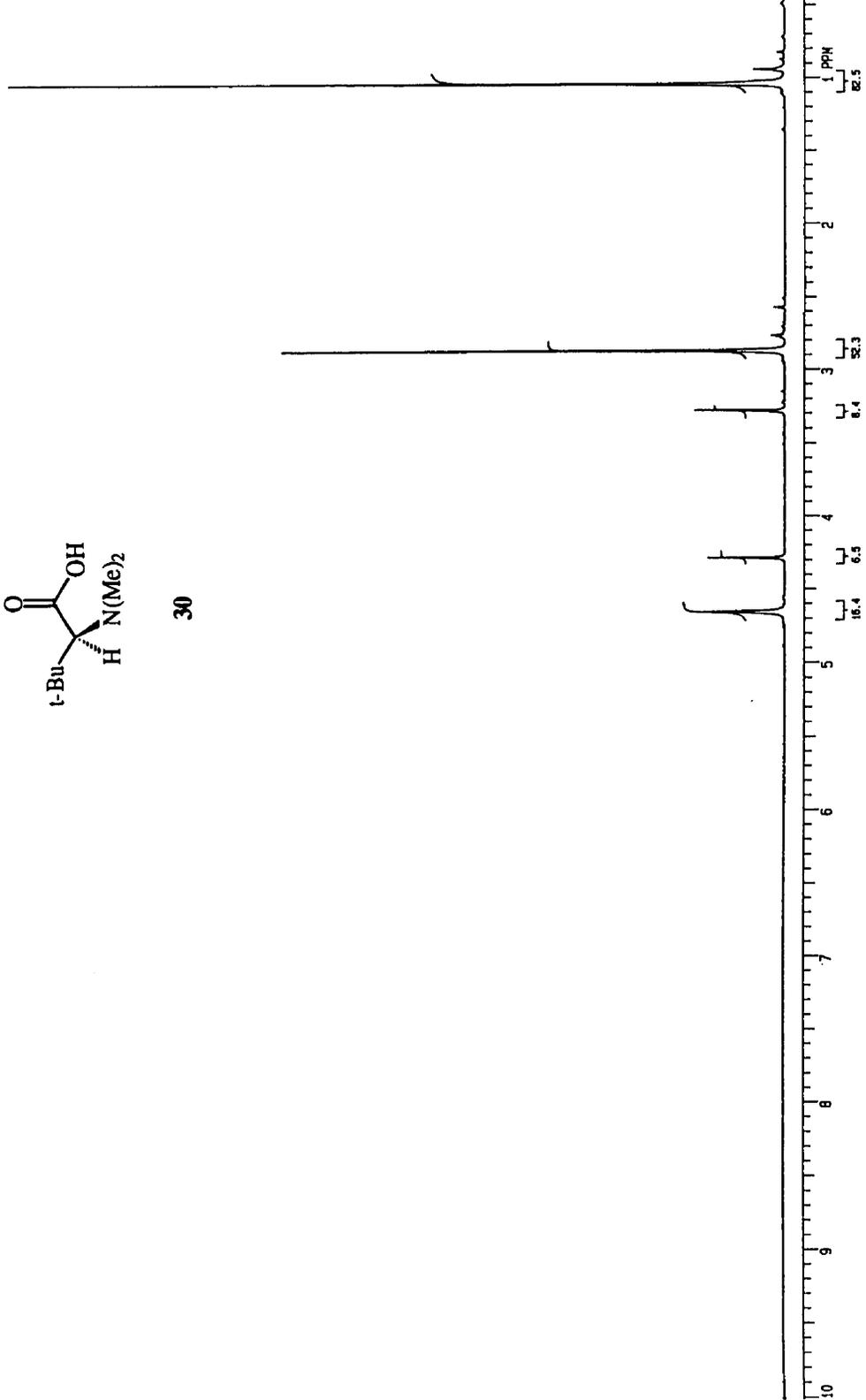
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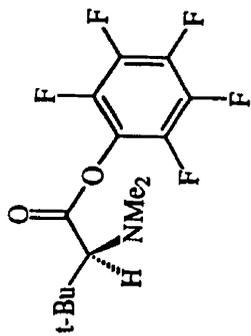
Appendix A

Selected ^1H NMR spectra of synthesized compounds

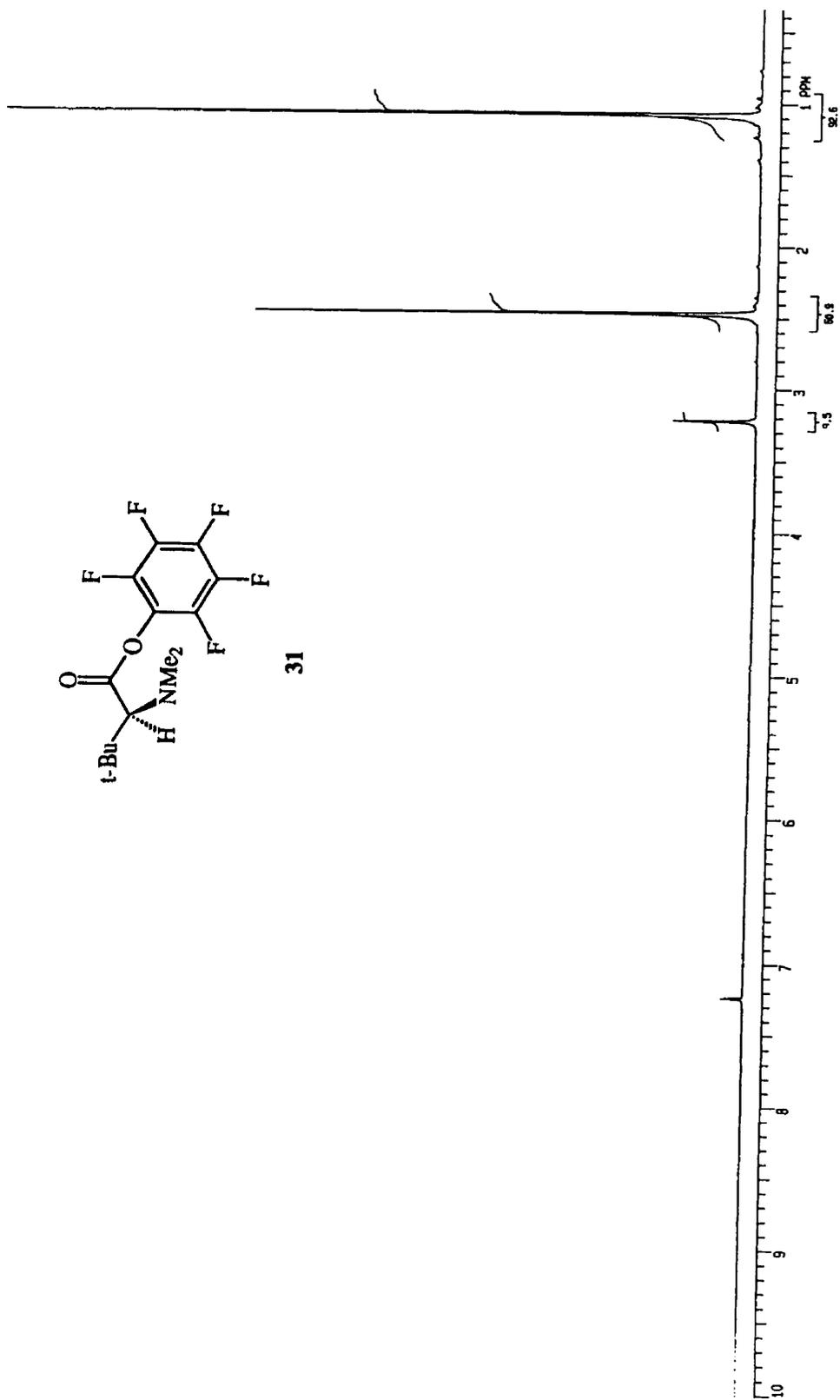


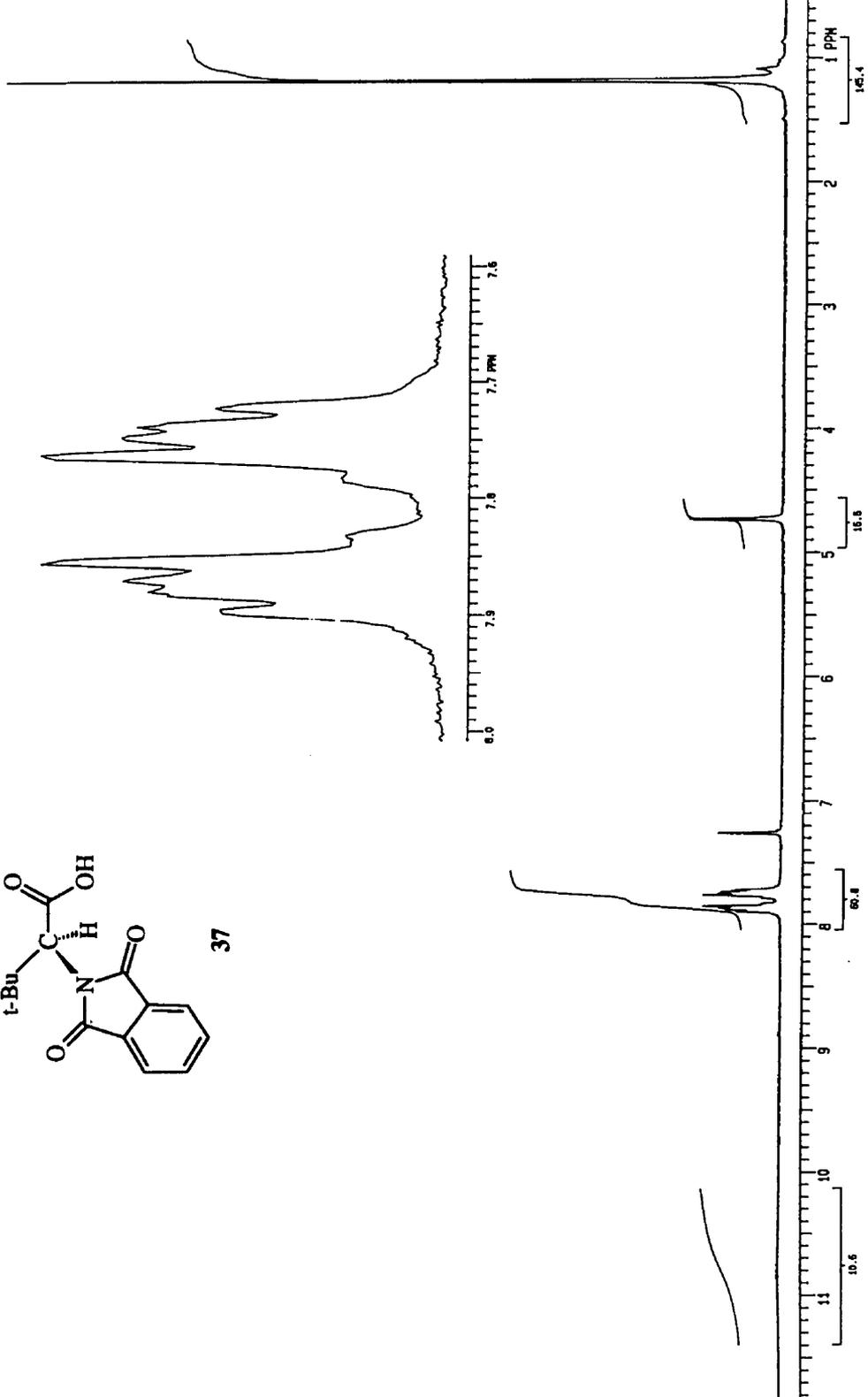
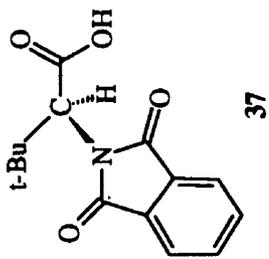
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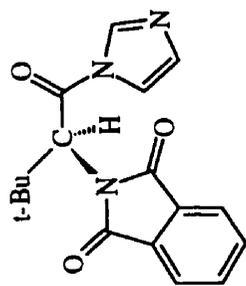




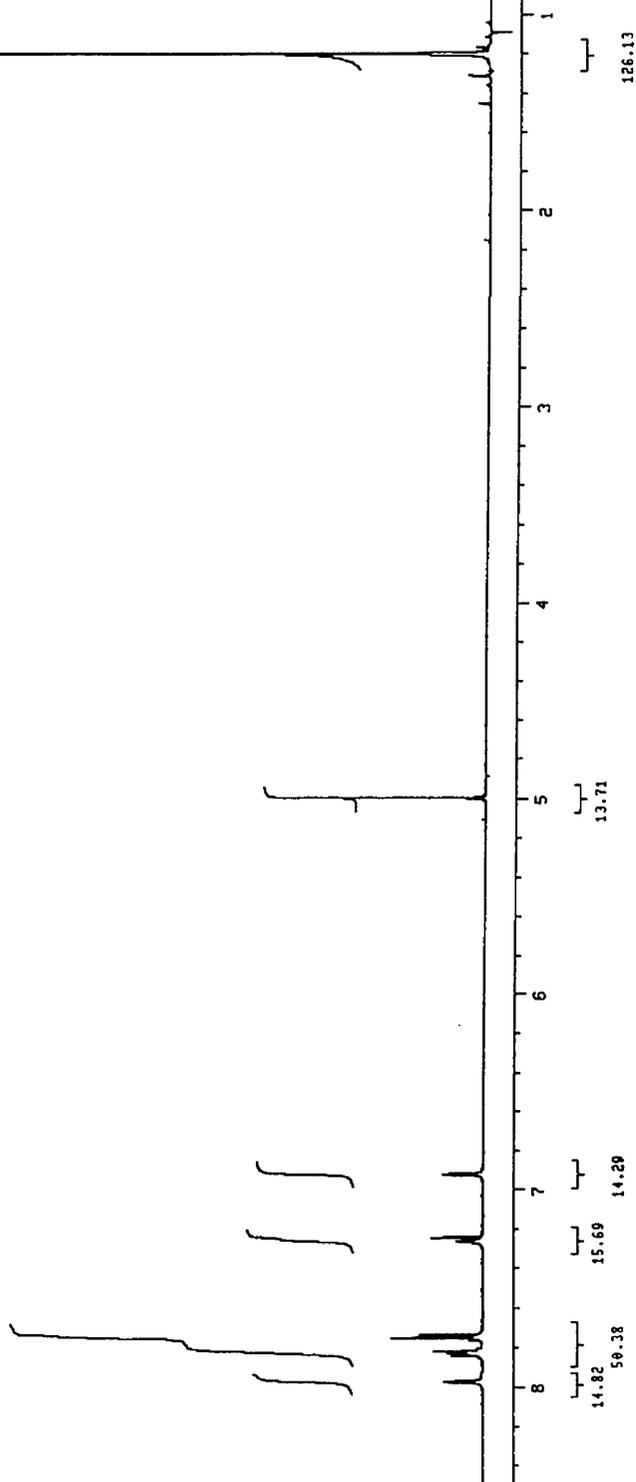
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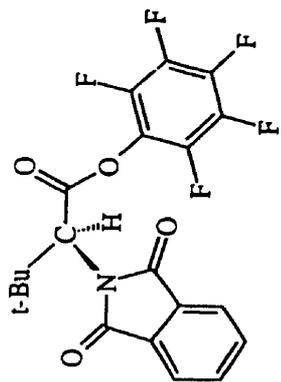




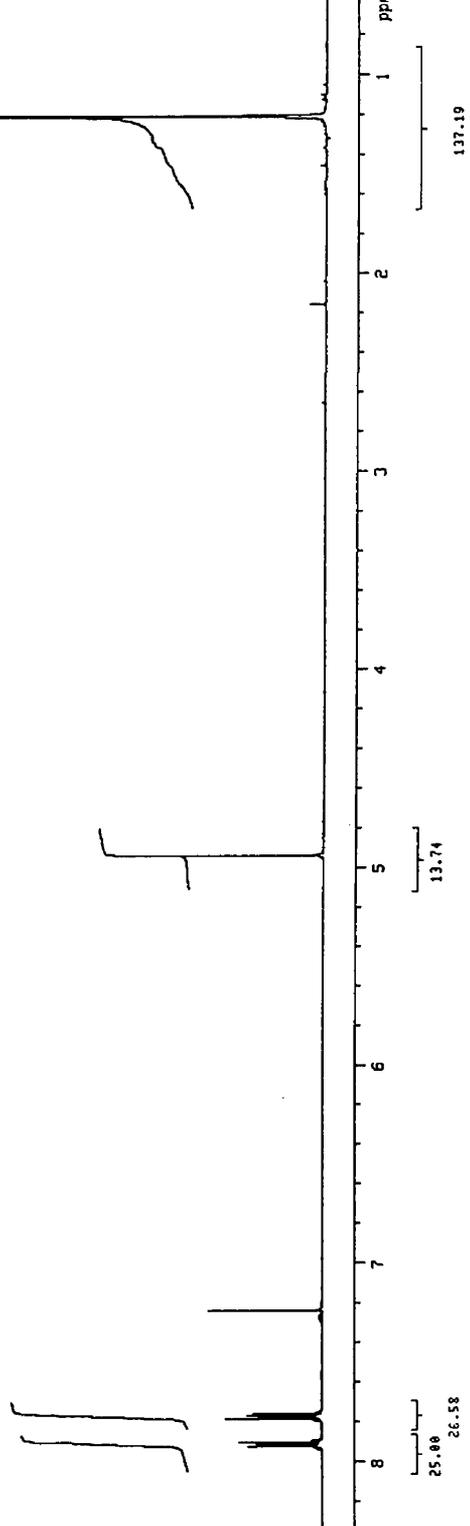


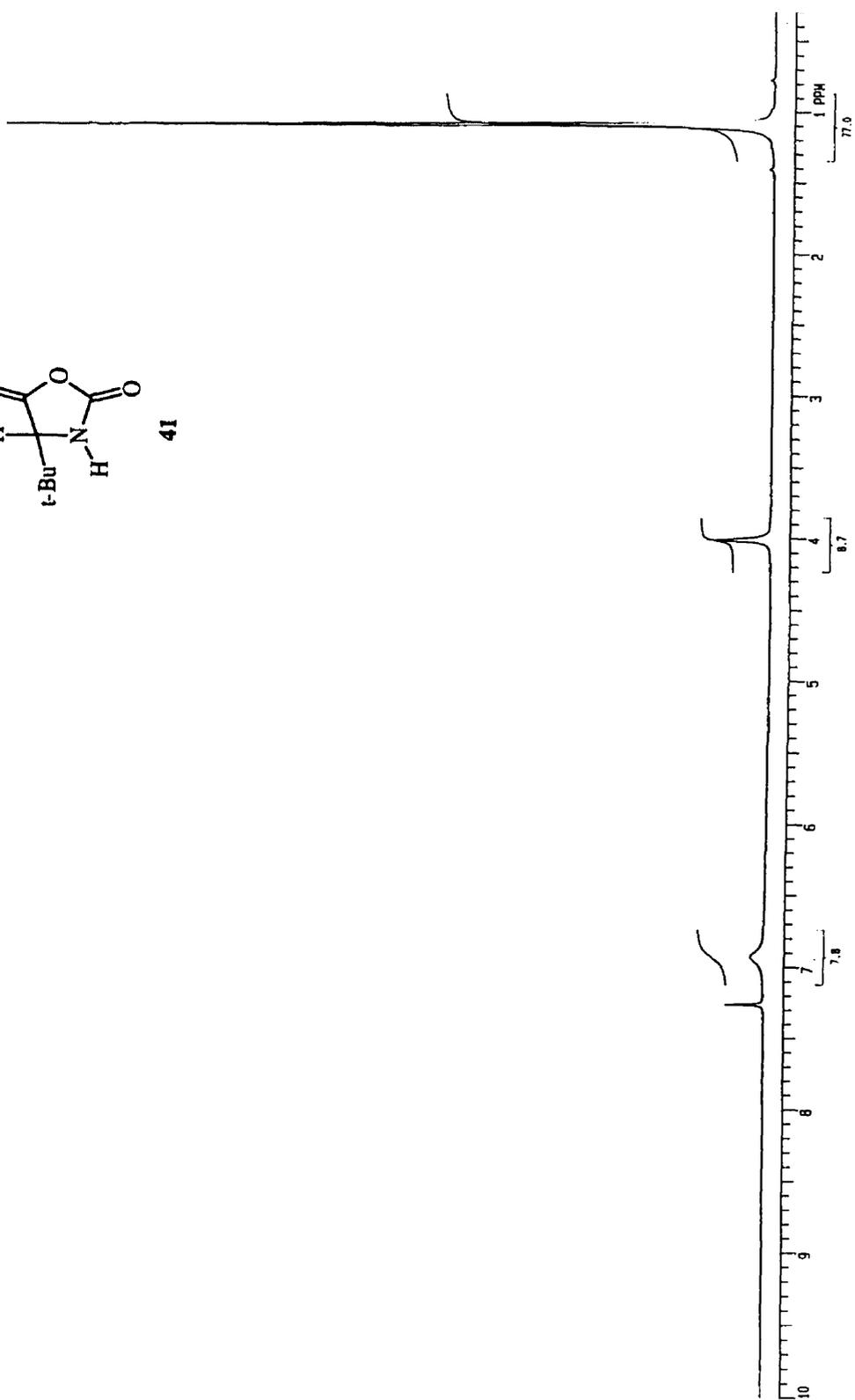
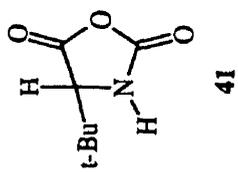
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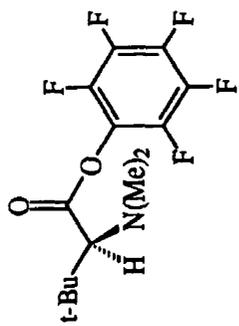
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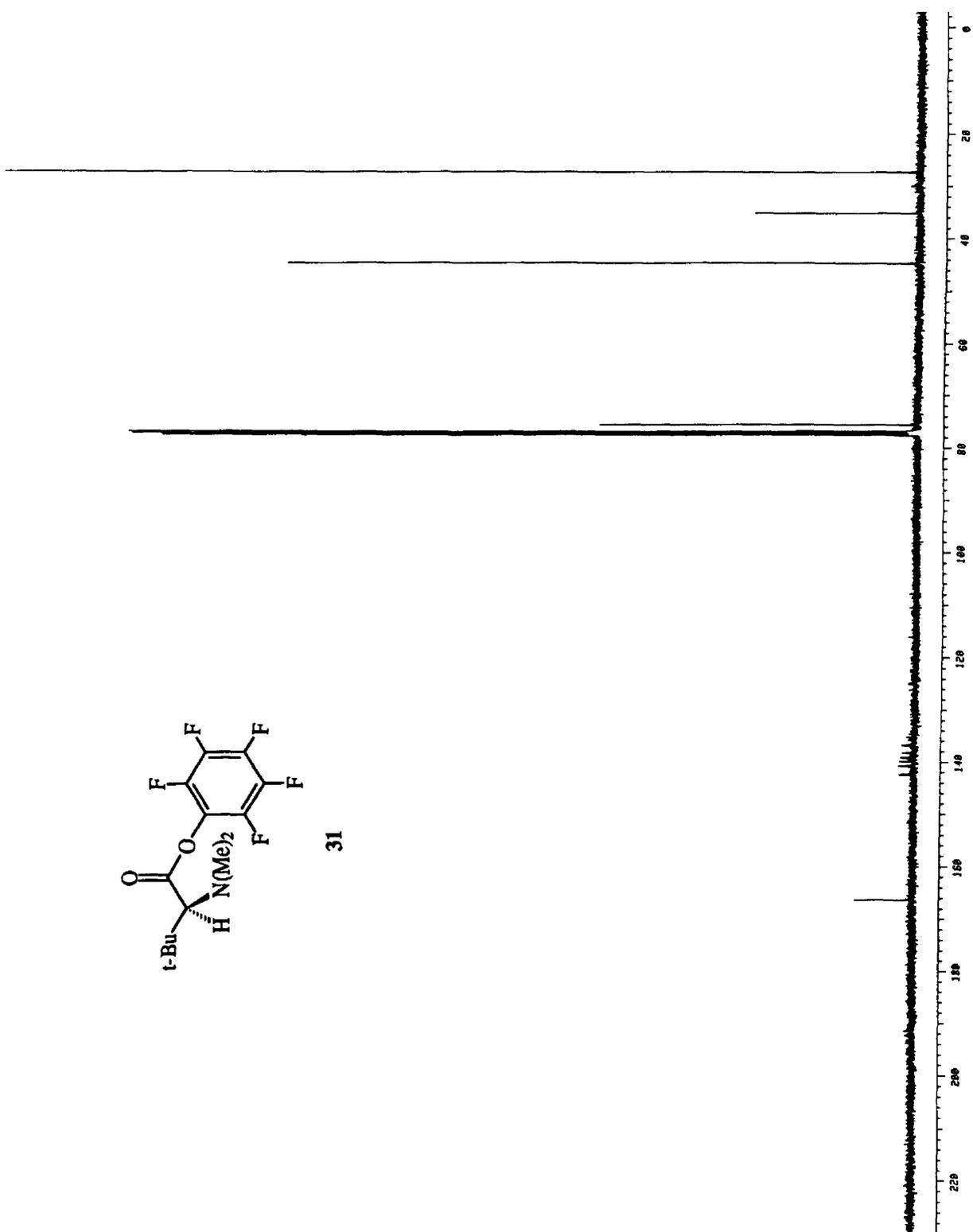


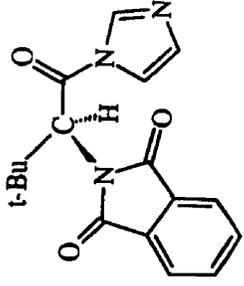
Appendix B

Selected ^{13}C NMR spectra of synthesized compounds

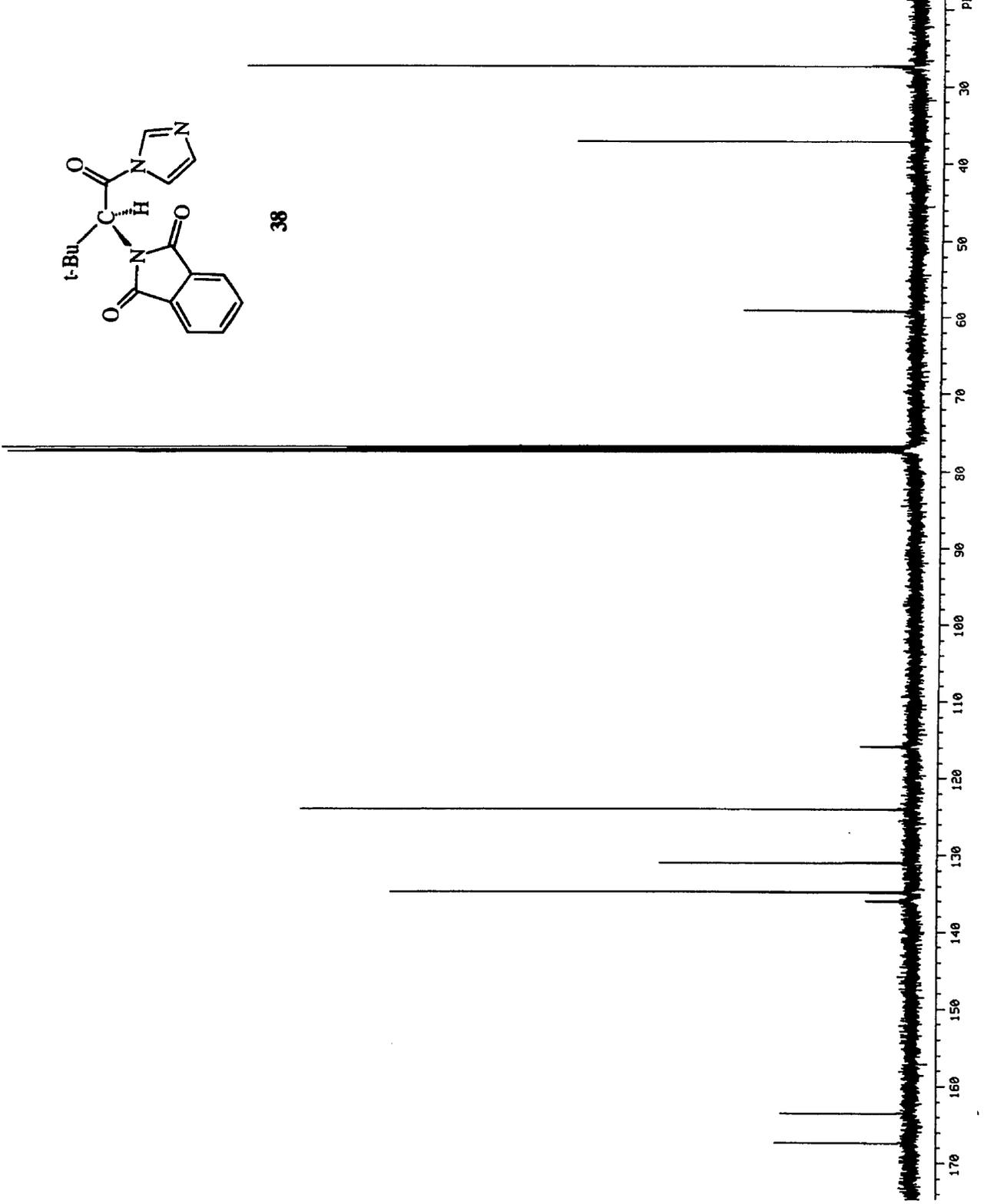


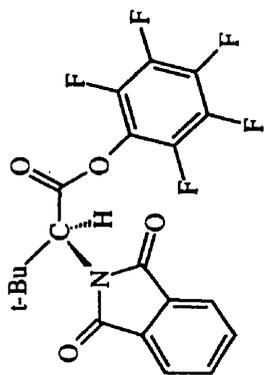
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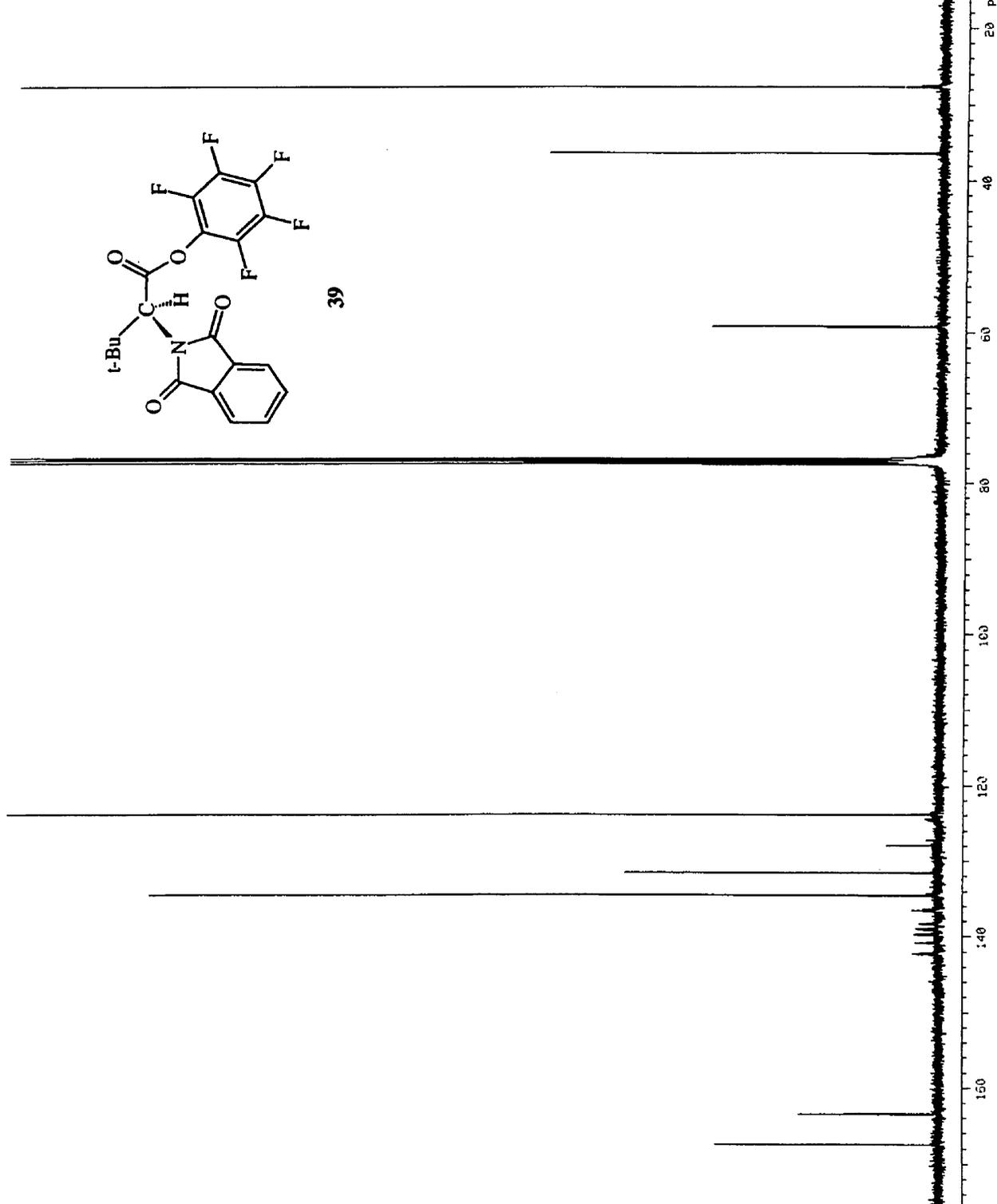


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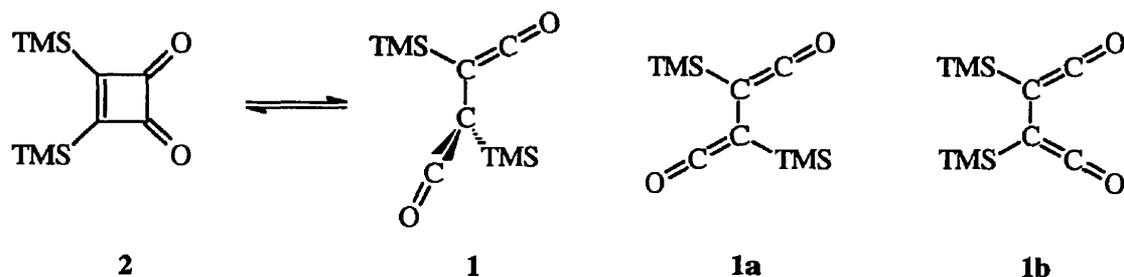


Nucleophilic Reactions of

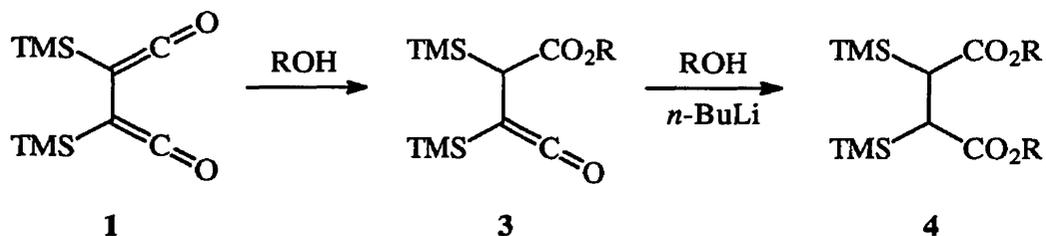
2,3-Bis(trimethylsilyl)buta-1,3-diene-1,4-dione

The title molecule (from here on referred to as **bisketene 1**) is the first persistent 1,2-bisketene prepared which is stable indefinitely in the absence of water, oxygen or other reactive materials.¹ Bisketene **1** can be generated either by photolysis or thermolysis of cyclobutenedione **2** (Figure 2.1). Calculations² have shown that the preferred geometry is twisted (**1**) rather than planar (**1a** and **1b**, see Figure 2.1) and this has been confirmed by X-ray crystallography.³ The twisted conformation minimizes the destabilizing interaction between the neighbouring electron rich β -carbons of the two ketenyl groups while not excessively crowding the trimethylsilyl (TMS) groups. The electropositive and bulky TMS groups stabilize bisketene **1** to the point that it is more stable than its corresponding cyclobutenedione **2**.

Figure 2.1

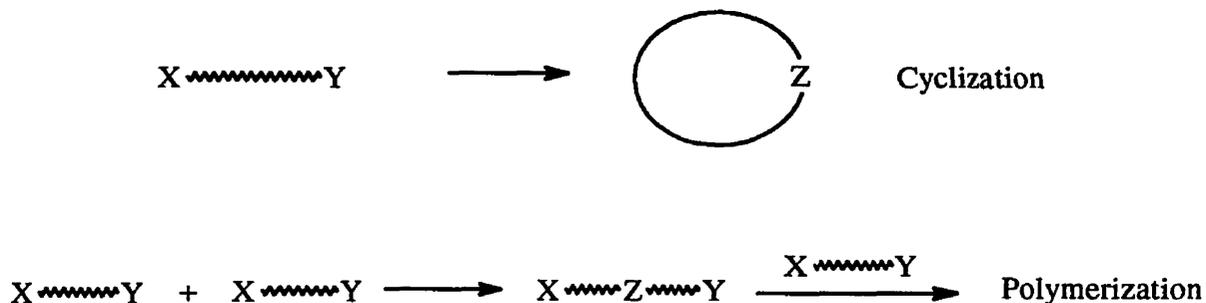


Frontier molecular orbital theory predicts that the highest occupied molecular orbital (HOMO) of ketenes is perpendicular to the ketene plane while the lowest unoccupied molecular orbital (LUMO) of ketenes is in the ketene plane (Figure 2.2). This electronic



The formation of cyclic lactones has long been of interest to chemists, especially since the discovery of many biologically important macrocycles. Cyclization is accomplished by the intramolecular reaction of two functional groups on the same molecule. A bifunctional substrate can however follow two reaction paths, namely cyclization and polymerization.

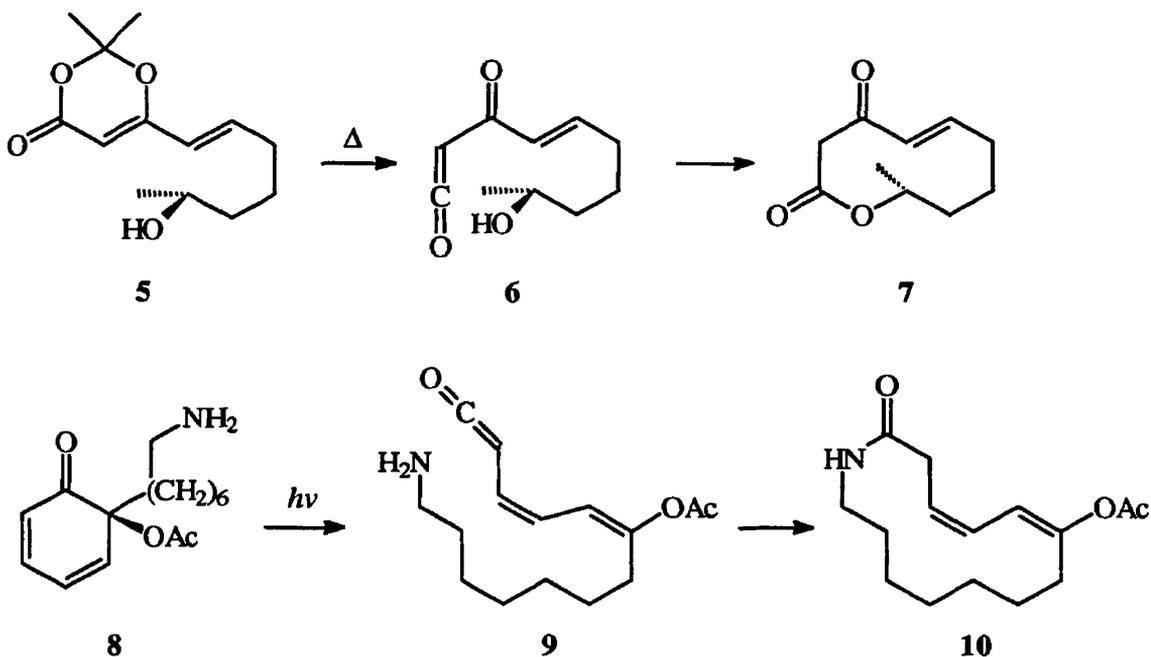
Scheme 2.3



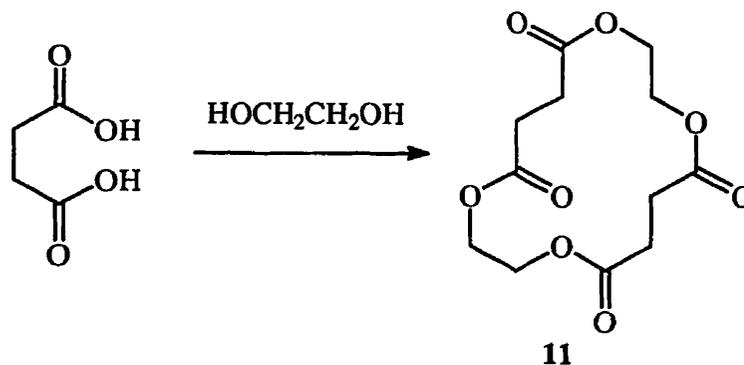
If polymerization is a bimolecular process then it would follow second order kinetics and should be favored at high concentrations whereas cyclization is first order and is favored in dilute conditions. Ziegler was the first to apply this high dilution method in the synthesis of a variety of medium-sized rings in the 1930's.⁷ Since then, many elegant synthetic methods have been developed⁸ to facilitate the ring closing process, which is often difficult to achieve.

cyclization via nucleophilic attack to yield the desired lactone, while ketenes containing amino groups intramolecularly cyclize to afford lactams.¹⁰

Scheme 2.4



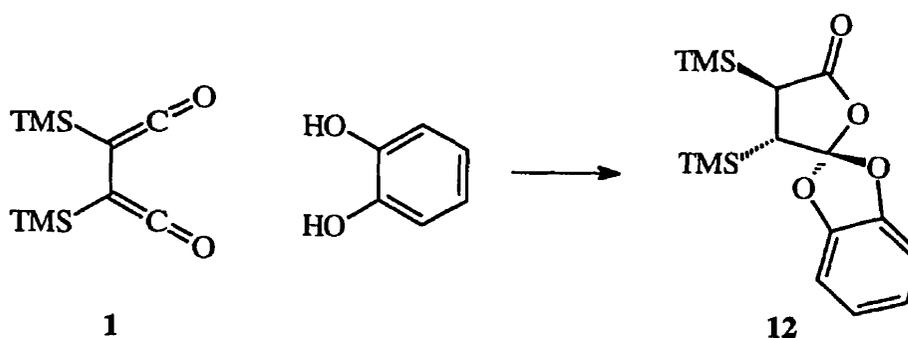
With the discovery of bicyclic ketene 1 comes the potential of ring formation via its reaction with dinucleophiles such as diols. The reaction of two bifunctional reagents was an early strategy used toward the synthesis of macrocyclic compounds. In 1930 as part of his pioneering polymer syntheses, Wallace Carothers employed this strategy with succinic acid and ethylene glycol in an attempt to form 8-membered bislactones.¹¹ The resulting product contained no bislactone and instead the major product was 16-membered tetralactone 11, a dimeric compound.



This result not only demonstrates the difficulty in forming 8-membered bislactones, but it represents a trend encountered in synthesizing lactones of all sizes using this synthetic strategy. Even in the cyclization of hydroxyketenes, dimeric macrocycles are the major product where formation of the desired monomer is either absent or minor, depending on the size and the degree of unsaturation of the ring.^{9c}

The reaction of bisketene **1** and catechol using *n*-BuLi catalyst has been studied,⁶ the result being a lack of formation of any 8-membered ring product. Instead, the major product was found to be *ortho* ester **12**.

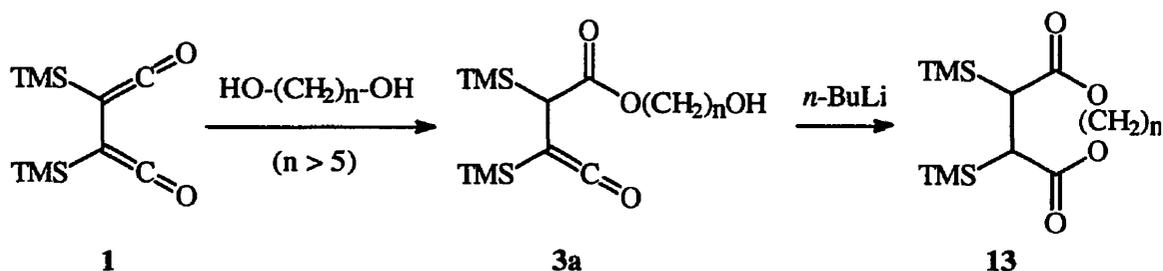
Scheme 2.6



ring forms for which bisketene **1** has shown preference in other reactions with difunctional reagents.⁶ Svensson reports¹² the formation of 8-membered rings using tetramethylsuccinoyl chloride and catechol in very low yields with 'pseudo esters' analogous to **12** being the major product.

The difficulty in formation of 8- to 11-membered rings has become a well known phenomenon. Regardless, the success of the catalyzed reaction of bisketene **1** and alcohols in making succinate esters makes the pursuit of larger ring systems (12 and higher), using diols in this same reaction scheme, an attractive one. The apparent high reactivity of monoketenyl esters **3** toward lithium alkoxides may reduce the barriers for cyclization reactions (Scheme 2.7) and this possibility is investigated within this chapter.

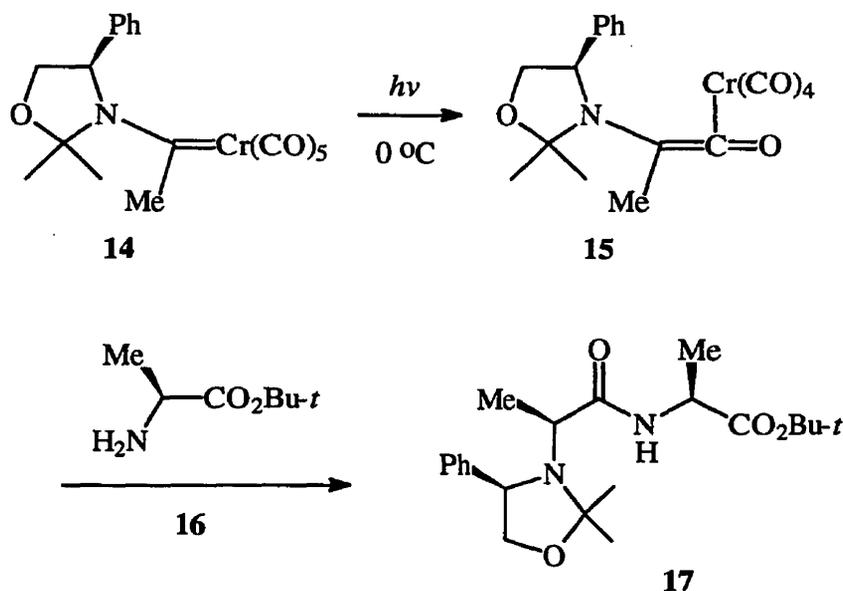
Scheme 2.7



The nucleophilic reaction of amines and ketenes is a well known route to amides. As with other nucleophiles, attack occurs at C_α giving an enol intermediate.¹³ One example of the potential usefulness of amide bond formation via ketenes is in peptide synthesis. The attack of amines (and other nucleophiles) on unsymmetrical ketenes creates a new chiral centre with stereochemistry determined in the proton delivery step. While the use of ketenes in the

success,¹⁴ one notable example involving optically active chromium amine complexes and esters of optically active amino acids gives dipeptides in a 98/2 diastereomeric ratio (Scheme 2.8); a reaction since used in solid state peptide synthesis.¹⁵

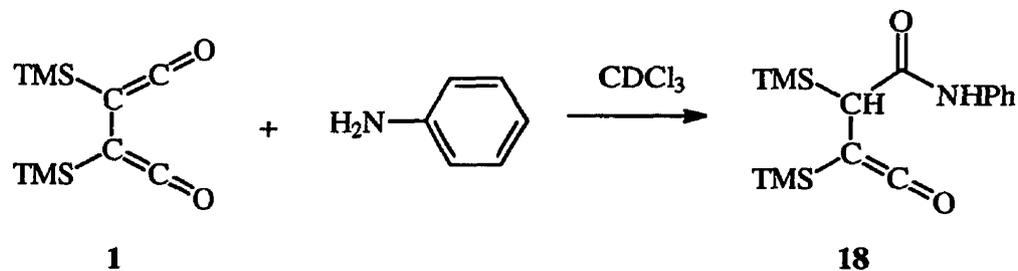
Scheme 2.8



As previously noted, ketenes with amino groups have been used successfully in intramolecular cyclizations. In the reaction of bisketene **1** and diamines, the possibility exists for cyclization or polymerization products, analogous to that described above with diols. For example, the reaction of diamines with dicarboxylic acid derivatives is widely used in the synthesis of nylons. Replacement of the dicarboxylic acid with a more reactive bisketene could lead to an alternative method for nylon synthesis.

uncatalyzed reaction with aniline which gave monoketenylamide **18** in 60% yield. However, **18** subsequently decomposed to unidentified products.

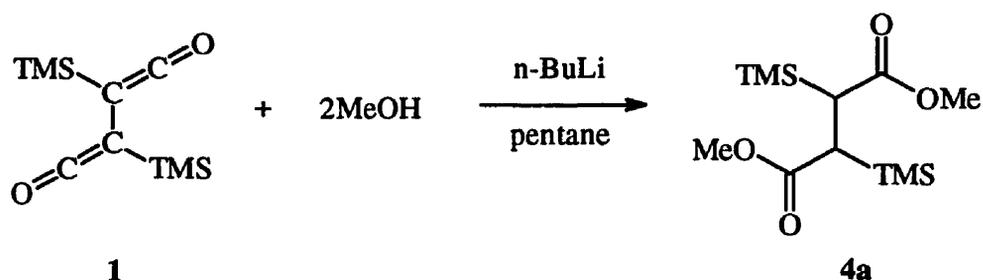
Scheme 2.9



Because of the high reactivity of ketenes with amines and the potential usefulness of products obtainable in the reaction of **1** with amines, these reactions were further investigated and the results are reported in this chapter.

A thorough investigation into the catalyzed reaction of 2,3-bis(trimethylsilyl)-1,3-butadiene-1,4-dione (**1**) and alcohols to form succinate esters has been undertaken and the results recently published.⁶ The n-BuLi catalyzed reaction between bisketene **1** and methanol (Scheme 2.10) will be discussed first to serve as a model for these nucleophilic reactions and in order to provide insight into the synthesis of macrolactones using the same catalyzed reaction between bisketene **1** and diols.

Scheme 2.10



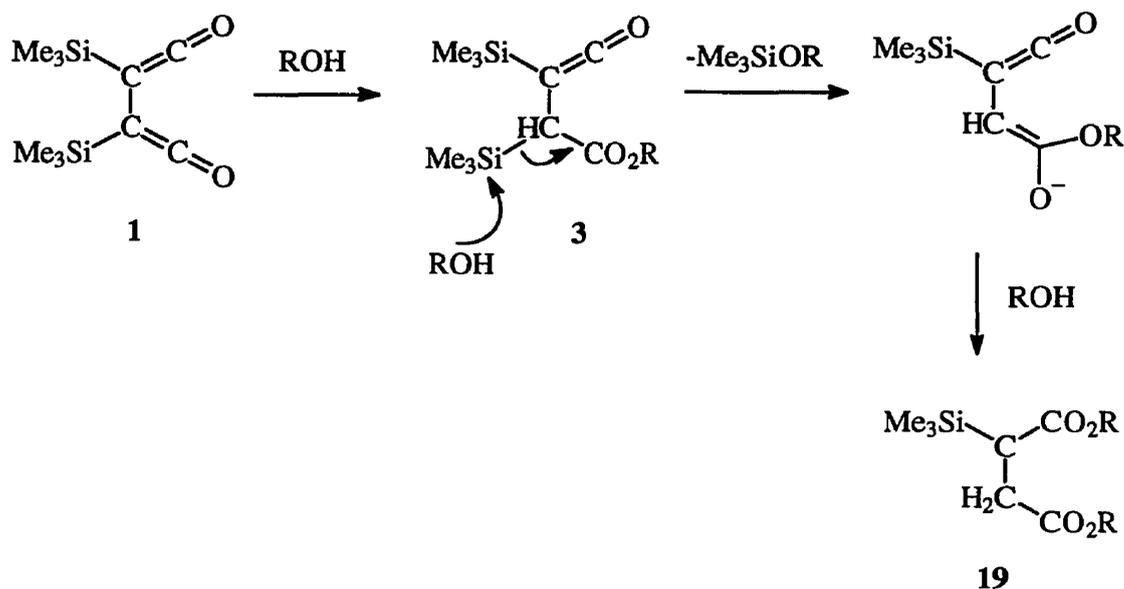
The reaction between bisketene **1**, excess methanol and 10 mol % n-BuLi (relative to MeOH) in pentane gives the succinate ester **4a** in 60% isolated yield with 15% desilylated product on completion of the reaction (75 min.). These results are anomalous when compared to the other alcohols used⁶ in the same reaction with bisketene **1**.

Looking at the series of alcohols *t*-butyl alcohol, isopropyl alcohol and ethanol it was found that the rate of reaction increased as the size of the alcohol decreased. It was also found that methanol was the only alcohol of the series that immediately gave any substantial amount of desilylated product.

maximum of 20 minutes (*t*-butyl alcohol), the same reaction with methanol/methoxide took 75 minutes to complete. There is no evidence for the cause of this difference but possible explanations include a lower nucleophilicity for methoxide since it is the conjugate base of the strongest acid of this series of alcohols and thus may be less reactive. A different solubility and state of aggregation of the lithium alkoxides in pentane may also play a role in the reaction rates of alkoxides with bisketene **1**. A small amount of solid was seen in the MeOH/MeOLi mixture in pentane, an observation not reported with the other alkoxides.

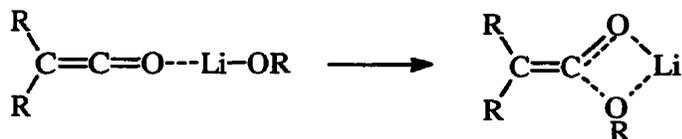
The uncatalyzed addition of alcohols to bisketene **1** leads to desilylated products. Experiments¹⁷ have led to the suggestion that desilylation occurs by the attack of alcohol on a trimethylsilyl group of the intermediate monoketenyl ester **3** giving mono(trimethylsilyl) succinate ester **19** as the product (Scheme 2.11).

Scheme 2.11



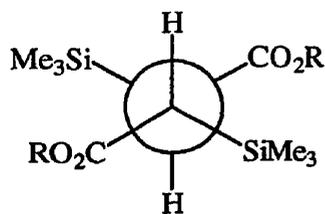
slower than the reaction between alcohols and bisketene 1^{1b} and hence the desilylation process shown in Scheme 2.11 readily competes. The use of n-BuLi as a catalyst circumvents this problem. It is proposed that the preferential attack of lithium alkoxides on ketenes rather than on silyl groups is induced by lithium coordination to the ketenyl oxygen (Figure 2.3).⁶

Figure 2.3

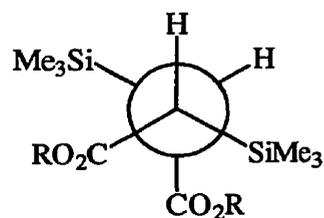


The observation that desilylation products can be observed immediately and in appreciable amounts in the reaction of bisketene 1 with methanol, immediately and in small amounts in the case of ethanol and only after longer reaction time in the case of isopropyl alcohol and *t*-butyl alcohol suggests that the smaller the nucleophile, the greater the extent of desilylation. It is also possible that the state of aggregation of the different lithium alkoxides plays a role in desilylation reactions as well.

Another important feature of these reactions is the creation of two stereocenters and hence the products are obtained as a pair of diastereomers (*meso* and *d,d*). MM⁺ molecular mechanics calculations have predicted the lowest energy conformations to be those shown in Figure 2.4 and this has been experimentally evidenced by ¹H NMR coupling constants of natural abundance ¹³C satellites and proven by X-ray crystallography.⁶



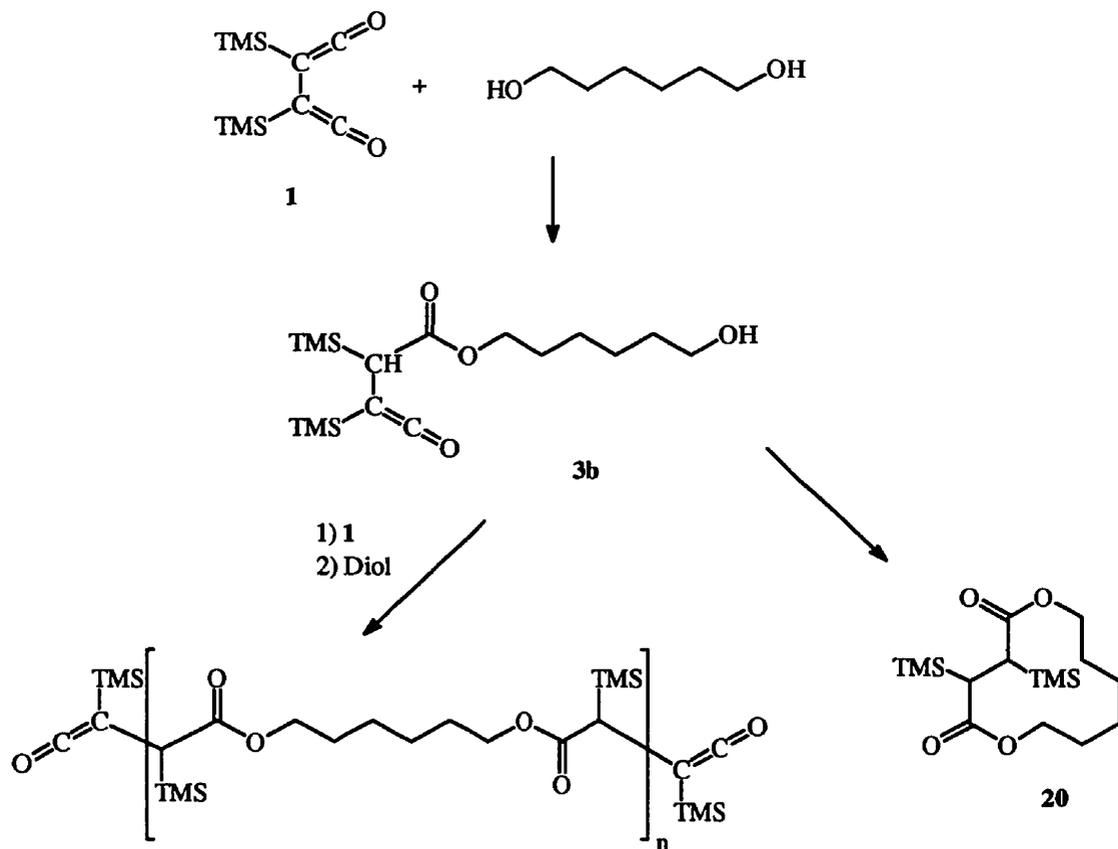
anti-meso-4



syn-d,l-4

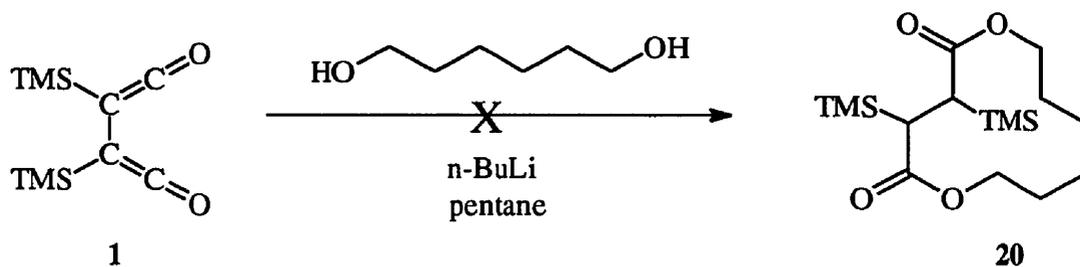
When *t*-butyl alcohol was used in the reaction there was a marked preference for the *d,l* isomers over the *meso* (92:8). The relative yield of *d,l* isomers to *meso* decreased when isopropyl alcohol was used (67:33) and finally, when ethanol was used there was little selectivity for the *d,l* isomers over the *meso* (55:45). When methanol was used in the reaction there was a definite preference for the *meso* isomer over the *d,l* (82:18). The decrease in relative yield of *d,l* isomers corresponding to the increasing extent of desilylation seen in the reaction could be taken as evidence for the selective desilylation of the *d,l* esters.⁶

While the reactions with bisketene 1 and diols were not examined under the same scrutiny as those with simple alcohols, the results of the diol reactions can be understood on the same grounds. As with any reaction between two bifunctional molecules, the reaction between bisketene 1 and 1,6-hexanediol could potentially give polymeric and/or cyclized products (Scheme 2.12).



The potential of bis-ketene **1** to react with diols to yield cyclized products was investigated. The reaction between 1,6-hexanediol and bis-ketene **1** (Scheme 2.13) was run using the same conditions employed for the nucleophilic addition of alcohols described above.

Scheme 2.13



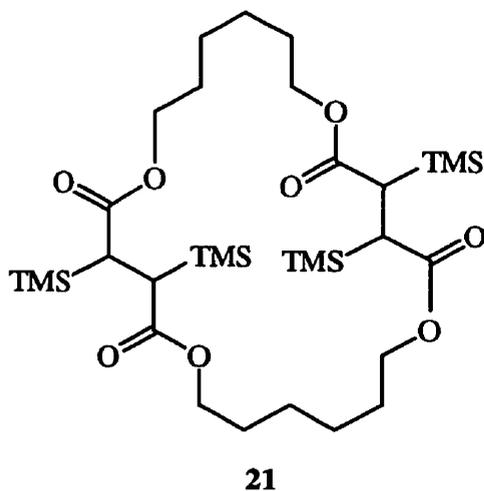
was obtained. ^1H NMR analysis revealed that the liquid was a mixture of different products. While one TMS signal ($\delta 0.07$) was dominant, a number of other significant signals in this region were also observed. Only two signals would be expected in the TMS region for bislactone **20**; one for each of the *meso* and *d,l* isomers. This observation, along with the presence of small multiplets in the region $\delta 2.2 - \delta 2.9$ that gave substantial signal integration, indicates that desilylation is occurring to a fairly large extent. Two triplets were also seen in the ^1H NMR spectrum; one at $\delta 3.65$ from excess 1,6-hexanediol and one at $\delta 3.57$, assigned to the methylene protons next to oxygen in $\text{TMSO}-(\text{CH}_2)_6\text{-OTMS}$.

A number of unidentified signals were seen in the ^1H NMR spectrum. However, the presence of singlets at $\delta 2.6$ and $\delta 2.3$ which have been characteristic of ROOC-CHTMS in these types of reactions and the presence of a strong carbonyl stretch at 1700 cm^{-1} in the IR spectrum confirmed ester linkages in the product mixture. Therefore there was still a strong possibility that bislactone **20** was among the products in the yellow liquid.

Separation of the various components of the product mixture by chromatography proved difficult mainly due to the limited solubility of the products in less polar solvents. Nonetheless, a clear colourless oil was eventually obtained as the only isolable component of the mixture. The ^1H NMR spectrum of the oil contained just two TMS signals ($\delta 0.07$ and $\delta 0.13$), two TMSCH singlets ($\delta 2.6$ and $\delta 2.3$) and a multiplet at about $\delta 4.0$ from R-COOCH_2 which integrated in the ratio 9:1:2. A lack of any ketene or alcohol absorption in the IR spectrum indicated that the oil was a cyclized product. Mass spectral analysis (CI) showed no observable signal at 344 m/z , expected for bislactone **20**. Instead, a molecular ion at 689 m/z

2.5).

Figure 2.5

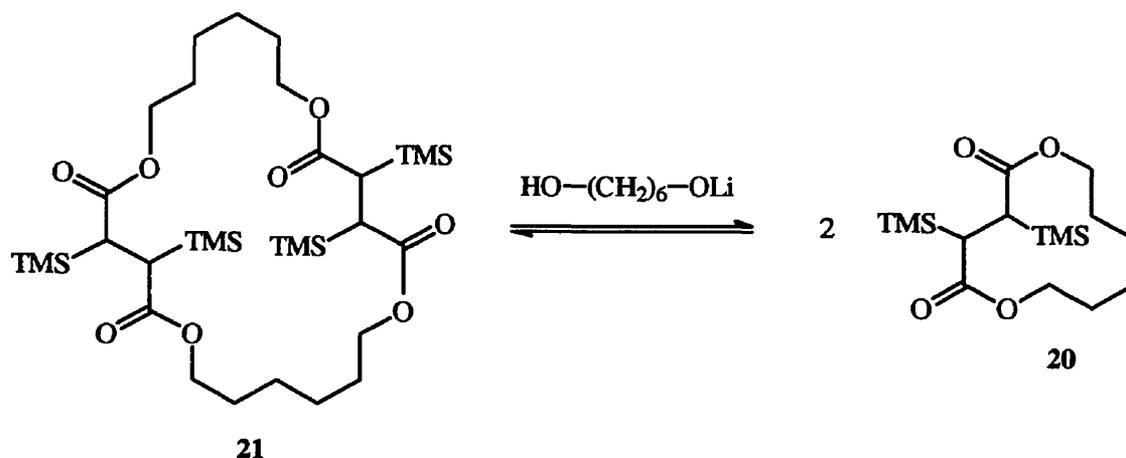


It has been predicted for lactone formation by ring closure that a 24-membered ring forms faster than a 12-membered ring¹⁸ (bis lactone **20**). However, the formation of tetralactone **21** would necessitate three intermolecular reactions before intramolecular ring closure, while formation of bis lactone **20** involves just one intermolecular reaction. Therefore it seems surprising that no 12-membered ring could be found at all. As mentioned in the introduction, the formation of dimeric ring products (**21**) over the monomeric rings (**20**) is a trend that had been observed as long ago as 1930 by Wallace Carrothers,¹¹ who found no 8-membered ring in reactions of succinic acid derivatives with ethylene glycol, but did obtain some 16-membered dimeric ring product. It has since been found that 8-membered lactone rings are conformationally unfavorable.¹⁹ However, no matter what the ring size, the trend

routes to medium size monomeric ring structures.

One theory²⁰ for the preferred formation of tetralactone **21** suggests that in the presence of lithium alkoxide, bislactone **20** and tetralactone **21** are in equilibrium (Figure 2.6).

Figure 2.6

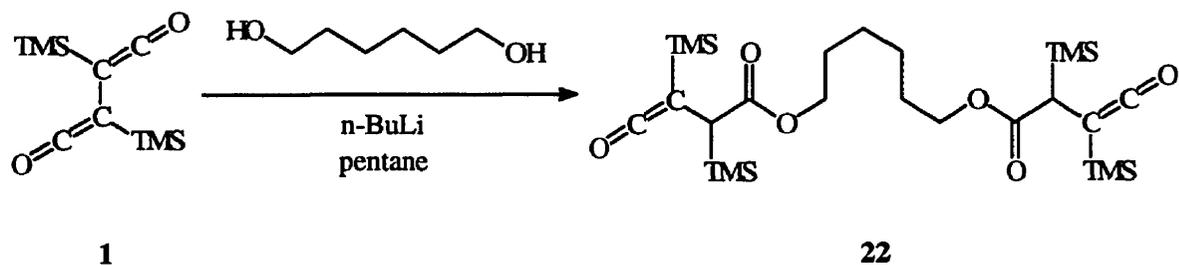


MM^+ calculations²⁰ of the free energy difference between the 24-membered tetralactone ring and the 12-membered bislactone ring without the TMS groups indicate that the larger ring is 15.98 kcal/mol more stable. When one considers that a free energy difference of 10 kcal/mol equates to an equilibrium constant of approximately 10^7 , it is easy to see why no trace of bislactone **20** can be isolated from the reaction mixture. Further calculations²⁰ involving smaller rings (8 - 20 membered) with TMS substituents indicated an even larger free energy difference between the respective monomeric and dimeric rings.

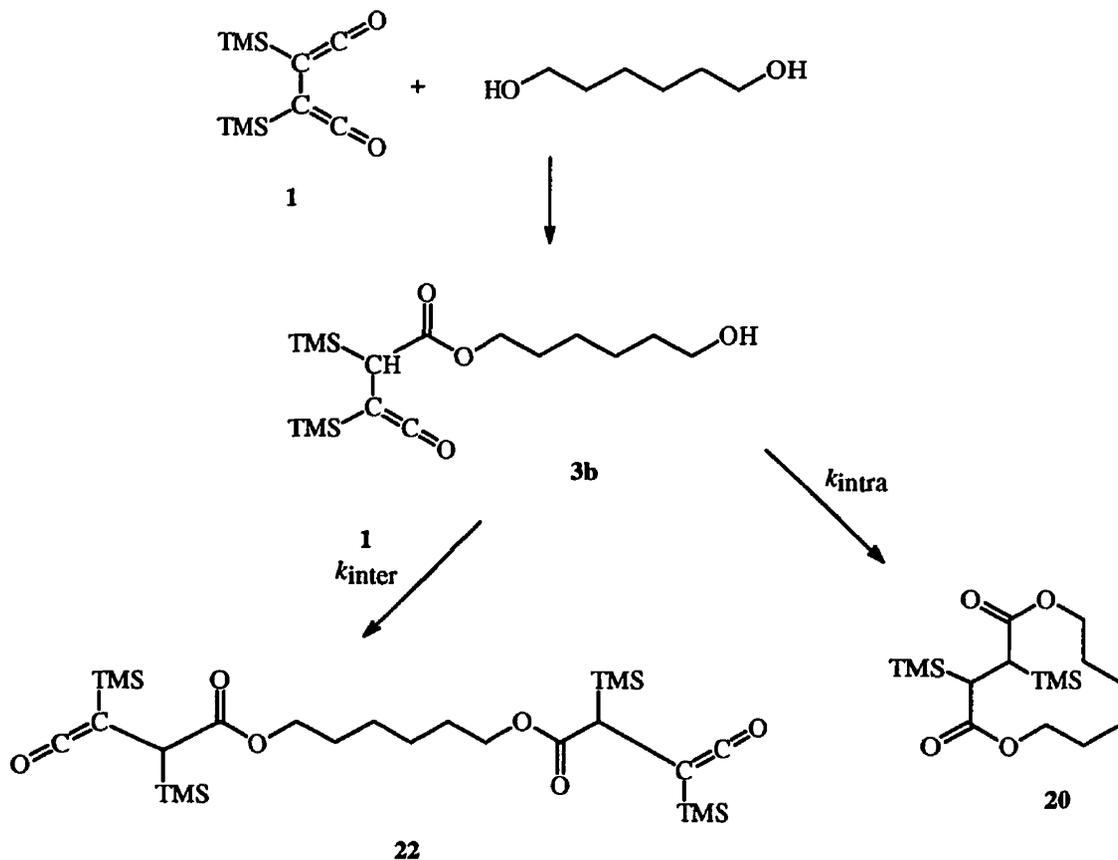
A reaction was run with bisketene **1** with half an equivalent of 1,6-hexanediol (Scheme 2.14). After 90 minutes at 0 °C, 30 minutes at RT, aqueous work-up and purification by radial chromatography, a faint yellow oil was obtained and identified as the 1,14-bisketene **22** by ^1H

tetralactone **21** and higher homologues.

Scheme 2.14



It would appear then, that the preferred formation of tetralactone **21** over bislactone **20** is not entirely a result of the stability or the energy of formation of the rings. It could be as much a result of the relative reactivity of the ketenyl groups of bisketene **1**, monoketene **3b** and bisketene **22**. It was earlier established (reaction of bisketene **1** with MeOH) that the reactivity of the first ketene group of bisketene **1** is much greater than that of the ketene group of the resulting monoketene **3b** (Scheme 2.15). Therefore in the case of ring forming reactions, the free hydroxy group of monoketene **3b** reacts faster with a second molecule of bisketene **1** than it does intramolecularly with its own ketene group ($k_{\text{inter}} > k_{\text{intra}}$). This makes an interesting rate comparison and is a testament to the large reactivity difference between a 1,2-bis-ketene and its corresponding monoketene.

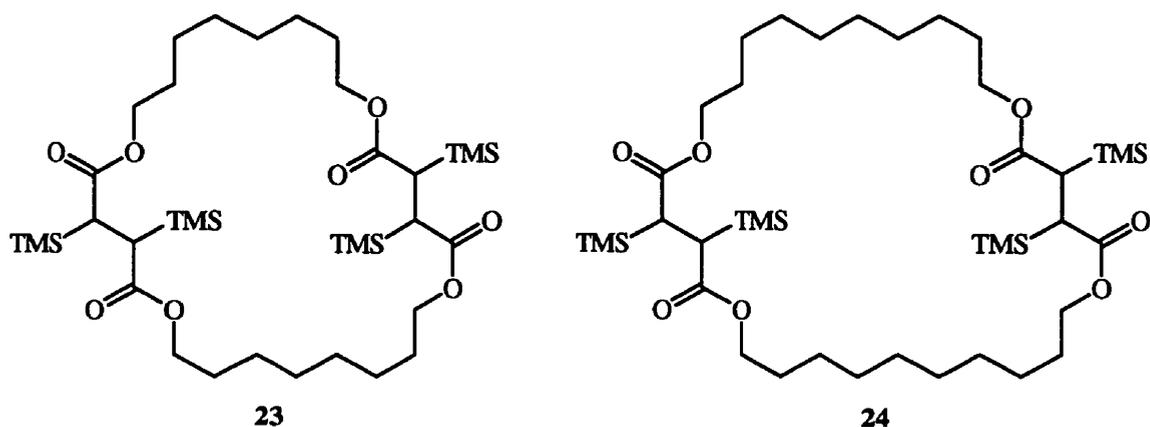


1,6-Hexanediol has little solubility in pentane. On addition of *n*-BuLi, a fine, dense white suspension formed. Assuming the solids are due to alkoxide formation, addition of bisketene 1 as a solution in pentane leads to heterogeneous conditions in which surface reactions may occur. This could lead to longer reaction times allowing desilylation reactions with unreacted diol to compete. Also of interest in this regard is a published report²¹ in which diols were reacted with diacid chlorides using phase transfer catalysis. Diacid chloride is added dropwise to a heterogeneous mixture of solid KOH, diol and triethylbenzylammonium chloride in benzene. Following work-up and purification, only dimeric tetralactone product is

bisketene **1**. No explanation for this result was given.

The reactions of bisketene **1** with 1,8-octanediol and with 1,10-decanediol were also done using the same reaction conditions as with 1,6-hexanediol. Similar results were obtained, with the only isolable and identifiable products being the 28-membered ring tetralactone **23** and the 32-membered ring tetralactone **24** (Figure 2.7).

Figure 2.7

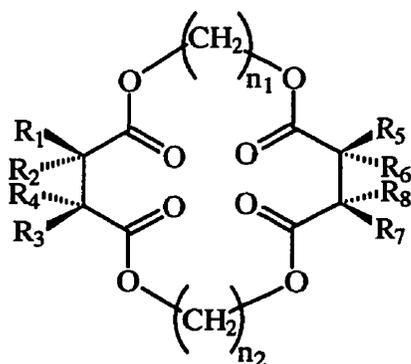


The isolated yields in all cases were low (tetralactone **21**, 5%; tetralactone **23**, 7%; tetralactone **24**, 4%). This is largely due to the competing desilylation reaction as well as polymerization reactions, which certainly would compete under the modestly dilute conditions employed for these reactions.

The isolated products in all cases are mixtures of isomers, with two distinct sets of ^1H NMR signals, analogous to the succinates formed in the reaction of bisketene **1** and simple alcohols. Four stereocenters are created which leads to seven different isomers of the tetralactone macrocycles (the five listed in Figure 2.8, two of which are optically active). Only

compounds. This essentially leaves three possibilities accounting for the two sets of signals (see Figure 2.8): a pair of cis-cis isomers, a pair of trans-trans isomers and a cis-trans isomer.

Figure 2.8



cis-cis: $R_1 = R_3 = R_5 = R_7 = \text{TMS}$
 $R_2 = R_4 = R_6 = R_8 = \text{TMS}$

trans-trans: $R_1 = R_4 = R_5 = R_8 = \text{TMS}$
 $R_2 = R_3 = R_6 = R_7 = \text{TMS}^*$

cis-trans: $R_1 = R_3 = R_5 = R_8 = \text{TMS}^*$

$n_1 = n_2 = 6, 8 \text{ or } 10$

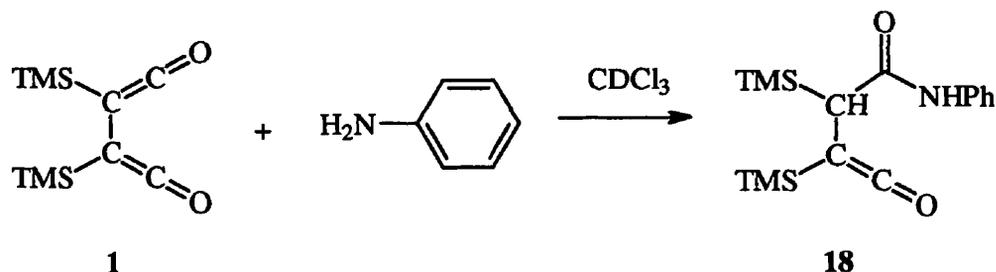
* = optically active

The isomers could not be separated so there is no direct way to establish the stereoselectivity for one isomer over the other. However, a cis arrangement of the bonds corresponds to the *meso* isomers in the acyclic succinates studied while a trans arrangement corresponds to the *d,l* isomers. Using this as a guideline it was found that there was a consistent preference for the cis arrangement of the TMS groups (or *meso*) over the trans arrangement (or *d,l*) in a 3:1 or 4:1 ratio, depending on the tetralactone. With all the different conformations possible for rings of this size, it can only be hypothesized that the cis arrangement of TMS groups minimizes steric crowding in the conformation adopted by the cyclized transition state. As noted above, with EtOH there was almost an equal preference for *meso* and *d,l* products.

The amination of bisketene 1 with a variety of amines was studied as another nucleophilic addition reaction of this unique molecule. As noted above, a reaction¹⁶ of

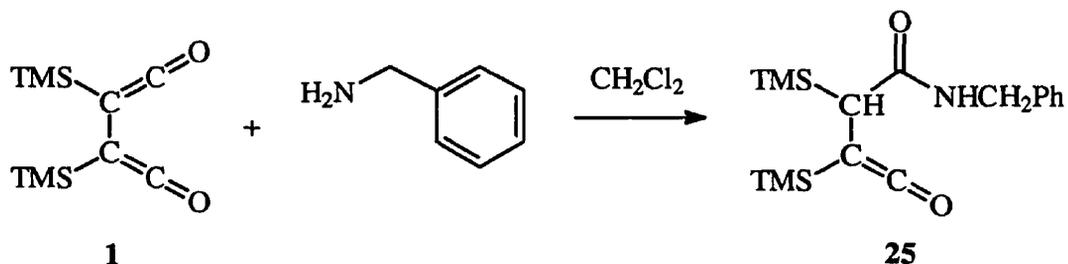
NMR spectra consistent with those of ketenylamide **18** (Scheme 2.9). This product proved to be unstable and decomposed to unidentified products.

Scheme 2.16



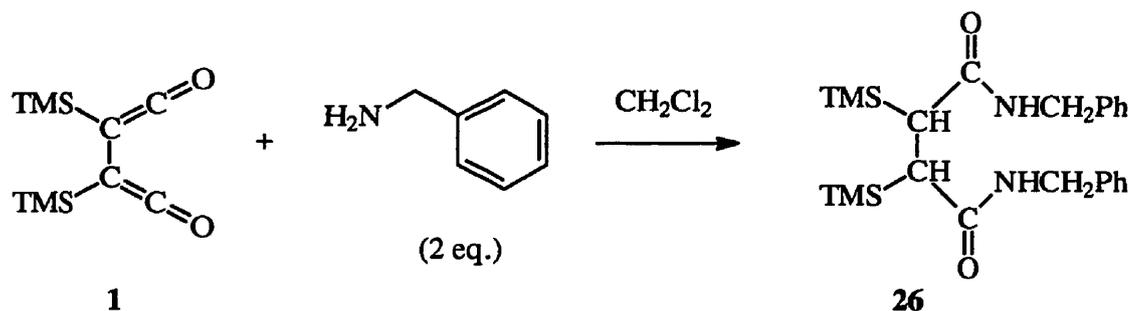
The inability of aniline to convert bisketene **1** to a succinamide is not surprising based on the results of the uncatalyzed reaction of **1** with alcohols. Though amines are generally more nucleophilic than alcohols, aniline is much less nucleophilic than aliphatic amines. Therefore the reaction with more reactive amines was investigated. The reaction of 1 equivalent of benzylamine with bisketene **1** in CH_2Cl_2 at room temperature immediately gave complete conversion to ketenylamide **25** as the only observable product by ^1H NMR (Scheme 2.17).

Scheme 2.17



benzylamine gave complete and immediate conversion to succinamide **26** (Scheme 2.18) in 92% crude yield and in 96% purity by ^1H NMR analysis.

Scheme 2.18

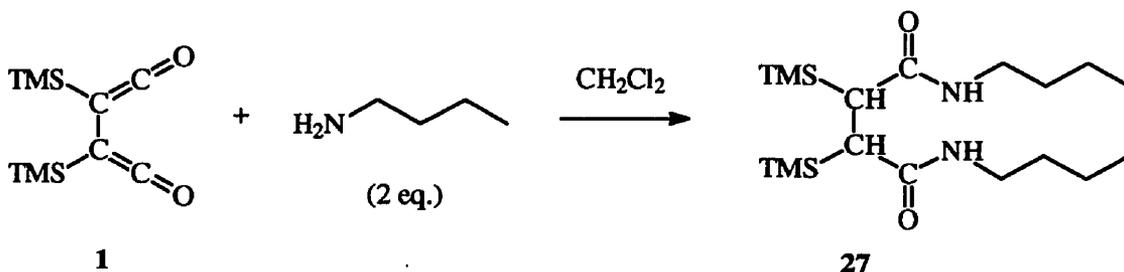


Succinamide **26** was obtained as a mixture of *meso* and *d,l* diastereomers. Stereochemistry was assigned in the same way as for the succinates⁶ where the ^1H NMR spectrum of the *meso* isomer had a Me_3SiCH proton signal that was consistently further downfield than that of the *d,l* isomer. The vicinal $J_{\text{H,H}}$ of the natural abundance ^{13}C satellites was always larger for the *meso* isomer ($J_{\text{H,H}} = 11.1$ Hz for **26**) than for the *d,l* isomer ($J_{\text{H,H}} = 5.1$ Hz for **26**). These satellites arise from succinates with one ^{13}C which lifts the degeneracy of the Me_3SiCH protons. There was no significant preference for the formation of one diastereomer over the other. The diastereomers were separated by radial chromatography on silica gel affording *meso*-**26** as a white solid in 22% yield and *d,l*-**26** as a white solid in 8% yield. It is believed that succinamide **26** is easily desilylated during purification. Several small multiplets are seen at $\delta 2.1 - \delta 2.9$ in the ^1H NMR spectrum of a compound that co-elutes with

26.

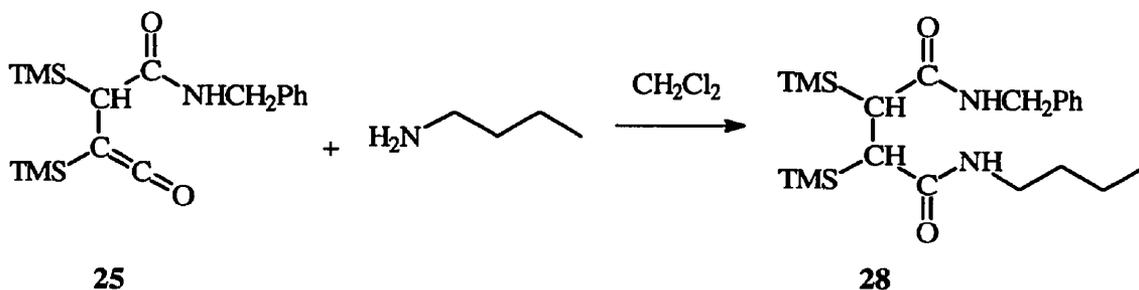
Similar results were obtained in the reaction of bisketene **1** and 2 equivalents of *n*-butylamine (Scheme 2.19). Diamide **27** was obtained in 85% crude yield and 89% purity as determined by ¹H NMR analysis of the product. There was a small preference for the formation of *meso*-**27** over *d,l*-**27** (3:2) in this reaction, as seen in the ¹H NMR spectrum of the product. No attempt at separating the diastereomers was made.

Scheme 2.19



The reaction of ketenylamide **25** with *n*-butylamine gave complete conversion to the mixed diamide **28** (Scheme 2.20) in 95% crude yield and 94% purity by ¹H NMR analysis of the product.

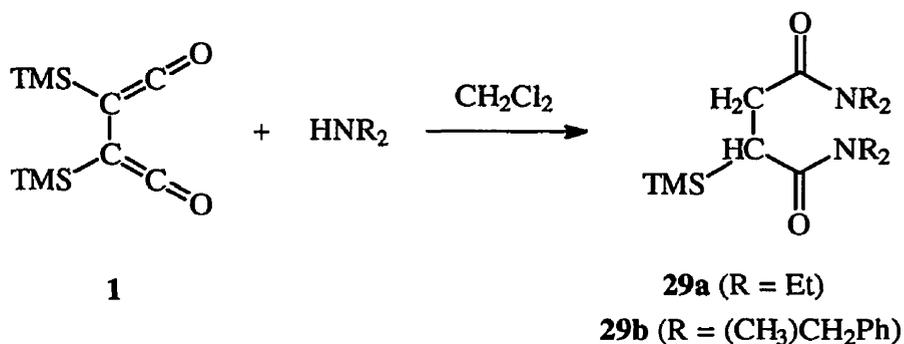
Scheme 2.20



(conformationally analogous to *meso* and *d,l* diastereomers in symmetric diamides) which were separated by radial chromatography on silica gel. The *erythro* isomer was isolated as a white solid in 27% yield while the *threo* isomer was isolated as a white solid in 9% yield. The degeneracy of the tertiary Me_3SiCH protons in this case is lifted by having two different amide groups, and therefore for one isomer, two doublets are seen from these protons in the ^1H NMR spectrum. For the *erythro* isomer, these doublets are seen at $\delta 2.318$ and $\delta 2.364$ with $J_{\text{H,H}}$ of 11.2 Hz and for the *threo* isomer they are seen at $\delta 1.975$ and $\delta 2.025$ with $J_{\text{H,H}}$ of 5.2 Hz. The stereochemistry is assigned to these structures based on these chemical shifts and coupling constants in the same fashion as for the symmetrical succinamides discussed above.

When bisketene **1** reacted with secondary amines (diethylamine and *N*-methylbenzylamine) the reactions appeared to be complete as quickly as with primary amines (Scheme 2.21). The ^1H NMR spectra of these products were consistent with those of other monodesilylated succinates⁶ and succinamides (small multiplets $\delta 2 - \delta 3$) previously identified.

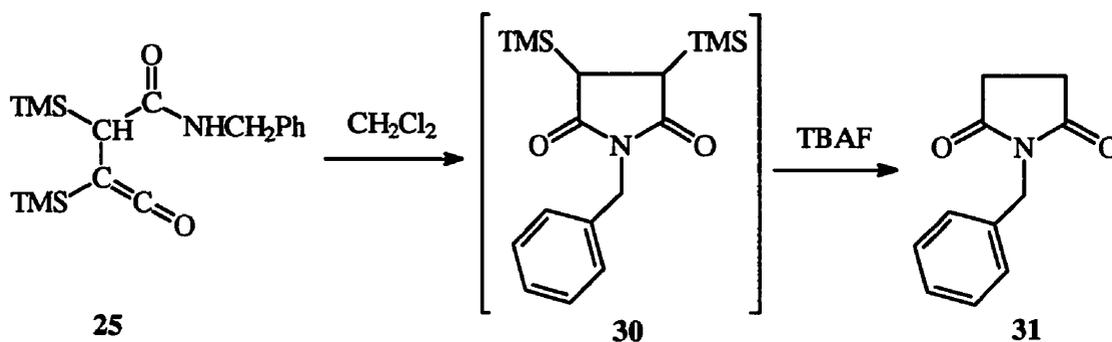
Scheme 2.21



steric crowding it desilylates quickly leaving succinamide **29** as the main reaction product. Alternatively desilylation of the intermediate ketenylamide may predominate due to a slower rate of the second amination relative to the same reaction with primary amines.

A solution of ketenylamide **25** was allowed to sit as a solution in CH_2Cl_2 for 8 days in a freezer. ^1H NMR analysis of the resulting mixture showed no trace of ketenylamide **25**. A number of proton signals were seen indicative of both bis(trimethylsilyl) and mono(trimethylsilyl) succinamides. Removal of the TMS groups with TBAF afforded succinimide **31** as a white solid (Scheme 2.22).

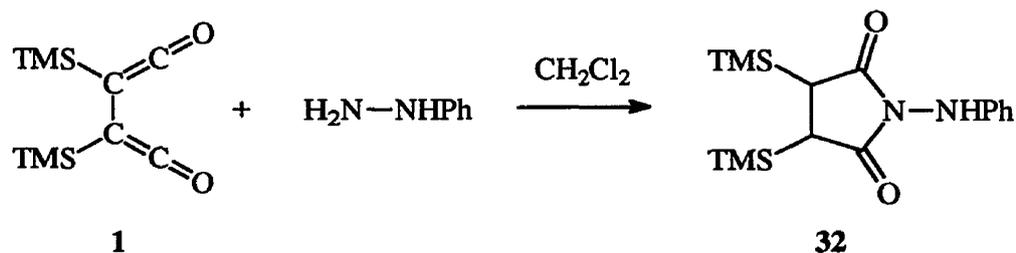
Scheme 2.22



So while ketenylamide **25** is a persistent enough species to identify and use for further reaction, after time it does decompose. It is interesting that an intramolecular cyclization of the ketenyl group and the amide group of **25** takes this amount of time considering a five membered ring is the product. The NH group of **25** is however deactivated by the adjacent carbonyl.

yield and in 97% purity by ^1H NMR analysis (Scheme 2.23).

Scheme 2.23

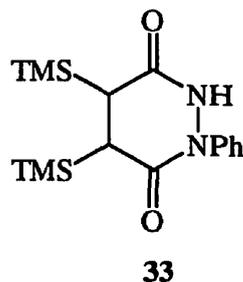


The product mixture was a 10:1 mixture of E (*d,l*) and Z (*meso*) isomers respectively. Only E-**32** was obtained pure by radial chromatography on silica gel and was identified by its upfield chemical shift of the Me_3SiCH protons in the ^1H NMR spectrum relative to that of Z-**32** in the crude ^1H NMR spectrum. The $J_{\text{H,H}}$ value (2.0 Hz) of the ^{13}C satellites was also typically small which agrees with the stereochemical assignment made for the corresponding E- and Z-succinic anhydrides.^{1b} Preference for E-**32** over Z-**32** is presumably due to steric crowding from the cis arrangement of TMS groups in the transition state for formation of the Z-isomer.

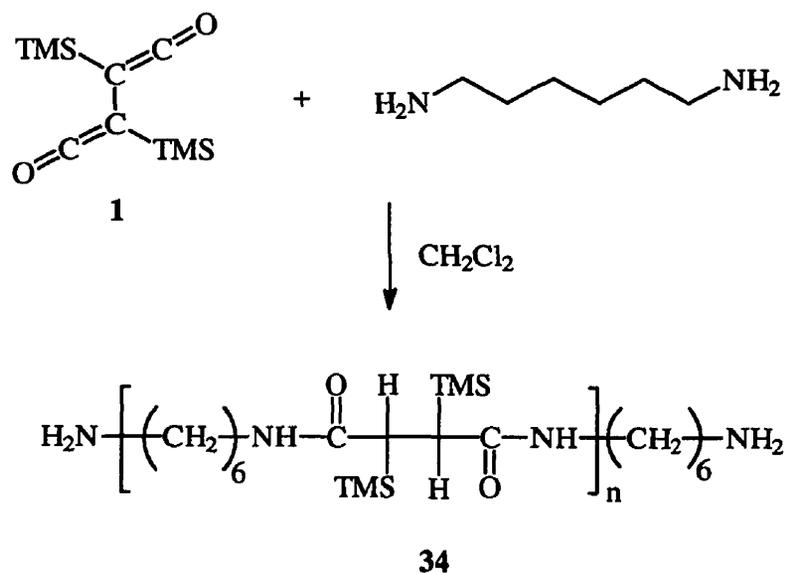
Two particularly interesting features of this reaction include how efficiently cyclization of the intermediate ketenylamide proceeds in comparison to the cyclization of ketenylamide **25**. The presence of an N-N bond must activate the amide group of the intermediate ketenylamide to the point that it is orders of magnitude more reactive than the benzylamido group of ketenylamide **25**. The other interesting feature is the lack of formation of any of the

for forming 5-membered rings when reacting with appropriate difunctional reagents.⁶

Figure 2.9



The immediate, high yielding conversion of bisketene **1** to succinamides with amines that involves no catalyst and virtually no side products is a potentially very useful reaction that may be modified for uses in peptide and polymer synthesis. Bisketene **1** was reacted with 1,6-hexanediamine and gave an off-white solid whose ¹H NMR and IR spectra were consistent with polyamide **34** (Scheme 2.24). Integration of the amine protons (δ 5.9) compared to the amide protons (δ 3.15) in the ¹H NMR spectrum suggests that the degree of polymerization is four ($n = 4$). Under the conditions used, no cyclized products were observed. The ease of formation of these oligomers is a positive sign that optimization of the reaction conditions may afford higher molecular weight polymers.



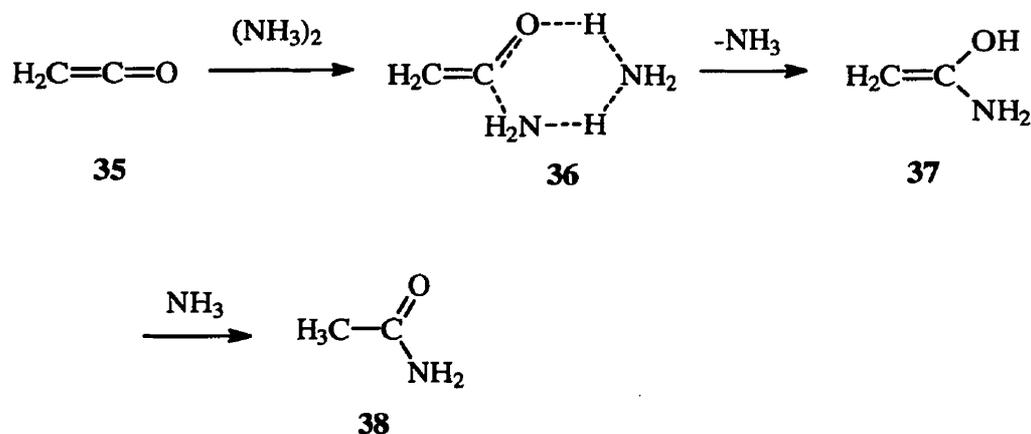
The ability of amines to react with both ketenyl groups of **1** with little or no desilylation occurring is in stark contrast to the reaction of **1** with alcohols. In fact, a number of kinetic studies have been done which indicate a much greater reactivity for amines with ketenes than for alcohols or water with ketenes. A competition study of the reaction of a dienylketene with a 1:5 mixture of *n*-BuNH₂ and *n*-BuOH gave an amide to ester product ratio of 9.5:1 indicating a 50-fold greater reactivity for the amine.²² The second order rate constant for amination of Ph₂C=C=O by *n*-BuNH₂ in water has been measured^{13a} to be 3.52 x 10⁵ M⁻¹ s⁻¹. In aqueous solution the second order rate constant for hydration of Ph₂C=C=O is calculated²³ to be 4.95 M⁻¹ s⁻¹. This gives an estimated rate ratio of $k(n\text{-BuNH}_2)/k(\text{H}_2\text{O}) = 7.1 \times 10^4$. The second order rate constant for amination of ketenes by amines in non-aqueous conditions (acetonitrile) was consistently found to be 2 orders of magnitude greater than for the

the hydrated amine must first be desolvated before it can quench the ketene.

The rate of reaction of bisketene **1** with *n*-BuNH₂ was studied²⁵ and it was found that the rate of the first addition of amine to **1** is 370 times greater than that of the second addition of the amine to the intermediate ketenyl amide. The rate ratio of bisketene **1** $k(n\text{-BuNH}_2)/k(\text{H}_2\text{O})$ was found to be 10^6 .

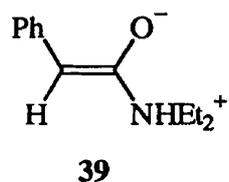
When the reaction of bisketene **1** with benzylamine was done at $-78\text{ }^\circ\text{C}$ in CH₂Cl₂, a deep pink colour was observed upon mixing of the reagents which was persistent at this temperature. The same observation was made in the reaction of **1** with other amines at $-78\text{ }^\circ\text{C}$. As the dry ice/acetone bath was removed and the reaction allowed to warm to room temperature, the pink colour slowly disappeared, replaced by an off-white suspension followed by a clear, nearly colourless solution. In another experiment, the reaction mixture was brought from $-78\text{ }^\circ\text{C}$ to $-23\text{ }^\circ\text{C}$ at which temperature the off-white suspension persisted.

Previously, theoretical studies into the mechanism of the reaction of ketenes with amines indicated that the amine initially added across the C=C bond.²⁶ It has since been shown that these studies used inadequate levels of theory and more recent experimental²⁴ and theoretical²³ studies have shown that the initial addition of the amine occurs at the C=O bond, though the amide product from C=C addition is more stable. The theoretical studies indicate that amine addition to ketene **35** going through the six-membered cyclic transition state **36** is favored which proceeds to amide enol **37** which then isomerizes to amide **38** (Scheme 2.25).



In fact the formation of the zwitterion **39** (figure 2.10) from $\text{PhCH}=\text{C}=\text{O}$ and Et_2NH concomitant with the disappearance of the ketene was observed by IR.²⁴ An amide enol analogous to **37** was also directly observed by ^1H NMR in the reaction of bis(2,4,6-triisopropylphenyl) acetic acid with dimethylamine.^{13b}

Figure 2.10

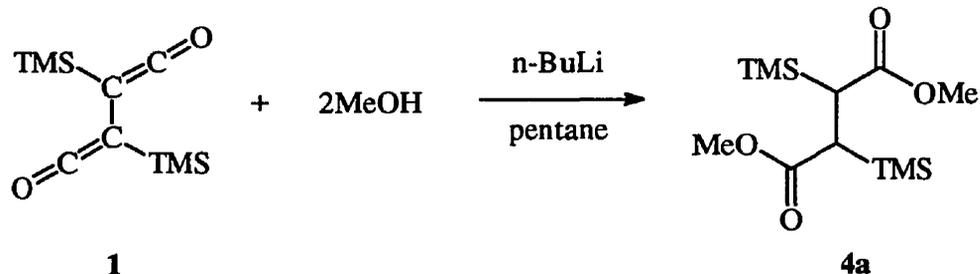


It could be speculated then that in the reaction of bisketene **1** with benzylamine at -78 $^\circ\text{C}$ that the pink colour seen is due to an intermediate complex, analogous to **36**, with the pink colour the result of a charge transfer. It is also possible that the white suspension seen at -23 $^\circ\text{C}$ is a result of a dichloromethane insoluble species, analogous to zwitterion **39**. Both variable temperature ^1H NMR spectroscopy (-80 $^\circ\text{C}$) and ESR spectroscopy (-80 $^\circ\text{C}$ to -85 $^\circ\text{C}$)

logistics problems in maintaining the pink colour while setting up equipment for spectroscopy were encountered and only ketenylamide **25** was observed by ^1H NMR. The ESR spectrum showed a weak signal indicating the presence of single electron, but it cannot be said whether this is a result of a slight excess of benzylamine adding to **25**, ring closure of **25** or whether **25** itself is responsible for the signal. This result does suggest that more experimental work into the mechanism of amine addition to bisketene **1** is warranted.

General:

All glassware was oven-dried (115 °C) overnight while all plastic equipment was blown dry with air and stored in a desiccator prior to use. All reactions were carried out under an atmosphere of argon. Tetrahydrofuran was distilled from Na/benzophenone just prior to use. Methanol was distilled from Mg/I₂ and stored over 4A sieves under argon in a sealed flask from which it was taken as needed. Pentane was dried over sodium metal ribbon. Dichloromethane was dried over 4A sieves. Bisketene 1 was generated thermally by injecting the corresponding cyclobutenedione into a Varian Aerograph Model 920 GC and collecting the product at the outlet. All other solvents and reagents were used as provided by commercial sources. Flash column chromatography was performed on 230-400 mesh Aldrich silica gel. Radial chromatography was performed on a Harrison Research Chromatotron, model 7924, with plates made from Merck TLC grade 7749 silica gel containing gypsum binder and fluorescent indicator. Thin layer chromatography was performed on TLC grade silica. Bands were detected using a portable UV lamp or else fractions were checked by ¹H NMR for compounds which had little or no UV absorption. ¹H NMR spectra were obtained at 200 MHz (Varian Gemini), 400 MHz or 500 MHz (Varian Unity). ¹³C NMR spectra were obtained at 100 MHz or 125 MHz (Varian Unity). IR spectra were obtained on either a Nicolet DX FT-IR spectrometer or a Perkin Elmer FT-IR Spectrum 1000 spectrometer. Ultraviolet spectra were obtained on a Perkin Elmer UV/Vis Spectrometer Lambda 12. Melting points were recorded on a Fisher-Johns melting point apparatus. ESR spectroscopy was performed on a Bruker ESP300 in room 302 of the Lash Miller building, courtesy of Prof. Geoffrey Ozin's group.

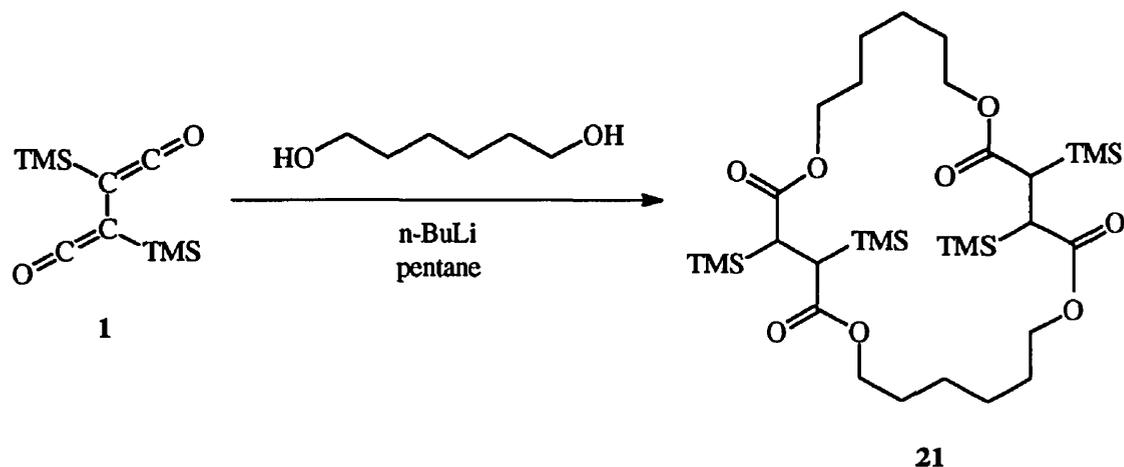


To a stirring solution of anhydrous pentane (1.5 mL) and anhydrous MeOH (83 μL , 2.1 mmol) at 0 $^{\circ}\text{C}$ and under an atmosphere of argon was added n-BuLi (128 μL , 1.6 M in hexanes, 0.21 mmol) dropwise by syringe. The ice bath was removed and a small amount of white solid was seen as the reaction warmed. The flask was allowed to come to room temperature and freshly prepared **1** (114 mg, 0.5 mmol) in anhydrous pentane (1.5 mL) was quickly added. After 75 minutes, water (5 mL) was added to the flask followed by hexanes (3 mL). The hexanes layer was kept and the water layer extracted again with hexanes (5 mL). The combined hexanes layers were washed with water (1 X 10 mL), dried over anhydrous MgSO_4 and filtered. Removal of the hexanes under reduced pressure gave crude **4a** as a clear, colourless liquid mixture of diastereomers in 60% yield. ^1H NMR (CDCl_3) analysis showed a preference for the *meso* isomer over the *d,l* in a ratio of 4:1. Also seen were the monodesilylated ester (9H singlet at δ 0.096; small multiplets δ 2.3 - 2.9; two methoxy singlets at δ 3.665 and δ 3.671) and bisdesilylated products. Purification and separation of the diastereomers was achieved by flash column chromatography on silica gel using 4% ethyl acetate in hexanes. The isolated diastereomers were obtained >97% pure by ^1H NMR: *meso*-**4a** (28% isolated yield, 41 mg, white crystals, m.p. = 44-44.5 $^{\circ}\text{C}$), ^1H NMR (CDCl_3) δ 0.051 (s,

δ 35.3 (TMSCH), δ 51.0 (OCH₃), δ 175.0 (CO); IR (CCl₄) 1715 cm⁻¹; EIMS m/z 290 (M⁺, 6), 275 (M⁺ -CH₃, 40), 260 (M⁺ -2CH₃, 6), 247 (M⁺ -CH₃ -CO, 47), 231 (M⁺ -CH₃-CO₂, 22), 186 (54), 171 (69), 143 (33), 127 (46), 73 (Me₃Si⁺, 100); HRMS m/z calc for C₁₂H₂₆O₄Si₂ 290.1370, found 290.1382. *d,l*-4a (10% isolated yield, 15 mg, clear, colourless liquid), ¹H NMR (CDCl₃) δ 0.125 (s, 18H, TMS); δ 2.302 (s, 2H, R₃CH); δ 3.637 (s, 6H, OCH₃); ¹³C NMR (CDCl₃) δ -0.965 (Me₃Si), δ 34.7 (TMSCH), δ 51.2 (OCH₃), δ 175.2 (CO); IR (CCl₄) 1729 cm⁻¹; EIMS m/z 290 (M⁺, 4), 275 (M⁺ -CH₃, 28), 260 (M⁺ -2CH₃, 9), (247 (M⁺ -CH₃ -CO, 27), 231 (M⁺ -CH₃-CO₂, 19), 186 (44), 171 (52), 143 44), 127 (39), 73 (Me₃Si⁺, 100); HRMS m/z calc for C₁₂H₂₆O₄Si₂ 290.1370, found 290.1385.

1,6,13,18-Tetraoxa-3,4,15,16-tetrakis(trimethylsilyl)cyclotetracosane-2,5,14,17-tetraone

(21):

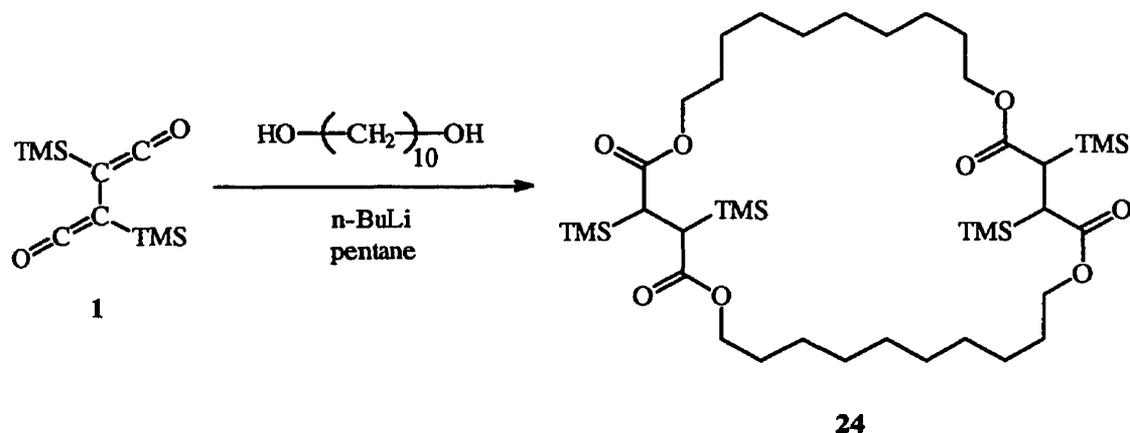


To a stirring heterogeneous mixture of 1,6-hexanediol (164 mg, 1.38 mmol) in pentane (6 mL) under an atmosphere of argon and cooled to 0 °C was added n-BuLi (1.45M in

min a white suspension was observed. After 10 min more of stirring a solution of bisketene **1** (171 mg, 0.755 mmol) in pentane (4 mL) was added all at once to the suspension. The reaction continued to stir for 1 hour at which time the contents of the flask were brown. The reaction mixture was added to H₂O (20 mL) in a separatory funnel and diluted with hexanes (10 mL). The organic layer was washed with H₂O (1 X 20 mL) and saturated NH₄Cl (1 X 15 mL), dried over anhydrous MgSO₄ and filtered. Removal of the solvents by reduced pressure gave a viscous yellow liquid mixture of products containing tetralactone **21**. ¹H NMR (CDCl₃) analysis revealed a 3:1 preference for the *meso* diastereomer (cis TMS arrangement) over the *d,l* diastereomers (trans TMS arrangement). Isolation and purification of tetralactone **21** was achieved by radial chromatography using a solvent system of 20% ethyl acetate in hexanes. The diastereomers could not be separated but tetralactone **21** was obtained 95% pure as determined by ¹H NMR with no change in the diastereomeric ratio (impurity was identified as silylated diol: δ 0.08, TMS; δ 3.62, t, TMSOCH₂). Tetralactone **21** (5% isolated yield, 26 mg, clear colourless oil), ¹H NMR (CDCl₃) *meso*-**21** δ 0.069 (s, 36H, TMS), δ 1.40 (m, 8H, OCH₂CH₂CH₂), δ 1.64 (m, 8H, OCH₂CH₂), δ 2.605 (s, 4H, COCHTMS), δ 3.98 (m, 8H, OCH₂CH₂); ¹H NMR (CDCl₃) *d,l*-**21** δ 0.134 (s, 36H, TMS), δ 1.40 (m, 8H, OCH₂CH₂CH₂), δ 1.64 (m, 8H, OCH₂CH₂), δ 2.251 (s, 4H, COCHTMS), δ 3.98 (m, 8H, OCH₂CH₂); ¹³C NMR (CDCl₃) *meso*-**21** δ -1.51 (TMS), δ 25.8 (OCH₂CH₂CH₂), δ 28.6 (OCH₂CH₂), δ 35.4 (COCHTMS), δ 62.9 (OCH₂CH₂), δ 174.60 (CO); ¹³C NMR (CDCl₃) *d,l*-**21** δ -0.68 (TMS), δ 25.8 (OCH₂CH₂CH₂), δ 28.6 (OCH₂CH₂) δ 34.7 (COCHTMS), δ 64.0 (OCH₂CH₂), δ 174.64

achieved by first triturating the yellow oil with MeOH, leaving a white solid with some oily residue. This mixture was then triturated with acetone and the acetone triturate was filtered through a cotton plug. Removal of acetone by reduced pressure yielded pure tetralactone **23** as a white solid mixture of the diastereomers with no significant change in the diastereomeric ratio as determined by ^1H NMR analysis. Tetralactone **23** (7% isolated yield, 44 mg, white solid, m.p. = 68-70 $^\circ\text{C}$), ^1H NMR (CDCl_3) *meso*-**23** δ 0.070 (s, 36H, TMS), δ 1.3 (m, 16H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 1.6 (m, 8H, OCH_2CH_2) δ 2.606 (s, 4H, COCHTMS), δ 3.95 (m, 8H, OCH_2CH_2); ^1H NMR (CDCl_3) *d,l*-**23** δ 0.135 (s, 36H, TMS), δ 1.3 (m, 16H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 1.6 (m, 8H, OCH_2CH_2) δ 2.248 (s, 4H, COCHTMS), δ 3.95 (m, 8H, OCH_2CH_2); ^{13}C NMR (CDCl_3) *meso*-**23** δ -1.54 (TMS), δ 26.0 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 28.6 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), δ 29.2 (OCH_2CH_2), δ 35.4 (COCHTMS), δ 64.2 (OCH_2CH_2), δ 174.8 (CO); ^{13}C NMR (CDCl_3) *d,l*-**23** δ -0.71 (TMS), δ 26.0 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 28.7 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), δ 29.7 (OCH_2CH_2) δ 34.6 (COCHTMS), δ 64.1 (OCH_2CH_2), δ 174.7 (CO); IR (CDCl_3) 1704 cm^{-1} ; EIMS m/z 746 (M^++2H , 7), 245 (21), 17 (23), 155 (43), 147 (30), 73 (Me_3Si^+ , 100), 55 (50); HRMS m/z calc. for $\text{C}_{36}\text{H}_{72}\text{O}_8\text{Si}_4+2\text{H}$ 746.4461 found 746.4472.

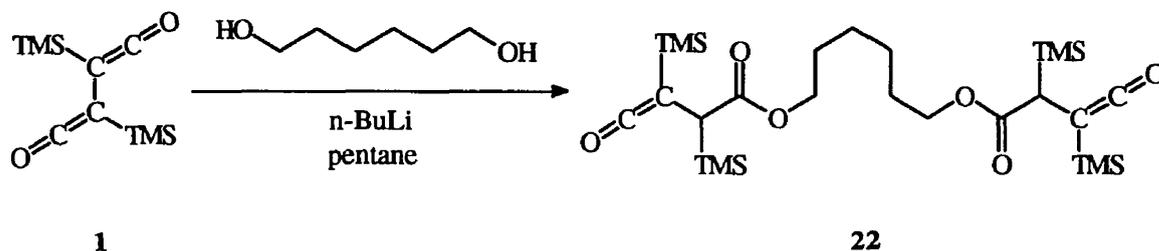
(24):



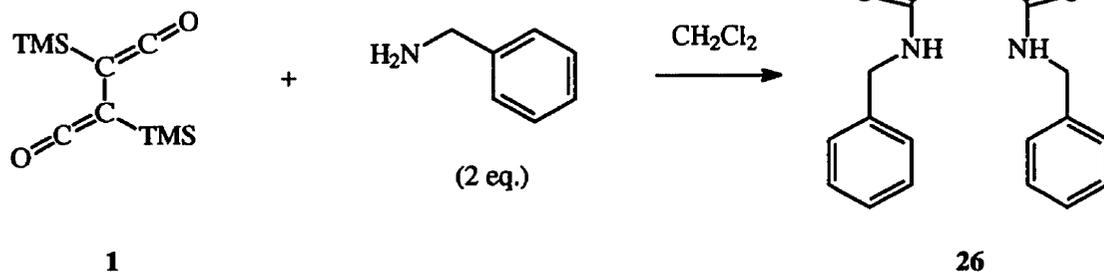
To a stirring heterogeneous mixture of 1,10-decanediol (289 mg, 1.66 mmol) in pentane (7 mL) under an atmosphere of argon and cooled to 0 °C was added n-BuLi (1.45M in hexanes, 300 μL, 0.44 mmol) dropwise by syringe. The ice bath was removed and after 10 min a white suspension was observed. After 20 min more of stirring a solution of bisketene **1** (192 mg, 0.848 mmol) in pentane (5 mL) was added all at once by syringe to the suspension. The reaction continued to stir for about 1 hour at which time the contents of the flask were brown and heterogeneous. The reaction mixture was added to H₂O (20 mL) in a separatory funnel and diluted with hexanes (10 mL). The organic layer was washed with H₂O (1 X 20 mL) and saturated NH₄Cl solution (1 X 20 mL), dried over anhydrous MgSO₄ and filtered. Removal of the solvents by reduced pressure gave a viscous yellow liquid mixture of products containing tetralactone **24**. ¹H NMR (CDCl₃) analysis revealed a 4:1 preference for the *meso* diastereomer (cis TMS orientation) over the *d,l* diastereomers (trans TMS orientation). Isolation and purification of tetralactone **24** was achieved by first triturating the yellow oil with

acetone and the acetone triturate was filtered through a cotton plug. Acetone was then removed by reduced pressure leaving a white solid. Trituration of this solid with acetone and subsequent collection of the acetone solution was repeated twice more. Removal of acetone by reduced pressure yielded tetralactone **24** in 91% purity (1,10-decanediol identified as impurity by ^1H NMR) as a white syrupy mixture of the diastereomers with no significant change in the diastereomeric ratio as determined by ^1H NMR analysis. Tetralactone **24** (4% isolated yield, 27 mg, white syrup), ^1H NMR (CDCl_3) *meso*-**24** δ 0.074 (s, 36H, TMS), δ 1.3 (m, 24H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 1.6 (m, 8H, OCH_2CH_2), δ 2.611 (s, 4H, COCHTMS), δ 3.95 (m, 8H, OCH_2CH_2); ^1H NMR (CDCl_3) *d,l*-**24** δ 0.140 (s, 36H, TMS), δ 1.3 (m, 24H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 1.6 (m, 8H, OCH_2CH_2), δ 2.253 (s, 4H, COCHTMS), δ 3.95 (m, 8H, OCH_2CH_2); ^{13}C NMR (CDCl_3) *meso*-**24** δ -1.49 (TMS), δ 26.1 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 28.6 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 29.3 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), δ 29.5 (OCH_2CH_2), δ 35.5 (COCHTMS), δ 64.3 (OCH_2CH_2), δ 174.7 (CO); ^{13}C NMR (CDCl_3) *d,l*-**24** δ -0.67 (TMS), δ 25.8 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 28.8 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), δ 29.4 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), δ 29.7 (OCH_2CH_2), δ 34.7 (COCHTMS), δ 63.1, (OCH_2CH_2), δ 174.6 (CO); IR (CDCl_3) 1701 cm^{-1} ; EIMS m/z 802 ($\text{M}^+ + 2\text{H}$, 7), 245 (21), 17 (23), 155 (43), 147 (30), 73 (Me_3Si^+ , 100), 55 (50).

1,6-Bis[4-oxo-2,3-bis(trimethylsilyl)but-3-enoyloxy]hexane (22):



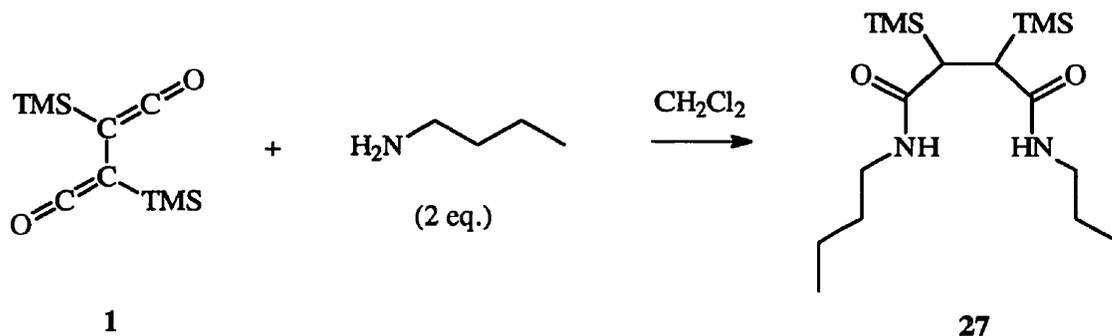
pentane (6 mL) under argon and cooled to 0 °C with an ice bath was added n-BuLi (1.45M in hexanes, 200 µL, 0.29 mmol) dropwise by syringe. A cloudy white suspension formed after 20 minutes of stirring. To this suspension was added **1** (131 mg, 0.579 mmol) as a solution in pentane (4 mL) which had been cooled to 0 °C prior to addition. The resulting yellow suspension stirred at 0 °C for 90 minutes at which point the ice bath was removed and the mixture was allowed to warm to room temperature. After 30 minutes of stirring at room temperature a brown suspension resulted which was diluted with hexanes (5 mL) and added to water (10 mL) in a separatory funnel. The organic layer was washed with saturated NH₄Cl (1 X 15 mL), dried over anhydrous MgSO₄ and filtered. Removal of the solvents by reduced pressure yielded **22** as the major product in a viscous light yellow oil, identified by a characteristic singlet at δ1.9 in the ¹H NMR spectrum and a strong ketene stretch at 2089 cm⁻¹ in the IR spectrum. Purification of **22** was done using radial chromatography on silica gel under argon (4% EtOAc in hexanes) giving bisketene **22** in 92% purity by ¹H NMR analysis. Bisketene **22** (18% isolated yield, 30 mg, clear light yellow liquid) ¹H NMR (CDCl₃) δ0.135 (s, 18H, TMS), δ0.145 (s, 18H, TMS), δ1.38 (m, 4H, OCH₂CH₂CH₂), δ1.64 (m, 4H, OCH₂CH₂) δ1.95 (s, 2H, COCHTMS), δ4.08 (m, 4H, OCH₂CH₂); ¹³C NMR (CDCl₃) δ-2.11, δ-0.80 (TMS), δ10.9 (CCO), δ25.7, (OCH₂CH₂CH₂), δ28.7, δ28.6 (OCH₂CH₂) δ30.3 (COCHTMS), δ64.8 (OCH₂CH₂), δ175.0 (CO), δ180.9 (CCO); IR (CDCl₃) 2089 cm⁻¹ (s), 1719 cm⁻¹ (m); UV (isooctane) λ_{max} = 334 nm; EIMS *m/z* 570 (M⁺, 4), 316 (16), 243 (46), 199 (16), 154 (21), 147 (30), 73 (Me₃Si⁺, 100).



To a stirring solution of benzylamine (198 μL , 1.81 mmol) and dichloromethane (3 mL) at room temperature and under an atmosphere of argon was added **1** (206 mg, 0.912 mmol) as a solution in dichloromethane (3 mL) all at once by syringe. A pink solution was seen momentarily as **1** was added but this quickly disappeared and the reaction mixture was a clear colourless solution within seconds of the addition of **1**. After two minutes of stirring, the dichloromethane was removed under reduced pressure giving **26** as a white solid mixture of diastereomers in 92% crude yield. ^1H NMR (CDCl_3) analysis showed that **26** was obtained in 96% purity, with no significant preference for one diastereomer over the other. The only impurity was believed to be a product of desilylation. Purification and separation of the diastereomers was achieved by radial chromatography on silica gel using 2% triethylamine in dichloromethane (note: noticeable desilylation of the products occurs on the silica when methanol/dichloromethane solvent systems are used). The isolated diastereomers were obtained in >95% purity by ^1H NMR and were identified as either *meso* or *d,l* based on coupling constants for the satellites of the α -protons ($^3J_{\text{H,H}}$ (*meso*) = 11.1 Hz; $^1J_{\text{C,H}}$ (*meso*) = 125 Hz; $^3J_{\text{H,H}}$ (*d,l*) = 5.1 Hz, $^1J_{\text{C,H}}$ (*d,l*) = 119 Hz): *meso*-**26** (22% isolated yield, 89 mg, white

δ 4.308 (d, 4H, PhCH₂), δ 5.894 (t, 2H, NH), δ 7.281 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ -1.20 (TMS), δ 37.2 (TMSCH), δ 44.0 (PhCH₂), δ 127.4 (*para*-Ph), δ 128.3 (*meta*-Ph), δ 128.5 (*ortho*-Ph), δ 138.0 (*ipso*-Ph), δ 173.6 (CO); IR (CDCl₃) 3446 cm⁻¹ (w), 1649 cm⁻¹, 1499 cm⁻¹; EIMS *m/z* 440 (M⁺, 14), 425 (M⁺-CH₃, 11), 349 (M⁺-PhCH₂, 26), 335 (M⁺-PhCH₂N, 11), 259 (16), 221 (28), 91 (PhCH₂⁺, 100), 73 (Me₃Si⁺, 54); HRMS *m/z* calc. for C₂₄H₃₆N₂O₂Si₂ 440.2315, found 440.2309. *d,l*-**26** (8% isolated yield, 32 mg, white solid, m.p. = 146-148 °C), ¹H NMR (CDCl₃) δ 0.073 (s, 18H, TMS), δ 2.048 (s, 2H, R₃CH), δ 4.347 (m, 4H, PhCH₂), δ 7.309 (m, 10H, PhH), δ 7.819 (s, broad, 2H, NH); ¹³C NMR (CDCl₃) δ -1.26 (TMS), δ 38.4 (TMSCH), δ 44.0 (PhCH₂), δ 127.2 (*para*-Ph), δ 128.1 (*meta*-Ph), δ 128.5 (*ortho*-Ph), δ 138.4 (*ipso*-Ph), δ 174.3 (CO); IR (CDCl₃) 3447 cm⁻¹ (w), 1649 cm⁻¹, 1503 cm⁻¹; EIMS *m/z* 440 (M⁺, 10), 425 (M⁺-CH₃, 7), 349 (M⁺-PhCH₂, 21), 335 (M⁺-PhCH₂N, 7), 259 (15), 221 (19), 187 (19), 106 (PhCH₂NH⁺, 32), 91 (PhCH₂⁺, 100), 73 (Me₃Si⁺, 40); HRMS *m/z* calc. for C₂₄H₃₆N₂O₂Si₂ 440.2315, found 440.2319.

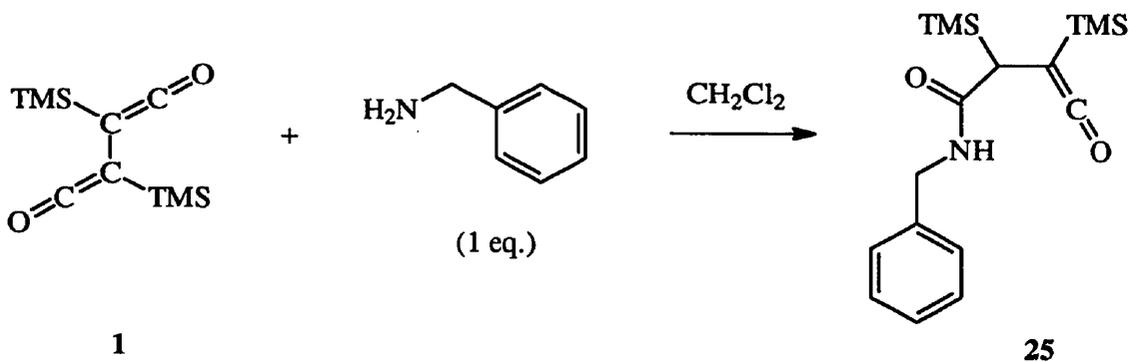
N,N'-Dibutyl-2,3-bis(trimethylsilyl)butanediamide (27):



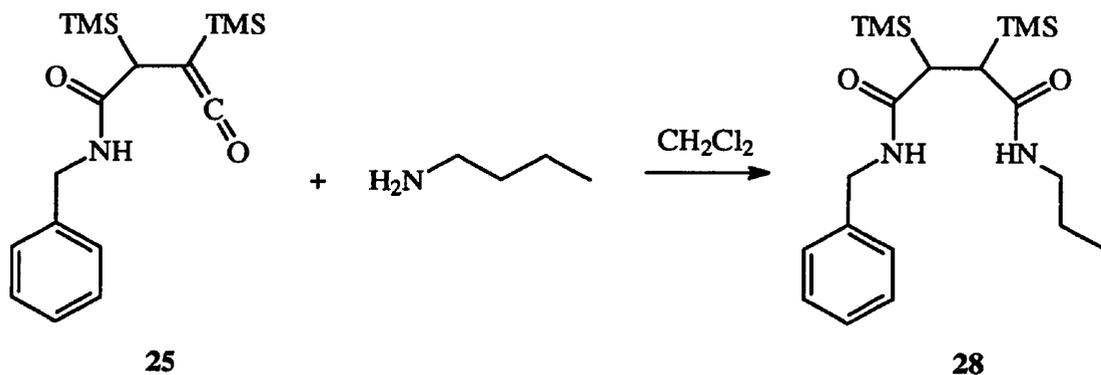
mL) at room temperature and under an atmosphere of argon was added **1** (182 mg, 0.804 mmol) as a solution in dichloromethane (3 mL) all at once by syringe. As with the reaction using benzylamine, a pink colour was seen momentarily as **1** was added but this disappeared within seconds and a clear colourless solution resulted. After ten minutes of stirring, the dichloromethane was removed under reduced pressure, giving diamide **27** as an off-white solid mixture of diastereomers in 85% crude yield. ^1H NMR (CDCl_3) analysis showed that diamide **27** was obtained in 89% purity, with a preference for the *meso* diastereomer over the *d,l* of about 3:2. The major impurity was believed to be the monodesilylated diamide.

^1H NMR (CDCl_3) *meso-27* δ 0.06 (s, 18H, TMS), δ 0.92 (t, 6H, CH_3), δ 1.4 (m, 8H, $\text{CH}_3\text{CH}_2\text{CH}_2$), δ 2.28 (s, 2H, R_3CH), δ 3.32 (m, 4H, R_2NCH_2), δ 5.4 (t, 2H, NH); ^1H NMR (CDCl_3) *d,l-27* δ 0.10 (s, 18H, TMS), δ 0.92 (t, 6H, CH_3), δ 1.4 (m, 8H, $\text{CH}_3\text{CH}_2\text{CH}_2$), δ 1.96 (s, 2H, R_3CH), δ 3.32 (m, 4H, R_2NCH_2), δ 7.4 (t, 2H, NH); IR (CDCl_3) 3447 cm^{-1} (m), 1651 cm^{-1} , 1508 cm^{-1} .

N-Benzyl-4-oxo-2,3-bis(trimethylsilyl)-but-3-eneamide (25):

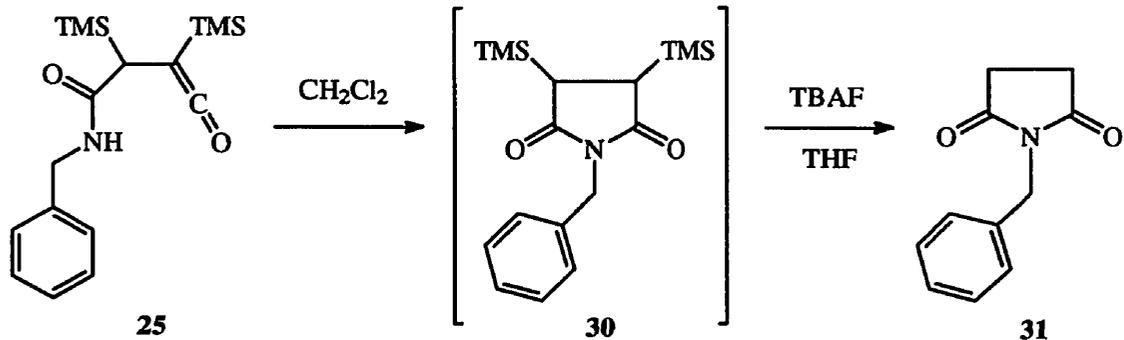


at room temperature and under an atmosphere of argon was added **1** (200 mg, 0.886 mmol) as a solution in dichloromethane (3 mL) all at once by syringe. Immediately a clear, very light yellow solution was seen. After five minutes the reaction mixture was placed in a dry ice/acetone bath to prevent decomposition of monoketene **25**. A 0.5 mL aliquot was removed from the flask and the dichloromethane removed by reduced pressure giving monoketene **25** as a clear, faint yellow oil. ^1H NMR analysis of the aliquot showed monoketene **25** as the only substantial product, calculated as 95% pure by signal integration. The IR spectrum of the aliquot also confirmed that the product did contain a ketene, showing a carbonyl stretch at 2081 cm^{-1} . Characterization of monoketene **25** was done without further purification due to the ease with which **25** decomposes. Monoketene **25** was kept at $-80\text{ }^\circ\text{C}$ as a solution in dichloromethane prior to any use in characterization or further reaction. ^1H NMR (CDCl_3) δ 0.132 (s, 9H, TMS), δ 0.155 (s, 9H, TMS), δ 1.917 (s, 1H, R_3CH), δ 4.438 (d, 2H, PhCH_2), δ 6.091 (t, 1H, NH), δ 7.294 (m, 5H, PhH); ^{13}C NMR (CDCl_3) δ -1.94 (TMS), δ -0.95 (TMS), δ 1.96 (CCO), δ 10.8 (TMSCH), δ 44.0 (PhCH_2), δ 127.3 (*para*-Ph), δ 127.8 (*meta*-Ph), δ 128.5 (*ortho*-Ph), δ 138.3 (*ipso*-Ph), δ 173.1 (CO), δ 179.6 (CCO); IR (CDCl_3) 3443 cm^{-1} (w), 2081 cm^{-1} , 1653 cm^{-1} ; EIMS m/z 333 (M^+ , 34), 290 (24), 242 (M^+ - PhCH_2 , 61), 232 (70), 91 (PhCH_2^+ , 70), 73 (Me_3Si^+ , 100); HRMS m/z calc. for $\text{C}_{17}\text{H}_{27}\text{NO}_2\text{Si}_2$ 333.1580, found 333.1577.



To a stirring clear, light yellow solution of **25** (0.71 mmol, generated in situ) in dichloromethane (8 mL) at room temperature and under an atmosphere of argon was added n-butylamine (70 μL , 0.71 mmol) all at once by syringe. Immediately a clear, colourless solution resulted. After three minutes of stirring, the dichloromethane was removed by reduced pressure, giving mixed diamide **28** as a white solid mixture of diastereomers in 95% crude yield. ^1H NMR analysis showed that **28** was obtained in 94% purity, with a 2:1 preference for the *erythro* isomer over the *threo* isomer. Purification and separation of the diastereomers was accomplished using radial chromatography on silica gel using 2% MeOH in dichloromethane. The isolated diastereomers were obtained in >95% purity by ^1H NMR and were identified as either *erythro* or *threo* based on coupling constants for the non-equivalent α -protons ($^3J_{\text{H,H}}$ (*erythro*) = 11.2 Hz; $^3J_{\text{H,H}}$ (*threo*) = 5.2 Hz): *erythro*-**28** (27% isolated yield, 78 mg, white solid, m.p. = 141-144 $^\circ\text{C}$), ^1H NMR (CDCl_3) δ 0.051 (s, 9H, TMS), δ 0.055 (s, 9H, TMS), δ 0.902 (t, 3H, CH_3), δ 1.314 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), δ 1.440 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), δ 2.318 (d, 1H, α -CH), δ 2.364 (d, 1H, α -CH), δ 3.164 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), δ 4.333 (dd, 2H,

(CDCl₃) δ-1.34 (TMS), δ-1.30 (TMS), δ13.8 (CH₃), δ20.2 (CH₂Me), δ31.7 (CH₂Et), δ37.18 (TMSCH), δ37.25 (TMSCH), δ39.3 (n-PrCH₂), δ44.0 (PhCH₂), δ127.4 (*para*-Ph), δ128.3 (*meta*-Ph), δ128.6 (*ortho*-Ph), δ138.1 (*ipso*-Ph), δ173.6 (CO), δ173.7 (CO); IR (CDCl₃) 3445 cm⁻¹, 3330 cm⁻¹, 1664 cm⁻¹, 1628 cm⁻¹; EIMS *m/z* 406 (M⁺, 22), 391 (M⁺-CH₃, 22), 315 (M⁺-PhCH₂, 40), 200 (29), 147 (24), 91 (PhCH₂⁺, 100), 73 (Me₃Si⁺, 77); HRMS *m/z* calc. for C₂₁H₃₈N₂O₂Si₂ 406.2472, found 406.2484. *threo*-**28** (9% isolated yield, 26 mg, white solid, m.p. = 126-128 °C), ¹H NMR (CDCl₃) δ0.079 (s, 9H, TMS), δ0.083 (s, 9H, TMS), δ0.921 (t, 3H, CH₃), δ1.367 (m, 2H, CH₂CH₂CH₃), δ1.498 (m, 2H, CH₂CH₂CH₂CH₃), δ1.975 (d, 1H, α-CH), δ2.025 (d, 1H, α-CH), δ3.124 (m, 1H, NHCHCH₂CH₂CH₃), δ3.269 (m, 1H, NHCHCH₂CH₂CH₃), δ4.303 (dd, 1H, PhCHNH), δ4.506 (dd, 1H, PhCHNH), δ7.28 (m, 5H, PhH), δ7.362 (s, broad, 1H, n-BuNH), δ7.866 (s, broad, 1H, PhNH); ¹³C NMR (CDCl₃) δ-1.37 (TMS), δ-1.30 (TMS), δ13.8 (CH₃), δ20.3 (CH₂Me), δ31.7 (CH₂Et), δ38.37 (TMSCH), δ38.49 (TMSCH), δ39.6 (n-PrCH₂), δ43.9 (PhCH₂), δ127.2 (*para*-Ph), δ128.1 (*meta*-Ph), δ128.5 (*ortho*-Ph), δ138.5 (*ipso*-Ph), δ174.30 (CO), δ174.35 (CO); IR (CDCl₃) 3445 cm⁻¹, 3257 cm⁻¹, 1656 cm⁻¹, 1621 cm⁻¹; EIMS *m/z* 406 (M⁺, 31), 391 (M⁺-CH₃, 25), 315 (M⁺-PhCH₂, 70), 225 (22), 200 (30), 91 (PhCH₂⁺, 100), 73 (Me₃Si⁺, 87); HRMS *m/z* calc. for C₂₁H₃₈N₂O₂Si₂ 406.2472, found 406.2470.

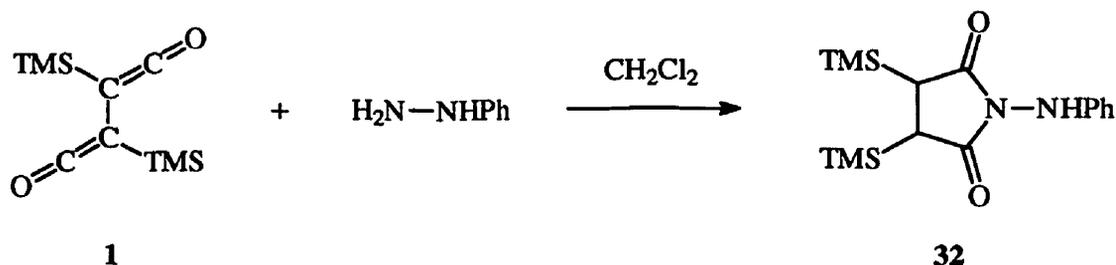


A solution of monoketene **25** (0.50 mmol) in dichloromethane (4.5 mL) under argon was placed in a freezer (0 °C) for eight days. After eight days, ¹H NMR and IR analysis showed no sign of monoketene **25**. The IR spectrum showed carbonyl absorption typical of amides while the ¹H NMR spectrum was much more complex than that of monoketene **25**. A number of small broad multiplets are seen in the region δ2.3 - δ3.3; typical of non-equivalent protons alpha to the carbonyl. The product mixture was believed to be succinimide **30**, which can have a cis or trans ring conformation, and possibly some monodesilylated succinimide **30**.

In order to positively identify the major decomposition product of monoketene **25**, desilylation of succinimide **30** was accomplished by adding TBAF (1.5 mL, 1.0 M in THF) to a stirring solution of succinimide **30** (quantity unknown) in THF (3 mL). Immediately the reaction mixture turned from clear, light yellow to a dark red/orange solution. After 10 minutes, the reaction mixture was added to 10 mL H₂O and diluted with 5 mL diethyl ether. The organic layer was separated, dried over anhydrous MgSO₄ and the solvents removed by reduced pressure giving crude succinimide **31** as a faint yellow oil, identified as the major product by ¹H NMR spectroscopy. Succinimide **31** was purified by radial chromatography on silica gel using 2%

yield, 24 mg, m.p. = 95-97 °C). ¹H NMR (CDCl₃) δ2.709 (s, 4H, RCH₂CH₂R), δ4.662 (s, 2H, PhCH₂), δ7.301 (m, 3H, PhH), δ7.382 (m, 2H, PhH); ¹³C NMR (CDCl₃) δ28.3 (RCH₂CH₂R), δ42.4 (PhCH₂), δ127.9 (*para*-Ph), δ128.6 (*meta*-Ph), δ128.8 (*ortho*-Ph), δ135.7 (*ipso*-Ph), δ176.7 (CO); IR (CDCl₃) 3443 cm⁻¹ (w), 1653 cm⁻¹; EIMS *m/z* 189 (M⁺, 100), 161 (43), 160 (50), 132 (44), 104 (59), 91 (PhCH₂⁺, 43), 77 (Ph⁺, 25); HRMS *m/z* calc. for C₁₁H₁₁NO₂ 189.0790, found 189.0791.

N-Phenylimino-3,4-bis(trimethylsilyl)succinimide (32):

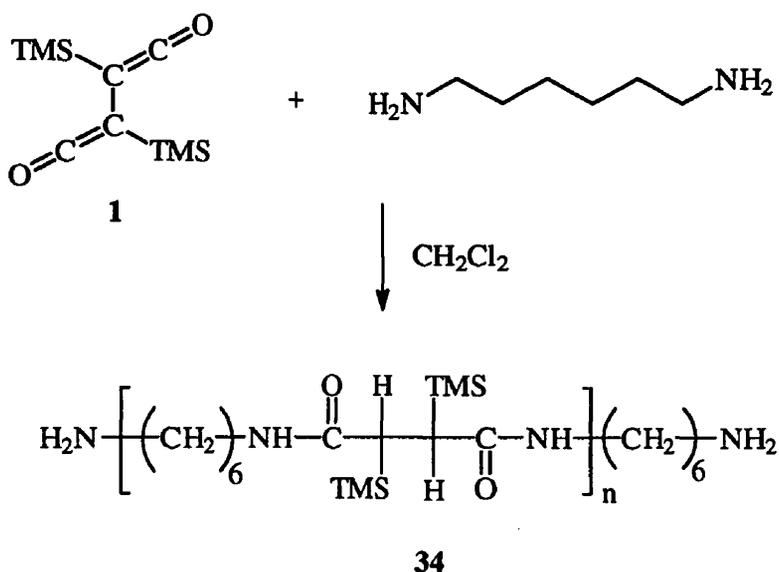


To a stirring solution of **1** (173 mg, 0.763 mmol) in dichloromethane (3 mL) under an atmosphere of argon was added phenylhydrazine (75 μL, 0.76 mmol) as a solution in dichloromethane. No change in colour was observed from the original bright yellow bisketene **1** solution. After 10 minutes of stirring, a 0.5 mL aliquot was removed from the flask and the dichloromethane removed under reduced pressure giving **32** quantitatively as a yellow liquid. ¹H NMR (CDCl₃) analysis showed that **32** was obtained in 97% purity, with a preference for the *d,l* diastereomer (*E*-**32**) over the *meso* (*Z*-**32**) in a ratio of 10:1, determined by signal integration. Due to the relatively small amount of *Z*-**32** isomer, only *E*-**32** isomer could be isolated, which was accomplished by radial chromatography using a solvent system of 10% EtOAc in hexanes. *E*-**32**

TMS), δ 2.341 (s, 2H, α -CH), δ 6.083 (s, broad, 1H, PhNH), δ 6.849 (m, 2H, *ortho*-PhH), δ 6.970 (m, 1H, *para*-PhH) δ 7.222 (m, 2H, *meta*-PhH); ^{13}C NMR (CDCl_3) δ -3.08 (TMS) δ 33.4 (α -CH), δ 115.6 (*para*-Ph), δ 122.7 (*meta*-Ph), δ 129.1 (*ortho*-Ph), δ 132.1 (*ipso*-Ph), δ 176.9 (CO); IR (CCl_4) 3344 cm^{-1} (w), 1703 cm^{-1} ; EIMS m/z 334 (M^+ , 42), 242 (M^+ -NHPH, 52), 150 (32), 91 (19), 73 (TMS^+ , 100); HRMS m/z calc. for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_2\text{Si}_2$ 334.1533, found 334.1525.

Note that the major diastereomer of **32** was identified as *d,l* (E-**32**) by the upfield chemical shift of the α -CH relative to the other diastereomer and by the small coupling constant of the ^{13}C satellites of the protons adjacent to the carbonyl group ($^3J_{\text{H,H}} = 2.0\text{ Hz}$).

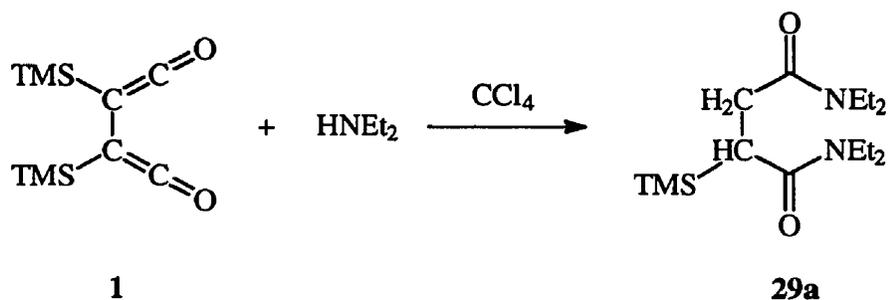
Polyamide (34):



To a stirring solution of 1,6-hexanediamine (55.8 mg, 0.480 mmol) in dichloromethane (3 mL) cooled to $-78\text{ }^\circ\text{C}$ and under an atmosphere of argon, was added **1** (about 0.5 mmol) as a solution in dichloromethane (3 mL) at $-78\text{ }^\circ\text{C}$. Immediately a deep pink solution appeared and

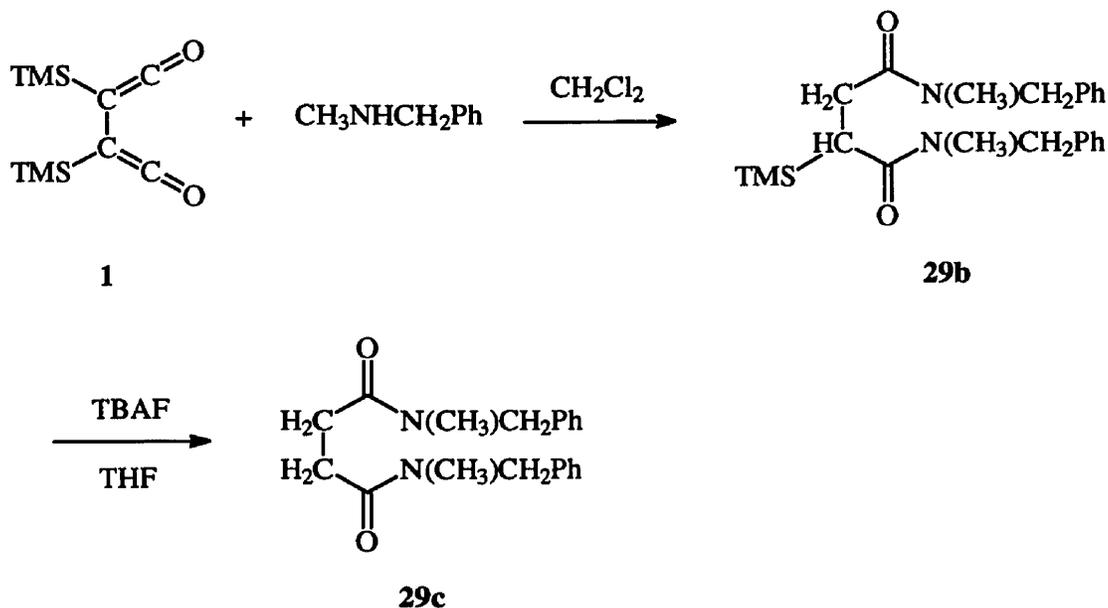
The pink colour disappeared and a white solid was observed. The solvent was removed by reduced pressure, giving an off white crystalline solid. Some of the solid was dissolved in CDCl_3 for ^1H NMR analysis, but not all the solid dissolved, so the sample was filtered through a cotton plug. The ^1H NMR spectrum revealed only two signals in the TMS region, while all the other signals in the spectrum were broad but corresponded to the expected signals for polyamide **34**. Integration of the amide protons ($\delta 5.9$) compared to the amine protons ($\delta 2.7$) suggests the degree of polymerization is four ($n=4$). The IR (CDCl_3) spectrum confirmed the likely identity of the product as polyamide **34** by its lack of ketene absorption at $2000\text{--}2100\text{ cm}^{-1}$ and the presence of amide carbonyl absorptions at 1650 cm^{-1} and 1499 cm^{-1} . ^1H NMR (CDCl_3) $\delta 0.07$ and $\delta 0.11$ (s, TMS), $\delta 1.35$ (broad, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), $\delta 1.5$ (broad, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), $\delta 2.1$ and $\delta 2.35$ (broad, COCHTMS), $\delta 2.7$ (broad, NH_2), $\delta 3.15$ (broad, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), $\delta 5.9$ and $\delta 7.8$ (broad, NH).

N,N'-Bis(diethyl)-2-trimethylsilylbutanediamide (29a):



To a stirring solution of diethylamine ($125\ \mu\text{L}$, $1.21\ \text{mmol}$) in carbon tetrachloride ($2\ \text{mL}$) at room temperature and under an atmosphere of argon is added **1** ($137\ \text{mg}$, $0.604\ \text{mmol}$) as a

immediately which got progressively lighter in colour until it turned brown after 2-3 hours. After nineteen hours carbon tetrachloride was removed under reduced pressure leaving a mixture of brown and white solids. Pentane was added to the mixture, the remaining solids filtered off through a cotton plug, and the pentane removed under reduced pressure leaving an off-white solid. ^1H NMR (CDCl_3) analysis of the solid revealed a large number of signals in the TMS region with the largest ones appearing at $\delta 0.07$, $\delta 0.14$ and $\delta 0.25$. Also, a number of singlets and multiplets were seen between $\delta 2.2$ and $\delta 3.0$ which indicated the presence of bis(trimethylsilyl) succinamides as well as **29a**. Purification of the product was done using flash column chromatography starting with 2% EtOAc in hexanes and gradually moving to 100% EtOAc. Succinamide **29a** was the only identifiable compound that eluted with this solvent system, as determined by ^1H NMR analysis. No yield was determined. Succinamide **29a** ^1H NMR (CDCl_3) $\delta 0.07$ (s, 9H, TMS), $\delta 1.04$, $\delta 1.06$, $\delta 1.17$, $\delta 1.23$ (4 triplets, 12H, NCH_2CH_3), $\delta 2.20$ (m, 1H, TMSCH), $\delta 2.85$ (m, 1H, R_3CH), $\delta 3.05$ (m, 1H, TMSCH), $\delta 3.0 - \delta 3.7$ (m, 8H, NCH_2CH_3); IR (CDCl_3) 1617 cm^{-1} ; EIMS m/z 300 (M^+ , 8), 285 ($\text{M}^+ - \text{CH}_3$, 18), 228 ($\text{M}^+ - \text{N}(\text{CH}_2\text{CH}_3)_2$, 100), 227 ($\text{M}^+ - \text{SiMe}_3$, 25), 212 (24), 200 (66), 184 (20), 110 (22), 73 (Me_3Si^+ , 66), 72 ($(\text{CH}_3\text{CH}_2)_2\text{N}^+$, 70).



To a stirring solution of N-methylbenzylamine (225 μL , 1.74 mmol) in dichloromethane (3 mL) under argon and cooled to $-78\text{ }^\circ\text{C}$ with a dry ice/acetone bath is added bisketene 1 (179 mg, 0.792 mmol) as a solution in dichloromethane (2 mL) which was also cooled to $-78\text{ }^\circ\text{C}$ before addition. Immediately the bright yellow colour of 1 disappeared and a very faint yellow clear solution resulted. Five minutes after the addition of 1, a 0.4 mL aliquot was removed from the reaction flask by syringe and the solvent removed under reduced pressure leaving a clear light yellow oil. ^1H NMR analysis of the oil revealed the presence of five significant signals in the TMS region (δ 0.05, δ 0.08, δ 0.12, δ 0.17, δ 0.30), a mixture of singlets and multiplets between δ 2.2 and δ 3.4, multiplets between δ 4.4 and δ 4.9 as well as some unreacted N-methylbenzylamine. The complex region between δ 2.2 and δ 3.4 suggests the major product is 29b. IR analysis of the oil confirmed that the reaction was complete by the lack of any ketene absorption ($\sim 2100\text{ cm}^{-1}$) and

of **29b** using radial chromatography on silica gel with a variety of solvent systems was unsuccessful.

In order to positively identify the product as a diamide, complete desilylation of the remaining oil believed to be **29b** (about 0.5 mmol) was done by dissolving the oil in THF (3 mL) and adding excess TBAF (3.0 mL, 1 M in THF) to this solution with stirring. After one hour the reaction mixture was diluted with diethyl ether (5 mL) and was then added to H₂O (10 mL) in a separatory funnel. The organic layer was washed once more with water (10 mL), dried over anhydrous MgSO₄, filtered through a cotton plug and the solvents removed under reduced pressure giving a yellowish oil identified as **29c** and some small baseline impurities as determined by ¹H NMR analysis. Purification of **29c** was done using radial chromatography on silica gel with 5% methanol in dichloromethane. Diamide **29c** was obtained as a clear, colourless oil as a mixture of three conformers (both N-methyl groups cis to carbonyl groups, both N-methyl groups trans to carbonyls, one N-methyl group trans and the other cis to the carbonyl groups), but these were not differentiated. No yield was determined. Succinamide **29c** ¹H NMR (CDCl₃) δ2.763, δ2.777, δ2.793, 2.809 (4 singlets, 4H, RCH₂CH₂R), δ2.952, δ2.968, 2.976, δ3.001, (4 singlets, 6H, NCH₃), δ4.604, δ4.613, 4.618, δ4.633 (4 singlets, 4H, NCH₂Ph), δ7.19-δ7.38 (m, 10H, PhH); ¹³C NMR (CDCl₃) δ28.2, 28.3, 28.5, 28.6 (RCH₂CH₂R), δ33.96, δ33.98, δ34.70, δ34.75, (NCH₃), δ50.9, δ51.0, δ53.2 (NCH₂Ph), δ126.3, δ127.1, δ127.4, δ127.7, δ128.4, δ128.7, δ136.6, 137.3 (Ph), δ172.0, δ172.3 (CO); IR (CCl₄) 1658 cm⁻¹, 1640 cm⁻¹; EIMS *m/z* 324 (M⁺, 8), 204 (M⁺-N(CH₃)CH₂Ph), 176 (11), 120 (PhCH₂(CH₃)N⁺, 76), 91 (PhCH₂⁺, 100); HRMS *m/z* calc for C₂₀H₂₄N₂O₂ 324.1838 found 324.1841.

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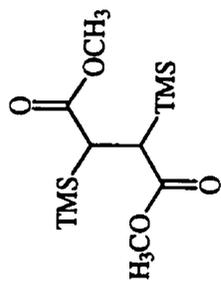
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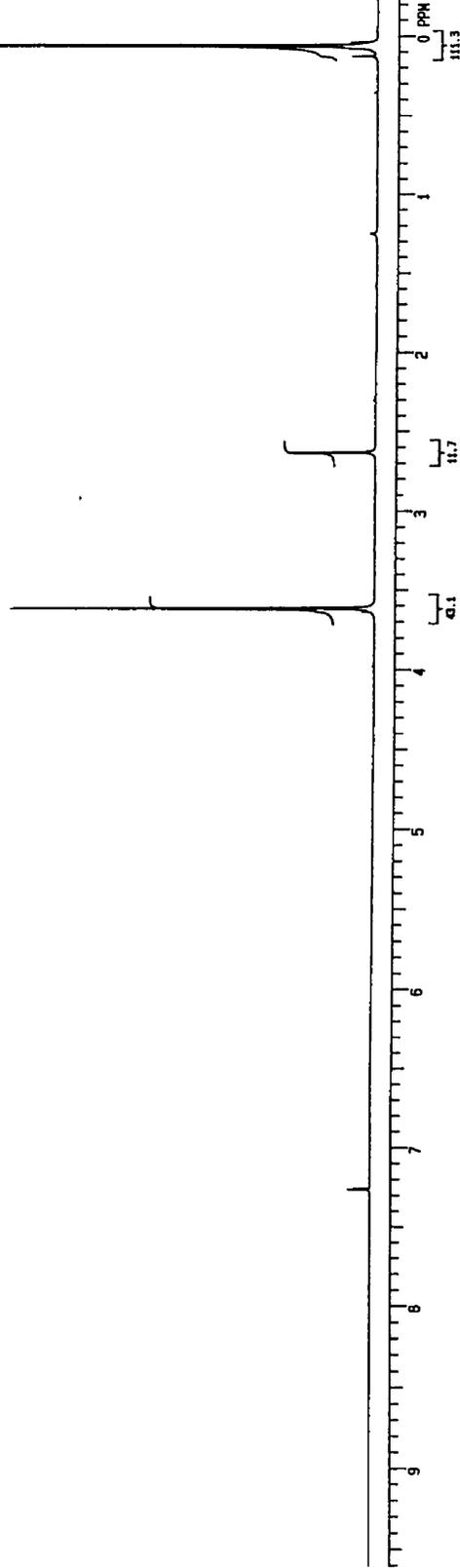
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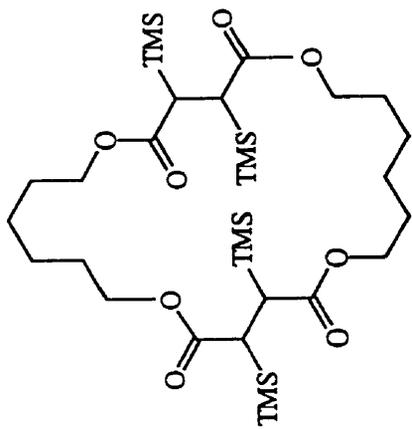
Appendix C

Selected ^1H NMR spectra of synthesized compounds

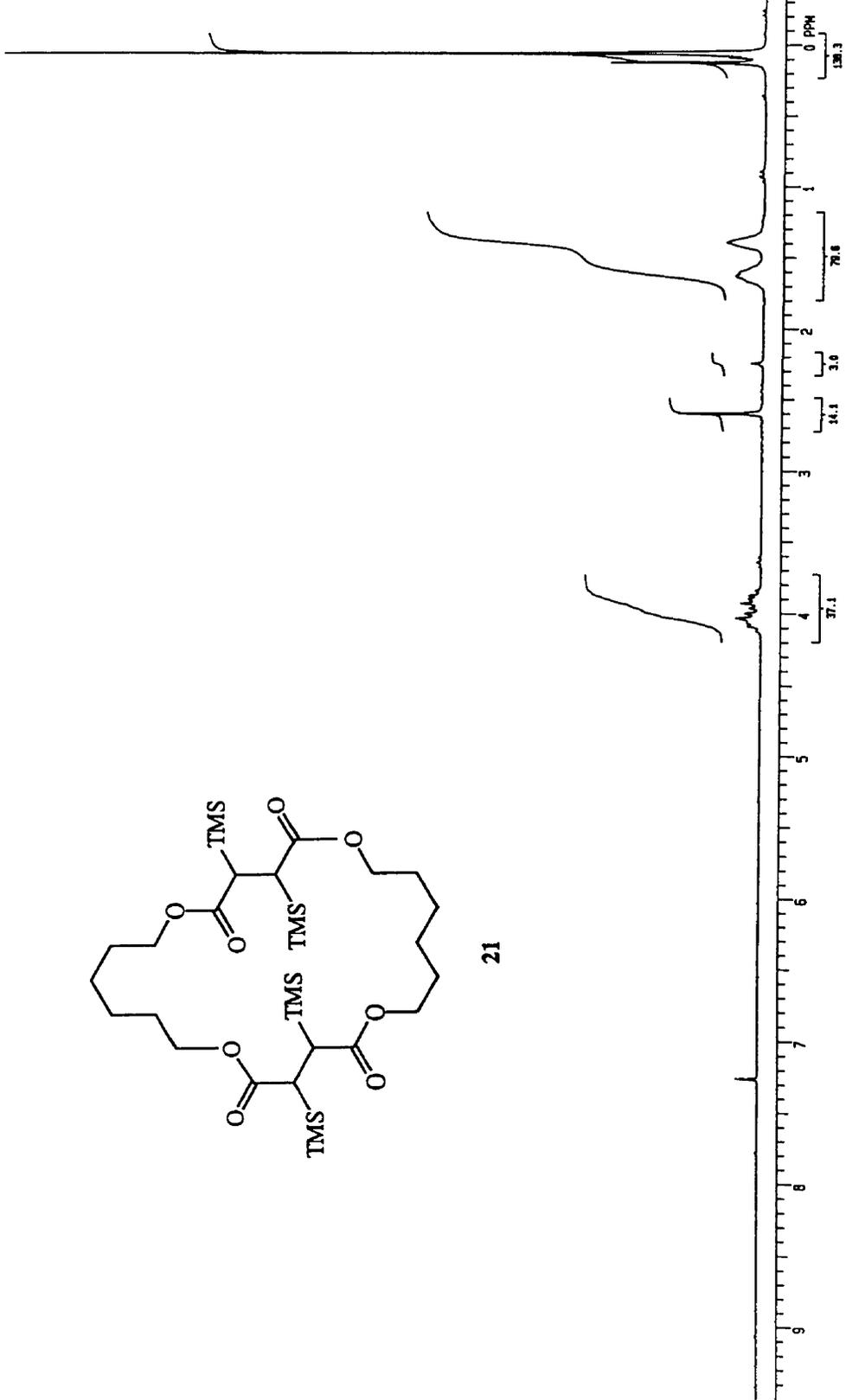


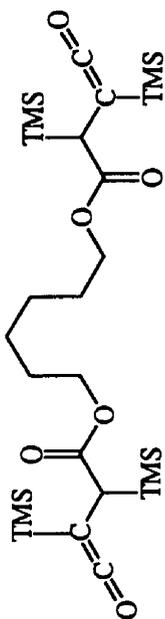
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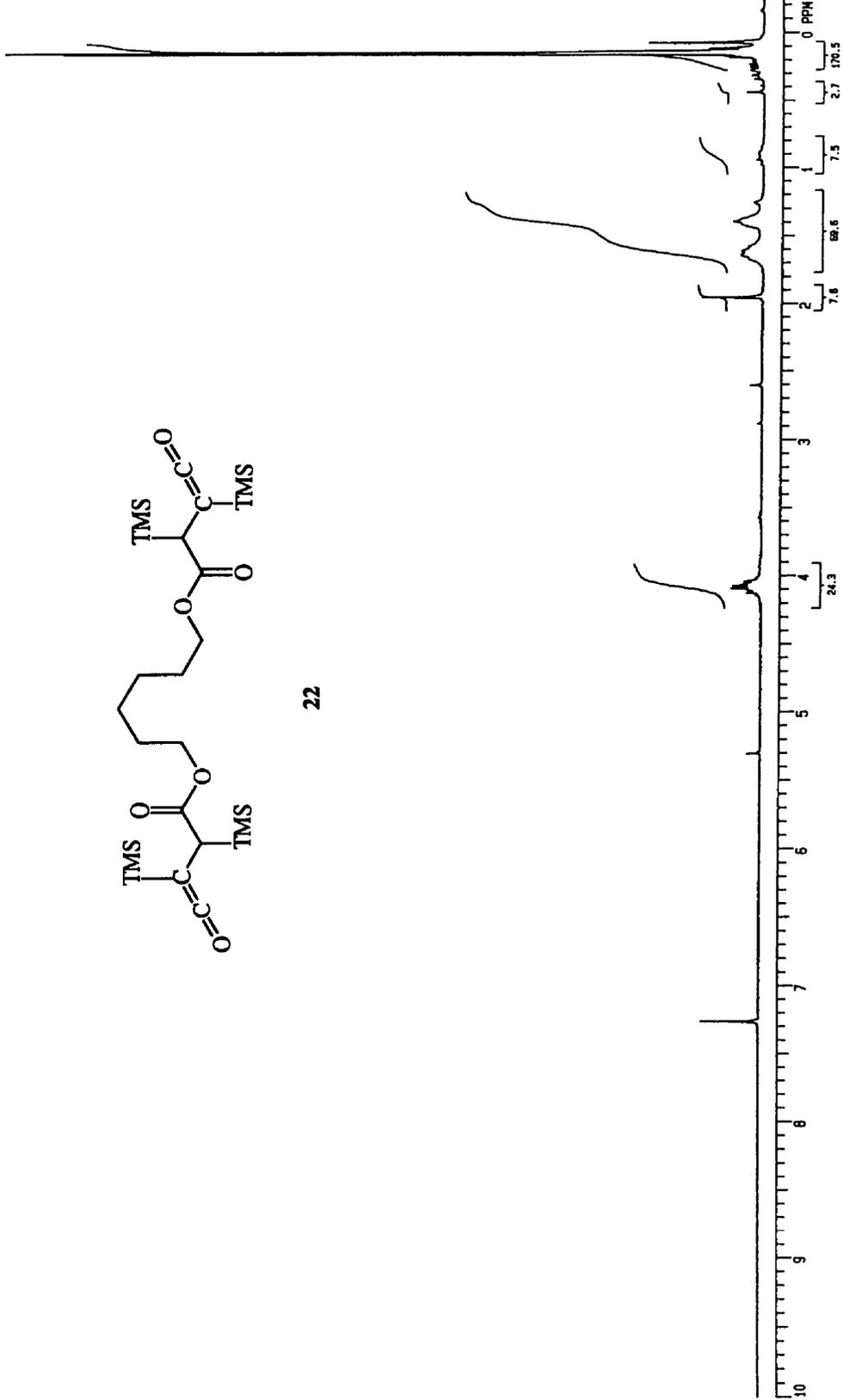


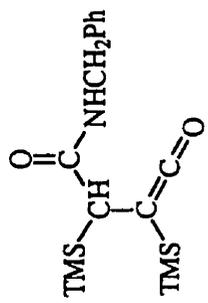
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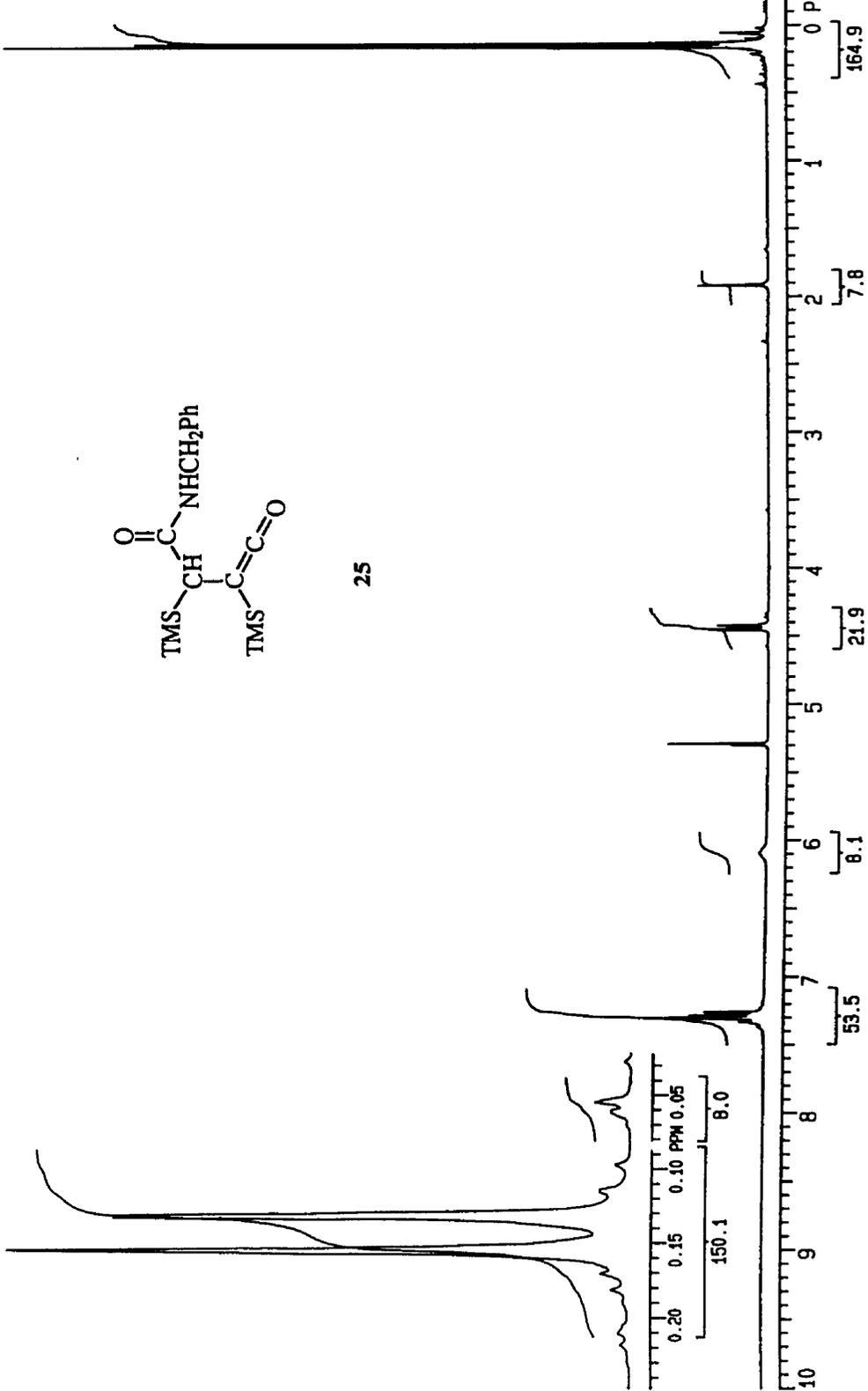


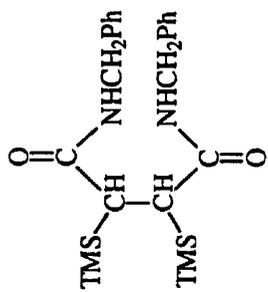
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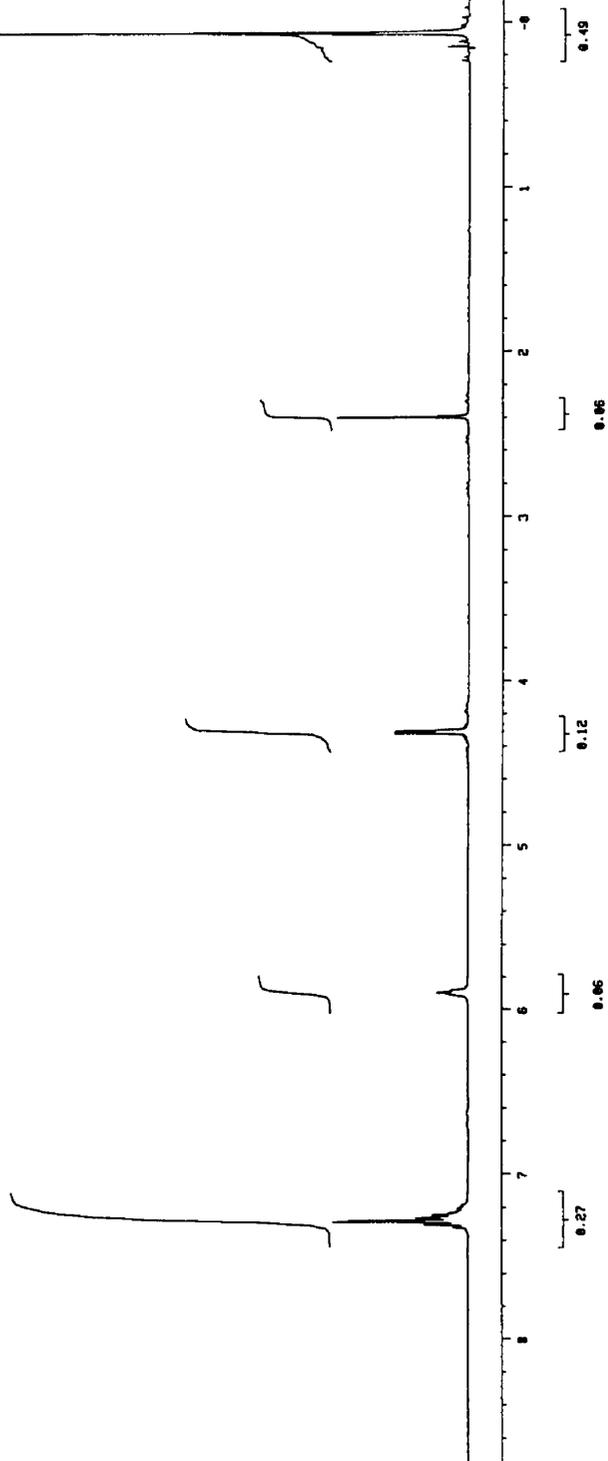


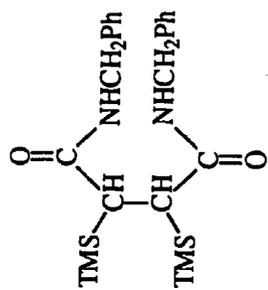
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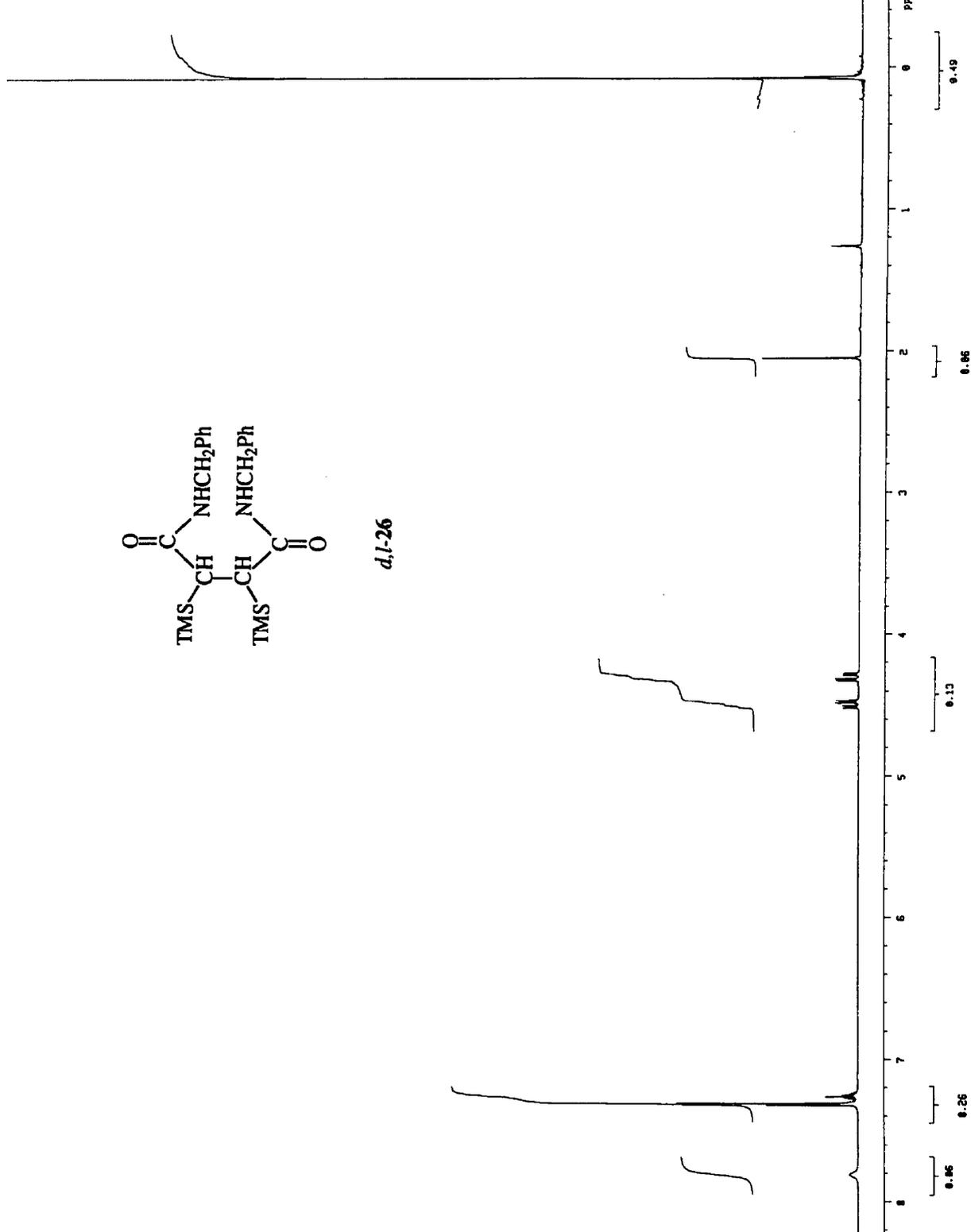


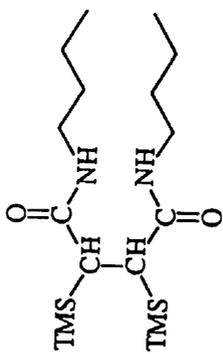
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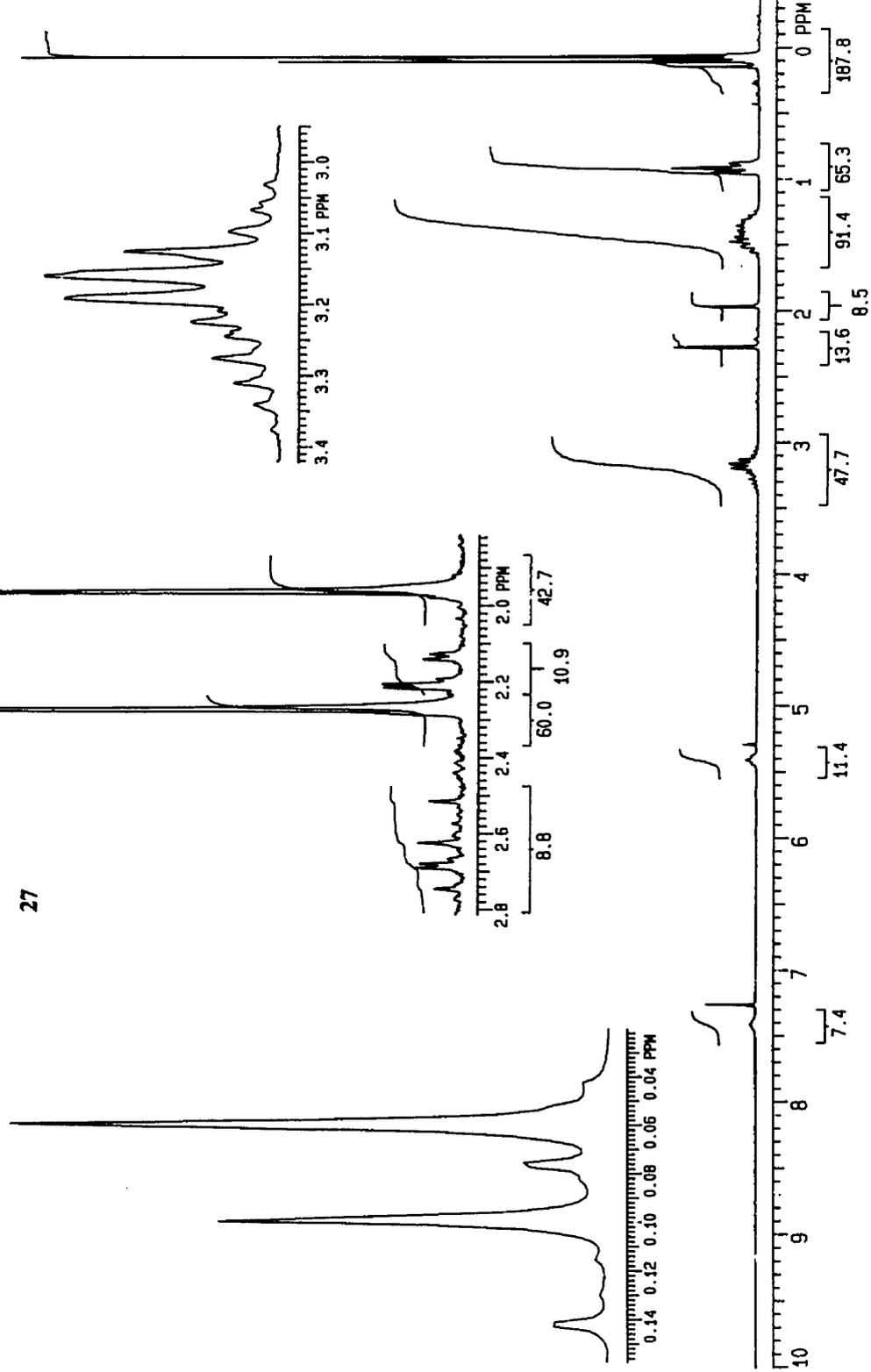


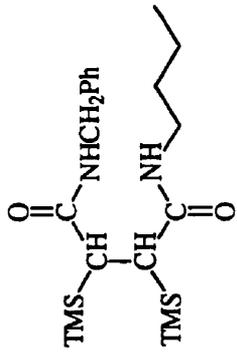
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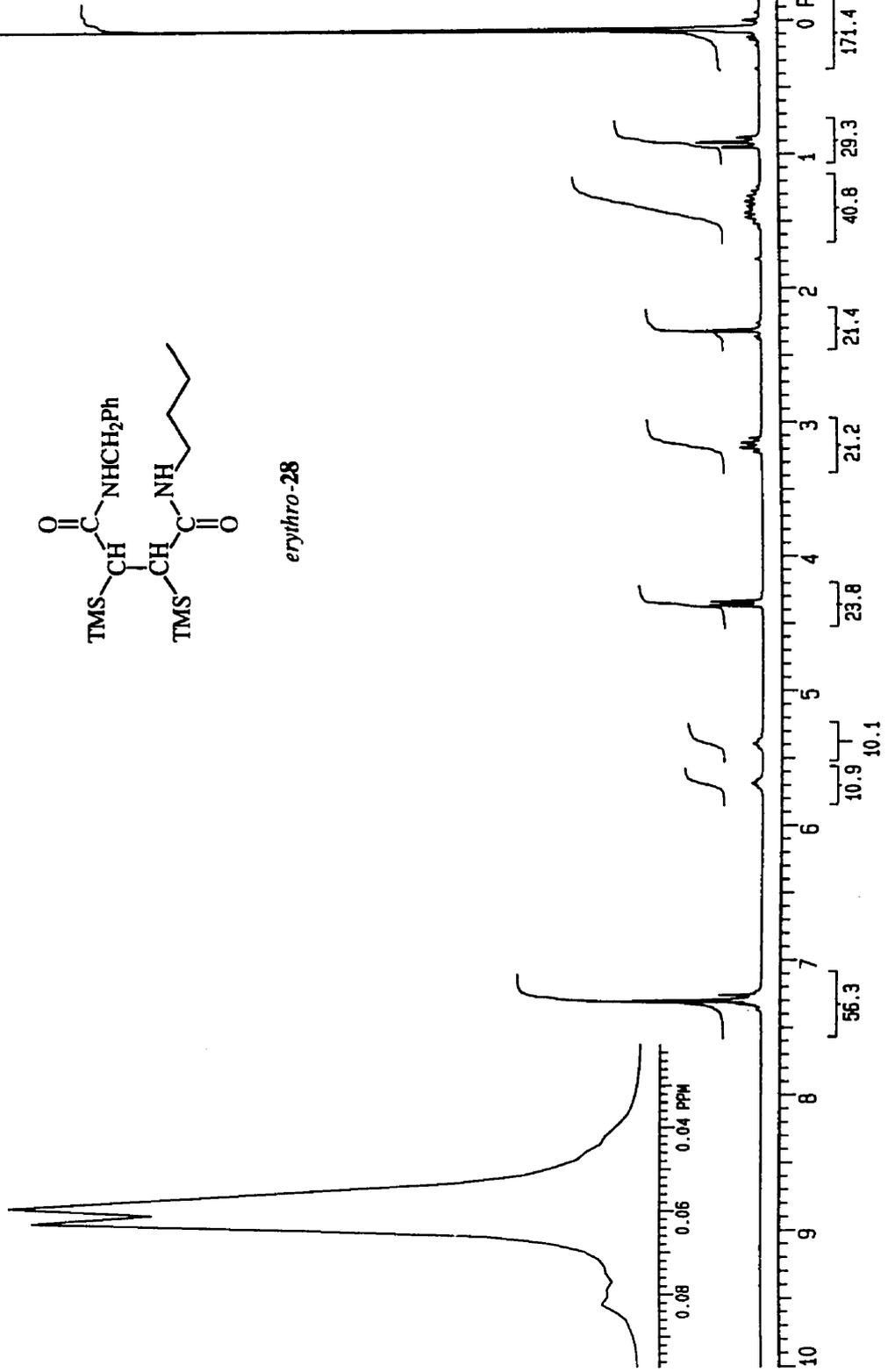


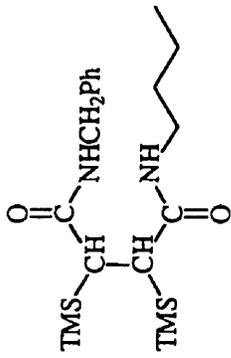
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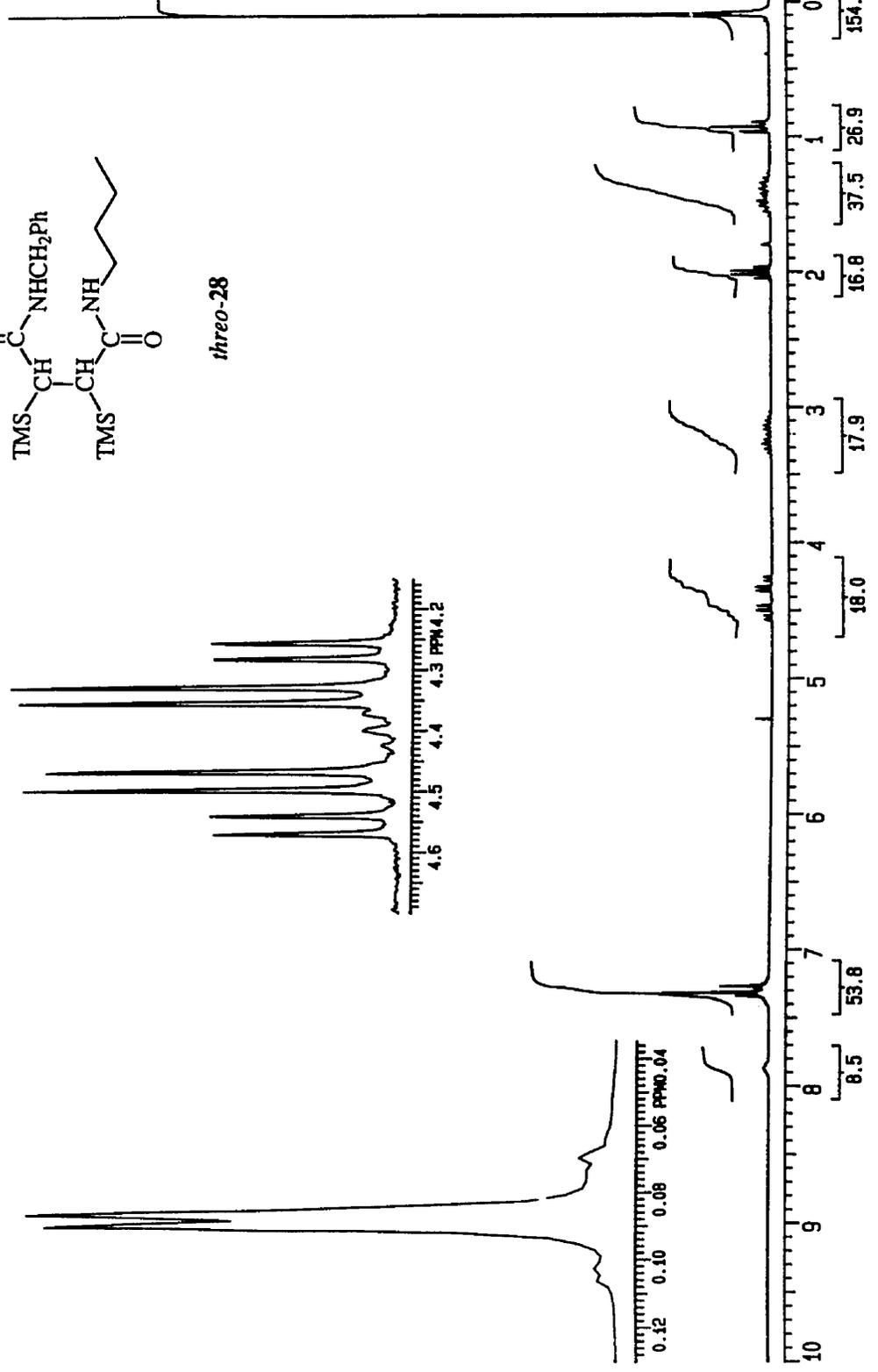


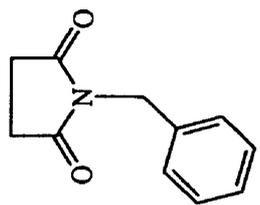
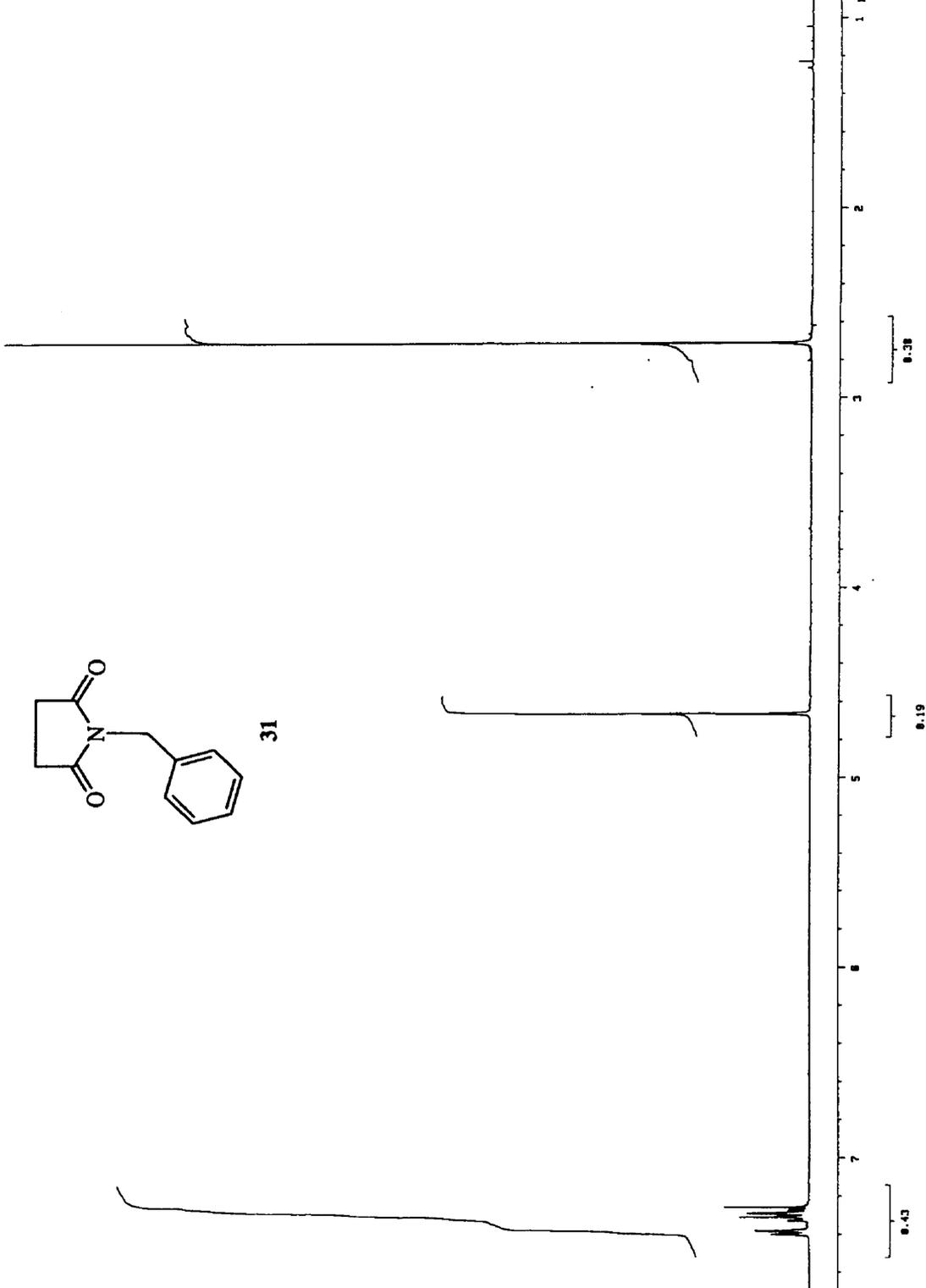
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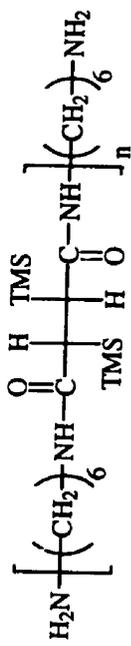


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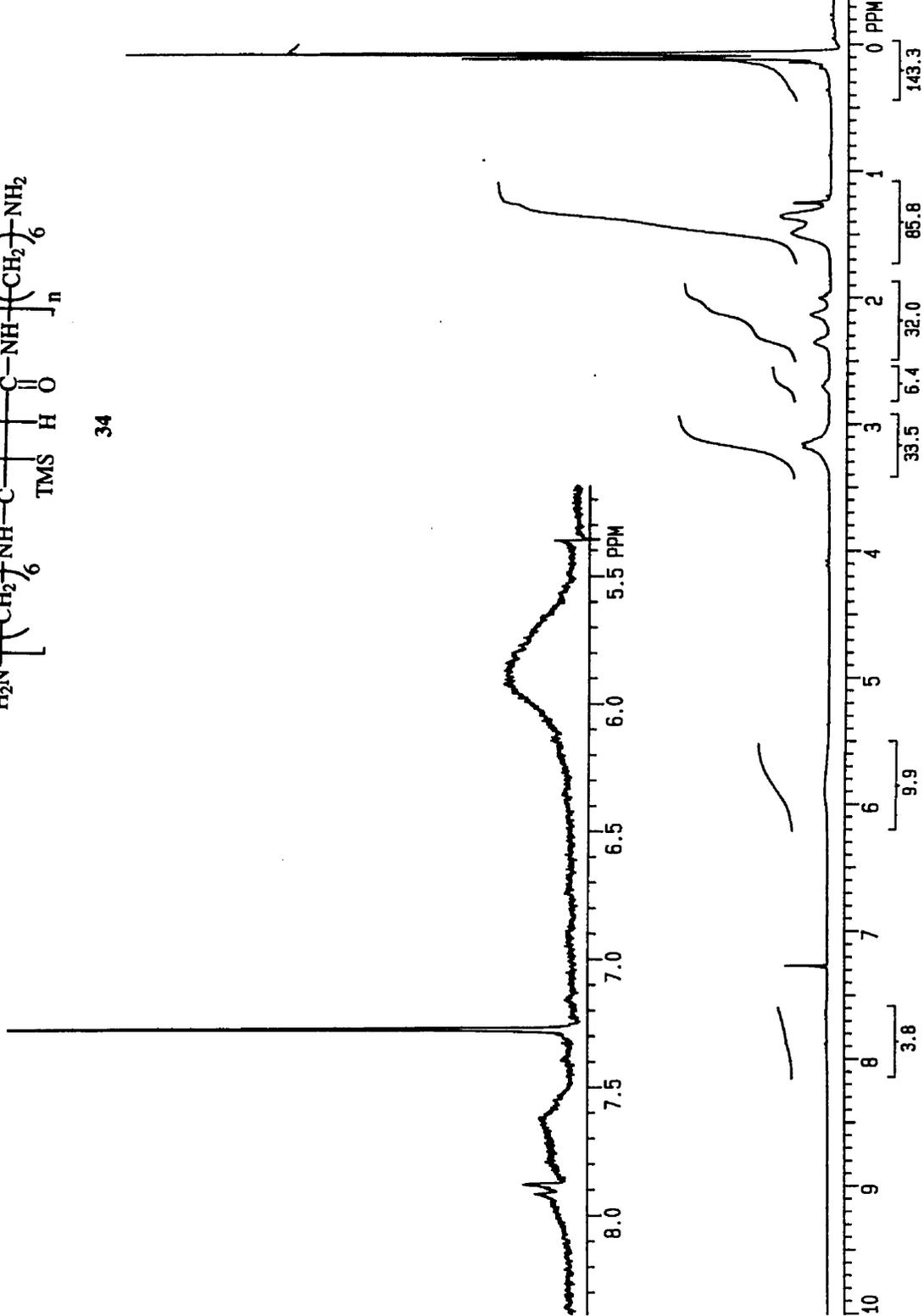


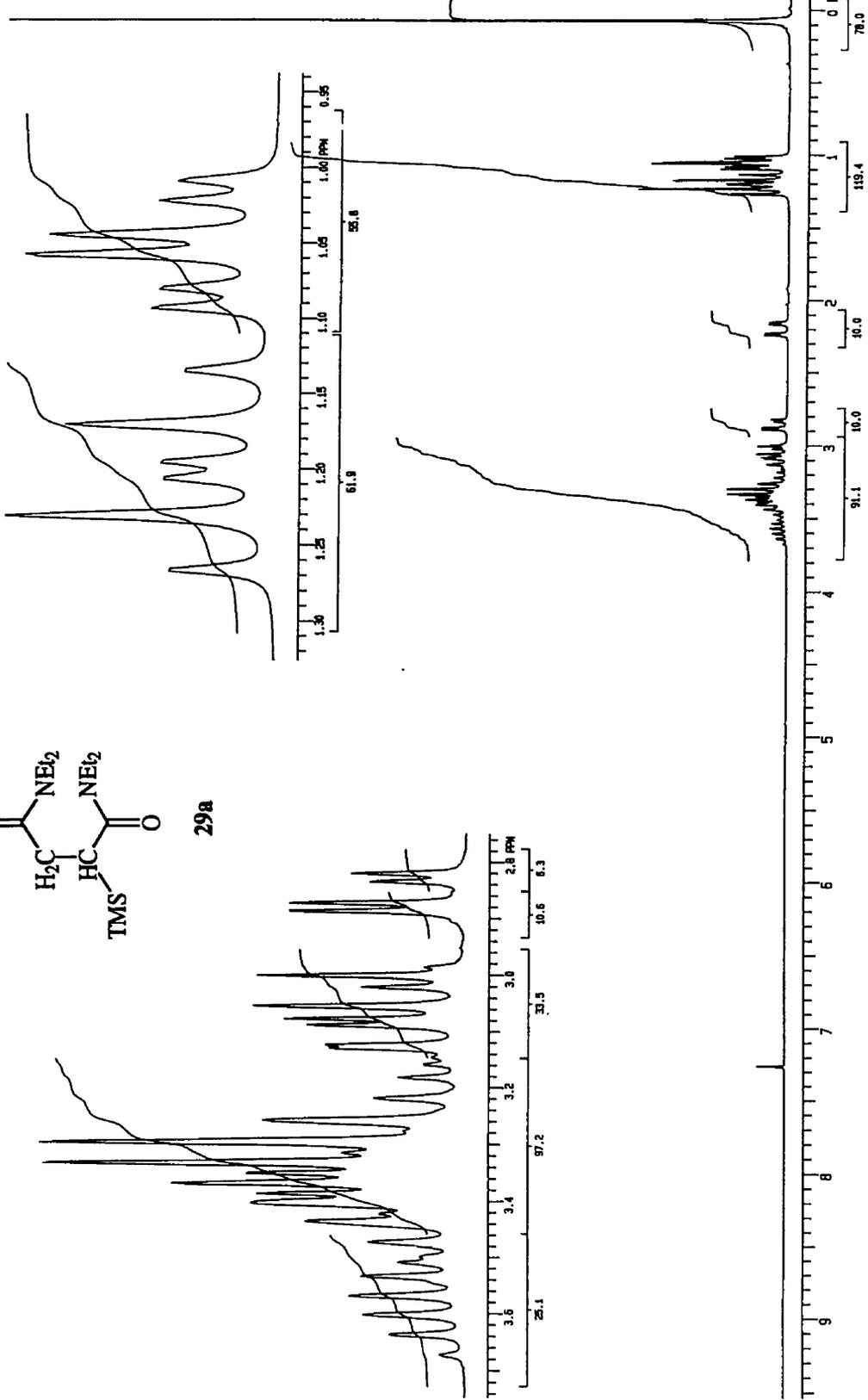
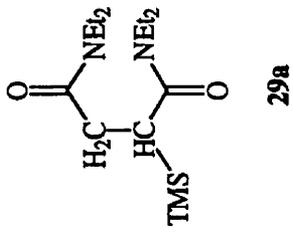


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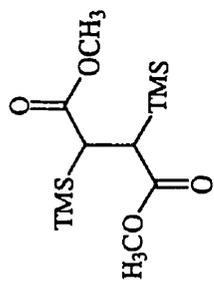
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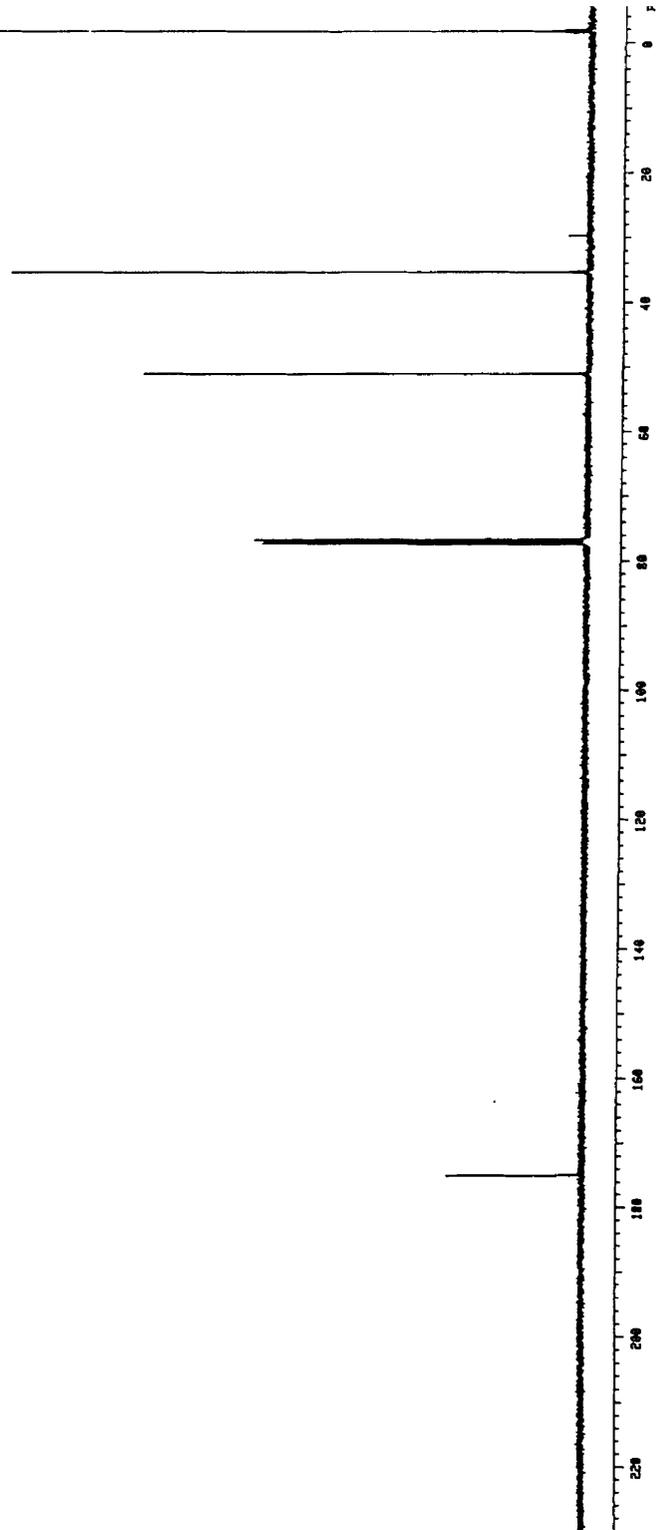


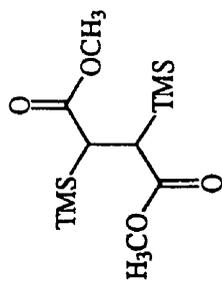
Appendix D

Selected ^{13}C NMR spectra of synthesized compounds

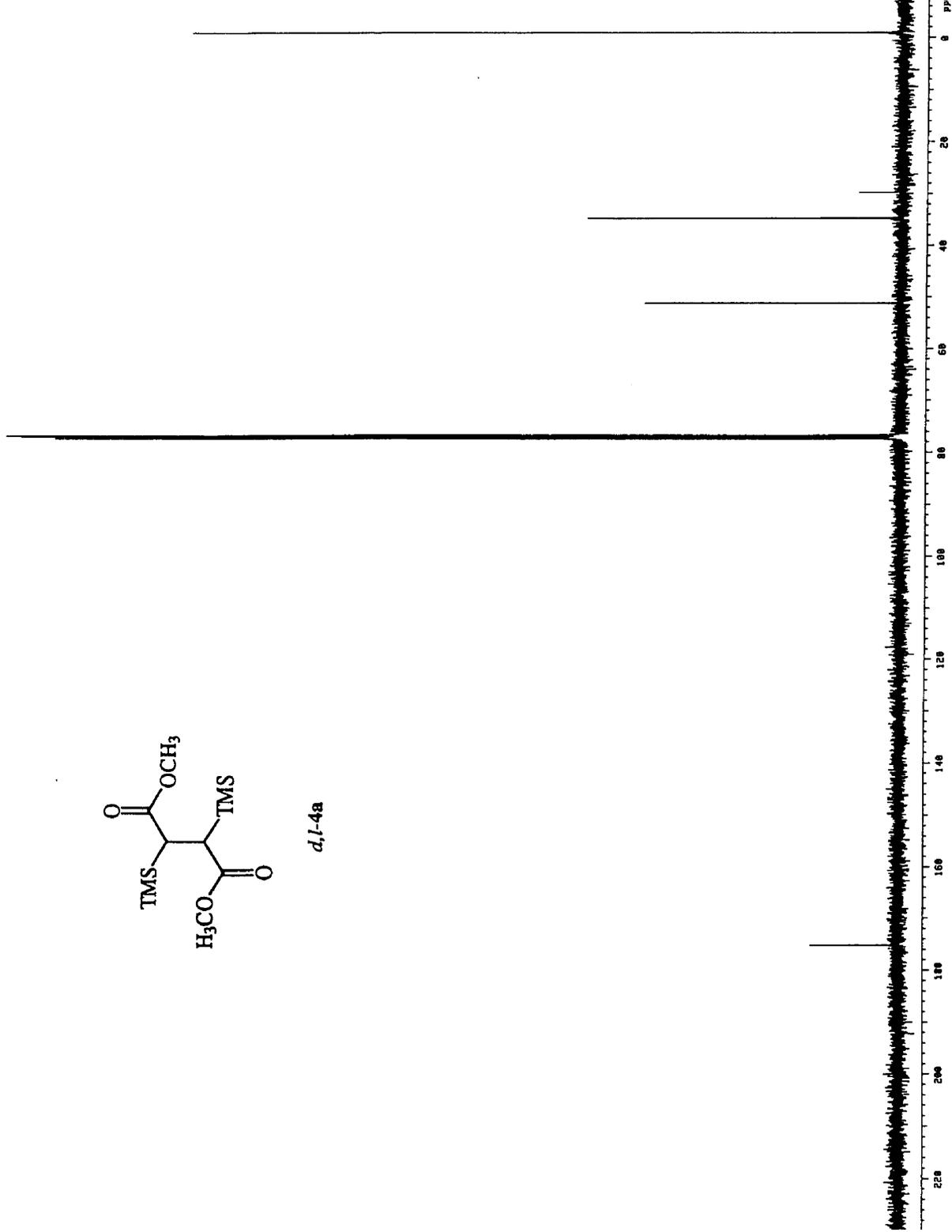


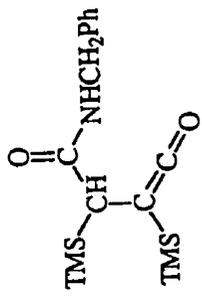
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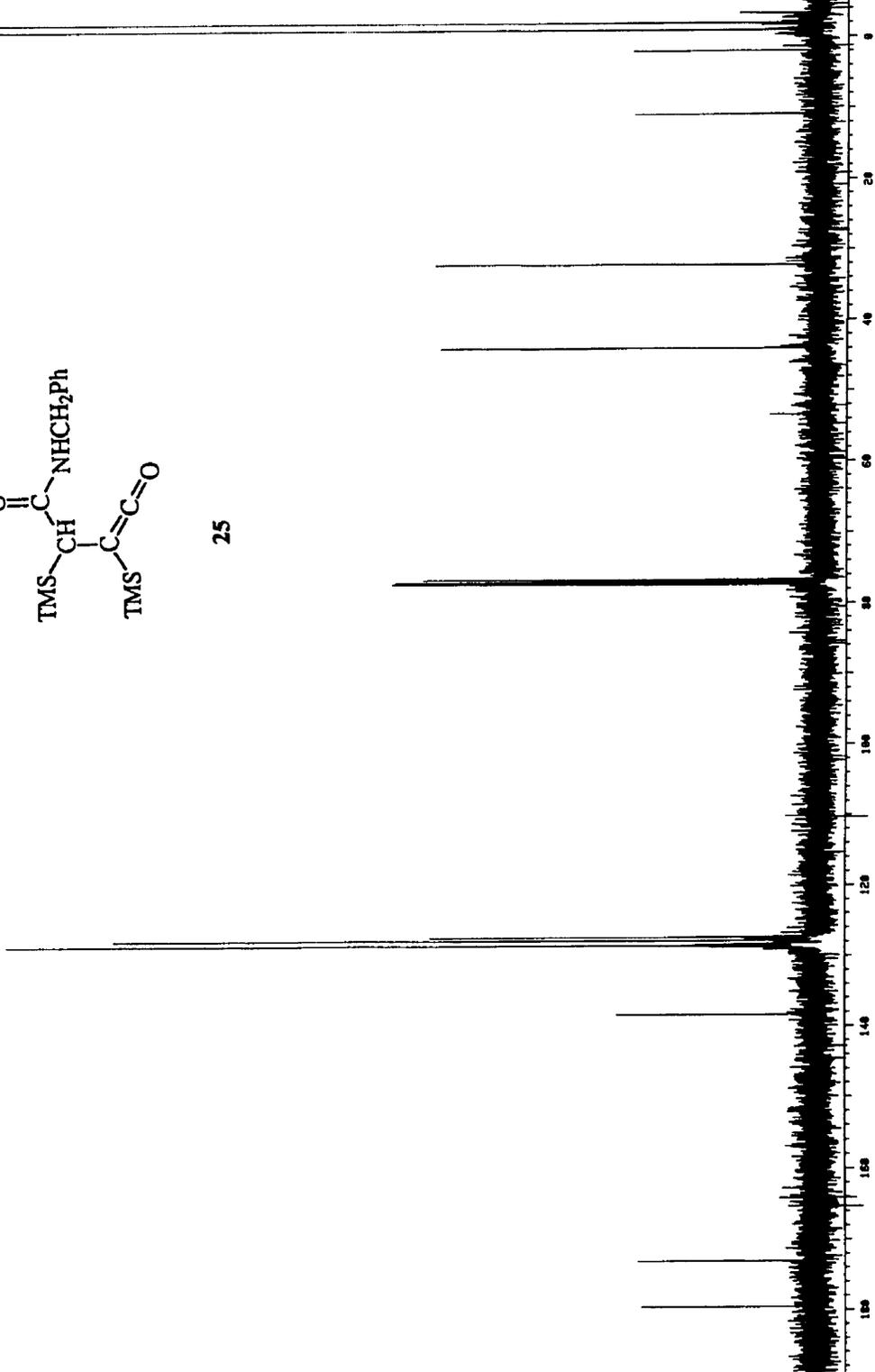


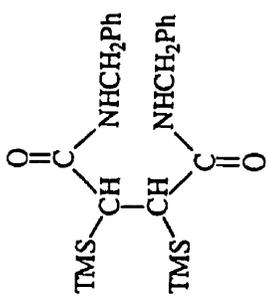
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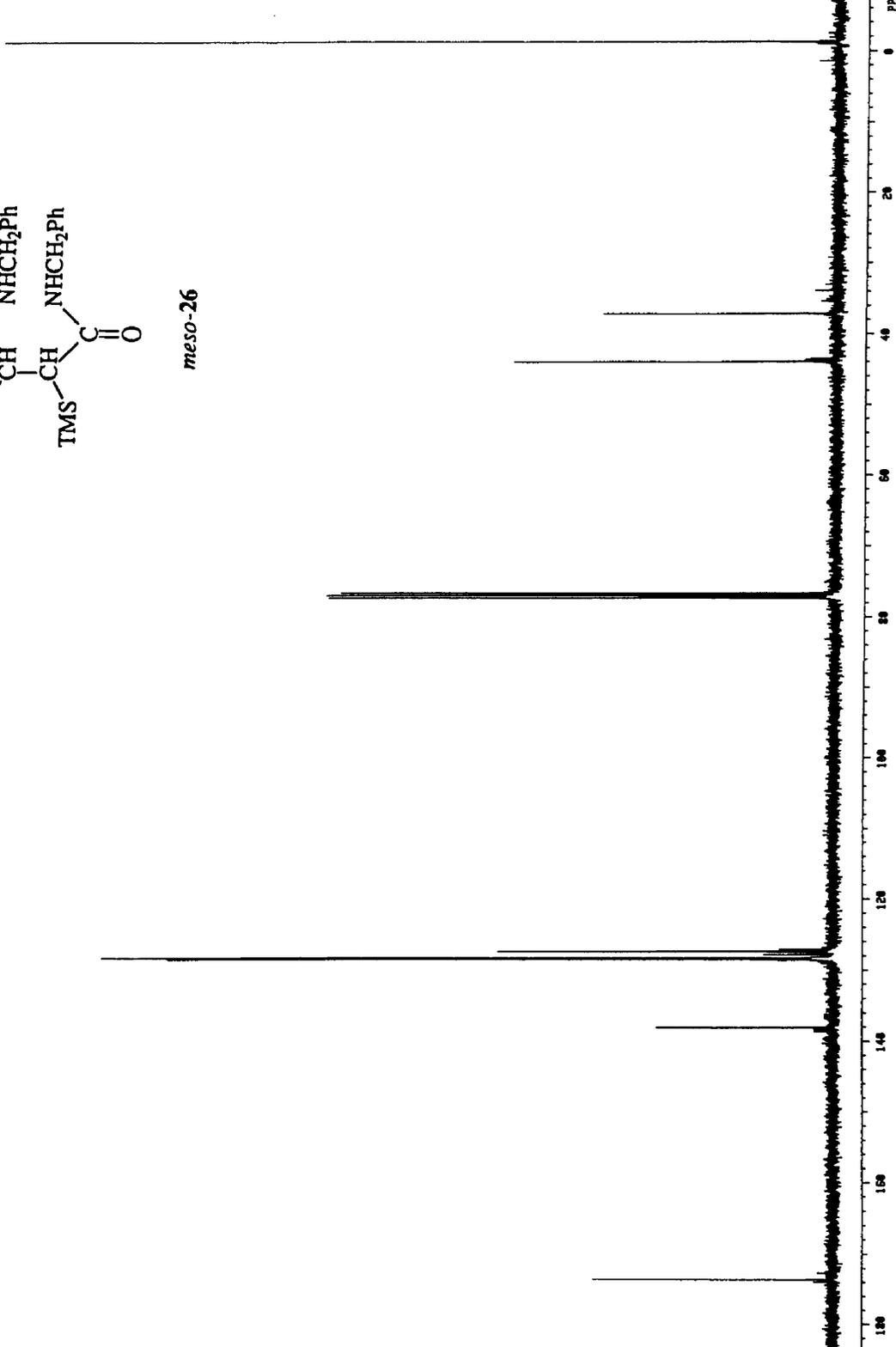


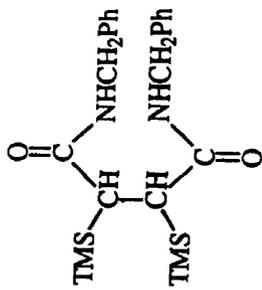
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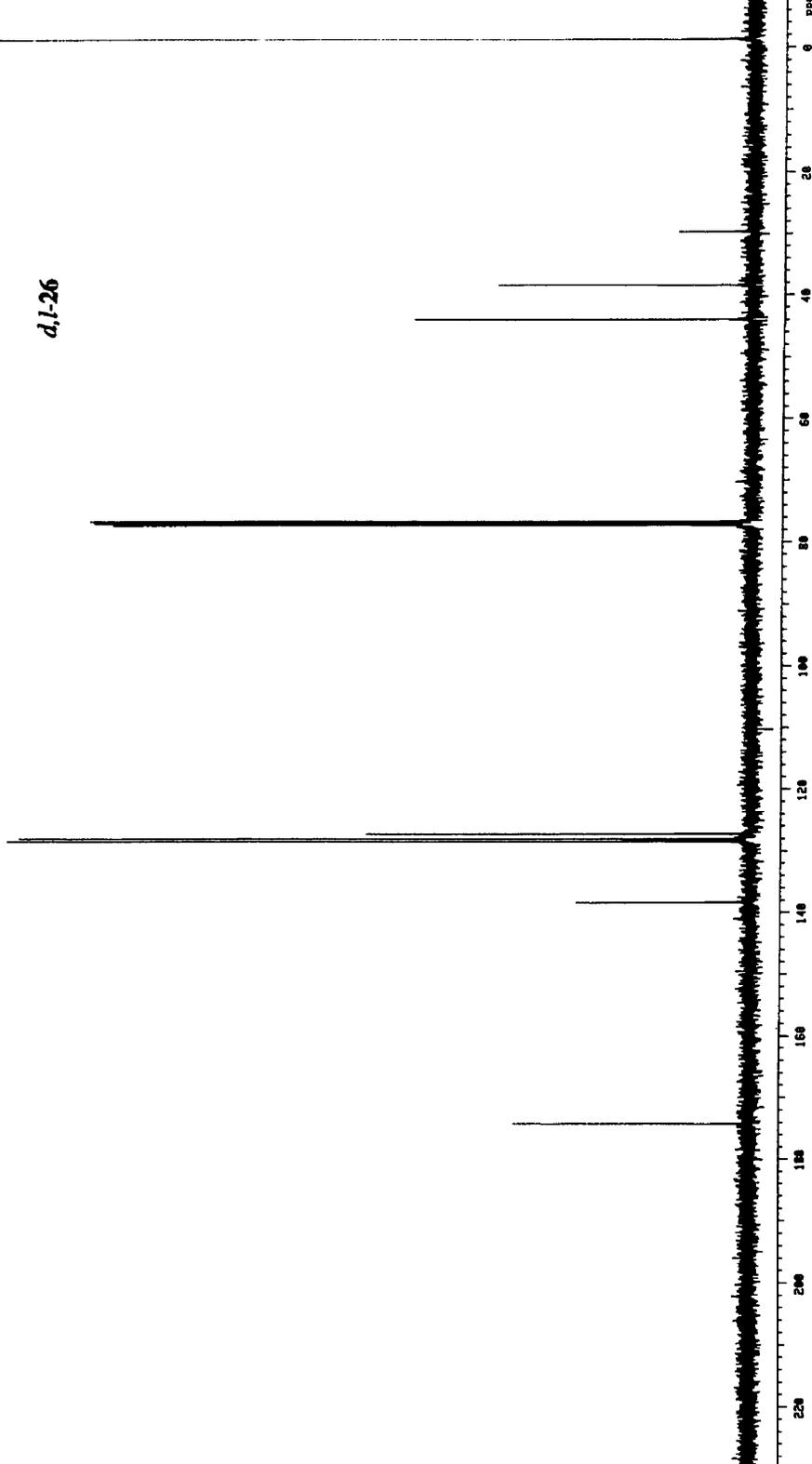


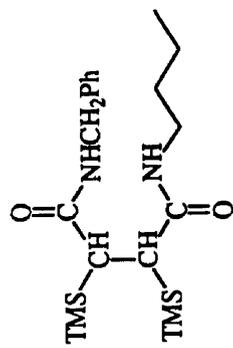
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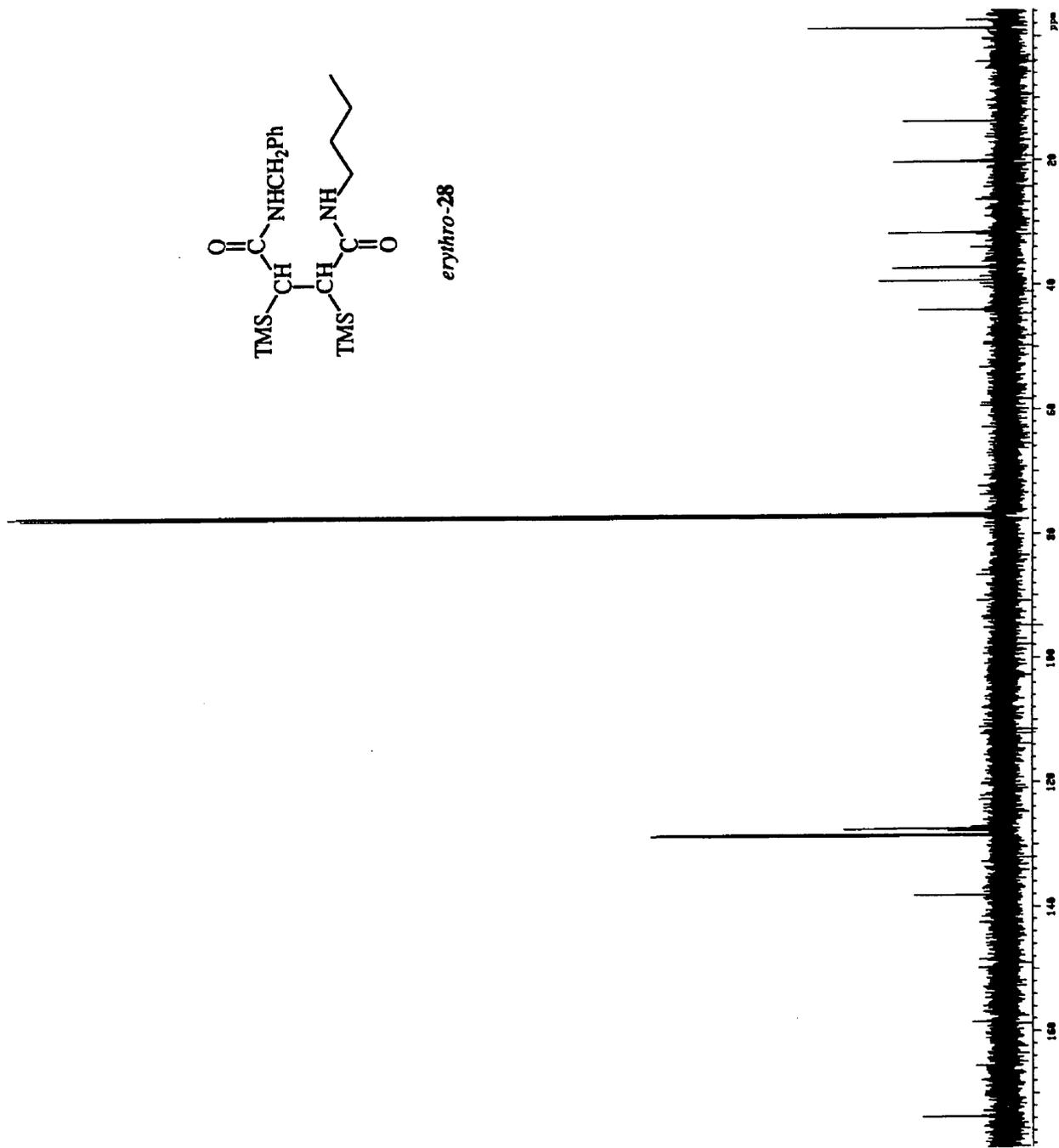


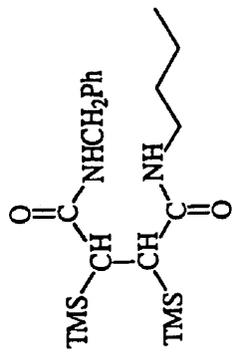
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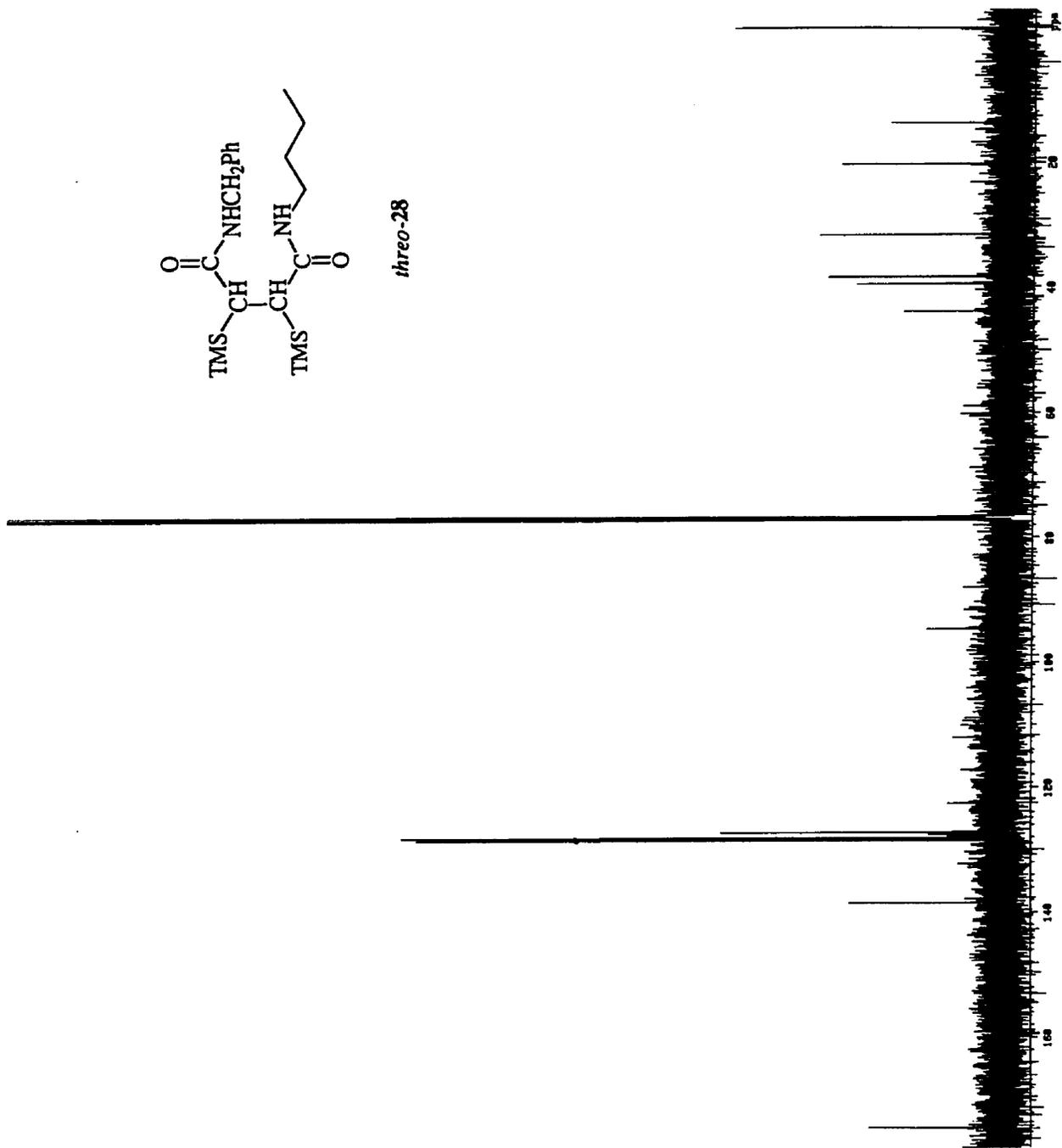


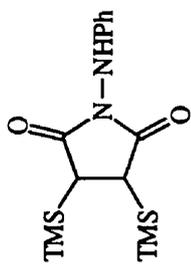
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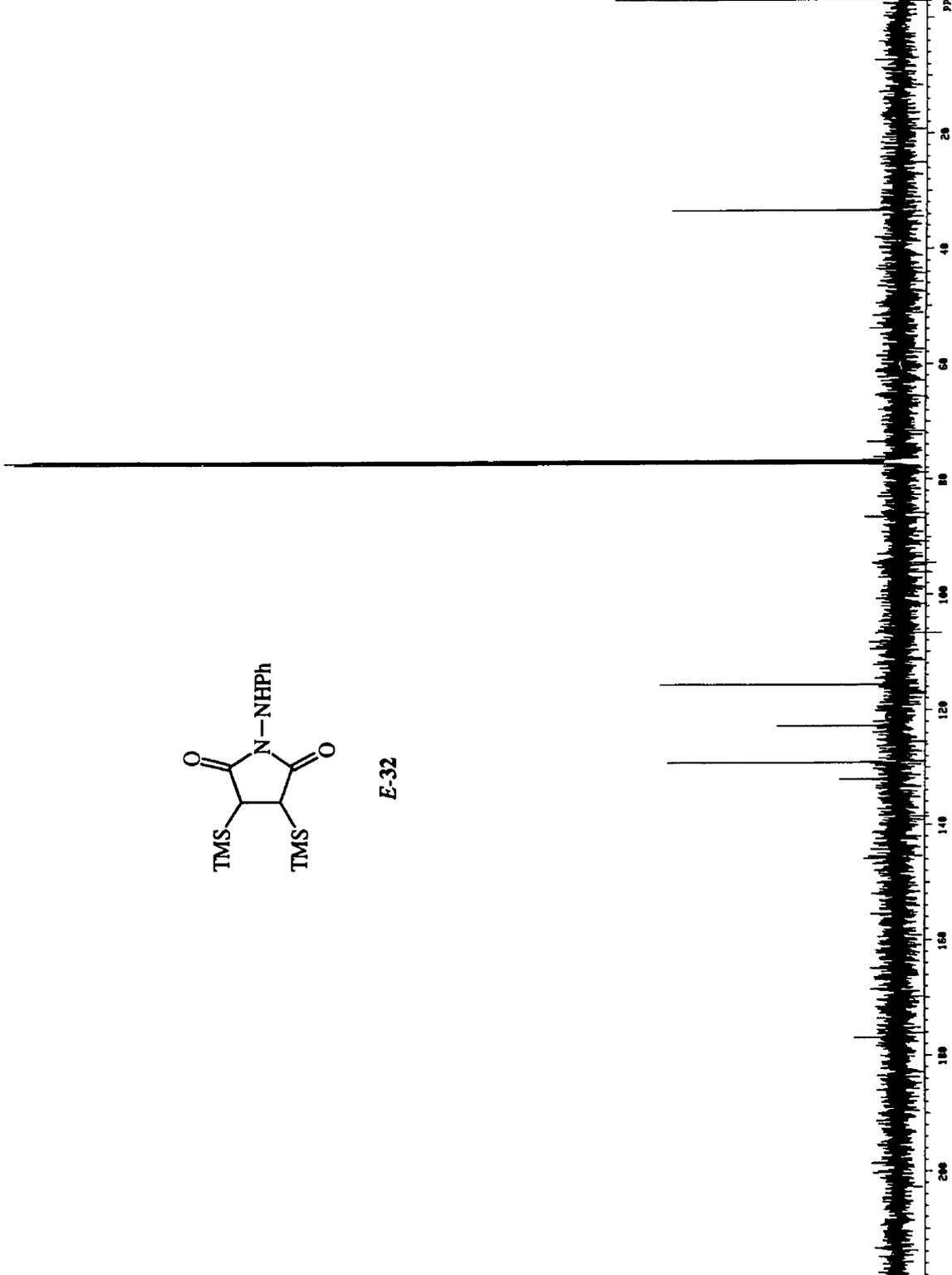


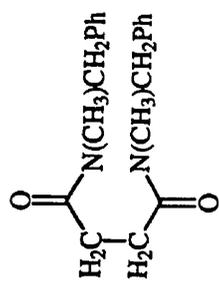
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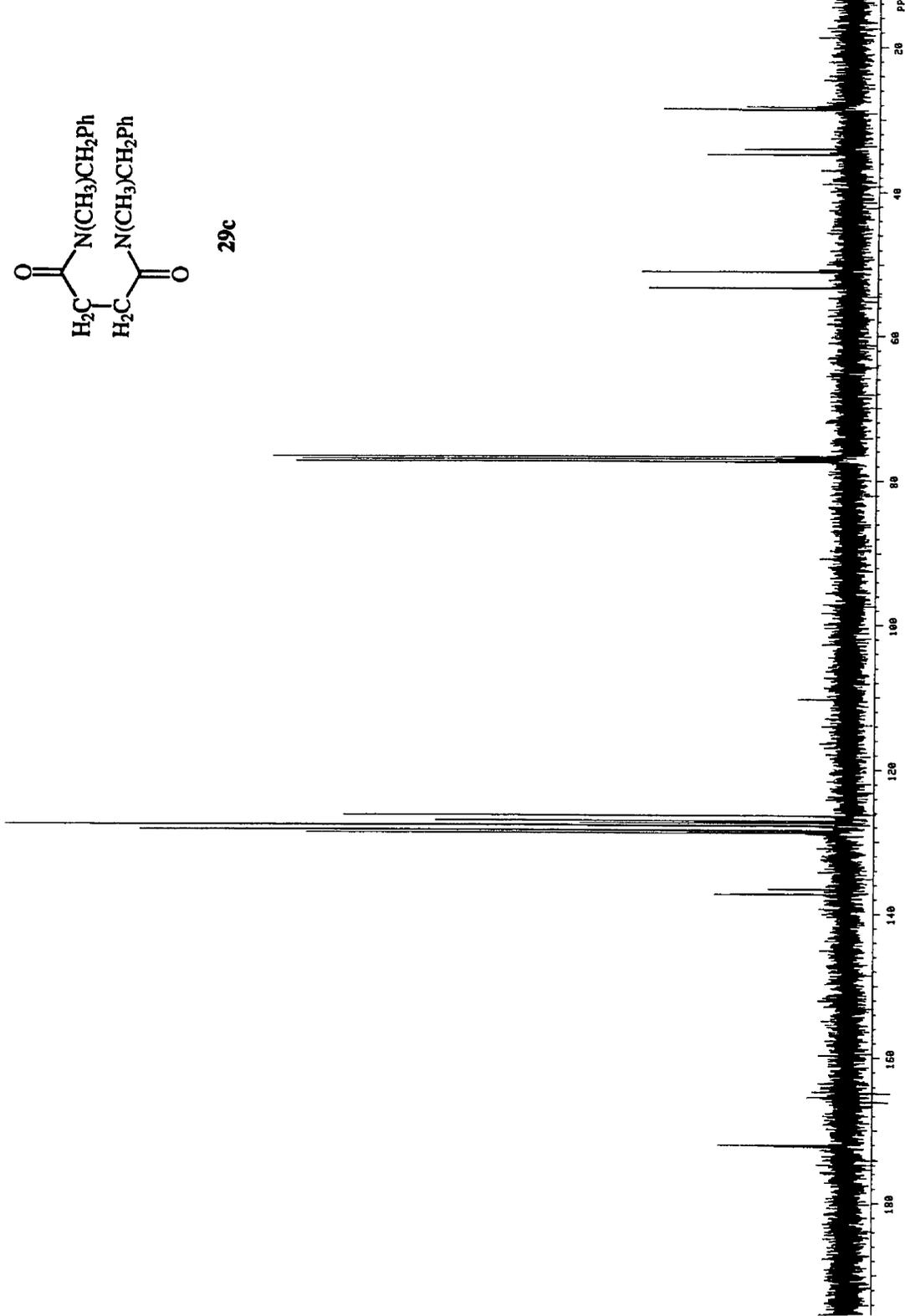


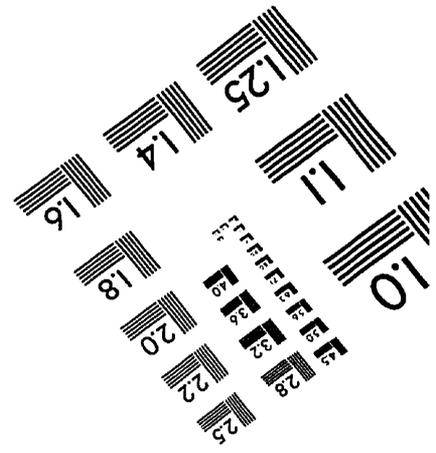
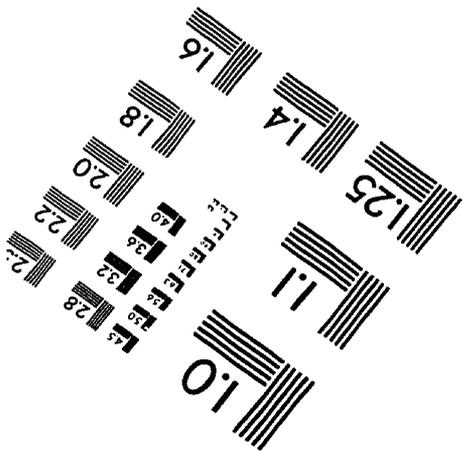
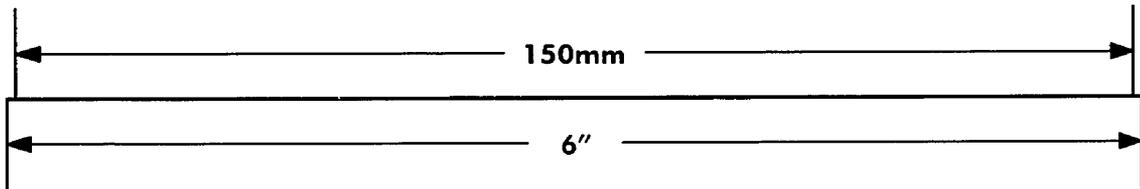
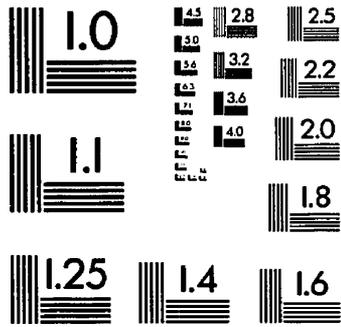
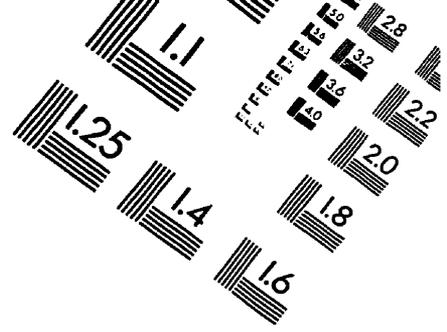
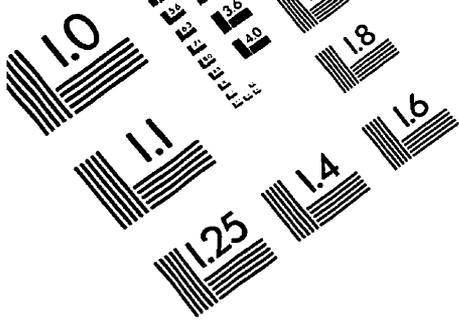
E-32





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