EXPLOITING THE GEMINAL ACYLATION REACTION TO PRODUCE A B-TURN PEPTIDOMIMETIC

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Abstract

The focus of this research was to develop a route to 5,6-fused 1-aza-2-oxobicycloalkane amino acids, beta-turn peptidomimetics, with carbon-based bridgehead substituents. The route that was developed proceeded as follows: Geminal acylation of the acetal derived from hex-5-en-2-one gave 2-(3-butenyl)-2-methyl-1,3-cyclopentanedione in 76% yield. Experiments with baker's yeast showed that desymmetricization of this 1,3-diketone could be carried out with very high enantioselectivity. Beckman rearrangement of (2*S*, 3*S*) 2-(3-butenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylcyclopentanone using *O*-mesitylenesulfonyl hydroxylamine provided the corresponding lactam, (3*S*, 4*S*)-1-Aza-6-(3-butenyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexanone. Cyclization of the lactam nitrogen onto the double bond was carried out with trimethylsilyl triflate and iodine in the presence of triethylamine which yielded the iodolactam (6*S*,5*S*,9*S*)-1-aza-5-[(*tert*-butyldimethylsilyl)oxy]-9-(iodomethyl)-6-methyl- bicyclo[4.3.0]nonan-2-one. This iodolactam was then converted into the propyl ester of (6*S*,5*S*,9*S*)-1-aza-5-[(*tert*-butyldimethylsilyl)oxy]-9-(hydroxymethyl)-6-methylbicyclo[4.3.0]nonan-2-one. The development of this route, including the elucidation of the structures of side-products, is discussed in detail.

Acknowledgments

I would like to express many thanks to my supervisor, Dr. D. Jean Burnell for his guidance, support and for giving me the opportunity to study under his supervision. I would also like to thank the Burnell group for their help throughout my research. My deepest appreciation is extended to following people: Mr. David O. Miller for NMR spectra and X-ray structure elucidation, Dr. Brian Gregory and Ms. Marion Baggs for mass spectral data, my supervisory committee, Dr. Paris Georghiou and Dr. John Bridson for evaluation of this document and my family and friends for their support, love and patience. Finally, I would like to thank Memorial University of Newfoundland for financial support.

List of Abbreviations

Ac	acyl
APT	attached proton test
BMS	$BH_3 \cdot SMe_2$
CBS	Corey, Bakshi, and Shibata
DMF	*N,N*-dimethylformamide
Et	ethyl
GC/MS	gas chromatograph-mass spectrometer
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectrometer
IR	infrared
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamine
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mL	milliliter
mp	melting point
MS	mass spectrum
MSH	*O*-mesitylenesulfonylhydroxylamine
NBS	*N*-bromosuccinimide

NMR	nuclear magnetic resonance
ORTEP	Oak Ridge thermal ellipsoids projection
OTf	triflate
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
p-TsOH	*para*-toluenesulfonic acid
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBS-Cl	chloro-*tert*-butyldimethylsilane
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMS-Cl	chlorotrimethylsilane
TMS-OTf	trimethylsilyl triflate
Tr	2,4,6-triisopropylbenzenesulfonyl
vis	visible

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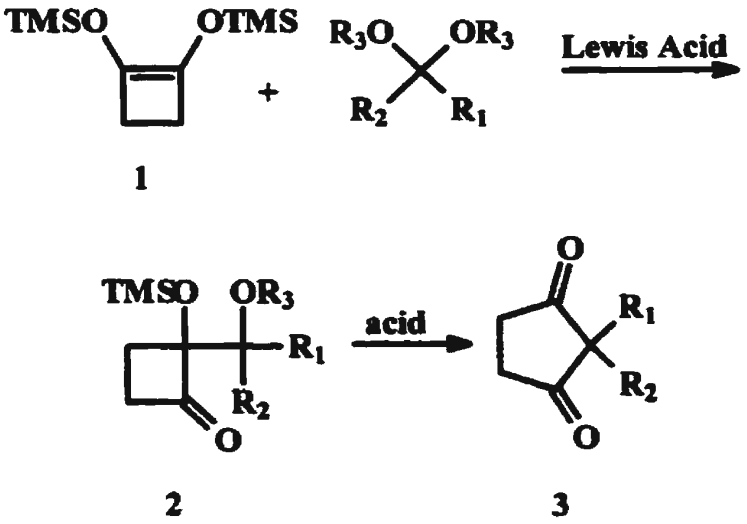
Introduction

Geminal acylation involves the replacement of the carbonyl moiety of a ketone or aldehyde directly, or via their acetals by two acyl groups. Kuwajima and co-workers[1] reported that an acetal or an aldehyde with 1,2-bis[(trimethylsilyl)oxy]cyclobutene 1 yielded a cyclobutanone derivative 2 under Lewis acid catalysis (Scheme 1). The transformation of the cyclobutanone intermediate 2 to the desired diketone 3 could be achieved by excess trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (*p*-TsOH) in hot benzene, $BF_3 \cdot Et_2O$, or trimethylsilyl triflate (TMS-OTf).

Scheme 1

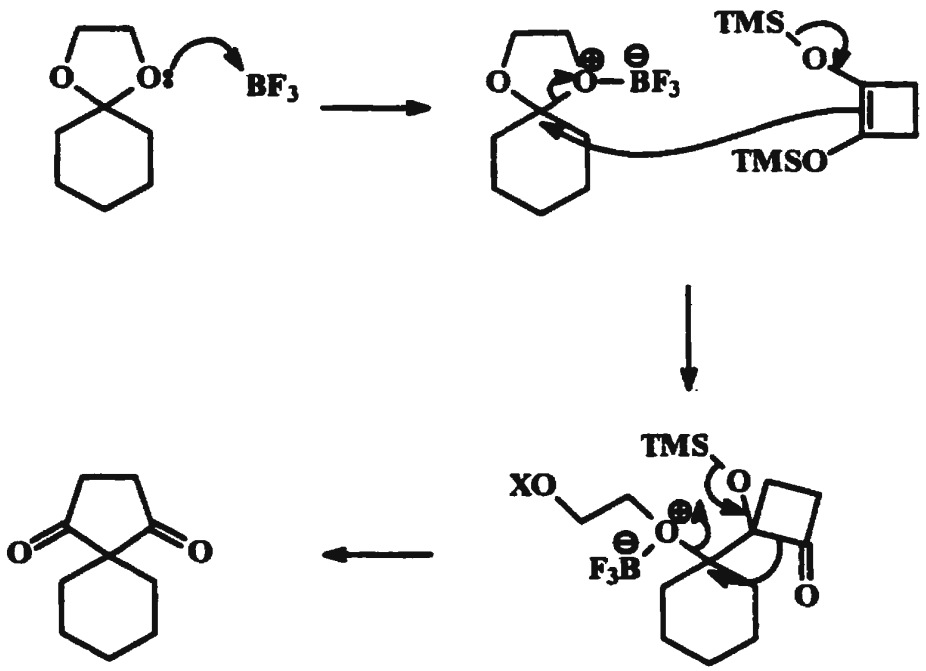


Kuwajima and co-workers[1] first introduced this methodology as a two-step procedure that involved isolation of cyclobutanone intermediate 2 (Scheme 1).

$TiCl_4$ was found to be the optimal Lewis acid to use for aldehydes and aliphatic acetals, however $BF_3 \cdot Et_2O$ was the reagent of choice for the more reactive acetals.

The mechanism for the formation of the geminal acylation products is shown in Scheme 2. The initial step in the geminal acylation reaction is a Mukaiyama-like aldol reaction that gives a cyclobutanone compound. The second step is an acid-initiated acyl migration similar to a pinacol rearrangement to provide a 1,3-diketone.

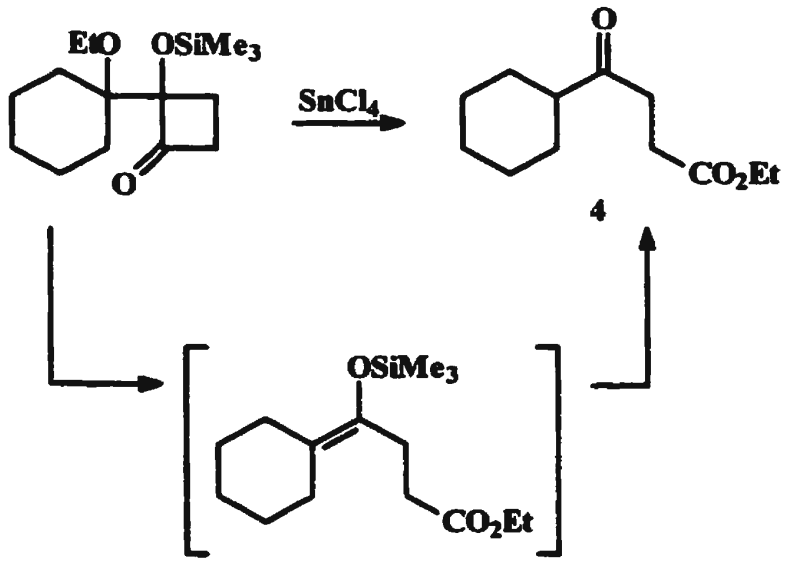
Scheme 2



Kuwajima also reported several instances in which the cyclobutanone ring underwent acid-catalyzed cleavage to furnish a γ-keto-ester such as 4 (Scheme 3). This process, called reductive succinoylation, was observed with a number of

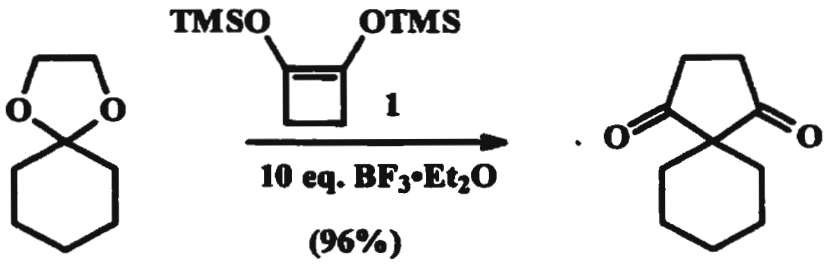
Lewis acids but could be accomplished in a single step using $SnCl_4$.[1] It was found that the facility of ring cleavage was related to the structure of the substrate.

Scheme 3



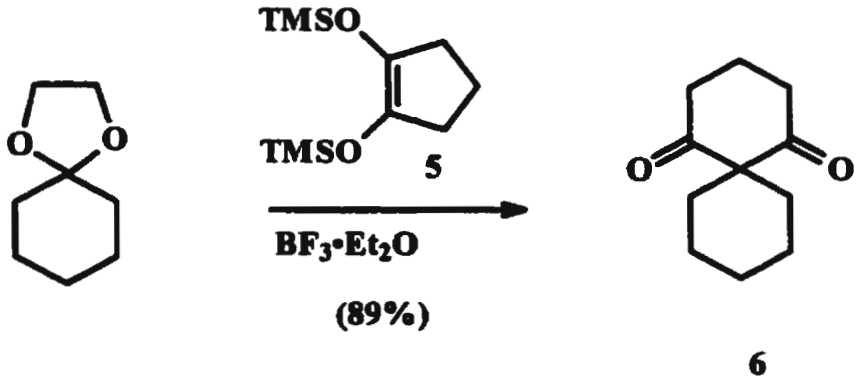
Several modifications to the original Kuwajima procedure have since been reported. Wu and Burnell[2] found that this reaction could be effected in a single step, usually in higher yield, by using two to three molar equivalents of **1** and a large excess of $BF_3 \cdot Et_2O$ (Scheme 4). The cyclobutanone intermediate was not isolated since in the presence of excess Lewis acid, the acyl migration readily occurs.

Scheme 4



In addition, Wu and Burnell[3] illustrated that the geminal acylation was applicable using 1,2-bis[(trimethylsily)oxy]cyclopentene **5** to produce the six membered 1,3-diketone **6** as shown in Scheme 5.

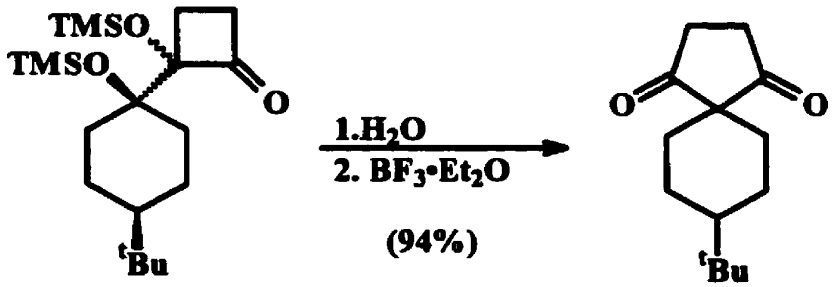
Scheme 5



Kuwajima stated that ketones are unreactive under the conditions of the initial aldol step[1], and that the one-pot procedure was not successful using ketones.[4] However, Jenkins and Burnell[4] reported an efficient synthesis of 2,2-disubstituted 1,3-cyclopentanediones by using 1.5 equivalents of **1** with an equivalent amount of $BF_3 \cdot Et_2O$. A small volume of water, approximately

equivalent to the volume of $BF_3 \cdot Et_2O$, was required, followed by a large excess of $BF_3 \cdot Et_2O$. It was believed that the addition of water and acid must have helped the rearrangement by hydrolyzing of one or both of the (trimethylsilyl)oxy groups of 7 (Scheme 6). An obvious advantage of this modification was the reduction in the number of synthetic steps required to generate the desired 1,3-diketone moiety.

Scheme 6



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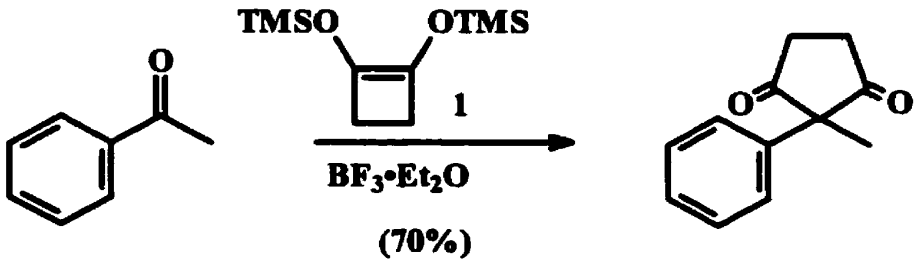
Crane and Burnell[5] improved the geminal acylation reaction for aromatic ketones such as **8** (Scheme 7) and α,β-unsaturated ketones. The geminal acylation of saturated ketones required the addition of water for the formation of 1,3-cyclopentanediones in good yield. However, aromatic and α,β-unsaturated ketones underwent this step readily under anhydrous conditions. This was attributed to allylic/benzylic stabilization of a positive charge in the transition state of the rearrangement.

Scheme 7



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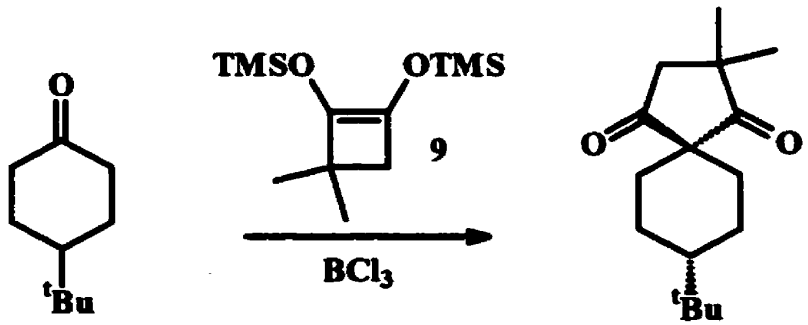
Geminal acylation reactions have also been reported for methyl-substituted analogues of 1,2-bis[(trimethylsilyl)oxy]cyclobutene (**9**).[6] BCl_3 is the preferred Lewis acid instead of $BF_3 \cdot Et_2O$ when using compound **9** as shown in Scheme 8. $BF_3 \cdot Et_2O$ facilitates an equilibration processes involving the aldol product - the cyclobutanone intermediate - which leads to the production of furanone by-products. The mechanism of action for BCl_3 is different, in that it inhibits the equilibration after initiating the initial aldol reaction, thereby resulting in improved yields of the desired diketone substrate.

Scheme 8



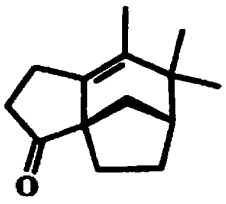
The geminal acylation reaction is a powerful carbon-carbon forming reaction. The creation of a spirocyclic center can be a challenging process for the synthetic organic chemist since such a center is necessarily sterically congested. Consequently, this reaction has gained synthetic utility for the synthesis of natural products (Figure 1). Wu and Burnell[2] synthesized isokhusimone, **10**, which is a derivative of the zizaane sesquiterpenes and may serve as common intermediate for all such sesquiterpenes.

Ogasawera and co-workers[7] synthesized (-)-chokel G **11**, a fungitoxic metabolite from the stromata of *Epichloetyphia*. Cephalotaxine, **12** has also been synthesized by a strategy employing geminal acylation methodology.[8] This compound is of interest since several members of this family exhibit anti-cancer properties.

Wu and Burnell[9] once again utilized geminal acylation methodology to yield (±)-*epi*-pentalenene, **13**, and (±)-pentalenene, **14**. Pentalenene is the biosynthetic precursor to the antibiotic sesquiterpenoid pentalenolactone.

The geminal acylation reaction was also a key step in the synthesis of β-bulnesene, **15**[10] and for the introduction of the unusual spirodiketone functionality present in fredericamycin A, **16**.[11] Compound **16** is of considerable interest because of its antitumor properties.

Figure 1: Natural products synthesized utilizing geminal acylation methodology



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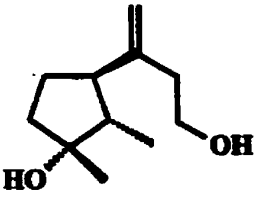

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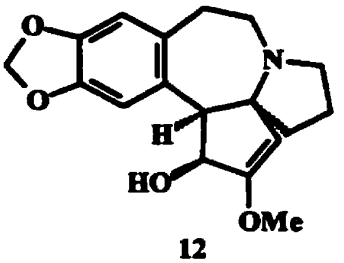

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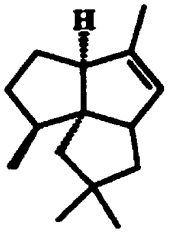

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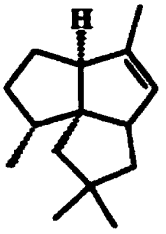

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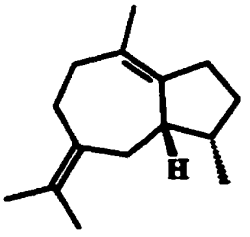

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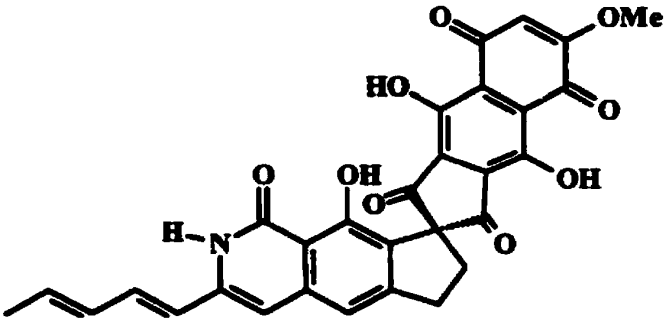

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Another potential use of the geminal acylation reaction is for the production of mimics for the turn regions present in naturally occurring peptides. During the past two decades there has been considerable interest in the rational design and production of highly active analogues of naturally occurring biologically active peptides.[12, 13] It is believed that such compounds could result in pharmaceuticals with enhanced selectivity and, as a result, reduced toxicity compared to the medications currently used.

Naturally occurring small linear peptides show biological activity as hormones, neurotransmitters, neuromodulators and immunologically-active peptides. As a result, these peptides are of great interest to the medicinal chemist. Small peptides are commonly used as initial lead compounds. However several limitations exist for these native peptides and this restricts their application as potential pharmaceuticals. Such limitations include[14]:

1. Rapid metabolism by proteolysis in the gastrointestinal tract, in the blood and in the numerous tissue beds.
2. Poor transport from the gastrointestinal tract to the blood and from the blood to the brain.
3. Rapid excretion by the liver and kidneys.
4. Lack of specificity of activity due to the conformational flexibility inherent to peptides.
5. Uncertainty about the relation between three-dimensional structure and activity.

Thus, the motivation for the development of peptide mimics

(peptidomimetics) is to overcome the aforementioned limitations. A generally applicable and successful method for the development of peptidomimetics has been the production of conformationally restricted analogues. Conformational restrictions enable such peptides to have improved metabolic stability since they are more resistant toward proteases.

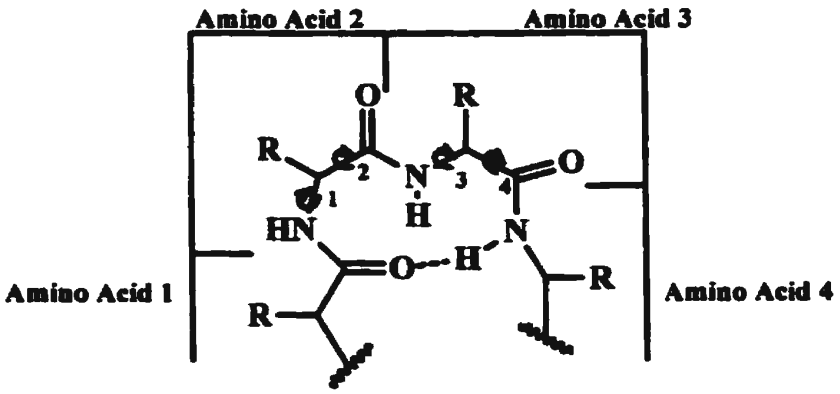
Two important factors should be considered[15] in the design of peptidomimetics as potential bioactive substances. First, a complimentary fit must take place between the desired peptidomimetic and the receptor. Second, the placement of certain structural elements such as functional groups, polar regions and hydrophobic regions must be in positions that favor interactions like hydrogen bonding, electrostatic interactions and hydrophobic interactions.

α-Helices, β-sheets and reverse turns are secondary structures of peptides that arise as a result of intramolecular hydrogen bonding. All have been targeted in the design of mimics, however most of the focus has centered on the reverse turns. Many of the turns in proteins are located on the surface of the protein. Thus, the surface locations and the predominance of residues containing potentially important pharmacophoric information has led to the hypothesis that turns play critical roles in numerous recognition events.[16,17]

Two types of turns exist, the α-turn and the β-turn. The β-turn consists of a four-amino-acid residue sequence in which the peptide chain reverses direction, by approximately 180°.[18] In the β-turn structure, the carbonyl of the first amino acid residue is aligned to form an intra-chain hydrogen bond with the amide

hydrogen of the fourth amino acid residue, and this forms a pseudo-ten membered ring[17] (Figure 2). β-Turns that do not exhibit hydrogen bonding are called open turns. However, about 60% of β-turns commonly found show an intramolecular hydrogen bond.[18] The α-turn structure is a three-amino-acid residue reverse turn. α-Turns are not as widespread as β-turns. In α-turns, the carbonyl of the first amino acid residue is aligned to form an intra-chain hydrogen bond with the amide hydrogen of the third amino acid residue, which then results in a pseudo-seven membered ring. The pseudo-cyclic systems can have different puckered conformations depending upon the orientation of the amide bonds and side chains on the residues making up the turn.[17] These side chains can then help with receptor recognition if the exposed functional groups of the amino acid residues allow a favorable fit.

Figure 2[17]. Classical view of a β-turn



Turns can be described by the distance from the C_α of the first amino acid residue

to the C_α of the fourth amino acid residue, and when this distance is less than 7Å and the tetrapeptide sequence is not in an α helical region it is considered to be a β-turn.[16] The most widely accepted system for the classification of β-turns is based upon the peptide backbone torsion angles of the second and third amino acids.[18] The predicted ideal torsion angles are given in Table 1, although they are rarely observed in proteins.

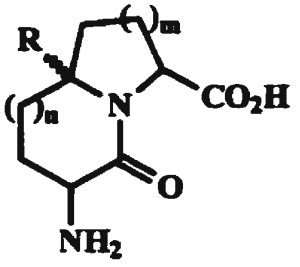
Table 1. Torsion angles (degrees) for classical β-turns

	Turn type					
Torsion Angle (Fig. 2)	I	I'	II	II'	III	III'
1	-60	60	-60	60	-60	60
2	-30	30	120	120	-30	30
3	-90	90	80	80	-60	60
4	0	0	0	0	-30	30

To prepare conformationally restricted analogues, reverse turn mimics are generally cyclic or bicyclic dipeptides. Many of these molecules feature the 1-azabicyclo[*X.Y.*0]alkane skeleton[19] (Figure 3). This basic ring system can also encompass heteroatom analogues in which a carbon is replaced by sulfur, oxygen, or nitrogen, although these sometimes have the disadvantage of reduced stability

under acidic conditions. In addition, any one of the methylene carbons in this 5,6-fused bicyclic system can have various substituents. All of the compounds that have been reported in the literature have R = H (Figure 3), so the production of analogues with R ≠ H is a fertile area for investigation.

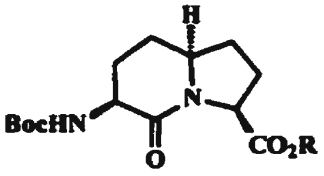
Figure 3. Azabicyclo[*X.Y.*0]alkane amino acid skeleton



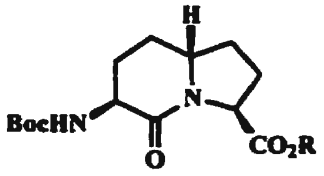
Compounds with this azabicyclo[*X.Y.*0]alkane amino acid skeleton have proved useful as β-turn mimics. Many others are still known only as potential β-turn mimics, based on conformational analysis.

Lubell and coworkers[20] synthesized **17a** and **18a** and found by conformational analysis that both have torsion angles similar to the second and third amino acid residues of an ideal type II' β-turn conformation. These have yet to be incorporated into peptides to explore their actual ability to induce a reverse turn. Compounds **19** and **20** also possess the azabicyclo[*X.Y.*0]alkane amino acid skeleton except that one of the methylene carbons is replaced by an oxygen.[21] No comment was made on their potential use or the ability of these to induce a reverse turn.

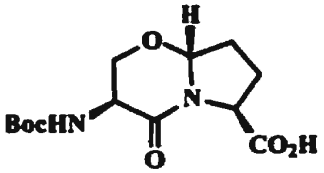
Scolastico and coworkers[22] synthesized **17b** and **18b** and found that their ability to act as reverse turn inducers was dependant on the stereochemisty at the bridgehead carbon. The isomers **17b** and **18b** were suggested to be potential reverse turn inducers based on conformational analysis, but their incorporation into real peptide chains was not performed. Colombo and co-workers[23] reported a stereoselective synthesis of compound **21**, and it was determined from molecular mechanics calculations that it also has the potential to invoke a reverse turn.



17a R = H
17b R = Me



18a R = H
18b R = Me



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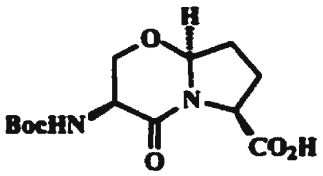

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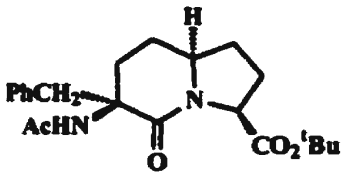

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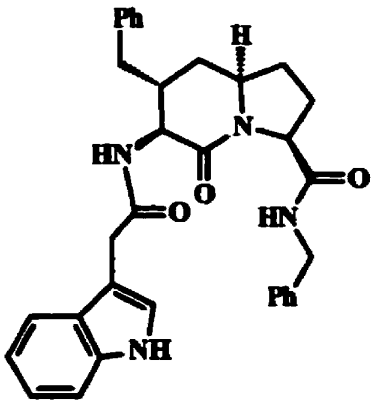
Compounds **22** and **23** were designed and synthesized by Hanessian and coworkers[24] as potential antagonists for the NK-2 receptor of the tachykinins. The physiological significance of tachykinins is still poorly understood, because of the absence of selective antagonists. The receptors for substance P and for neurokinins A and B are designated NK-1, NK-2, and NK-3, respectively. The

effects of substance P have been examined the most and it has been found that it triggers contraction of the smooth muscles of the respiratory, gastrointestinal, and urogenital tracts. In addition, substance P is a potent stimulator for the secretion of saliva, pancreatic juice, and bile. Neurokinin A has effects similar to those of substance P, but neurokinin B operates as a pain reliever by the release of ligands of the opiate receptor.[13]

Antagonists for the NK-1 and NK-3 receptors are known, but the NK-2 receptor has been somewhat more elusive. It was determined that **22** has no affinity for the NK-1 receptor, but it does have a low affinity for the NK-2 receptor and this led to the modification seen in **23**.[24a] Compound **23** revealed selective antagonist activity for the NK-2 receptor.[24b] Further modifications should result in a more useful analogue.



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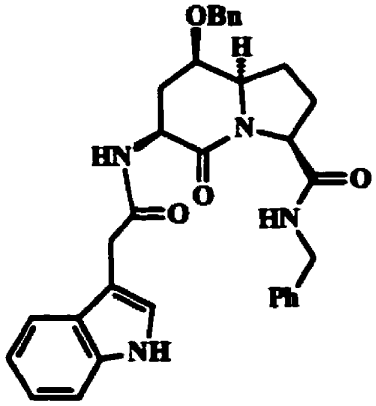


23

Compound **24** was designed to be a thyrotropin-releasing-hormone (TRH)

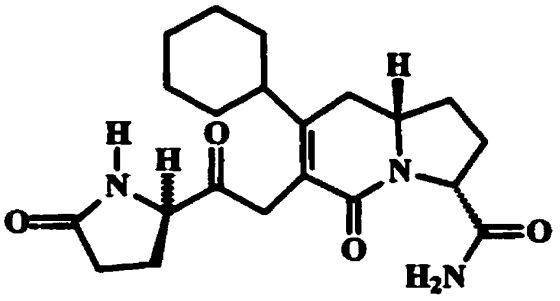
analogue.[25] TRH is the hypothalamic tripeptide that controls the release of thyroid stimulatory hormone from the anterior pituitary gland. TRH also displays effects in the brain, blood, spinal cord and the gut. The potency and binding of **24** was dependent on the ring fusion stereochemistry in that the isomer with *R* stereochemistry was found to be much more potent than the *S* isomer. However, at high concentrations both stereoisomers displaced 100% of the TRH bound to the receptor, but stereoisomer **24** is 4.7 times more potent and had 3.4 times greater affinity for the TRH receptor.

Structure **25** was designed as a non-peptide mimic of an immunosuppressing peptide, tuftsin.[26] This peptide is a naturally-occurring tetrapeptide that displays immunostimulatory activity. It was found that **25** blocks the stimulatory effect of tuftsin in a sheep red-blood-cell assay in a dose-dependant fashion.

Nagai and co-workers[27] synthesized **26** in which a sulfur atom is incorporated into the 1-azabicyclo[*X.Y.*0]alkane skeleton. This compound is a gramicidin S (GS) analogue. GS is a cyclic decapeptide antibiotic that contains two β-turns in its structure. When **26** was incorporated in the turn regions of GS, the antibiotic activity of this analogue was found to be the same as that of natural GS.

L-Prolyl-L-leucyl-glycinamide (PLG) is an endogenously derived peptide that has been shown to control dopamine neurotransmission within the central nervous system. Compound **27** was found to exhibit a pharmacological profile

similar to PLG in terms of activity in binding to dopamine receptors.[28] A type II β-turn has been postulated to be the bioactive conformation of PLG, and this spiro bicyclic lactam, **27**, is believed to mimic this region effectively.



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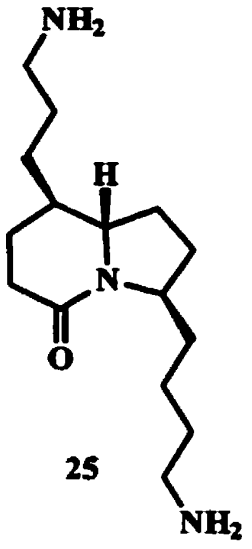
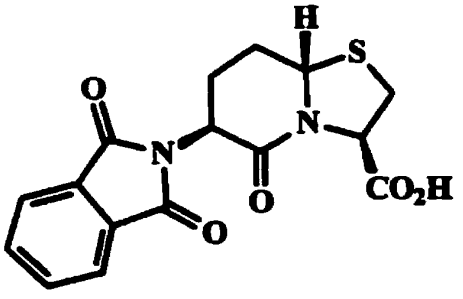


25



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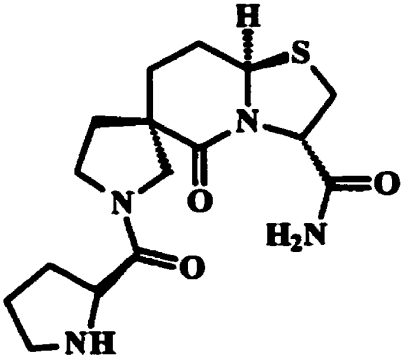


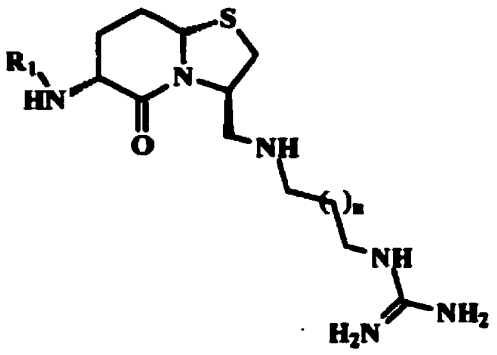
27

Compounds **28a**, **28b**, **28c**, **29a**, **29b**, and **29c** were investigated as thrombin inhibitors.[29] Thrombin is a trypsin-like serine protease. It is the key terminal protease in the coagulation cascade, and it plays a central role in hemostasis and thrombosis. Thrombin catalyzes the proteolytic cleavage of the soluble plasma

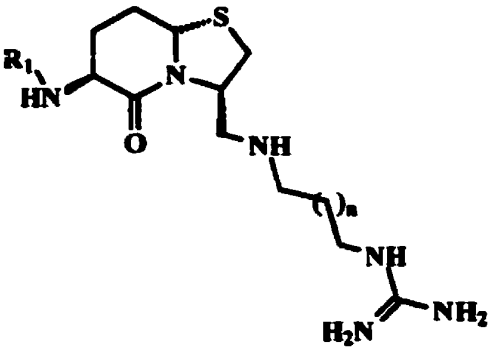
protein fibrinogen to form insoluble fibrin leading to clot formation. The 5,6-fused bicyclic core is postulated to fill the pocket of the active site of thrombin. Chromogenic assays were performed with important serine proteases including thrombin, trypsin and plasmin. All six compounds were found to be inactive against plasmin. Compounds **28c** and **29c** showed some selectivity for trypsin, whereas **28a** and **29a** were thrombin-selective. However, **28b** and **29b** exhibited a greater potency than **28a** and **29a** in terms of thrombin inhibition.

This wide representation of examples illustrates that there is a wide variety of potential targets for β-turn peptidomimetics which contain an azabicyclo[X.Y.0]alkane skeleton.

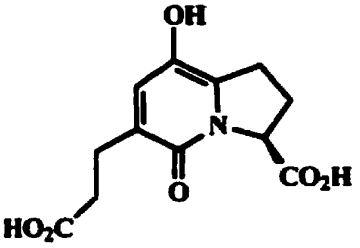
Another synthetic goal involving these 5,6-fused bicyclic systems could include synthesizing analogues of compound **30**. (-)-A58365A **30** is a natural product that was isolated from the fermentation broth of a soil bacterium.[30] This compound is a powerful inhibitor of angiotensin-converting enzyme, and, as a result, this could make the synthesis of analogues of this compound relevant for the design of blood-pressure-lowering drugs. Thus, this is a promising area for the investigation of other compounds with a similar 5,6-bicyclic backbone.



28a. n = 1; R_1 = H
28b. n = 1; R_1 = BenzylSO_2^-
28c. n = 2; R_1 = H



29a. n = 1; R_1 = H
29b. n = 1; R_1 = BenzylSO_2^-
29c. n = 2: R_1 = H



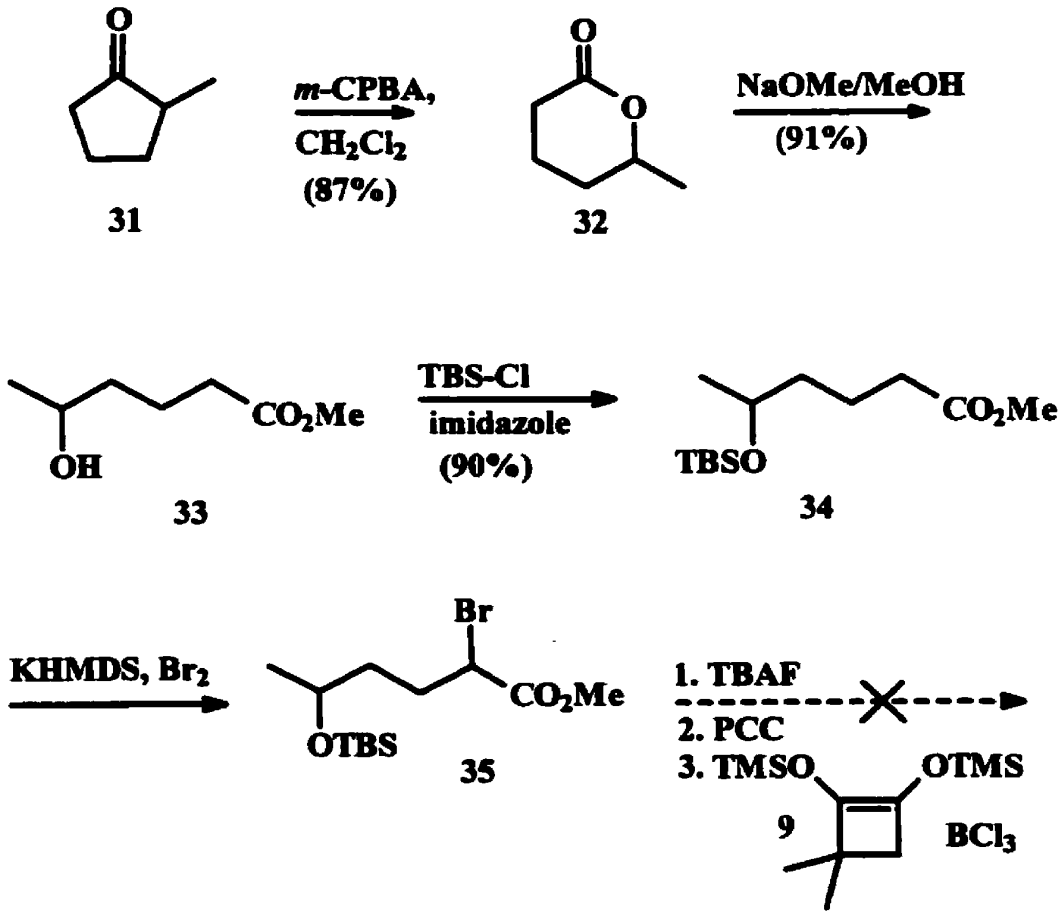
30

Results and Discussion

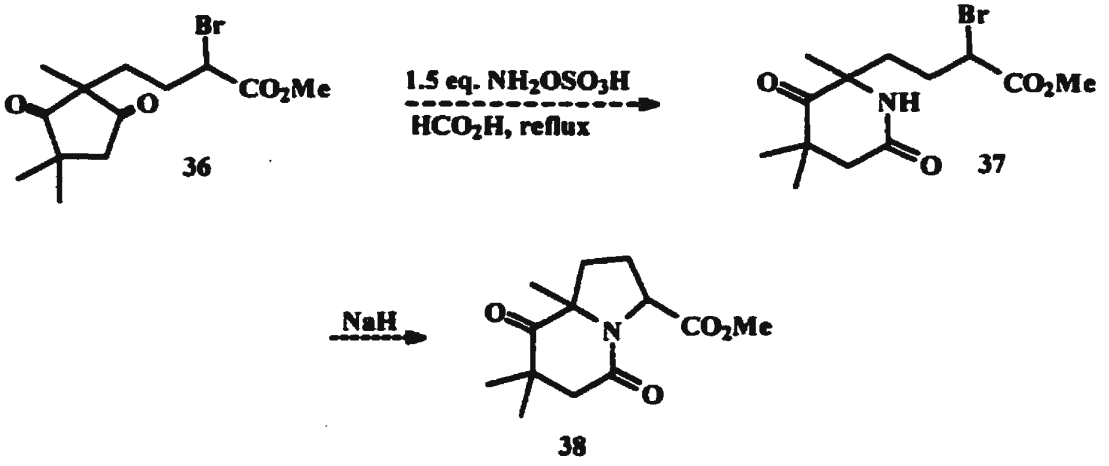
Initial Attempts

Several routes were initially proposed to produce a β-turn peptidomimetic, many of which proved to be unsuccessful. First, it was thought that the 5,6-fused bicyclic system could be synthesized using the synthetic route shown in Scheme 9.

Scheme 9



Scheme 9 (continued)

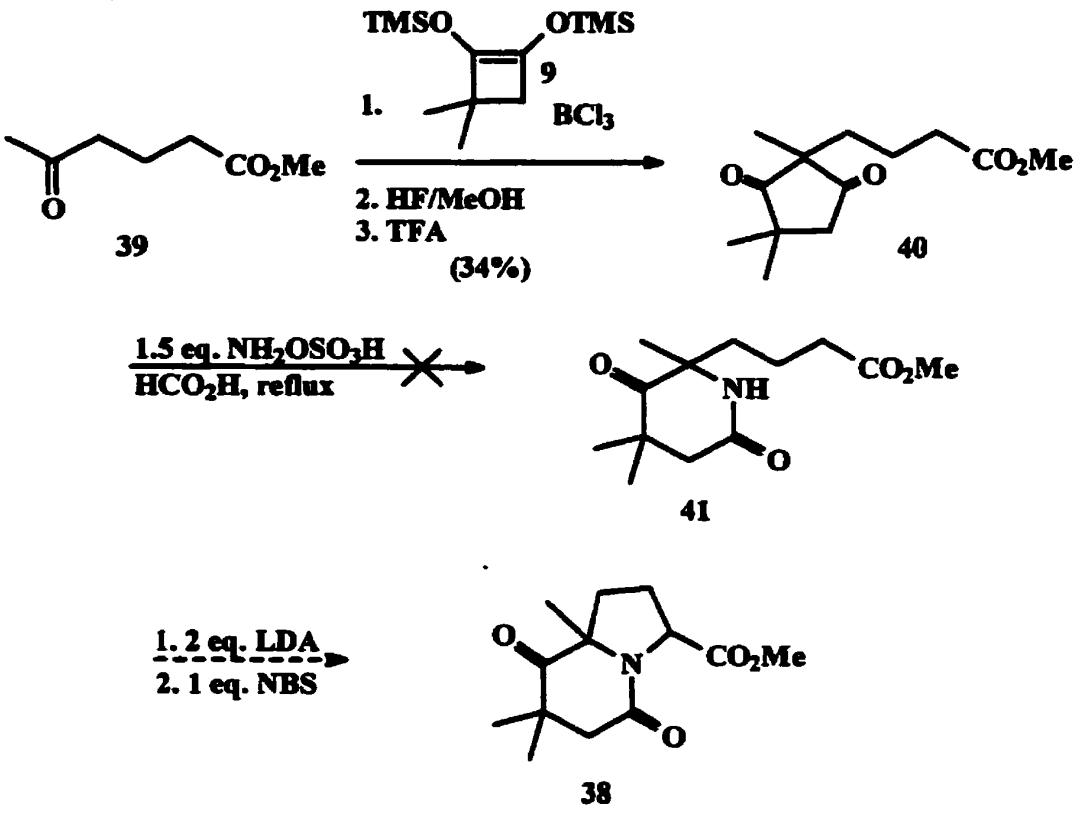


In our initial plan the group at the ring junction of the peptidomimetic **38** would be a methyl. It was thought that generation of the lactam would be from an α-bromoester **37**. Treatment of **37** with 1 equivalent of a base such as NaH would result in the removal of the hydrogen atom on the nitrogen of **37** and this anion could displace the bromine to generate the desired bicyclic structure **38**. The synthetic sequence began with 2-methylcyclopentanone **31**. A Baeyer-Villiger reaction was performed using *m*-CPBA to produce the lactone **32** in good yield. No product with the oxygen inserted on the less hindered side of the ketone was detected.[31] Subsequent solvolysis of **32** under basic conditions yielded compound **33**. Next, the secondary alcohol was protected using TBS-Cl. This was followed by bromination of the carbon α to the ester using KHMDS to generate the intermediate enolate, to give compound **35**. The bromination step did not proceed

to completion. Since four diastereomers are possible for **35**, it was impossible by ^{1}H NMR spectroscopy to determine the extent of the reaction completion and thus the approximate yield. An attempt at separating the starting material **34** from **35** by flash chromatography proved to be unsuccessful. There was also some concern about decomposition of compound **35**. As a result, it was decided to isolate the desired product in the next step. Removal of the silyl group from **35** using TBAF resulted in an alkoxide which unfortunately appeared to displace the bromine to generate a cyclic ether. The mass spectrum of the reaction mixture after this attempt showed that a bromine atom was not present in the structure. Also, the ^{1}H NMR spectrum revealed signals at δ 3.75 (1H) and 3.40 (3H) which is indicative of the ether-type product that would arise from such a process involving compound **35**.

The next approach involved a small variation of the previous attempt. Compound **38** was now postulated to be produced by the synthetic sequence shown in Scheme 10.

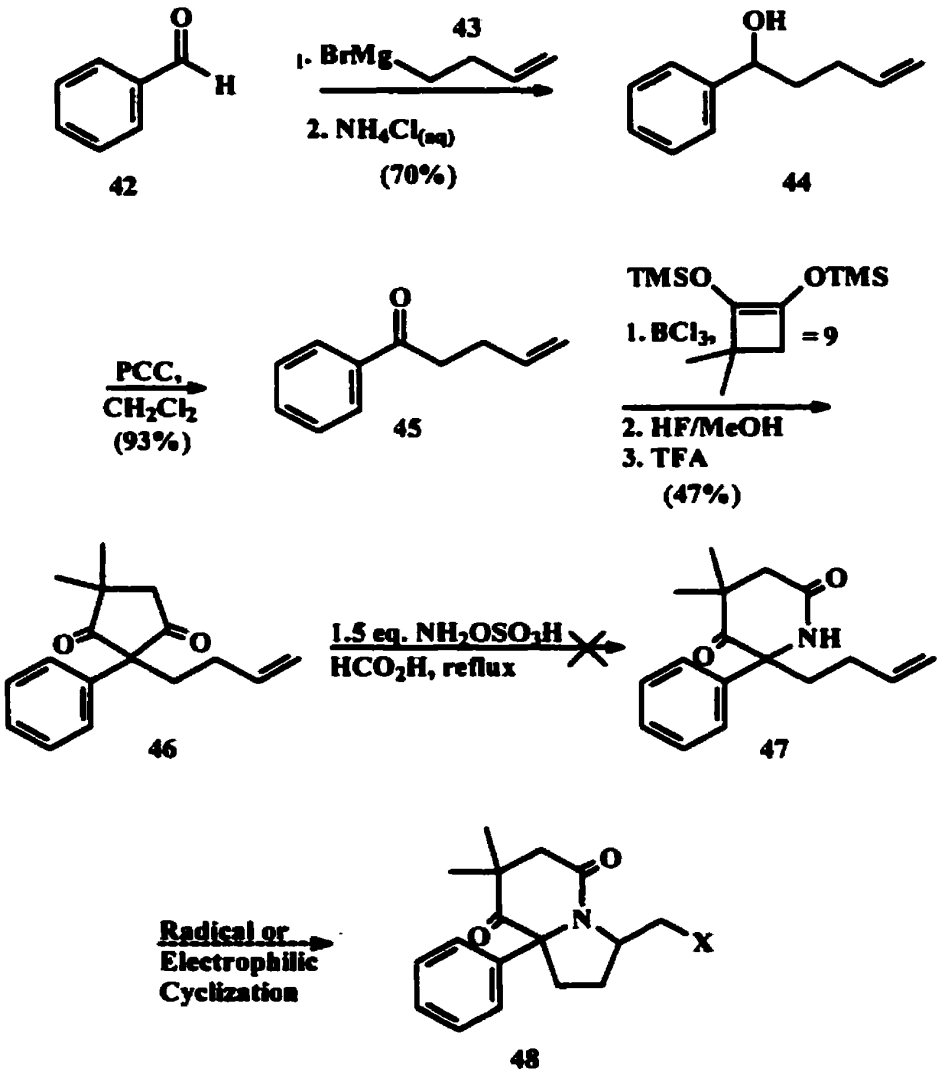
Scheme 10



The starting compound **39** was obtained by oxidation of the alcohol **33** using PCC. Geminal acylation using the BCl_3 modification with **9** was conducted to afford **40**. The yield for this step was low at 34%. However, this can be accounted for by partial hydrolysis of the ester functionality during treatment with TFA. Next, the Beckmann reaction to produce lactam **41** was attempted without success. This reaction produced an intractable mixture of many compounds. As a result, focus was shifted to an alternative route (shown in Scheme 11) that was being pursued at the same time. If the formation of the lactam **47** were successful,

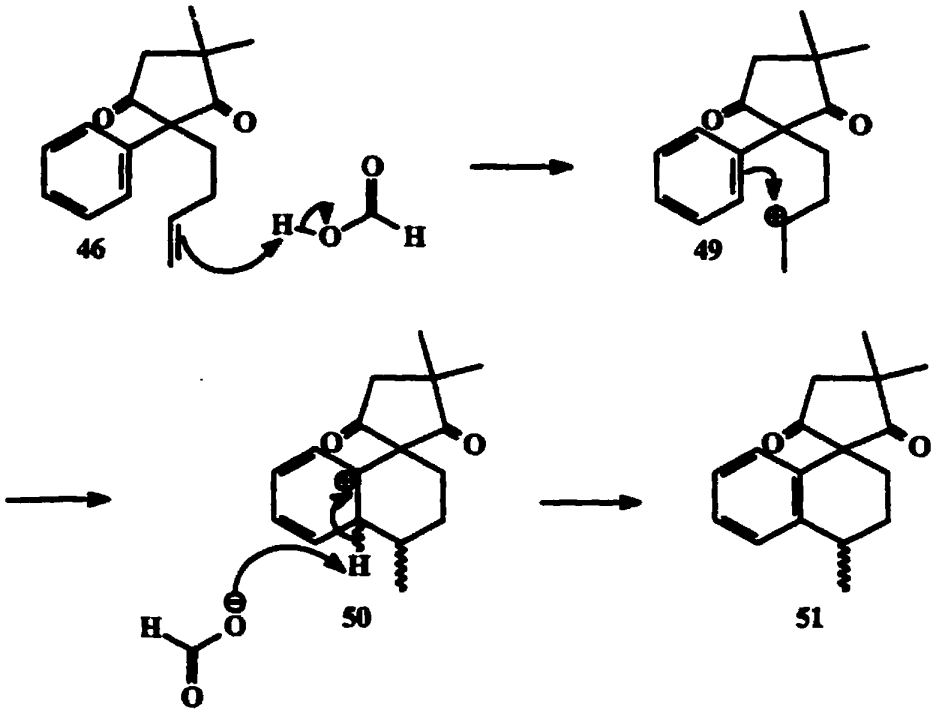
then either a radical or an electrophilic cyclization could be performed to generate the desired 5,6-bicyclic system. The group denoted CH_2X in **48** could be some functionality that could easily be converted into a carboxylic acid.

Scheme 11



A Grignard reaction was performed with benzaldehyde **42** and the organomagnesium reagent derived from 4-bromobutene **43** to produce the alcohol **44.** Subsequent oxidation using PCC furnished ketone **45.** Next, the geminal acylation reaction with **9** provided compound **46.** The Beckmann reaction was attempted on this substrate, but the result, once again, was not the desired lactam **47.** Several products were produced, but the major product was isolated and identified as the diketone **51.** A mechanism for its formation is proposed in Scheme 12. The formic acid might protonate the double bond before the oxime has had a chance to form. This would generate a secondary carbocation **49,** which would then be attacked by the aromatic ring to produce the benzenonium ion **50,** followed by regeneration of the aromatic ring to yield compound **51** as a mixture of epimers. All spectral information indicate that the assignment of **51** is correct but the ^{13}C NMR spectrum is complicated by the presence of both epimers.

Scheme 12

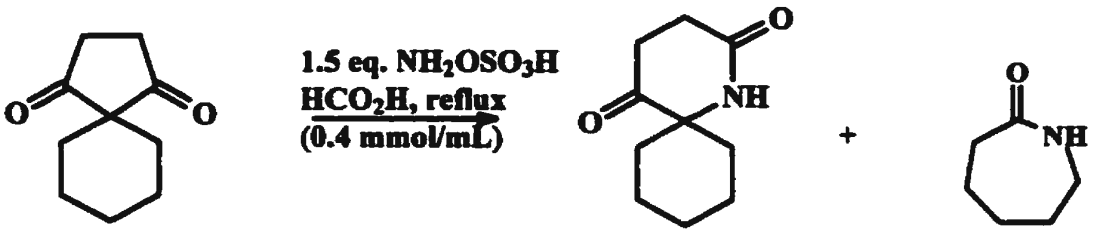


Investigation of the Beckmann Reaction

Each time the Beckmann reaction was attempted using conventional conditions, such as using hydroxylamine *O*-sulfonic acid in refluxing formic acid,[32] the result was the destruction of the starting material. It became obvious that an investigation of conditions required for the Beckmann reaction was necessary. Also, it seemed preferable to initially use a diketone without an aromatic ring or a double bond. Subsequently, molecules with double bonds or aromatic systems could then be examined. The first Beckmann investigation involved spiro[4.5]decane-1,4-dione **52** at a concentration of less than 0.4 mmol of diketone per mL of formic acid. The result was the desired lactam **53**, and

recovered starting material **52**.

Scheme 13

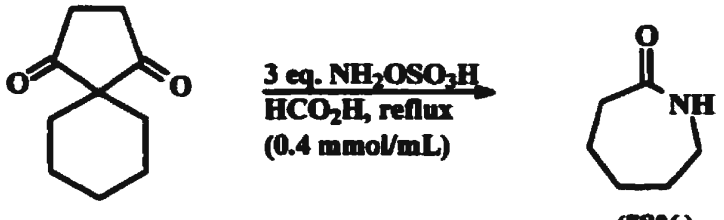


(46%) (9%)

52 **53** **54**

When the concentration was adjusted to 0.4 mmol of diketone per mL of formic acid, the result was the formation of the desired amide **53** and ϵ-caprolactam **54** (Scheme 13) without any **52** being recovered. Further investigation revealed that when 3 equivalents of the aminating reagent were used at the same concentration, the result was the formation of mainly ϵ-caprolactam as seen in Scheme 14.

Scheme 14

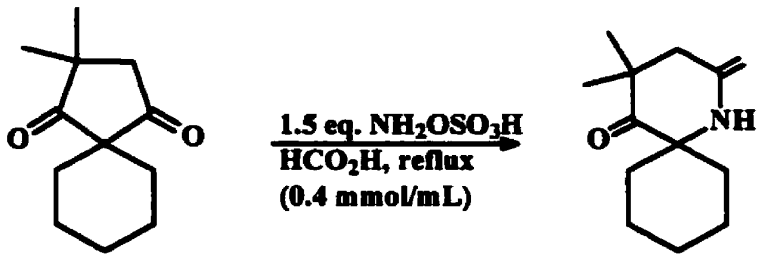


(78%)

52 **54**

When 4,4-dimethylspiro[4.5]decane-1,3-dione **55** was subjected to the same conditions as shown in Scheme 13, the result was the formation of only the desired amide **56** (Scheme 15) without any starting material remaining. In addition, when the number of equivalents of the aminating reagent was increased to 5 equivalents, compound **56** was still the only observed product.

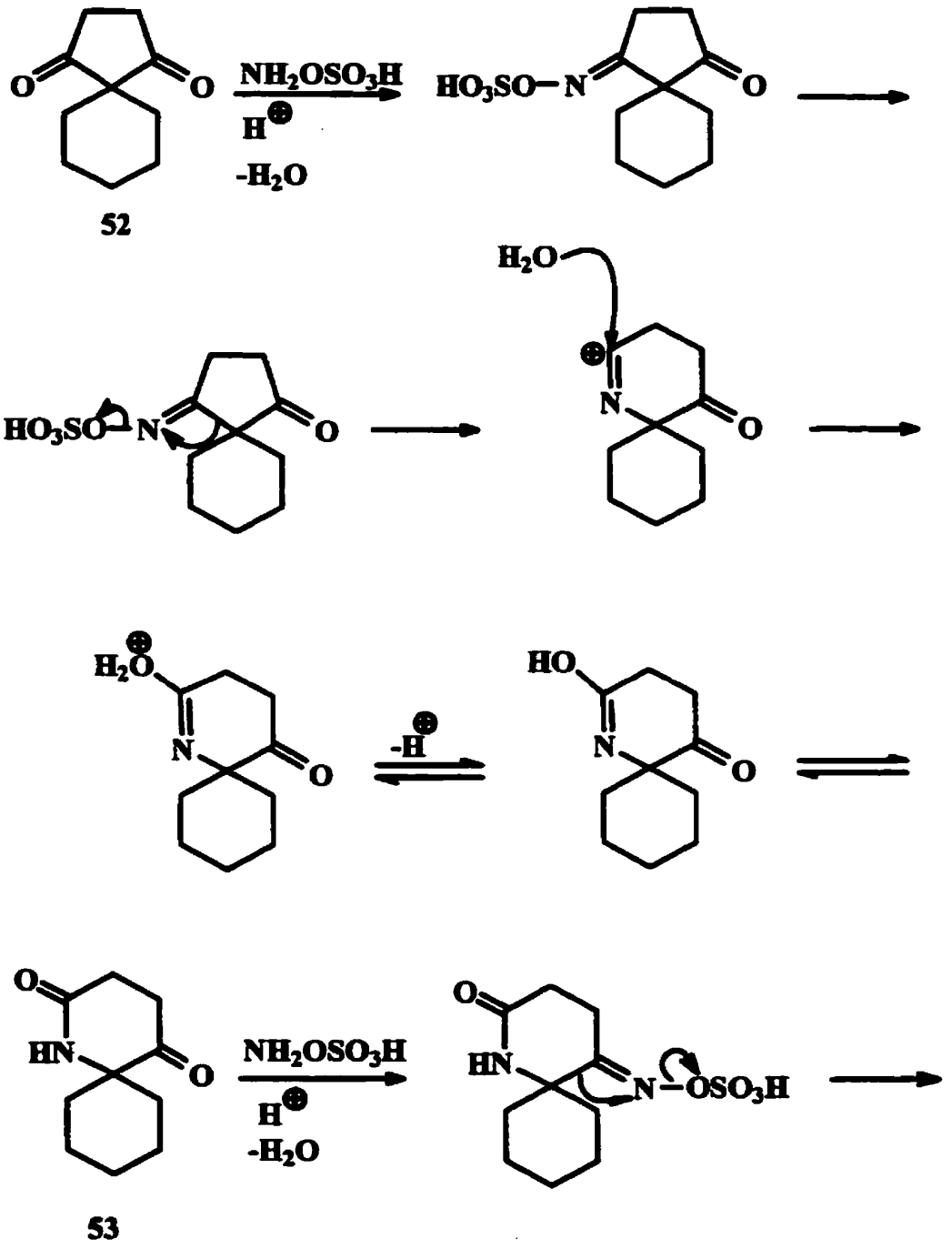
Scheme 15



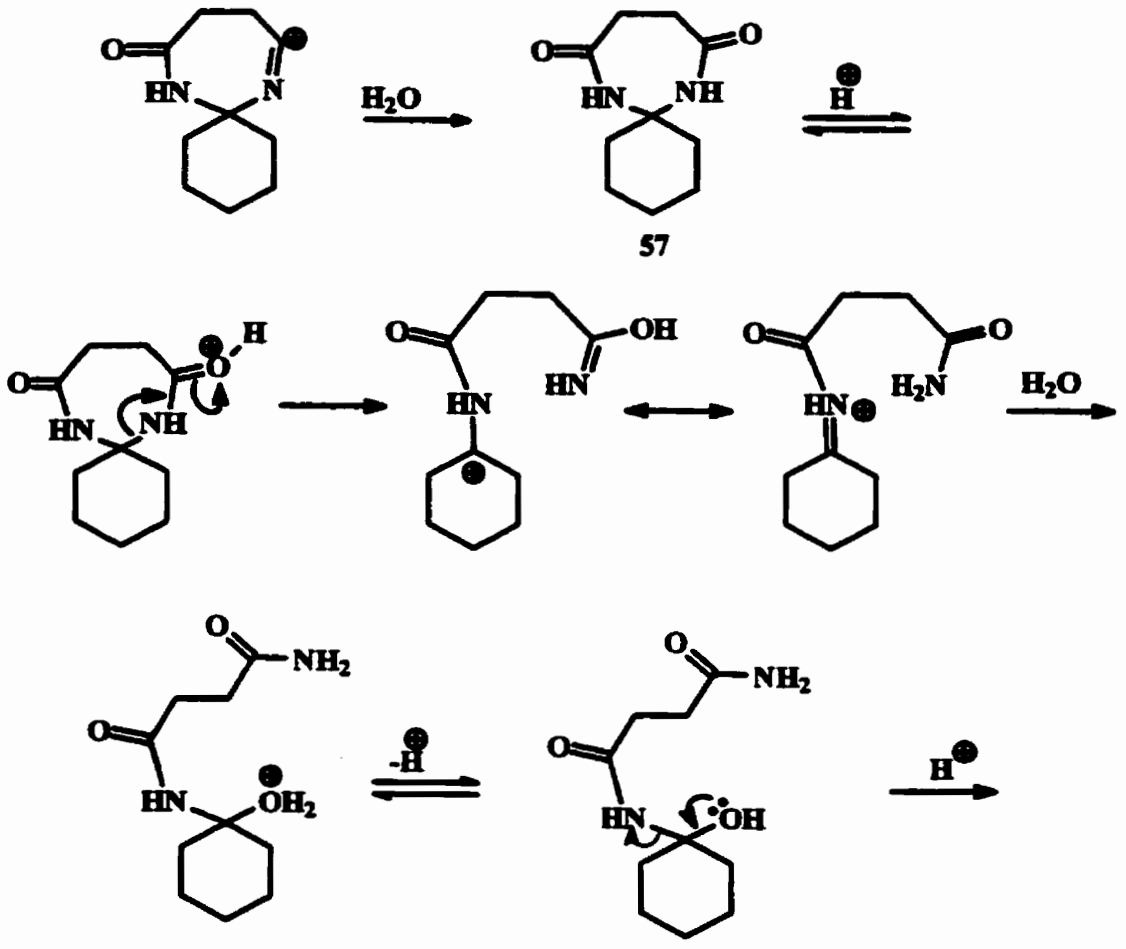
55 (79%) **56**

The efficient formation of ϵ-caprolactam from **52** with three equivalents of the aminating reagent is due to the formation of oximes from both sterically unhindered carbonyls, as shown in Scheme 16.

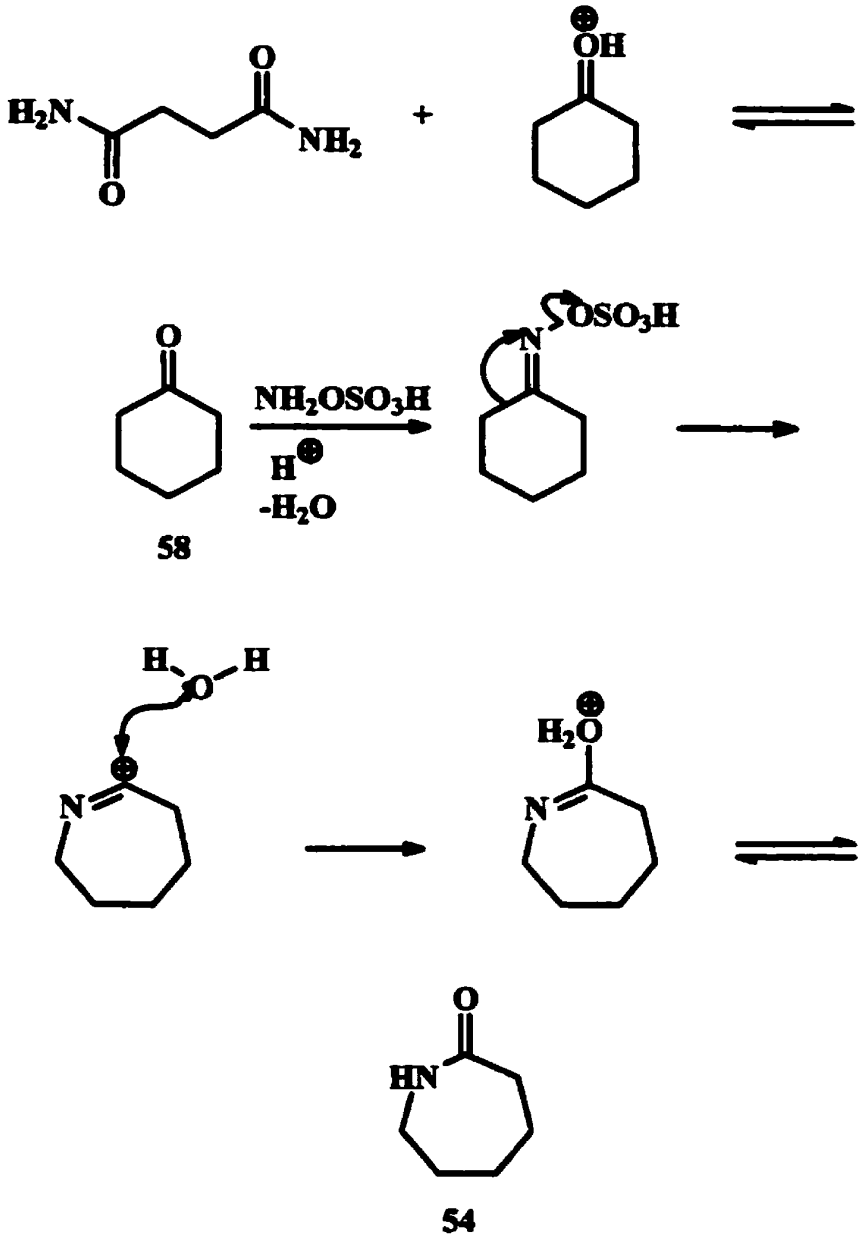
Scheme 16



Scheme 16 (continued)



Scheme 16 (continued)

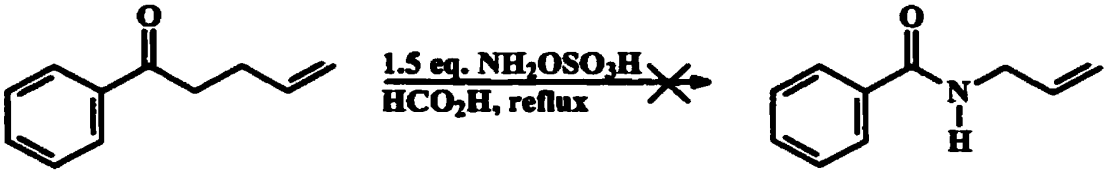


The first equivalent of the aminating reagent forms the oxime on one carbonyl of compound **52**, followed by migration of the quaternary carbon, which is succeeded by attack of a molecule of water. After the formation of the lactam **53**, a second oxime is formed on the second ketone moiety. Migration of the quaternary center produces the diamide **57**. Compound **57** resembles an acetal and hydrolysis of this diamide is analogous to hydrolysis of an acetal. This results in the production of cyclohexanone **58**, which would react with the third equivalent of the aminating reagent furnish an intermediate oxime, followed by migration to produce ϵ-caprolactam **54**. Thus, even though 1.5 equivalents of the aminating reagent was used under the "normal" Beckmann conditions, the bimolecular process involving the formation of the second oxime must have been in competition with the unimolecular process of migration to produce the monoamide product. Both processes must have similar rates.

An attempt to perform the Beckmann rearrangement with compound **59** (Scheme 17) did not yield **60**, or any significant amount of product with the double bond intact. After flash chromatography only one fraction included the signal for an amide proton in its ^{1}H NMR spectrum. Unfortunately, this fraction, which appeared to be homogeneous by TLC, contained two components. GC/MS revealed that the two components probably had molecular masses of 100 and 115. The component with a molecular mass of 100 was suspected to be γ-valerolactone while the second component could have been 2-phenylaziridine.

The ^{1}H NMR spectrum of this mixture contained signals with the same chemical shifts as those seen with a commercially available sample of γ-valerolactone.

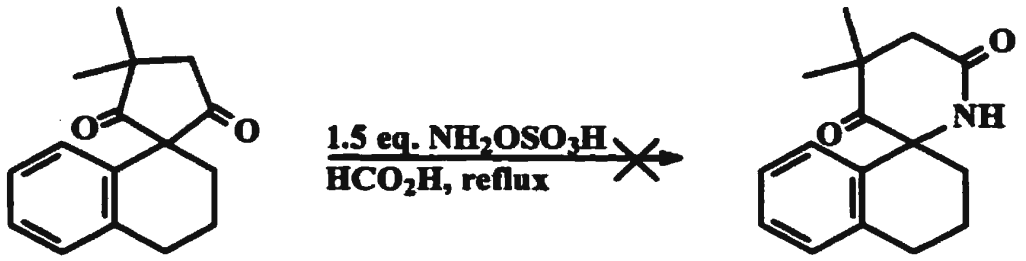
Scheme 17



59 **60**

Finally, the diketone **61** was subjected to the conditions of the Beckmann reaction (Scheme 18), but it was found that the amide **62** was not produced in any significant amount. Instead, several compounds were formed, one of which may have been a derivative of naphthalene. This conclusion is supported by both the ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum contained the majority of its signals in the aromatic region, with the exception of two signals. One signal could be attributed to the methyl groups and the other was consistent with methylene hydrogens α to the carbonyl. As well, the ^{13}C NMR spectrum contained ten signals for aromatic carbons. The ratio of recovered **61** to this napthalene by-product was 1:1.8.

Scheme 18



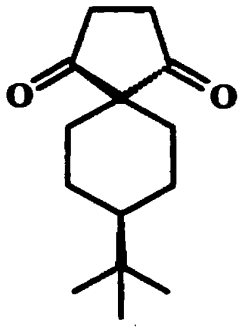
61 **62**

Thus, after this investigation of the Beckman reaction using conventional conditions, the conclusion was reached that these conditions were not compatable with our diketones. Diketones derived from 1,2-bis-(trimethylsilyl)oxycyclobutene **1** would undergo a double Beckmann and hydrolysis process. As well, substrates with a double bond in the position shown in Scheme 17 were destroyed as were compounds with an aromatic ring.

Another investigation, (unrelated to the previous work) involving the Beckmann reaction was carried out (Scheme 19). It involved trying to determine the position of nitrogen insertion for ketones conformationally locked into axial and equatorial positions. The Beckmann reaction with compound **63** showed little chemoselectivity. Two products **64a** and **64b** were formed in a ratio of 1:2. Oxime formation and therefore ultimately the position of the nitrogen was not influenced much by the carbonyl being either axial or equatorial. However, in **65** the equatorial carbonyl is flanked by quaternary centers. Steric hindrance would not allow oxime formation on the equatorial carbonyl, therefore only an axial

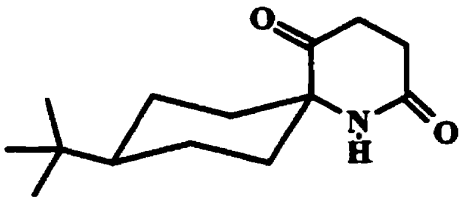
nitrogen was found in the product. Both NOE and X-ray data support these results for the position of nitrogen insertion with these substrates.

Scheme 19

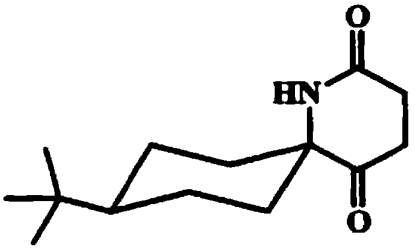


63

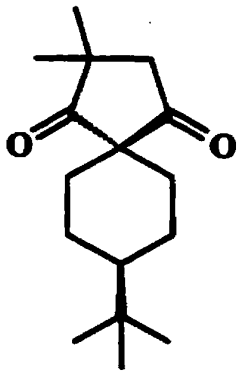
1.5 eq. NH_2OSO_3H
HCO_2H, reflux
(0.4 mmol/mL)



64a

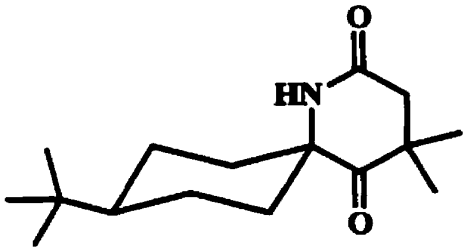


64b



65

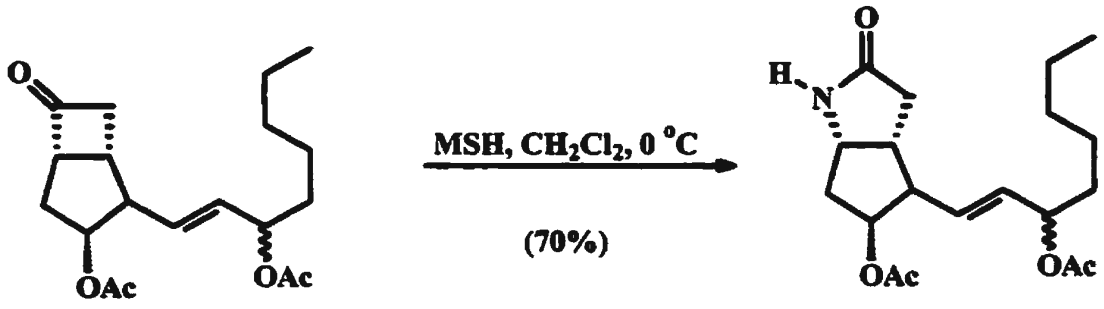
1.5 eq. NH_2OSO_3H
HCO_2H, reflux
(0.4 mmol/mL)



66

Once it was realized that conventional Beckmann conditions were unsuitable with our substrates it was decided to pursue a more gentle aminating reagent. *O*-Mesitylenesulfonylhydroxylamine (MSH) was then investigated because of the example shown in Scheme 20.[33]

Scheme 20



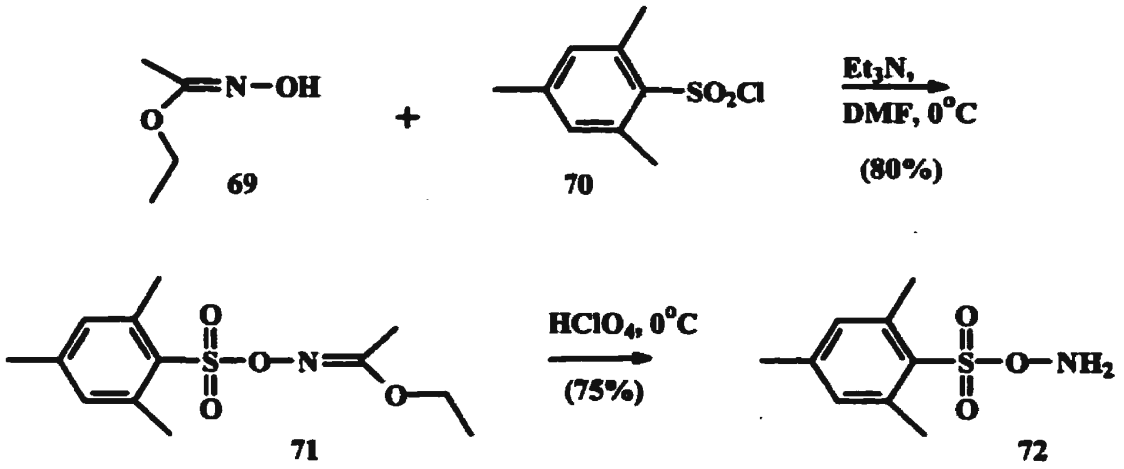
67 **68**

21% of the other regioisomer

With MSH and **67**, oxime formation and the subsequent migration occurred under very mild conditions, 0 °C in CH_2Cl_2, to produce the lactam **68**. This substrate is obviously higher in energy than our diketones since it has a four-membered ring, but this result was very encouraging. A drawback to the use of this aminating reagent is that it is not commercially available. It must be prepared from ethyl acetohydroxamate **69** and mesyl chloride **70**, as shown in Scheme 21.[34] MSH can be stored below 0 °C, but only for a short period of time in order to remain

effective, otherwise it decomposes.

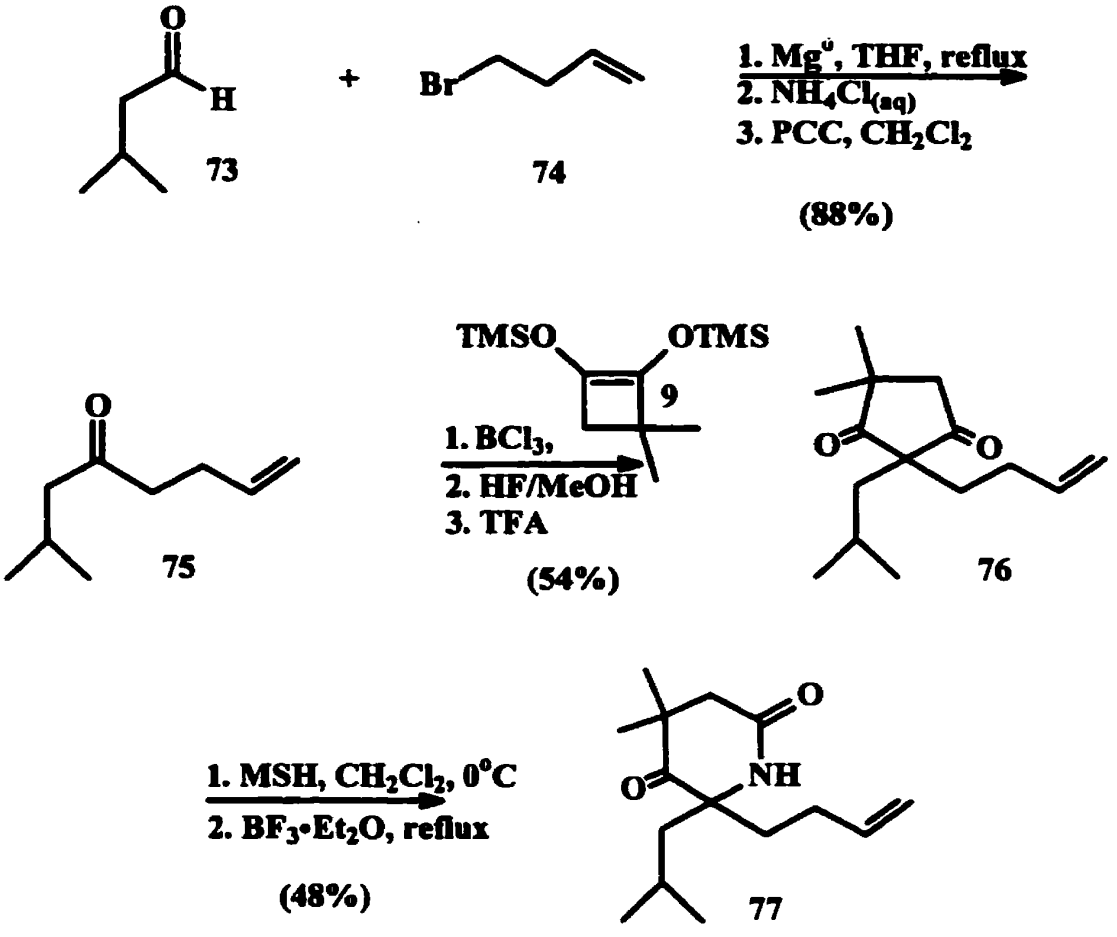
Scheme 21



The next step involved after the preparation of this aminating reagent **72** (MSH) was to test it using the diketone substrate **76** (Scheme 22).

The synthesis of **76** began with the Grignard reaction between isovaleraldehyde **73** and the organomagnesium reagent derived from 4-bromobutene **74** to furnish an alcohol, which was oxidized by PCC to yield the ketone **75**. The geminal acylation reaction produced the diketone **76**, and the Beckmann reaction was performed with MSH to give **77**. The formation of compound **77** was clearly evident by the amide proton present in the ^{1}H NMR spectrum of the product.

Scheme 22



Initially, there was a problem with the Beckmann reaction using MSH and substrate **76**. The oxime formation was observed by ^{1}H NMR spectroscopy but the subsequent migration did not occur. Thus, conditions had to be found that would promote the migration. Flushing a benzene solution of an oxime through basic alumina has been reported to effect migration.[35] The result of this process with the oxime derived from **76** however only afforded recovery of the unchanged

oxime. Another reagent that has been found to promote migration, is $BF_3 \cdot Et_2O$. An example[36] of the use of this Lewis acid is shown in Scheme 23.

Scheme 23

78 **(97 %)** **79**

95% plus 5% of the other isomer

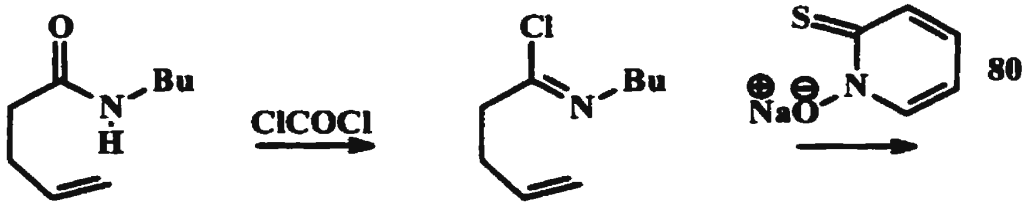
Thus, $BF_3 \cdot Et_2O$ was also used to promote the migration of the oxime derived from compound **76** (Scheme 22). Two interesting aspects of compound **77** is complexity observed for the amide proton in the ^1H NMR spectrum and the complexity of the ^{13}C NMR spectrum. Initially, it was thought that **77** existed in the amide form as well as its enol form. It was concluded that these spectra would have to be acquired at a higher temperature to observe a simpler spectrum (any enol form would convert back to the amide form). However, when higher temperatures were attempted during the acquisition of both the ^1H NMR and ^{13}C NMR spectra, no difference was observed. It was then noticed that the integration values for the olefinic protons do not correspond well to the integration for the rest of the peaks in the ^1H NMR spectrum. This implied that the double bond in **77** might have been protonated in an earlier step involving TFA and the resultant

carbocation would be stabilized by a counterion. This could explain the complexity of the spectra for compound **77**. The hypothesis of protonation was determined after the subsequent cyclization attempts because the variable temperature NMR could not be performed as quickly as required.

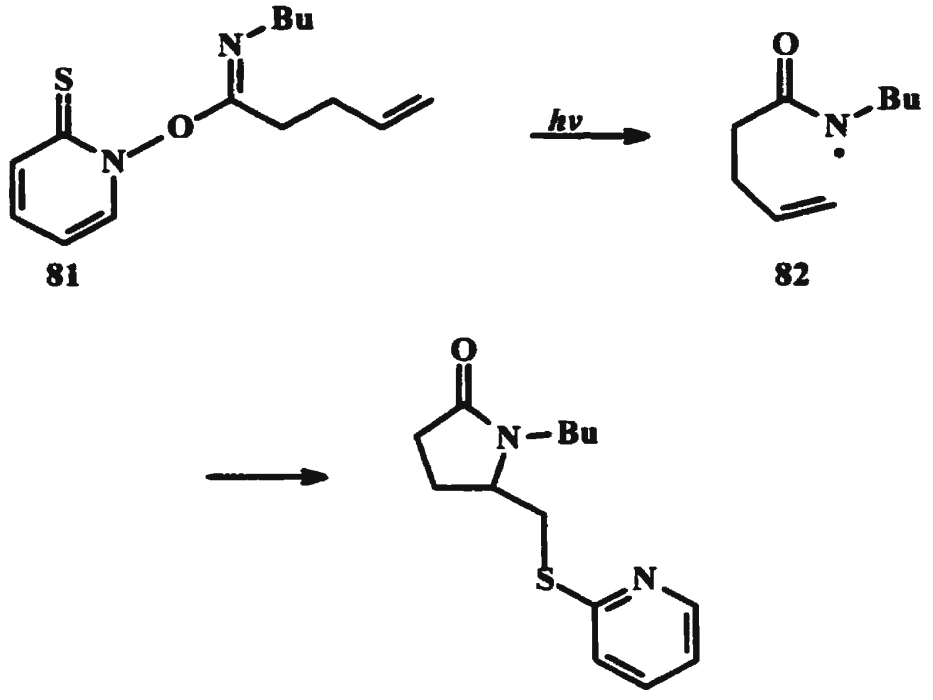
Subsequent Attempts at Cyclization

The next step in this synthetic sequence is crucial since it will form the 5,6-fused bicyclic system. Initially as proposed in Scheme 11, it was intended to proceed with the cyclization either by a radical or an electrophilic method. It was decided to first pursue the radical method exemplified[37] in Scheme 24.

Scheme 24

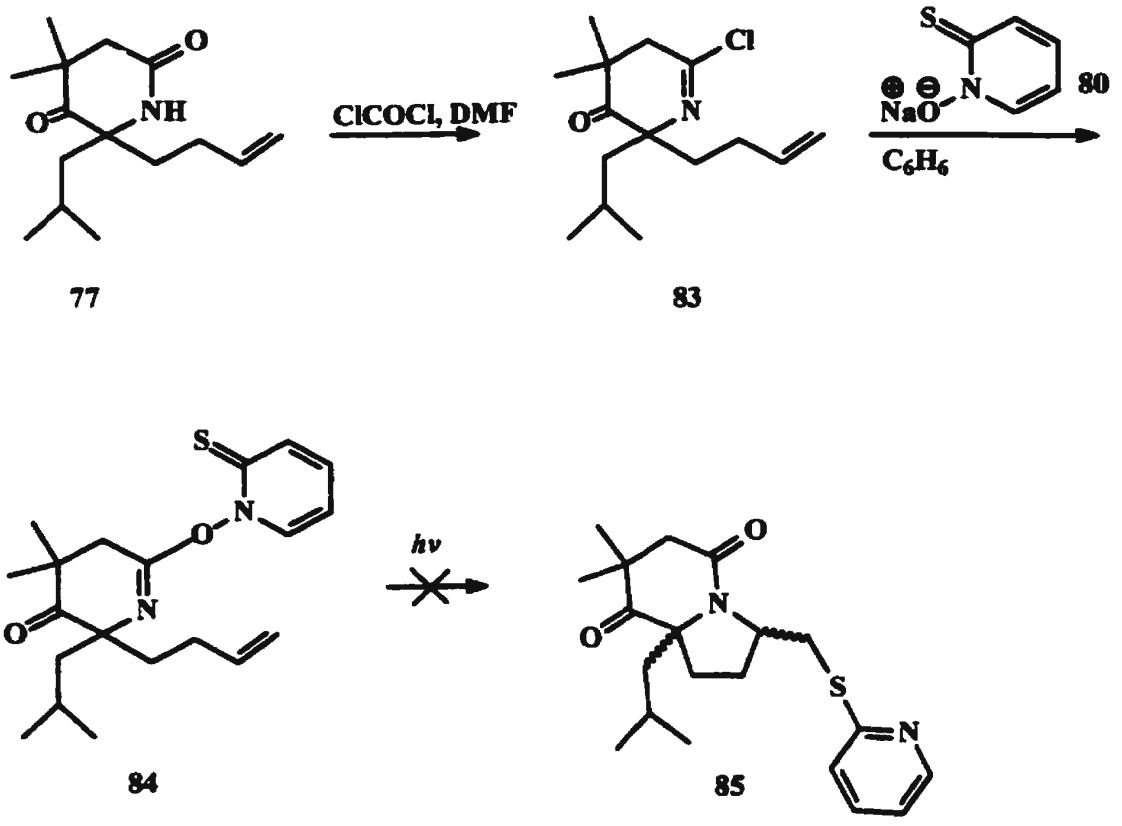


Scheme 24 (continued)



The amidyl radicals such as **82** are produced from *N*-hydroxypyridine-2-thione imidate esters such as **81** and allow for 5-*exo*-cyclizations to produce γ-lactams. These esters are related structurally and in their reactions to Barton's pyridine-2-thioneoxycarbonyl esters, which are important carbon-centered radicals. A radical trapping agent can be added if required. Otherwise, the carbon-centered radical that arises after the cyclization has occurred can also be trapped by the radical produced by the 2-thiopyridyl moiety of the intermediate. Thus, this process was attempted with the lactam **77**, as shown in Scheme 25.

Scheme 25



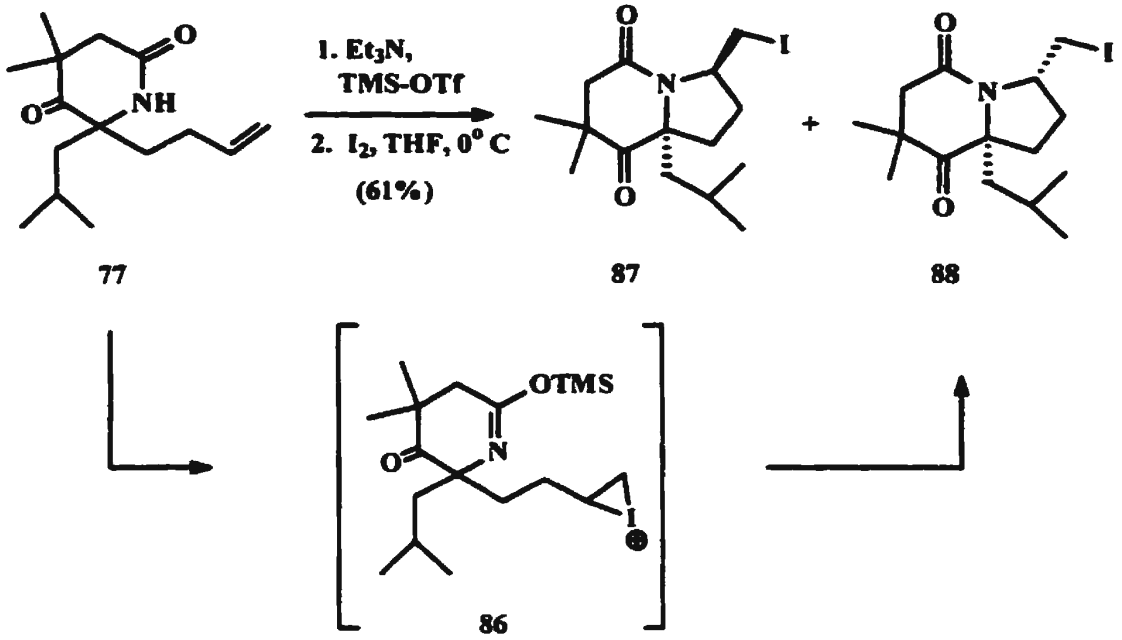
The lactam **77** was converted to the imidoyl chloride **83** using phosgene. The formation of the imidoyl chloride was followed by ^{1}H NMR spectroscopy and the conversion occurred smoothly as shown by the complete disappearance of the amide proton in the ^{1}H NMR spectrum. Then the sodium salt of 2-mercaptopyridine *N*-oxide **80** was added to the reaction mixture to produce the imidate ester **84**. The formation of the imidate ester was also monitored by ^{1}H NMR spectroscopy, and although this step was sluggish, it did appear to occur.

However, the photochemical step proved to be a failure. Irradiation with visible light should have generated the amidyl radical, which would then have attacked the double bond to form the five-membered product **85**. Signals for compound **77** and the mercaptopyridine could be observed in the ^{1}H NMR spectrum of the crude material, but upon subjecting the mixture to column chromatography it became apparent that these moities were not connected to each other. None of the desired cyclized product could be found.

Attention was then turned to the electrophilic cyclization process shown in Scheme 26. Treating the amide **77** with trimethylsilyl trifluoromethanesulfonate yielded a silyl imidate,[38] which was then treated with iodine to furnish the iodonium intermediate **86**. Subsequently, cyclization occurred to generate the *trans* and *cis* iodolactams, **87** and **88** in a 4.8:1.0 ratio, respectively. The relative stereochemistry of **87** was determined by X-ray diffraction to be a *trans* arrangement. Both the *cis* and *trans* product are useful since there are many examples throughout the literature in which both types have been shown to be β-turn peptidomimetics.

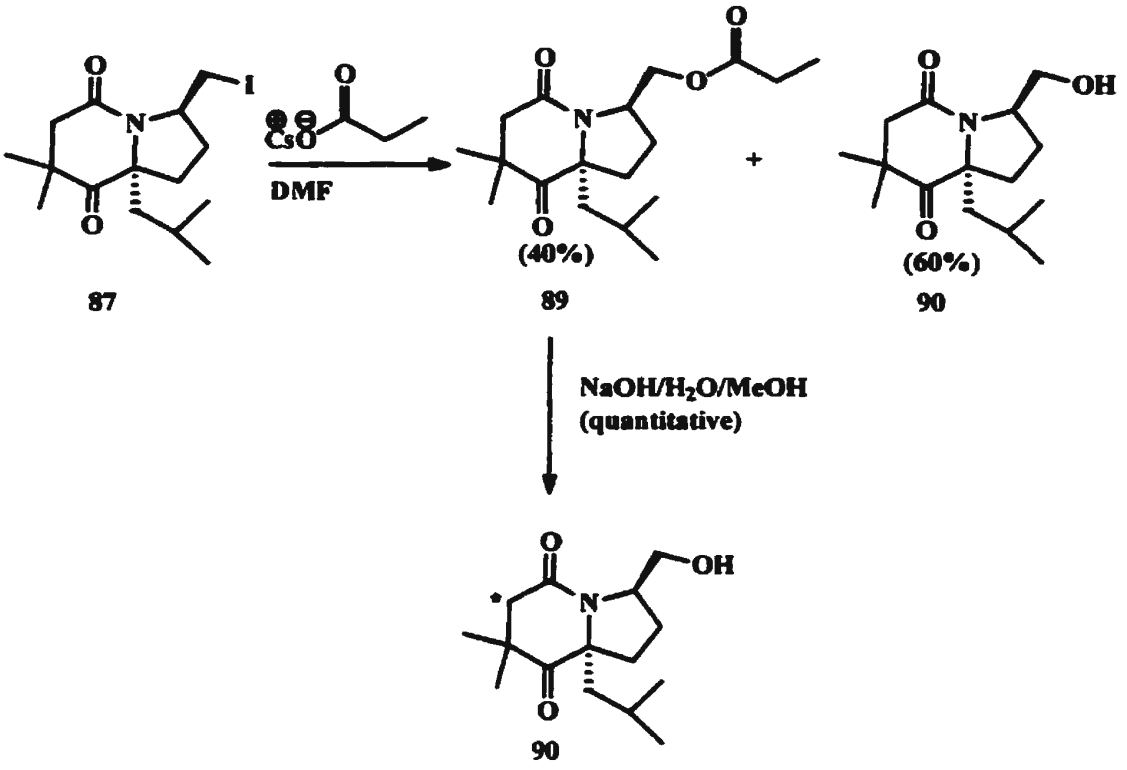
The last few steps that are required in order to generate a β-turn peptidomimetic involve conversion of the iodine to an oxygen functionality and introduction of the amino group α to the amide carbonyl.

Scheme 26



Cesium propionate had been chosen for the conversion of the iodine to an oxygen function because it is fairly soluble in DMF,[39] and also a gentle reagent was required since the stability of the iodolactam was not known. Cesium propionate attacked the major isomer **87** in a simple S_N2 reaction to generate the ester **89** and the alcohol **90** (Scheme 27).

Scheme 27

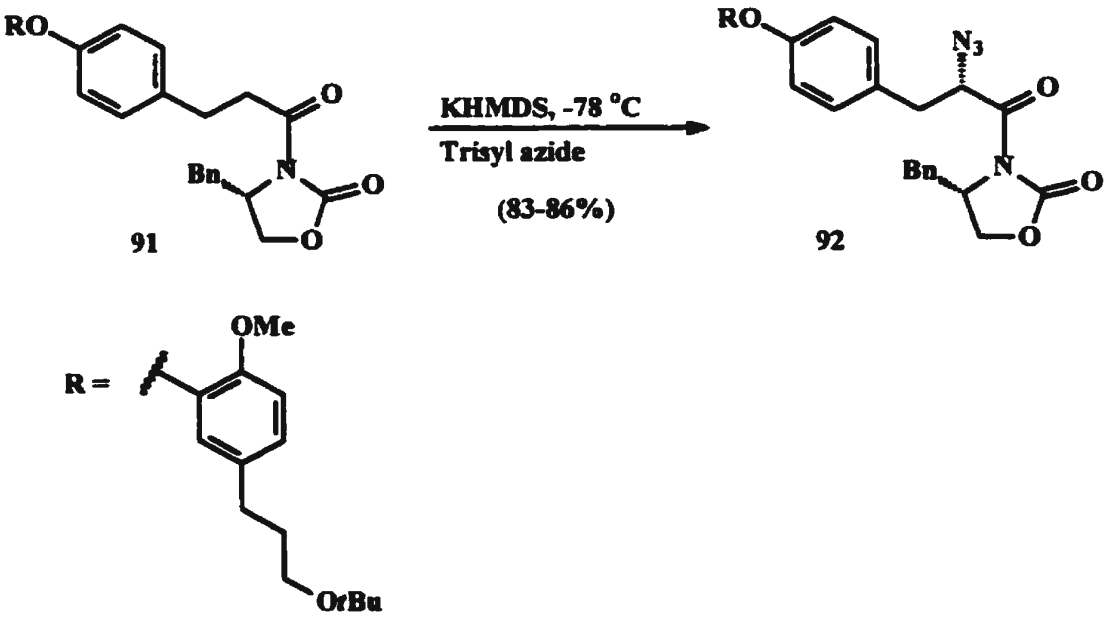


The formation of the corresponding alcohol **90** in this step was not a concern since the ester **89** was to be hydrolyzed to the alcohol **90** in the subsequent step. However, alcohol formation was more likely due to the presence of cesium hydroxide which would have facilitated the partial hydrolysis of the ester once it had formed.

The next step would have been the introduction of the amino moiety. This step was not pursued with **90** because the position of introduction (denoted by *) is at a neopentyl carbon. Our planned approach for the introduction of the amino group in a less hindered substrate, was as follows; first, the primary alcohol would

have to be protected, then treatment with a strong base, such as KHMDS, should generate the anion α to the carbonyl of the amide. Introduction of trisyl azide should then result in the addition of an azide function. Trisyl azide has been used for the introduction of azide α to an amide,[40a] as shown for compound **91**. This reagent is generated from trisyl chloride and sodium azide.[40b] The example shown in Scheme 28 indicates that the azide moiety can be introduced stereoselectively, to furnish **92**.

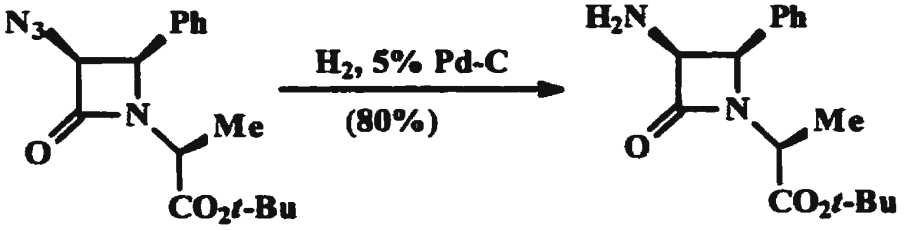
Scheme 28



Hydrogenolysis would then be used to reduce the azide to the amine while leaving the amide carbonyl intact. For example, the azide in compound **93** has been

selectively reduced to yield **94** while leaving the carbonyls of the amide and ester untouched (Scheme 29).[41]

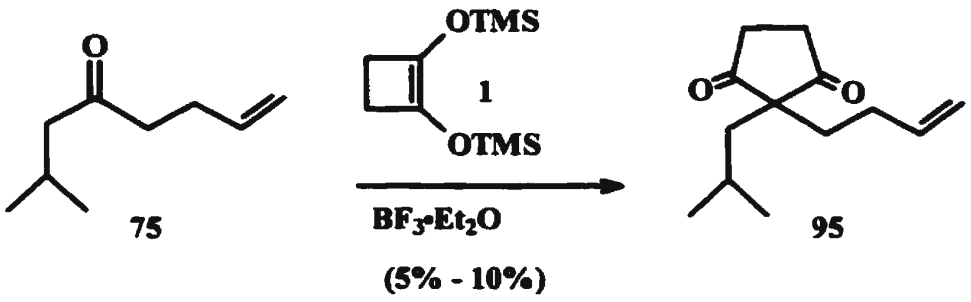
Scheme 29



93 **94**

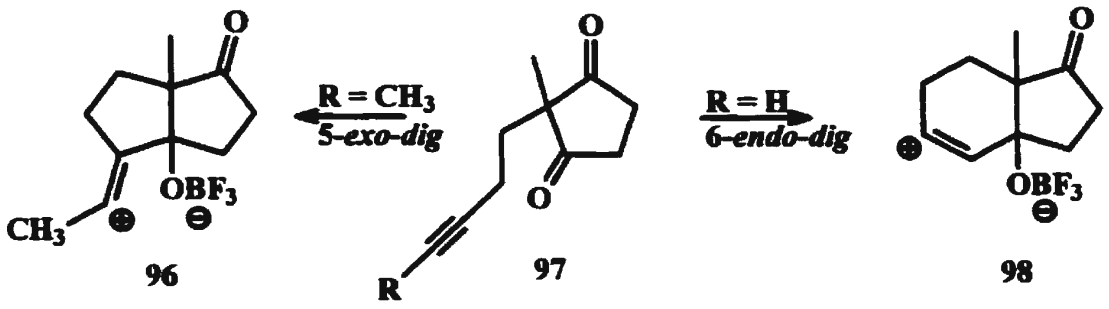
With a successful cyclization method in place, it was decided to synthesize the analogous substrate derived from 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1**. This should provide a substrate in which the amino moiety could be more easily introduced. Now the problem encountered was the geminal acylation reaction. Very low yields of diketone **95** were obtained from **75** or from its corresponding acetal (Scheme 30). Various modifications of the conditions were tried, such as changing the Lewis acid, the time of the reaction, and the temperature, but to no avail.

Scheme 30



Curran and co-workers[42] had seen poor yields when the diketone products had unsaturation at the δ-position. They reported a set of conditions to effect a one-step condensation of **1** and ω-alkynyl acetals in the presence of excess BF_3•Et_2O at room temperature to provide polycyclic enediones after formation of the 1,3-diketone **97**. The BF_3•Et_2O-promoted cyclization of the alkynyl ketone occurs either via a 5-*exo-dig* process to produce compound **96** or a 6-*endo-dig* process to produce **98** if the alkyne is terminal (Scheme 31).

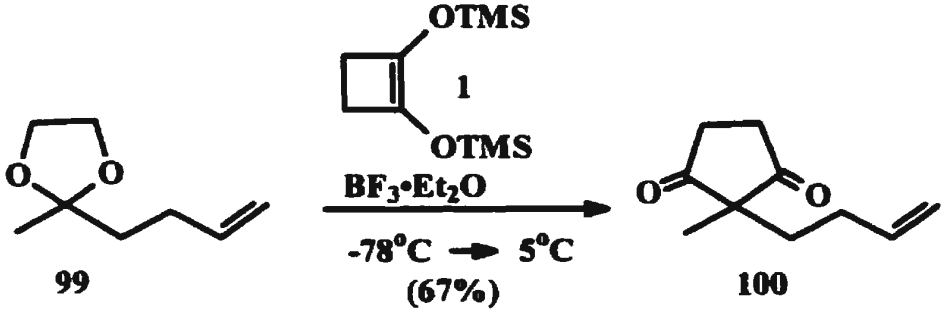
Scheme 31



However, they found that if there is a double bond at the δ position of the dione substrate, the subsequent π-cyclization occurs but the cyclized product cannot be isolated due to decomposition. In a subsequent paper, Curran and co-workers[43] disclosed that the addition of a nucleophile such as Bu_4NBr with these substrates was necessary in order to stabilize the carbocation intermediate, otherwise the result was the complete decomposition of the substrate.

This explained our problem with the geminal acylation shown in Scheme 30 since the ^1H NMR spectrum of the crude product indicated a lot of polymerization. Nonetheless, careful control of the temperature and the time of the reaction could reduce the Lewis acid catalyzed π-cyclization, as shown by Curran and co-workers[42] when they successfully performed the geminal acylation reaction using the acetal of allyl acetone **99** (Scheme 32). Their addition of the reagents was carried out at -78 °C, the reaction was stirred for 3 hours, and then it was slowly warmed to 5 °C and quenched after 10 minutes.

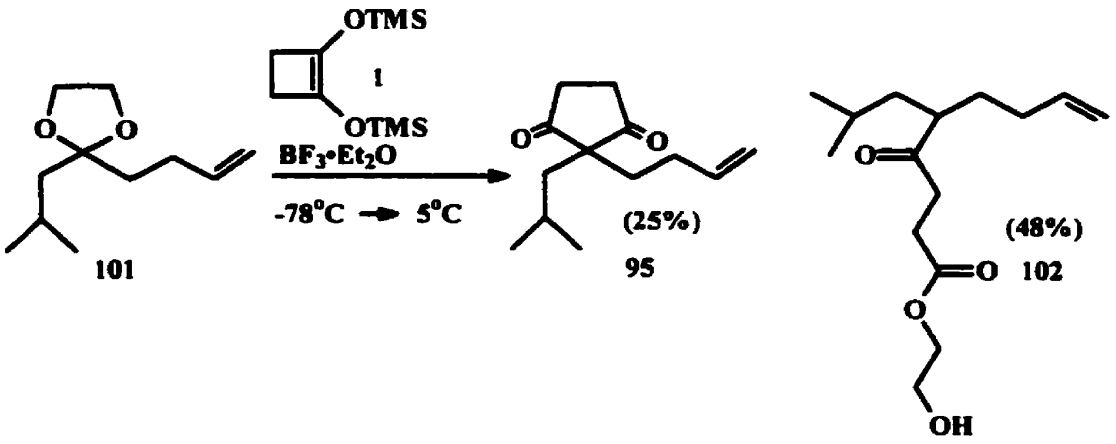
Scheme 32



99 100

When this procedure was applied to our acetal **101**, the result was the formation of the desired diketone **95**, but in only 25% yield, along with a significant amount of reductive succinoylation product **102** (Scheme 33).

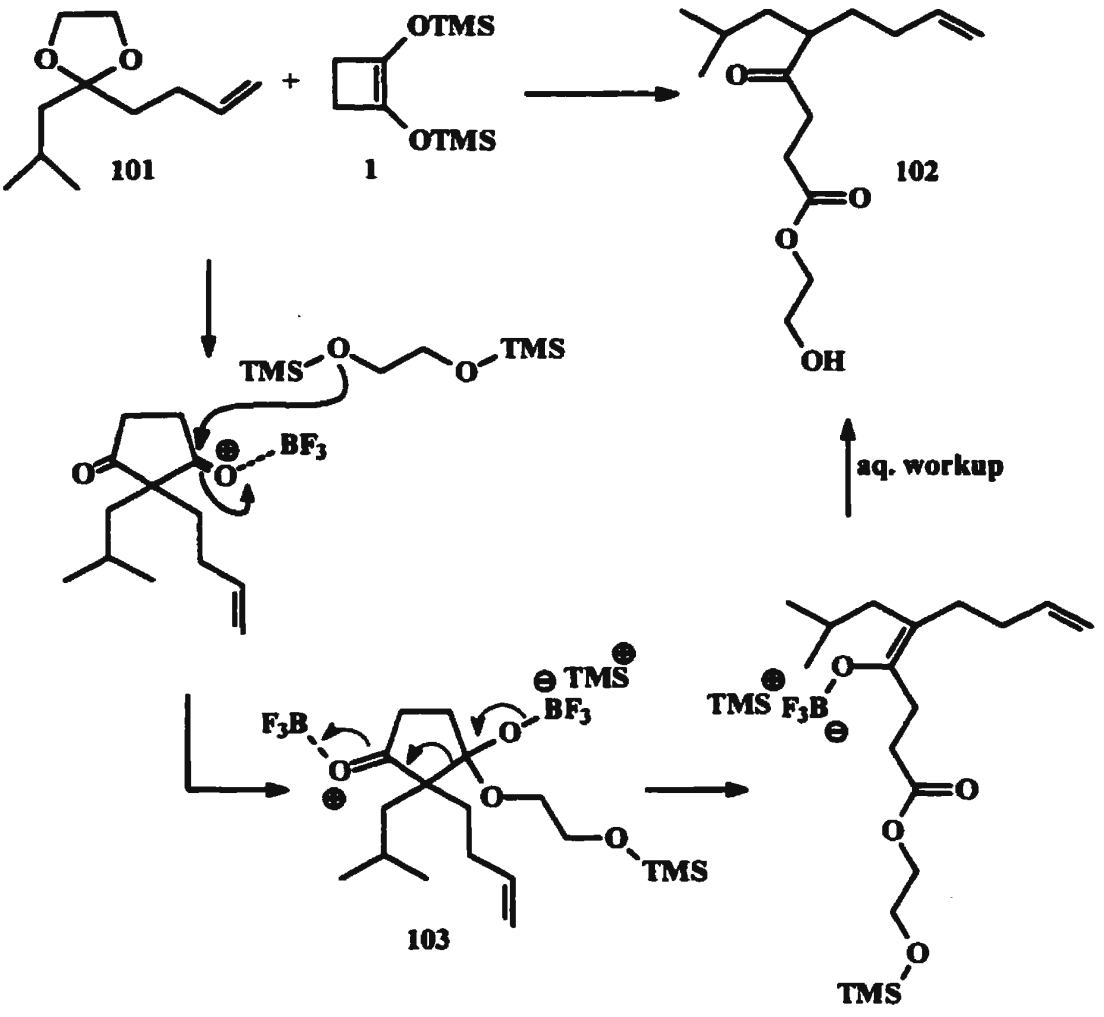
Scheme 33



Attempt to Prevent Reductive Succinyolation

Reductive succinoylation originally reported by Kuwajima and co-workers[1] is the Lewis acid-catalyzed ring-opening of the diketone product to produce a γ-keto ester. The geminal acylation reaction has been proven to be very sensitive to congestion about the acetal carbon. A series of acetals derived from ketones with α-methyl groups and 1,2-ethanediol were previously examined by Burnell and co-workers,[2c] and the yields of the bisacylation products ranged from modest to nonexistent because of this reductive succinoylation process. A mechanism for the formation of the keto-ester **102** is proposed in Scheme 34.

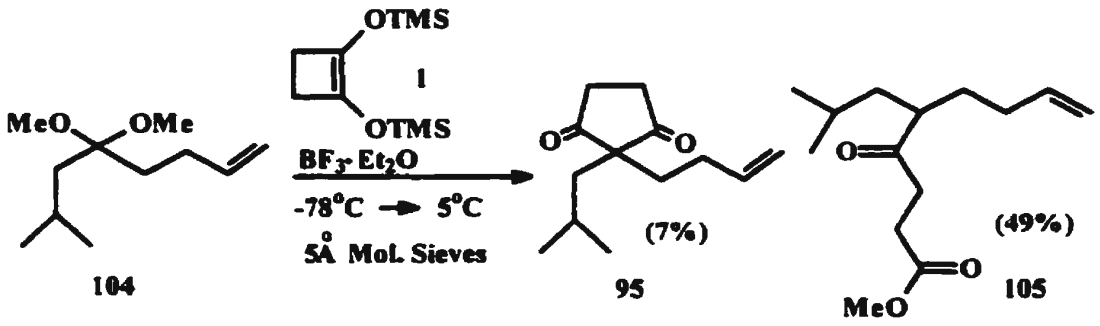
Scheme 34



The Lewis acid complexes with one of the carbonyls of the diketone and this is followed by nucleophilic attack at that carbonyl. Regeneration of a carbonyl can take place with the rupture of the ring and generation of an enol, as shown by structure **103** in Scheme 34. Upon aqueous workup, compound **102** is produced. Several attempts were made to stop this acid catalyzed ring opening.

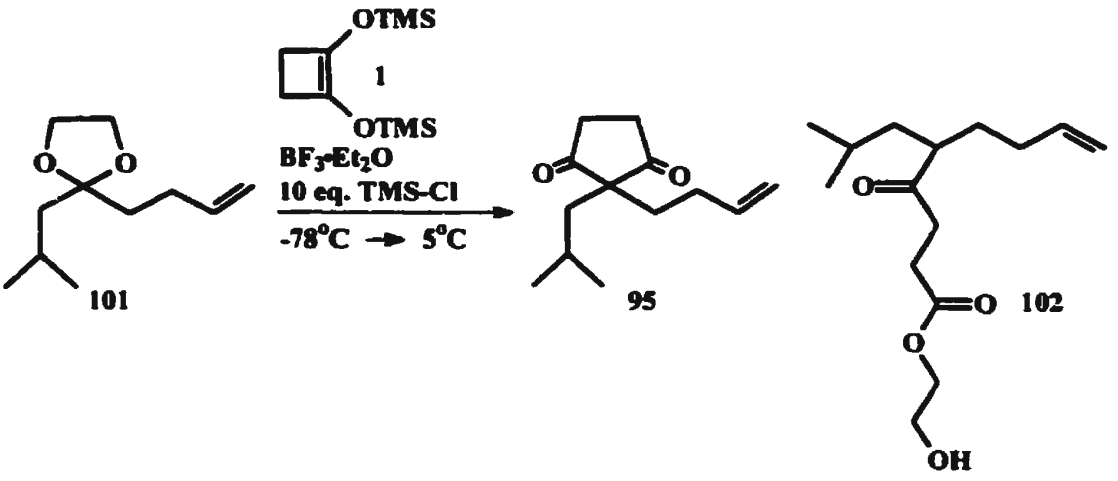
The first involved the use of the dimethyl acetal **104** instead of one derived from 1,2-ethanediol. The idea was to carry out the reaction in the presence of 5Å Molecular Sieves, using the time and temperature conditions reported by Curran and co-workers,[42] but then methanol might be trapped before it could initiate the reductive succinoylation process (Scheme 35). The use of the Molecular Sieves did not improve the disappointing result.

Scheme 35



Another attempt used 10 equivalents of chlorotrimethylsilane, which might leave the oxygen moieties of the ethylene glycol less nucleophilic and thus stop the ring-opening process. The result was also not promising (Scheme 36).

Scheme 36

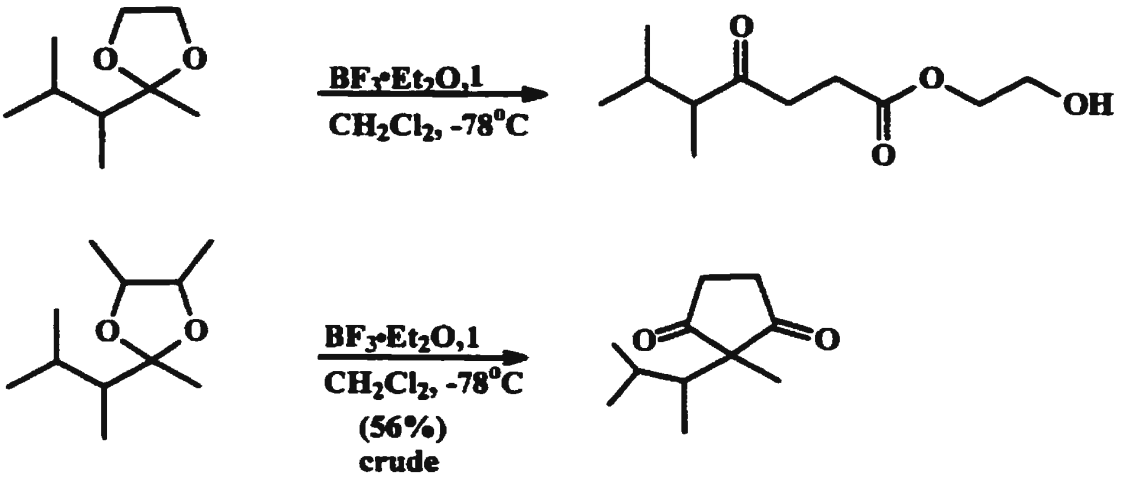


95:102 = 1:4.3

The yield was not determined in this reaction since the formation of the reductive succinoylation product was clearly evident in the crude ^{1}H NMR spectrum. The ratio of compound **95** to compound **102** was 1:4.3.

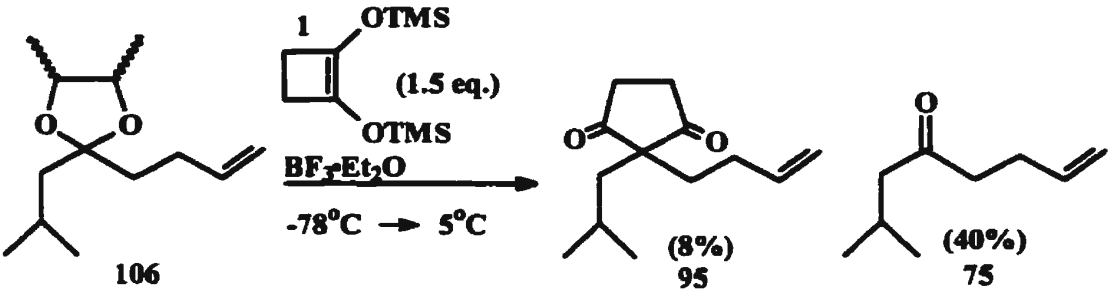
In the past, there had been some success in curbing reductive succinoylation in our laboratory using an acetal derived from a more hindered diol,[2c] as shown in Scheme 37. The increased bulk of the diol made it less capable of approaching the diketone to cause the ring opening process.

Scheme 37

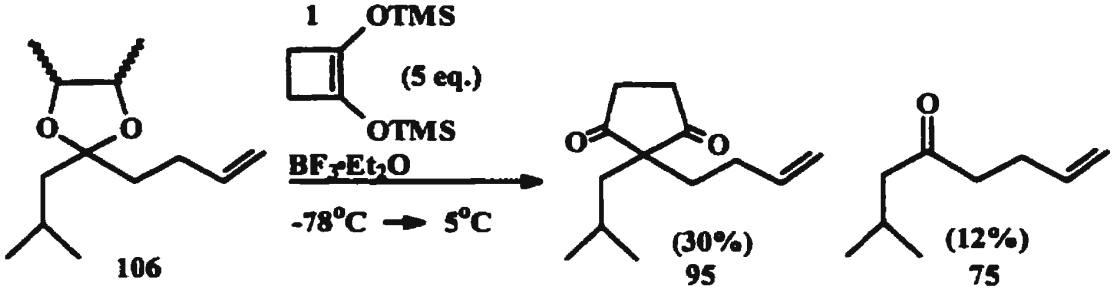


It was decided to try the geminal acylation with the acetal **106**, which was made from technical grade (±)-2,3-dimethylbutanediol (Scheme 38). The geminal acylation reaction proved to be very sluggish. Much of the parent ketone **75** was recovered along with the desired diketone substrate **95**. It was proposed that the diketone product might be produced in better yield if the number of equivalents of 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1** were increased. This was certainly the case, as can be seen in Scheme 38. An interesting aspect of this reaction is that the acetal recovered was entirely the (±) form of the acetal **106a**, which led to the conclusion that the meso-form of the acetal reacted more readily.

Scheme 38



plus 5% of the acetal, 106a

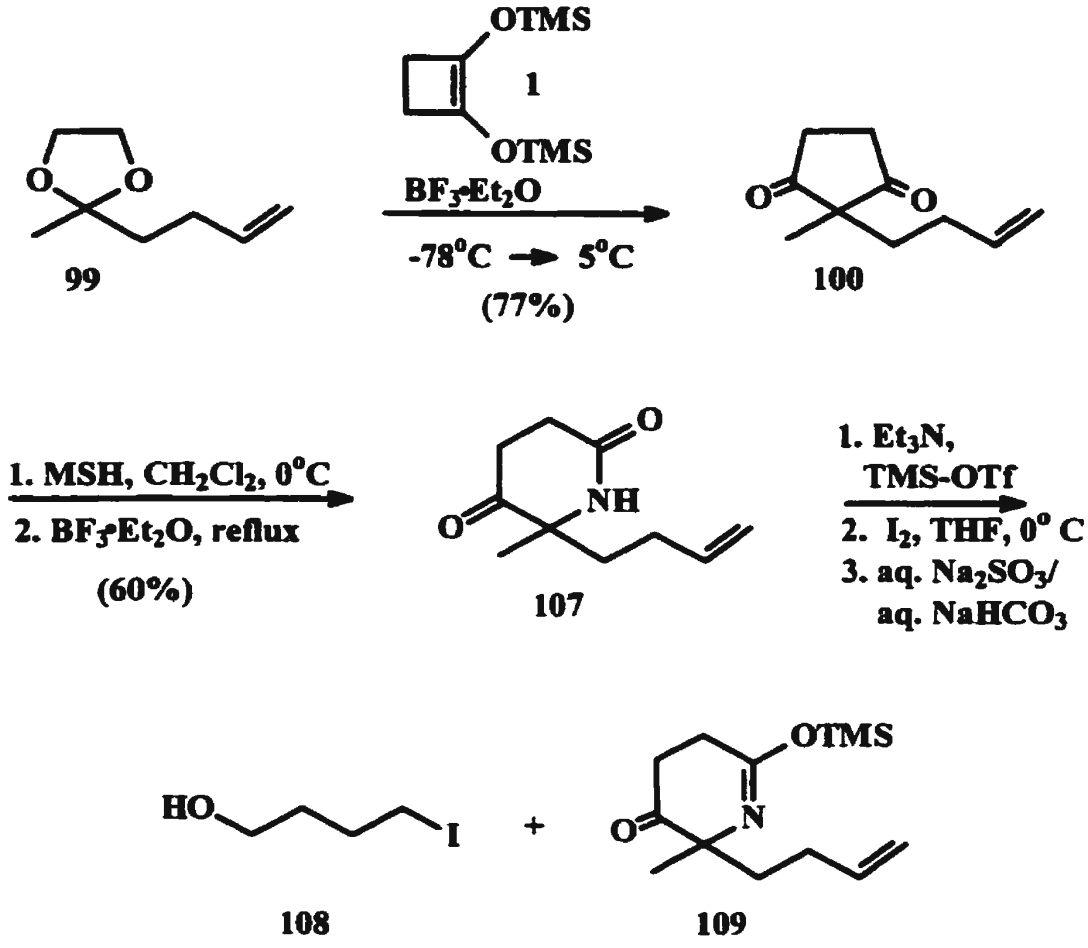


plus 25% of the acetal, 106a

Cyclization Using an Alternative Substrate

At the same time as pursuing the problem of reductive succinoylation it was decided to proceed with the synthesis of a simpler β-turn peptidomimetic. Since Curran and co-workers[42] had shown that the geminal acylation of allyl acetone could proceed in 67% yield, this substrate was utilized in this synthesis. The geminal acylation reaction of the acetal **99** gave the desired diketone **100** in a better yield than that reported by Curran and co-workers[42] (Scheme 39).

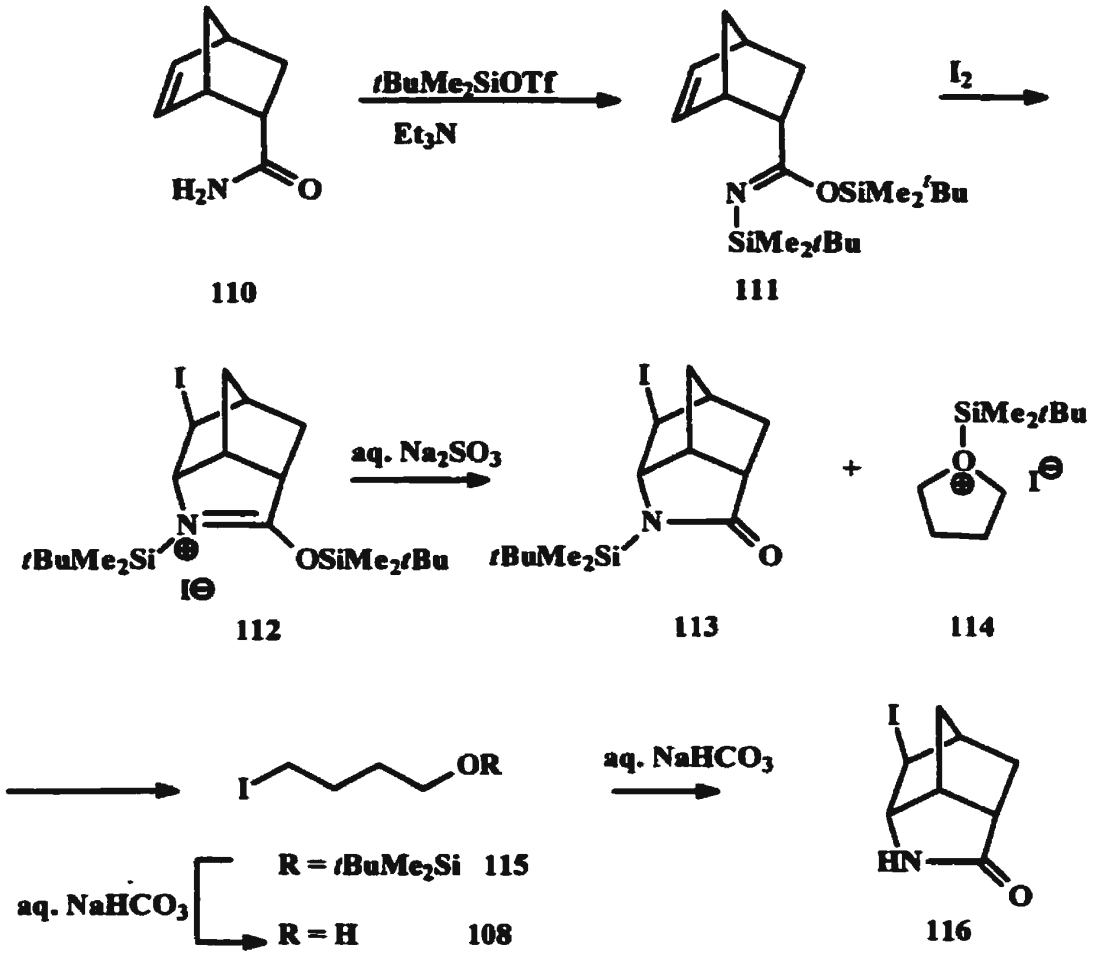
Scheme 39



The next step was the Beckmann reaction of compound **100** using MSH. It was not known if the conditions required for the migration of the quaternary center (BF_3•Et_2O, reflux) would also result in undesired Lewis acid catalyzed π-cyclization. Curran and co-workers[43] reported that the π-cyclization could occur with **100**. However, this was not the case since the yield of **107** was fairly good at 60%. The next step proved to be fatal in this route since 4-iodobutanol **108**, formed from THF, was isolated instead of the desired cyclized product. In

addition, the intermediate **109** was thought to be present in the crude mixture as determined by the ^{1}H NMR spectrum. There is a precedent[38b] for the formation of 4-iodobutanol during the synthesis of other iodolactams. The only reasonable source of **108** was from the solvent THF, which suggests that THF becomes silylated during the course of the reaction and is ultimately cleaved upon workup. When this same cyclization was performed with *endo*-5-norborene-2-carboxamide **110** (Scheme 40) using *tert*-butyldimethylsilyl trifluoromethane sulfonate as the silylating agent, the result was the formation of the *N,O*-bis(silyl) derivative **111**. This was treated with I_2 in THF, and work-up consisted of adding sodium sulfite only and omitting the sodium bicarbonate, although both are used in the "usual" work-up for this cyclization step. The result was the formation of the *N*-(*tert*-butyldimethylsilyl)lactam, **113** and the silylether of 4-iodobutanol **115** as shown in Scheme 40. Further treatment with water produced 4-iodobutanol **108**. Thus, the cyclization occurred to provide initially the iminium species **112**, the *O*-silil group of which was transferred to the oxygen of THF to give the siloxonium species **114**. Compound **114** was then opened by either iodide or triiodide leading to the silyl-protected form of 4-iodobutanol **115**. Treatment of **113** with aqueous $NaHCO_3$ resulted in the formation of the desired compound **116**.

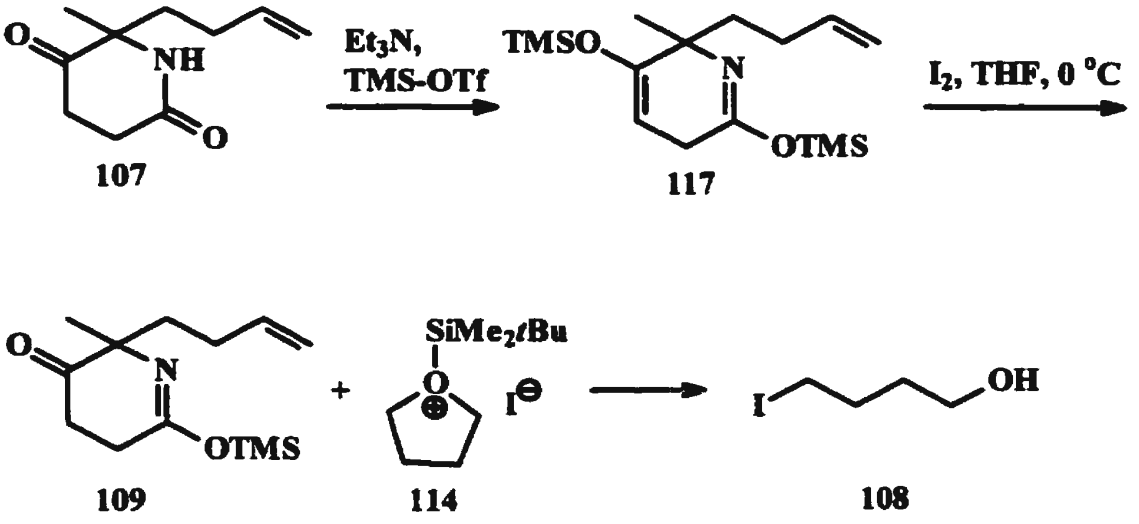
Scheme 40



It is likely that in our case the formation of species **117** was involved in this ring cleavage of THF since 2.2 equivalents of both Et_3N and TMS-OTf were used (Scheme 41). This was not possible with compound **88** in Scheme 26 since the α-carbon of the ketone was quaternary. Consequently, when THF is added to the reaction mixture, one of the silyl groups from groups **117** can transfer to the oxygen of THF allowing for iodide or triiodide to cleave THF. This leaves little or no iodine to add across the double bond of compound **109**. As a result, the

cyclization could not occur and the intermediate **109** was still present in the reaction mixture as seen by the ^{1}H NMR spectrum.

Scheme 41

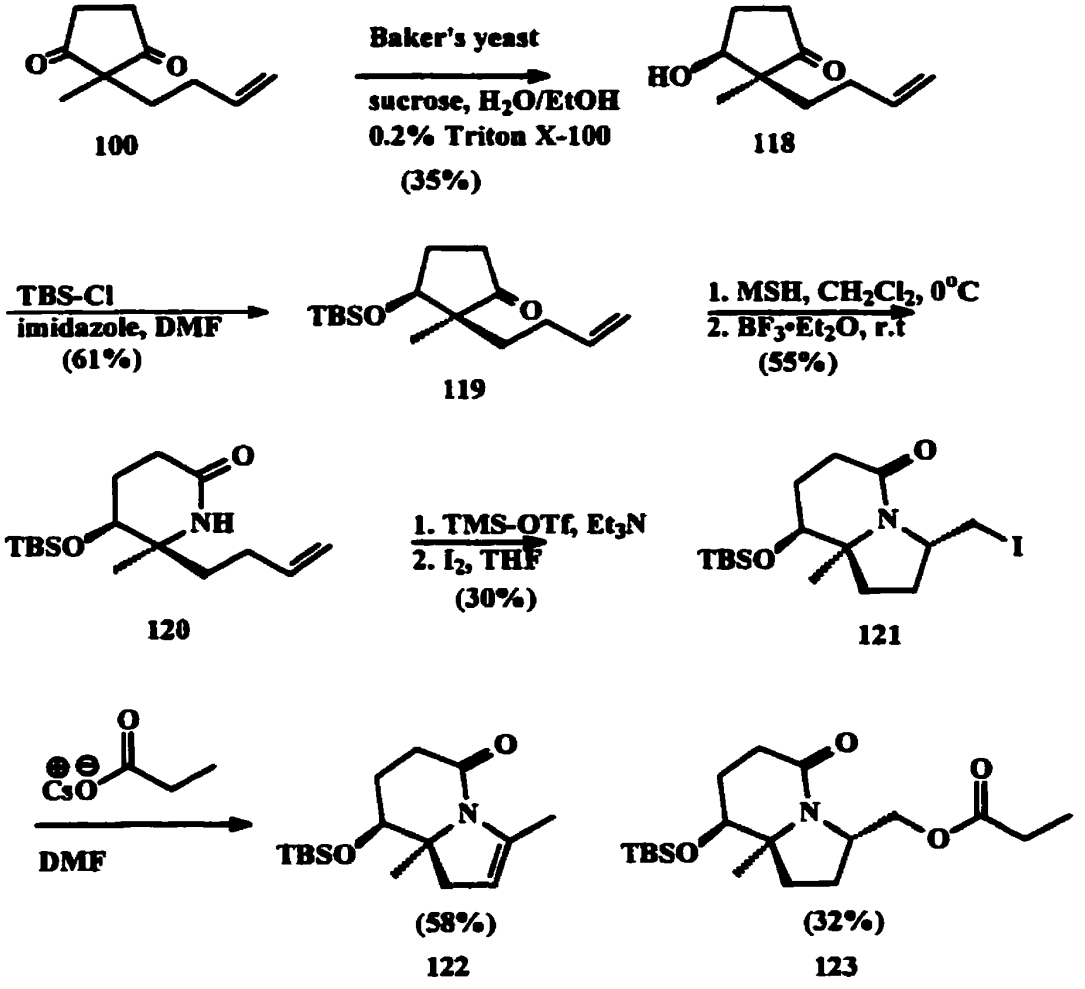


In order to avoid this it was necessary to either reduce selectively one of the ketones before cyclization so that double enol formation cannot occur, or use a different solvent. A number of solvents have previously been examined for this cyclization such as pentane, dichlormethane, toluene, acetonitrile, carbon tetrachloride, ether and dioxane but all proved to be less than satisfactory.[38b] The efficacy of THF is due in part to its ability to dissolve I_2 and its Lewis basicity. As a consequence, the selective reduction of one of the ketone moities was pursued. This was ultimately going to be done anyway since the original proposal was for a chiral, non-racemic route to a potential β-turn peptidomimetic.

Chiral, Non-racemic Route

The monoreduction of the diketones was planned to occur by the use of baker's yeast.[9b] This was investigated as outlined in Scheme 42. In addition, microbial monoreduction was also attempted with the cyclic amide **107**, but only starting material was recovered.

Scheme 42



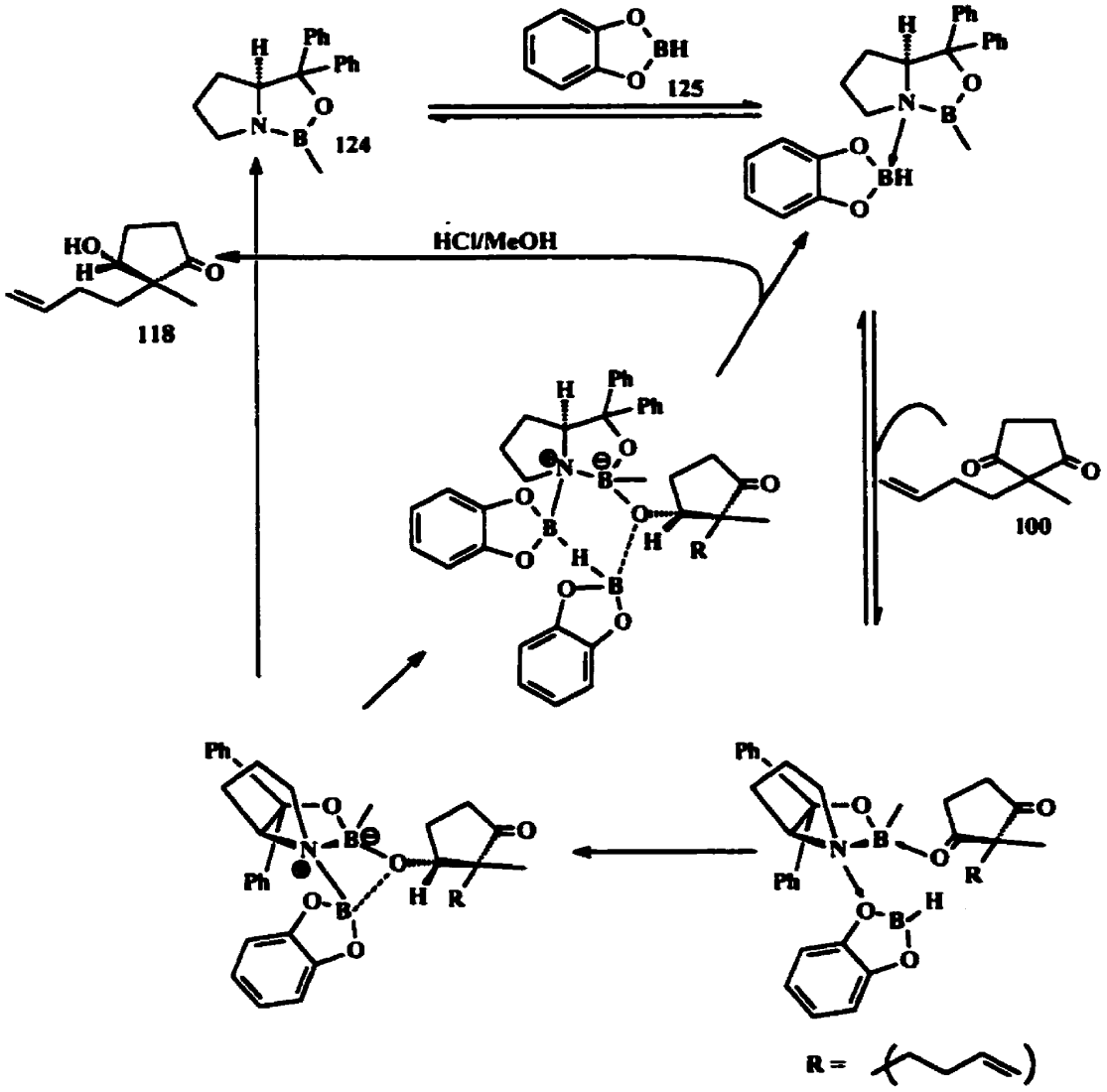
The diketone **100** underwent microbial reduction to produce the alcohol **118** in a 1:9 diastereomeric ratio. Difficulty was encountered in trying to separate these alcohols by flash chromatography at this point, so the mixture was protected using TBS-Cl. The Beckmann reaction was performed with **119** using MSH to produce the desired lactam **120**. The cyclization to furnish the iodolactam **121** was carried out, but the yield was only 30%. A fraction containing only the major isomer **121** was isolated after column chromatography with a yield of 14%. A mixture of the two isomers was also observed with a yield 16% and a ratio of 4.2:1.0 for **121** and its isomer. The relative and absolute stereochemistry of **121**, the major isomer, was determined using X-ray diffraction.

The next step in the synthetic sequence was the S_N2 reaction using cesium propionate to produce the ester **123**. A significant amount of the E2 elimination product **122** was also observed. This was attributed to decomposition of the cesium propionate to cesium hydroxide. A strong base is required in order to facilitate this elimination. As a result, when this reaction is carried out again in the future freshly prepared cesium propionate should be used. The last step required for the synthesis of a potential β-turn peptidomimetic would be the introduction of the amine moiety α to the amide carbonyl, but this step was not conducted due to a lack of material. It was felt that a more pressing matter was an effort to diastereoselectively reduce a diketone such as **100** using chemical

methods. The reduction of **100** with (*S*)-CBS-oxazaborolidinone **124** (Scheme 43) could be accomplished on a larger scale than was practical with yeast. Initially, there were concerns that the reduction would occur on either or both of the carbonyl carbons, as well as reduction of the double bond. The reduction was executed using both BMS and then BH_3•THF but reduction of more than one of the carbonyls was observed in the ^1H NMR spectrum. Next, the reduction was also performed using catecholborane, **125** a less reactive monohydride reagent. This reagent permits CBS reductions to occur (with excellent enantioselectivity)[44] at temperatures as low as -126 °C in noncoordinating solvents such as dichloromethane or toluene. Also, the decreased reactivity of catecholborane compared to BH_3, especially at lower temperatures, minimizes both the uncatalyzed ketone reduction and hydroboration of sensitive functional groups such as double and triple bonds as well as other carbonyl moieties within the ketonic structure.[44] The proposed mechanism for the CBS reduction of **100** is shown in Scheme 43. Based on this mechanism it is relatively easy to predict the major diastereomer, (2*S*,3*S*)-2-(3-Butenyl)-3-hydroxy-2-methyl- cyclopentanone **118**, for the chemical reduction using (*S*)-CBS-oxazaborolidine. The diastereomeric ratio for the chemical reduction of compound **100** was 1:9. The major diastereomer from the chemical reduction and the microbial reduction were the same, as shown from the ^1H NMR spectra for both. Thus, the prediction of the major diastereomer from Scheme 42 is consistent with the determination of the

absolute stereochemistry from X-ray diffraction analysis for compound **121**.

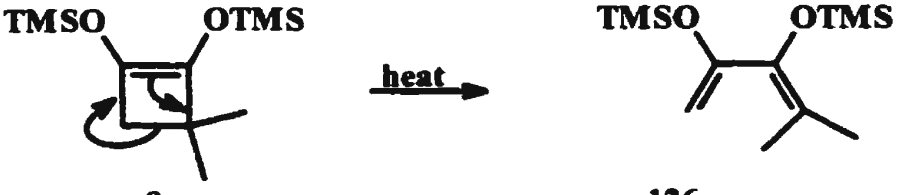
Scheme 43



Ring opening of 2,2-dimethyl-*bis*-[(trimethylsilyl)oxy]cyclobutene (9)

An interesting and unexpected result that was found during the course of this work occurred during the first attempt at the acyloin condensation reaction to produce 3,3-dimethyl-1,2-bis[(trimethylsilyl)oxy]cyclobutene **9**. During the course of synthesizing compound **9**, solvent is removed by simple distillation. The first attempt at the acyloin condensation reaction resulted in the application of too much heat, and **9** began to distill. Subsequent, high vacuum distillation gave a mixture of the desired product **9** as well as the ring-opened product **126** (Scheme 44). The structure of **126** was deduced from the following spectroscopic data: the ^{1}H NMR spectrum showed two signals indicative of olefinic protons at δ 4.40 and 4.29 as well as two distinct methyl signals at δ 1.77 and 1.65. Compound **9** contains two methyl groups as well, but they are chemically equivalent.

Scheme 44



9 **126**

These two isomers could not be separated by high vacuum distillation. In order to trap diene **126**, a Diels-Alder reaction using *N*-phenylmaleimide **127** was conducted (Scheme 45)

Scheme 45

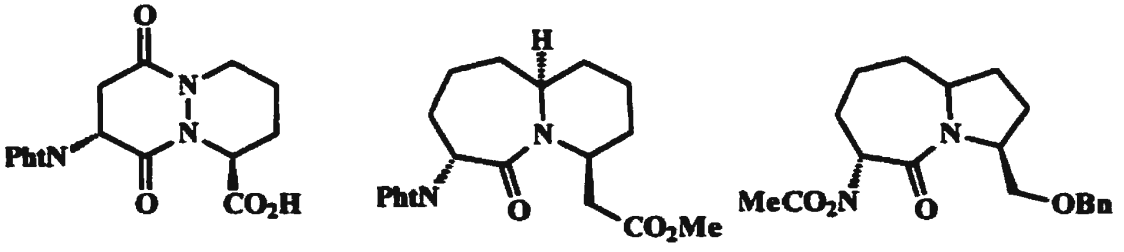
127 **126** **128**

After flash chromatography using a very short column, a fraction was isolated for which the ^{1}H NMR spectrum was consistent with the structure of adduct **128**. Signals for aromatic protons were clearly evident as well as two signals indicative of the protons at the ring junctions at δ 3.34 and 3.22. Also, signals at δ 2.92 and 2.53 were speculated to be the allylic protons. The low resolution mass spectroscopy clearly showed a mass indicative of the product **128** with a loss of a methyl group. Unfortunately, when the ^{13}C NMR spectrum was acquired, some evidence of hydrolysis was observed. Two signals were present which were characteristic of the amide carbonyls but there was also a ketonic carbonyl signal. Thus, the results were not conclusive, but there was some evidence to indicate that the diene **126** had been trapped to produce the desired Diels-Alder adduct.

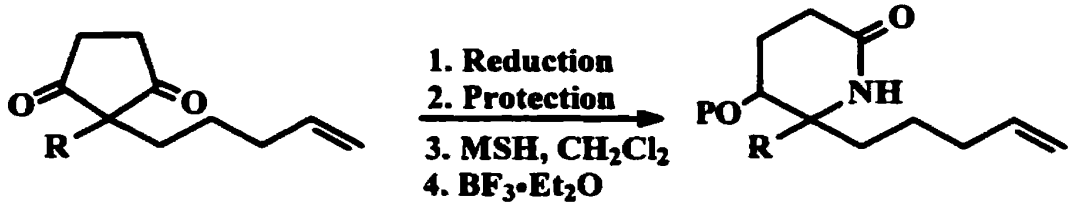
Considerations for Future Work

Several other sizes of fused-bicyclic ring systems could also be used as potential β-turn peptidomimetics. Throughout the literature there are many instances of similar ring systems being used to mimic different types of β-turn peptidomimetics as shown in Figure 4.[12] As stated before, the group located at the ring junction of these potential peptidomimetics in the literature[12] is exclusively hydrogen. Future work would consist of generating several of these differently-sized bicyclic ring systems. The synthesis of such compounds might be accomplished using the lactams shown in Scheme 46. These lactams could be synthesized using the reduction, protection and Beckmann reactions shown in Scheme 42. Compound **129** could be used to generate the 6,6-bicyclic system, while **130** and **131** could be used to produce the 5,7- and the 6,7-fused bicyclic systems.

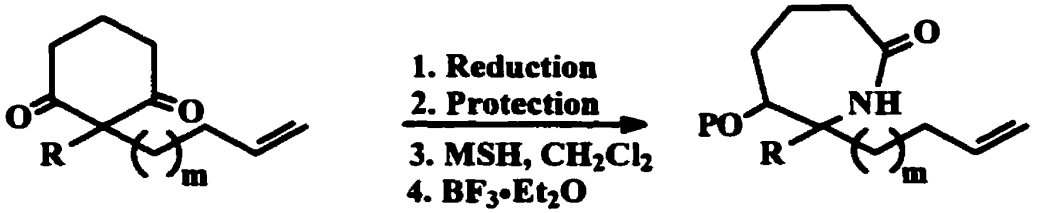
Figure 4: Examples of Other Fused-Ring Systems



Scheme 46



129



m = 1
m = 2

130: m = 1
131: m = 2

These bicyclic systems have not been as widely investigated as the 5,6-system but this would definitely be an area to focus on in future.

Finally, the chemical reduction would have to be pursued further to make this synthetic sequence viable so that the introduction of the amino moiety can be accomplished.

Experimental Section

General Procedures:

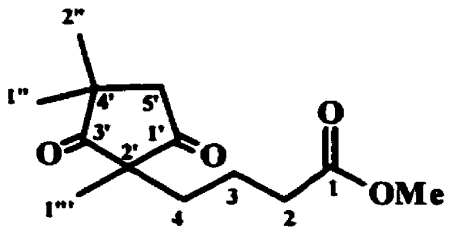
Compounds 1 and 9 were prepared by the method of Bloomfield and Nelke.[45] Flash chromatography ("chromatography") used 240-400 mesh silica gel. IR spectra were recorded on the Mattson FT-IR instrument as thin films, unless otherwise stated. Relative intensities of the absorption bands are recorded using the following abbreviations: s (strong), m (medium), w (weak), and b (broad). ^{1}H NMR spectra were obtained on either a General Electric GE-300 NB spectrometer at 300 MHz in $CDCl_3$ or a Bruker Avance spectrometer with a TXI inverse-detect gradient probe at 500 MHz in $CDCl_3$. Unless otherwise stated, shifts are relative to internal tetramethylsilane and coupling constants are in Hz. The following abbreviations are used in the description of multiplicities in the ^{1}H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) n (narrow), b (broad), and sep (septet). The ^{13}C NMR spectra were recorded at 75 MHz on the General Electric GE-300 NB spectrometer, and at 125 MHz on the Bruker Avance 500 MHz instrument. Shifts were measured relative to a solvent resonance. The number of attached protons was determined by an attached proton test (APT) and heteronuclear correlations for the GE-300 NB spectrometer, and by using distortionless enhancement by polarization transfer (DEPT) and heteronuclear multiple quantum correlation (HMQC) on the Bruker Avance 500

MHz instrument. NMR free induction decay data were processed using WinNuts (Acorn NMR software). Low resolution mass spectral data were recorded on the V.G. Micromass 7070HS instrument. High resolution mass spectra were obtained from the University of Ottawa mass spectral facility. Melting points were determined using a Fisher-Johns hot stage apparatus and were uncorrected. Mr. David Miller obtained data for the X-ray structures of compounds **64a**, **66**, **87**, and **121** on a Rigaku AFC6S difractometer. The data solution and refinement were performed using teXsan software. Dichloromethane, DMF, and pentane were distilled from CaH_2. THF and toluene were distilled from sodium metal.

General Procedure for Geminal Acylation.

Compounds **40**, **46**, and **76** were prepared based on the methods developed in our laboratory.[4,5,6] Compounds **52** and **63** were prepared based on the method of Jenkins and Burnell.[4] Compounds **55**, **61**, and **65** were provided by Dr. Sheldon Crane. Compounds **95** and **100** were generated based on the method of Curran and coworkers.[43]

Methyl 4-(2,4,4-trimethyl-1,3-dioxocyclopent-2-yl)butanoate (40)

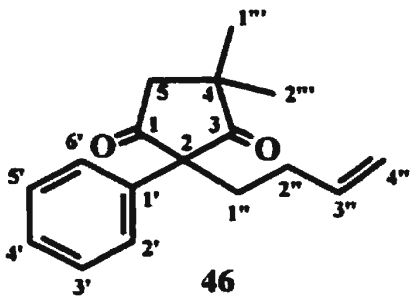


40

BCl_3 (12.8 mL, 12.8 mmol) and then **9** (3.33 g, 12.9 mmol) in CH_2Cl_2 (4 mL) were added to a solution of **39** (1.15 g, 7.99 mmol) in CH_2Cl_2 (16.5 mL) at -78°C and warmed to rt overnight. The mixture was recooled to -78°C before a

solution of 50% HF (6.4 mL) in MeOH (14 mL) was added and the mixture was stirred for 15 minutes. The mixture was warmed to rt and stirred for 1 hour. The mixture was concentrated under reduced pressure. TFA (24 mL) was added and the mixture was stirred at rt for 24 hours. Aqueous workup consisted of adding H_2O (100 mL) and CH_2Cl_2 (50 mL). Solid $NaHCO_3$ was added until neutral pH was obtained. The organic layer was washed with H_2O (100 mL) and the aqueous layer was back extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. Flash chromatography using 50% ethyl acetate/hexanes furnished **40** (653 mg, 34%) as a yellow liquid: IR ν_{max} 2962 (m), 1752 (bs), 1722 (bs) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.65 (3H, s, Me), 2.68 (1H, d, J = 18.3 Hz, H-5'), 2.60 (1H, d, J = 18.3 Hz, H-5'), 2.25 (2H, t, J = 6.8 Hz, H-2), 1.52 (4H, m, H-3, H-4), 1.25 (6H, s, H-1" and H-2"), 1.17 (3H, s, H-1'''). ^{13}C NMR ($CDCl_3$): δ 221.1 (0, C-3'), 216.4 (0, C-1'), 173.3 (0, C-1), 56.3 (0, C-2'), 51.8 (3, Me), 51.1 (2, C-5'), 46.5 (0, C-4'), 35.1 (2, C-4), 34.1 (2, C-2), 26.8 (3, C-1" or C-2"), 25.1 (3, C-1" or C-2"), 21.0 (3, C-1'''), 20.5 (2, C-3). MS *m/z* (%): 240 (10, M^+), 166 (26), 153 (10), 128 (40), 125 (15), 113 (21), 97 (12), 83 (32), 82 (33), 74 (16), 69 (83), 68 (17), 59 (11), 56 (19), 55 (27), 43 (21), 41 (100), 39 (27), 29 (18), 27 (19). HRMS calcd for $C_{13}H_{20}O_4$: 240.1360; found: 240.1348.

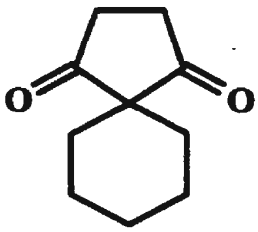
2-(3-Butenyl)-4,4-dimethyl-2-phenyl-1,3-cyclopentanedione (46)



46

A solution of **45** (328 mg, 2.35 mmol), **9** (833 mg, 3.22 mmol), and $BF_3 \cdot Et_2O$ (0.41 mL, 3.2 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 25 hours. Aqueous workup consisted of adding H_2O (30 mL) followed by CH_2Cl_2 (30 mL). The organic layer was washed with H_2O (2 × 30 ml) and the aqueous layer was back extracted with CH_2Cl_2 (3 × 30 mL). The solution was concentrated under vacuum. Flash chromatography using 40% ethyl acetate/hexanes provided **46** (248 mg, 47%) as a yellow liquid: IR ν_{max} 3064 (m), 1751 (s), 1721 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.29 (5H, m, H-2', H-3', H-4', H-5', H-6'), 5.68 (1H, m, H-3''), 4.93 (2H, m, H-4''), 2.71 (1H, d, J = 18.1 Hz, H-5), 2.50 (1H, d, J = 18.1 Hz, H-5), 1.91 (4H, m, H-2'' and H-1''), 1.22 (3H, s, H-1''' or H-2'''), 1.16 (3H, s, H-1''' or H-2'''). ^{13}C NMR ($CDCl_3$): δ 218.2 (0, C-3), 213.2 (0, C-1), 137.6 (1, C-3''), 136.4 (0, C-1'), 129.4 (1, C-6' and C-2'), 128.0 (1, C-4'), 126.7 (1, C-3' and C-5'), 115.5 (2, C-4''), 65.4 (0, C-2), 51.5 (2, C-5), 46.8 (0, C-4), 36.6 (2, C-1''), 30.0 (2, C-2''), 26.9 (3, C-1''' or C-2'''), 25.7 (3, C-1''' or C-2'''). MS *m/z* (%): 256 (1, M^+), 215 (19), 202 (30), 131 (71), 103 (100), 77 (14), 41 (11). HRMS calcd for $C_{17}H_{20}O_2$: 256.1462; found: 256.1460.

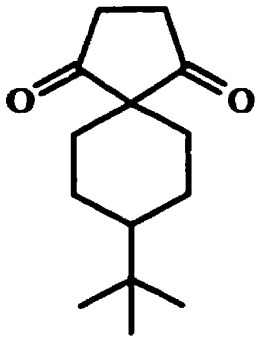
Spiro[4.5]decane-1,4-dione (52)



52

To a solution of cyclohexanone (620 mg, 6.32 mmol) and $BF_3 \cdot Et_2O$ (0.96 mL, 7.6 mmol) in CH_2Cl_2 (25 mL) at -78°C was added **1** (2.21 g, 9.67 mmol) in CH_2Cl_2 (14 mL). The mixture was stirred at this temperature for 3 hours before it was allowed to attain rt. H_2O (0.96 mL) was added, and the mixture was cooled again to -78°C before more $BF_3 \cdot Et_2O$ (14.4 mL, 113 mmol) was added. The mixture was allowed to attain rt overnight. Aqueous workup involved washing the mixture with H_2O (2 × 100 mL), back-extracting with CH_2Cl_2 (3 × 100 mL), washing the combined organic layers with brine (100 mL) and drying over anhydrous $MgSO_4$. The solvent was reduced in volume to 50 mL and the resulting solution was flushed through a Florisil column containing activated charcoal to yield **52** (956 mg, 91%) as a white solid: mp 60-62°C (lit.[2b] 61-62°C). ^1H NMR ($CDCl_3$): δ 2.74 (4H, s), 1.73-1.46 (10H, m). ^{13}C NMR ($CDCl_3$): δ 215.6, 55.8, 34.2, 29.1, 24.9, 20.4.

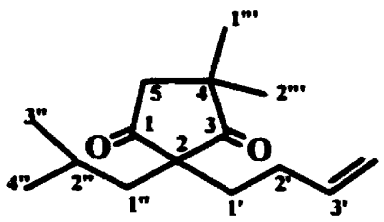
8-*tert*-Butylspiro[4.5]decane-1,4-dione (63)



63

To a solution of *tert*-butylcyclohexanone (490 mg, 3.17 mmol) and $BF_3 \cdot Et_2O$ (0.49 mL, 3.9 mmol) in CH_2Cl_2 (20 mL) at -78°C was added **1** (1.11 g, 4.86 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at this temperature for 3 hours before it was allowed to attain rt. H_2O (0.49 mL) was added, and the mixture was cooled again to -78°C before more $BF_3 \cdot Et_2O$ (6.1 mL, 48 mmol) was added. The mixture was allowed to attain rt overnight. Aqueous workup involved washing the mixture with H_2O (2 × 100 mL), back-extracting with CH_2Cl_2 (3 × 100mL), washing the combined organic layers with saturated NaCl (140 mL) and drying over anhydrous $MgSO_4$. The solvent was reduced to 50 mL and the resulting solution was flushed through a Florisil column containing activated charcoal to yield **63** (549 mg, 78%) as a white solid: mp 81-83°C (lit.[4] 82.5-84°C). ^1H NMR ($CDCl_3$): δ 2.76 (4H, b s), 1.75-1.46 (9H, m), 0.88 (9H, s). ^{13}C NMR ($CDCl_3$): δ 216.0, 215.9, 55.8, 46.9, 34.5, 34.3, 32.4, 30.1, 27.3, 21.6.

2-(3-Butenyl)-2-isobutyl-4,4-dimethyl-1,3-cyclopentanedione (76)

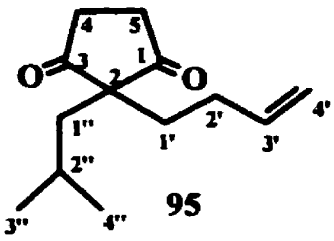


76

BCl_3 (28.0 mL, 28.0 mmol) and then **9** (11.0 g, 42.5 mmol) in CH_2Cl_2 (18.5 mL) were added to a solution of **75** (3.84 g, 27.4 mmol) in CH_2Cl_2 (50 mL) at -78°C, and warmed to rt overnight. The

mixture was recooled to -78°C before a solution of 50% HF (22.6 mL) in MeOH (48.5 mL) was added, and the mixture was stirred for 15 minutes. The mixture was warmed to rt and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure. TFA (77 mL) was added and the mixture was stirred at rt for 24 hours. Aqueous workup consisted of adding of water (200 mL) and solid $NaHCO_3$ until neutral pH was obtained. The organic layer was washed with H_2O (100 mL) and the aqueous layer was back extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was conducted eluting with 10% ethyl acetate/hexanes to yield **76** (3.46 g, 54%) as a colorless liquid: IR ν_{max} 2960 (bm), 1761 (s), 1720 (s) cm^{-1}. ^1H NMR($CDCl_3$): δ 5.69 (1H, m, H-3'), 4.96 (2H, m, H-4'), 2.69 (1H, d, *J* = 18.8 Hz, H-5), 2.60 (1H, d, *J* = 18.8 Hz, H-5), 1.89 (2H, m, H-2'), 1.68 (5H, m, H-1', H-1" and H-2"), 1.30 (3H, s, H-1"' or H-2"'), 1.25 (3H, s, H-1"' or H-2"'), 0.83 (6H, apparent t, *J* = 5.32 Hz, H-3" and H-4"). ^{13}C NMR ($CDCl_3$): δ 220.7 (0, C-1 or C-3), 215.9 (0, C-1 or C-3), 137.3 (1, C-3'), 115.5 (2, C-4'), 61.0 (0, C-2), 51.2 (2, C-5), 45.8 (0, C-4) , 43.8 (2, C-1' or C-1"), 34.8 (2, C-1' or C-1"), 28.7 (2, C-2'), 26.6 (3, C-1"' or C-2"'), 26.3 (3, C-1"' or C-2"'), 24.9 (1, C-2"), 24.3 (3, C-3" or C-4"), 24.2 (3, C-3" or C-4"). MS *m/z* (%): 182 (37, M^+- C_4H_6), 140 (42), 139 (10), 111 (85), 109 (25), 93 (20), 81 (30), 79 (10), 67 (16), 56 (16), 55 (59), 53 (18), 43 (31), 41 (100), 40 (12), 39 (32), 29 (32), 27 (32).

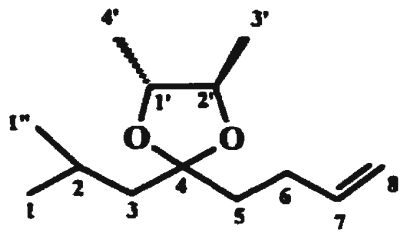
2-(3-Butenyl)-2-isobutyl-1,3-cyclopentanedione (95)



95

BF_3•Et_2O (0.63 mL, 5.0 mmol) was introduced slowly to a solution of **106** (105 mg, 0.496 mmol) in CH_2Cl_2 (4.95 mL) at -78°C. After 10 minutes, **1** (0.60 g, 2.6 mmol) was added to the mixture, and the mixture was stirred at -78°C for 3 hours. The mixture was slowly warmed to 5°C, and after ten minutes the mixture was diluted with Et_2O (15 mL), H_2O (15 mL) and then extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (25 mL) and dried over anhydrous $MgSO_4$. Flash chromatography was performed eluting with 20% ethyl acetate/hexanes to yield **95** (31.0 mg, 30%) as a yellow liquid. The recovery of the starting material **106a** was entirely the *d/l* form (25%). IR ν_{max} 2958 (bm), 1764 (s), 1722 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.63 (1H, m, H-3'), 4.95 (2H, m, H-4'), 2.76 (4H, s, H-4 and H-5), 1.92 (2H, m, H-2'), 1.62 (5H, m, H-1', H-1" and H-2"), 0.77 (6H, d, J = 6.7 Hz, H-3" and H-4"). ^{13}C NMR ($CDCl_3$): δ 217.4 (0, C-3 and C-1), 137.3 (1, C-3'), 115.9 (2, C-4'), 60.4 (0, C-2), 44.5 (2, C-1' or C-1"), 36.3 (2, C-1' or C-1"), 36.2 (2, C-4 and C-5) , 28.8 (2, C-2'), 25.2 (3, C-3" or C-4"), 24.0 (2C, 1 and 3, C-2" and C-3" or C-4"). MS *m/z* (%): 208 (1, M^+), 154 (60, M^+- C_4H_6), 152 (12), 125 (14), 112 (100), 111 (37), 107 (15), 81 (13), 67 (11), 55 (31), 53 (11), 43 (22), 41 (47), 39 (17), 29 (19), 28 (16), 27 (23).

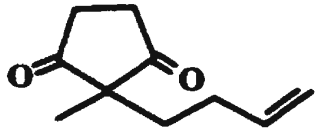
(*d/l*)-2-Methyl-pentyl-7-octen-4-one, 2,3-butanediol acetal (106a)



106a

Colorless liquid: ^{1}H NMR ($CDCl_3$): δ 5.84 (1H, m, H-7), 4.97 (2H, m, H-8), 3.61 (2H, m, H-1', H-2'), 2.13 (2H, m, H-6), 1.78 (1H, m, H-2), 1.71 (2H, m, H-5), 1.53 (2H, d, J = 6.2 Hz , H-3), 1.24 (3H, s, H-3' or H-4'), 1.22 (3H, s, H-3' or H-4'), 0.95 (6H, apparent t, J = 6.7 Hz , H-1 and H-1") . ^{13}C NMR ($CDCl_3$): δ 139.3 (1, C-7), 114.5 (2, C-8), 111.2 (0, C-4), 79.0 (1, C-1' or C-2'), 78.7 (1, C-1' or C-2'), 47.3 (2, C-3), 38.2 (2, C-5), 28.3 (2, C-6), 24.6 (3, C-3' or C- 4'), 24.3 (3, C-3' or C-4'), 17.3 (3, C-1 or C-1'), 17.0 (3, C-8 or C-1').

2-(3-Butenyl)-2-methyl-1,3-cyclopentanedione (100)



100

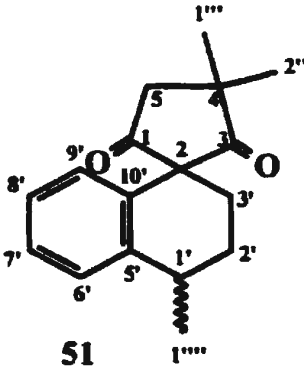
Compound **99** (758 mg, 5.33 mmol) was dissolved in CH_2Cl_2 (53 mL) and the reaction mixture was cooled to -78°C. BF_3•Et_2O (6.76 mL, 53.4 mmol) was added dropwise and after ten minutes, **1** (1.61 g, 7.00 mmol) was introduced slowly. The mixture was stirred at -78°C for 3 hours before it was warmed to 5°C . The mixture was stirred at this temperature for ten minutes, then the mixture was diluted with Et_2O (35 mL) followed by H_2O (35 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (75 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was performed eluting with

33% ethyl acetate/hexanes to produce **100** (677.1 mg, 76%) as a colorless liquid: IR ν_{max} 2927 (s), 1765 (m), 1722 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.64 (1H, m), 4.94 (2H, m), 2.77 (4H, m), 1.96 (2H, m'), 1.77 (2H, m), 1.12 (3H, s). ^{13}C NMR ($CDCl_3$): δ 216.8, 137.5, 116.0, 56.4, 35.3, 34.3, 29.3, 20.3. MS *m/z* (%): 166 (3, M^+), 125 (28), 112 (100), 97 (15), 69 (37), 41 (55), 39 (19), 28 (17), 27 (20).

General Procedure for the Beckmann Reaction using NH_2SO_3H/HCO_2H

Compounds **51**, **53**, **56**, **64a**, **64b**, and **66** were prepared based on the method of Olah and Fung.[32]

1',2',3',4'-Tetrahydro-1',4,4-trimethylspirocyclopentane-2-naphthalene (51)

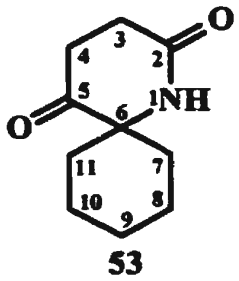


51

A solution of NH_2OSO_3H (180 mg, 1.60 mmol) and **46** (258 mg, 1.00 mmol) in 98% formic acid (2.5 mL) was heated under reflux for 2 days. The mixture was cooled to rt, then in an ice bath which was followed by the addition of H_2O (10 mL). The mixture was adjusted to a pH of 9-10 using 20% NaOH. Workup consisted of extracting with $CHCl_3$ (4 × 50 mL) and drying the combined organic extracts over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was performed using 20% ethyl acetate/hexanes to yield **51** as the major product (15.3 mg, 6%) a tan colored resin. The ^{13}C NMR spectrum was complicated by the presence of both epimers. IR ν_{max} 2962 (m), 1765 (m), 1721 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.41-7.17 (3H, m, H-6', H-7' and H-8'), 6.64 (1H, d,

J = 7.3 Hz, H-9'), 3.11 (2H, m, H-1' and H-5), 2.79 (1H, m, H-5), 2.24-2.01 (3H, m, H-2' and H-3'), 1.82 (1H, m, H-3'), 1.56 (3H, 2 s, H-1''' or 2'''), 1.55 (3H, 2 s, H-1''' or 2''') 1.45 (3H, dd, J = 1.3 Hz, 30.2 Hz, H-1'''). ^{13}C NMR ($CDCl_3$): δ 220.1, 219.6, 143.9, 143.8, 129.1, 128.9, 128.7, 128.0, 126.5, 120.5, 51.0, 50.9, 46.7, 32.2, 32.0, 30.4, 29.9, 26.9, 26.8, 26.5, 26.3, 26.1, 25.9, 23.1, 23.0, 22.8, 22.7. MS *m/z* (%): 256 (0.2, M^+), 146 (9), 117 (11), 104 (100). HRMS calcd for $C_{17}H_{20}O_2$: 256.1462; found: 256.1443.

1-Azaspiro[5.5]undecane-2,5-dione (53)

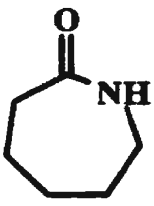


53

A solution of NH_2OSO_3H (106 mg, 1.00 mmol) and **52** (103.6 mg, 0.6233 mmol) in 98% formic acid (1.56 mL) was heated under reflux for 2 hours. The mixture was cooled to rt, then in an ice bath which was followed by the addition of H_2O (10 mL). The mixture was adjusted to a pH of 9-10 using 20% NaOH. Workup consisted of extracting with $CHCl_3$ (5 × 30 mL) and drying the combined organic extracts over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was performed using 75% acetone/hexanes to yield **53** (51.1 mg, 45%) and **54** (6.2 mg), both as white solids. Physical data for compound **53**: mp 187-189°C. IR (Nujol) ν_{max} 3425 (m), 1713 (m), 1657 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.94 (1H, bs, H-1), 2.69 (4H, s, H-3 and H-4), 1.52-1.80 (10H, m, H-7, H-8, H-9, H-10, H-11). ^{13}C NMR ($CDCl_3$): δ 208.9 (0, C-5), 171.6 (0, C-2), 63.3 (0, C-6), 32.0 (2, C-4), 31.6 (2, C-7 and C-11), 26.2 (2, C-3), 21.8

(2, C-8 and C-10), 17.7 (2, C-9). MS *m/z* (%): 181 (0.1, M^+), 153 (62), 110 (18), 98 (59), 97 (100), 96 (16), 82 (18), 81 (11), 69 (34), 57 (22), 56 (12), 55 (17), 54 (41), 42 (12), 41 (34), 39 (18), 30 (14), 29 (15), 28 (39), 27 (35). HRMS calcd for $C_{10}H_{15}NO_2$: 181.1102; found: 181.1080.

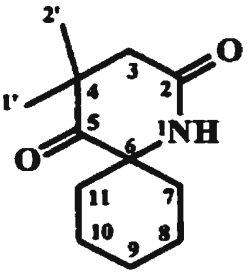
ϵ-Caprolactam (54)



54

mp 66-69°C (lit.[46] 70-72°C). ^{1}H NMR ($CDCl_3$): δ 7.16 (1H, b s), 3.20 (2H, m), 2.45 (2H, m,), 1.69 (6H, m). ^{13}C NMR ($CDCl_3$): δ 197.6, 42.8, 36.8, 30.7, 29.8, 23.3.

1-Aza-4,4-dimethylspiro[5.5]undecane-2,5-dione (56)

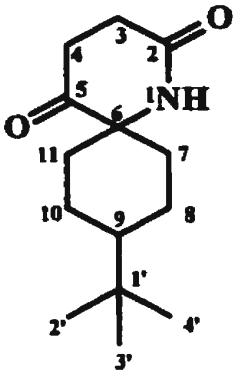


56

A solution of NH_2OSO_3H (77.9 mg, 0.689 mmol) and **55** (86.3 mg, 0.444 mmol) in 98% formic acid (1.1 mL) was heated under reflux for 3 hours. The mixture was cooled to rt, then in an ice bath which was followed by the addition of H_2O (15 mL). The mixture was adjusted to a pH of 9-10 using 20% NaOH. Workup consisted of extracting with $CHCl_3$ (4 × 30 mL) and drying the combined organic extracts over anhydrous $MgSO_4$. The solution was concentrated under vacuum to yield **56** (73.3 mg, 79%) as a white solid: mp 186-189°C. IR (CCl_4) ν_{max} 2928 (m), 1721 (m), 1672 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.45 (1H, b s, H-1), 2.51 (2H, s, H-3), 1.79 (4H, m, H-7, H-11), 1.37 (5 H, m, H-8, H-10 and H-9), 1.20 (6H, s, H-1' and H-2'). ^{13}C NMR ($CDCl_3$): δ 212.4 (0, C-

5), 170.2 (0, C-2), 62.8 (0, C-6), 42.6 (2, C-3), 42.2 (0, C-4), 34.6 (2, C-7 and C-11), 24.5 (3, C-1' and C-2'), 24.3 (2, C-9), 20.3 (2, C-8 and C-10). MS *m/z* (%): 209 (3, M^+), 181 (54), 138 (22), 110 (13), 98 (100), 97 (99), 96 (12), 82 (13), 81 (10), 69 (20), 57 (10), 56 (29), 55 (23), 54 (39), 53 (11), 42 (11), 41 (57), 39 (25), 29 (20), 28 (30), 27 (17).

***cis*-1-Aza-9-*tert*-butylspiro[5.5]undecane-2,5-dione (64a)**

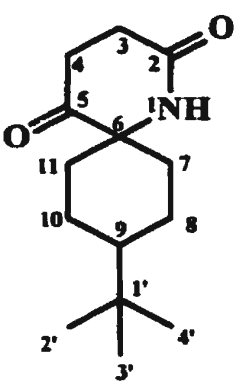


64a

A solution of NH_2OSO_3H (23.4 mg, 0.207 mmol) and **63** (25.5 mg, 0.145 mmol) in 98% formic acid (1.6 mL) was heated under reflux for 3 hours. The mixture was cooled to rt, then in an ice bath which was followed by the addition of H_2O (10 mL). The mixture was adjusted to a pH of 9-10 using 20% NaOH. Workup consisted of extracting with $CHCl_3$ (4 × 25 mL) and drying the combined organic extracts over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was performed using 75% acetone/hexanes to yield a mixture of **64a** and **64b** (11.7 mg, 41%) as a white solid. The yield based on recovered starting material was 56%. Flash chromatography was preformed on the mixture using 50% acetone/hexanes to yield **64a** (3.4 mg) and **64b** (7.1 mg). Physical data for compound **64a**: mp 160-162°C. IR (CCl_4) ν_{max} 3196 (m), 3088 (m), 2967 (s), 1712 (s), 1659 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.91 (1H, b s, H-1), 2.68 (4H, s, H-3 and H-4), 2.16 (2H, m, H-7 and H-11, equatorial), 1.58 (4H, m, H-8 and H-10),

1.32 (2H, m, H-7 and H-11, axial), 1.02 (1H, m, H-9), 0.87 (9H, s, H-2', H-3', and H-4'). ^{13}C NMR ($CDCl_3$): δ 208.0 (0, C-5), 171.8 (0, C-2), 61.7 (0, C-6), 46.9 (1, C-9), 37.5 (2, C-7 and C-11), 35.1 (2, C-3 or C-4), 32.6 (0, C-1'), 29.3 (2, C-3 or C-4), 27.7 (3, C-2', C-3', C-4'), 23.4 (2, C-8 and C-10). MS *m/z* (%): 238 (3), 209 (58), 194 (30), 154 (24), 153 (19), 152 (26).

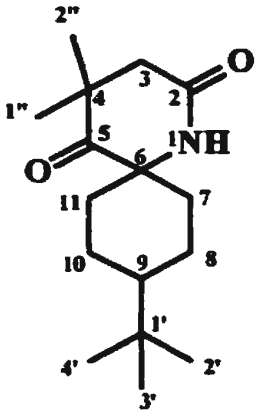
***trans*-1-Aza-9-*tert*-butylspiro[5.5]undecane-2,5-dione (64b)**



64b

White solid: mp 230-233°C. IR (CCl_4) ν_{max} 3193 (m), 2933 (m), 1722 (m), 1660 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.12 (1H, b s, H-1), 2.69 (4H, m, H-3 and H-4), 1.78 (6H, m, H-8 or H-10, H-7, and H-11), 1.11 (3H, m, H-8 or H-10, H-9), 0.87 (9H, s, H-2', H-3', and H-4'). ^{13}C NMR ($CDCl_3$): δ 208.6 (0, C-5), 171.1 (0, C-2), 63.5 (0, C-6), 47.0 (1, C-9), 35.1 (2, C-3 or C-4), 35.0 (2, C-7 and C-11), 32.7 (0, C-1'), 29.2 (2, C-3 or C-4), 27.6 (3, C-2', C-3', C-4'), 21.7 (2, C-8 and C-10). MS *m/z* (%): 238 (1), 209 (63, M^+ - CO), 194 (41), 154 (30), 153 (20), 152 (28), 138 (25), 125 (57), 110 (59), 100 (14), 97 (33), 96 (61), 95 (10), 82 (20), 81 (15), 74 (12), 70 (15), 69 (100), 67 (14), 57 (8), 55 (31), 54 (23, 43 (20), 42 (11), 41 (54), 29 (31), 28 (31), 28 (43), 27 (15). HRMS calcd for $C_{14}H_{23}NO_2$: 237.1728; found: 237.1698.

1-Aza-9-*tert*-butyl-4,4-dimethylspiro[5.5]undecane-2,5-dione (66)

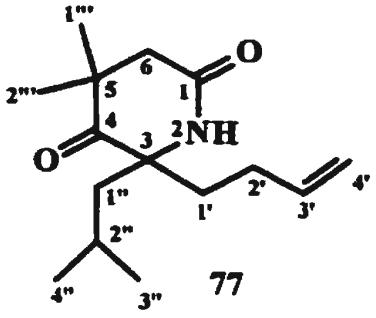


66

A solution of NH_2OSO_3H (370 mg, 3.27 mmol) and **65** (542 mg, 2.16 mmol) in 98% formic acid (5.4 mL) was heated under reflux for 20 hours. The mixture was cooled to rt, then in an ice bath which was followed by the addition of H_2O (25 mL). The mixture was adjusted to a pH of 9-10 using 20% NaOH. Workup consisted of extracting with $CHCl_3$ (4 × 50 mL) and drying the combined organic extracts over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was performed using 10% acetone/hexanes to yield **66** (306 mg, 54%) as a beige solid: mp: 251-253°C. IR (Nujol) ν_{max} 3213 (m), 3091 (m), 1712 (s), 1666 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.35 (1H, b s, H-1), 2.53 (2H, s, H-3), 1.84-1.70 (8H, m, H-7, H-11, H-8 and H-10), 1.20 (6H, s, H-1"and H-2"), 1.12 (1H, m, H-9), 0.87 (9H, s, H-2', H-3' and H-4'). ^{13}C NMR ($CDCl_3$): δ 212.8 (0, C-5), 170.3 (0, C-2), 63.1 (0, C-6), 46.7 (1, C-9), 43.0 (2, C-3), 42.6 (0, C-4), 35.6 (2, C-7 and C-11), 32.7 (0, C-1'), 27.6 (3, C-2', C-3' and C-4'), 24.9 (3, C-1" and C-2"), 21.7 (2, C-8 and C-10). MS *m/z* (%): 250 (7, M^+ - Me), 237 (58), 222 (17), 180 (12), 154 (77), 153 (35), 138 (73), 112 (11), 97 (43), 96 (49), 83 (19), 82 (23), 81 (13), 70 (12), 69 (57), 67 (12), 57 (98), 56 (46), 55 (48), 54 (29), 53 (12), 43 (22), 42 (14), 41 (100), 39 (19), 29 (42), 28 (23), 27 (15). HRMS calcd for $C_{16}H_{27}NO_2$: 250.1806 (M^+-Me); found: 250.1825.

General Procedure for Beckmann Rearrangement using MSH. Compounds **77**, **107**, and **120** were prepared using the method of Tamura and co-workers[35] with some modifications. The MSH was prepared using the method Tamura and co-workers,[34] and the reagent was stored below 0°C.

1-Aza-6-(3-butenyl)-6-isobutyl-4,4-dimethyl-2,5-cyclohexadione (77)

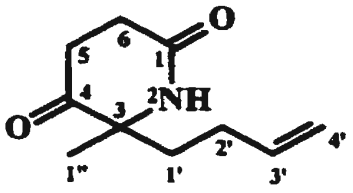


77

A solution of **72** (318 mg, 1.49 mmol) in CH_2Cl_2 (1.0 mL) was added to solution of **76** (188 mg, 0.798 mmol) in CH_2Cl_2 (1.6 mL) at 0°C. The mixture was stirred at this temperature for 20 minutes, warmed to rt overnight and then heated under reflux for 6 hours. $BF_3 \cdot Et_2O$ (0.30 ml) was added, and the mixture was heated under reflux for 30 minutes. Aqueous workup consisted of washing with saturated $NaHCO_{3(aq)}$ (2 × 10 mL), back-extracting aqueous layers with CH_2Cl_2 (3 × 10 mL), and drying the combined organic layers over anhydrous $MgSO_4$. Flash chromatography was performed using 25% acetone/hexanes to yield **77** (97.9 mg, 49%) as a white solid. The ratio of **76** to **77** in the crude mixture as determined by ^{1}H NMR spectroscopy was 0.5:1. mp 69-71°C. IR (CCl_4) ν_{max} 3198 (m), 3083 (m), 2961 (m), 1718 (s), 1673 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.64 (1H, m, H-2), 5.73 (1H, m, H-3'), 4.99 (2H, m, H-4'), 2.53 (2H, m, H-6), 2.08 (1H, m, H-2'), 1.98-1.75 (2H, m, H-2', H-1'), 1.71-1.59 (1H, m, H-1''), 1.54-1.43 (2H, m, H-1', H-1''), 1.29 (1H, m, H-2''), 1.22 - 1.19 (6H, dd, J = 3.9 Hz, 11.1 Hz, H-1''' and 2'''), 0.96 - 0.94 (3H,

dd, J = 1.4 Hz, 6.6 Hz, H-3" or 4"), 0.91 - 0.88 (3H, dd, J = 4.3 Hz, 6.9 Hz, H-3" or 4"). ^{13}C NMR ($CDCl_3$): δ 212.6, 212.3 (0, C-4), 171.1 (0, C-1), 137.2 (1, C-3'), 115.9, 115.8 (2, C-4'), 67.8, 67.6 (0, C-3), 48.2, 48.1 (2, C-1"), 43.4 (2, C-6), 42.4, 42.3 (0, C-5), 40.0 (2, C-1'), 39.2 (2, C-1'), 28.5 (2, C-2'), 26.3 (2, C-2'), 25.5 (2, C-2'), 26.3, 25.5 (3, C-1"' or 2"'), 25.54, 25.50 (3, C-1"' or 2"'), 25.4 (3, C-4" or 3"), 24.9, (3, C-4" or 3"), 24.8 (3, C-4" or 3"), 24.5 (2, C-1'), 23.1 (2, C-1'), 14.1 (2, C-2"). MS *m/z* (%): 223 (15, M^+-CO), 196 (12), 182 (37), 180 (11), 142 (15), 140 (71), 124 (18), 112 (12), 98 (15), 97 (31), 96 (33), 84 (16), 83 (26), 82 (28), 57 (60), 56 (46), 55 (54), 53 (14), 43 (43), 42 (32), 41 (100), 40 (10), 39 (40), 29 (55), 28 (28), 27 (42).

1-Aza-6-(3-butenyl)-6-methyl-2,5-cyclohexadione (107)

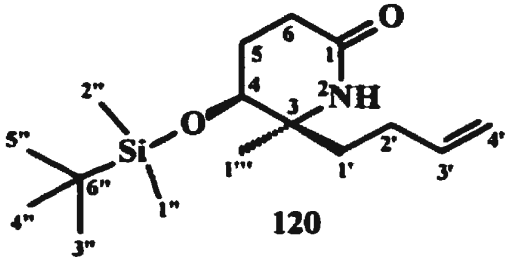


107

A solution of **72** (316 mg, 1.45 mmol) in CH_2Cl_2 (1.2 mL) was added to a solution of **100** (188 mg, 1.13 mmol) in CH_2Cl_2 (2.3 mL) at 0°C. The mixture was stirred at this temperature for 10 minutes then at rt overnight. BF_3•Et_2O (0.42 mL) was added, and the mixture was stirred at rt for 3.5 hours, followed by heating to reflux for 3.5 hours. Aqueous workup consisted of washing with saturated $NaHCO_{3(aq)}$ (2 × 10 mL), extracting the combined aqueous layers with CH_2Cl_2 (3 × 20 mL) and drying the organic solutions over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography was performed using 50% acetone/hexanes to yield **107** (127.8

mg, 62%) as a white solid: mp 115-117°C. IR (CCl_4) ν_{max} 3195 (bs), 1729 (s), 1674 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ (1H, b s, H-2), 5.75 (1H, m, H-3'), 5.06 (2H, m, H-4'), 2.68 (4H, m, H-5 and H-6), 2.62 (1H, m, H-1'), 2.13 (2H, m, H-1' and H-2'), 1.59 (1H, m, H-2'), 1.38 (3H, s, H-1''). ^{13}C NMR ($CDCl_3$): δ 208.6 (0, C-4), 172.0 (0, C-1), 137.1(1, C-3'), 115.8 (2, C-4'), 64.2 (0, C-3), 39.7 (2, C-1'), 35.4 (2, C-5 or C-6), 29.1 (2, C-5 or C-6), 28.5 (2, C-2'), 27.2 (3, C-1''). MS *m/z* (%): 181 (0.2, M^+), 153 (34, M^+ - CO), 138 (12), 126 (31), 112 (25), 98 (100), 97 (48), 96 (30), 82 (37), 81 (13), 57 (24), 56 (22), 55 (20), 42 (58), 41 (25), 39 (15), 29 (10), 28 (33), 27 (22).

(3*S*, 4*S*)-1-Aza-6-(3-butenyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexanone (120)



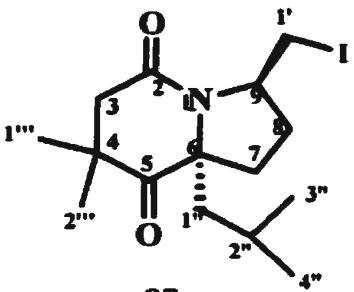
120

A solution of **72** (760 mg, 3.53 mmol) in CH_2Cl_2 (1.70 mL) was added to a solution of **119** (436 mg, 1.54 mmol) in CH_2Cl_2 (3.1 mL) at 0°C. The mixture was stirred at this temperature for 20 minutes than at rt overnight. $BF_3 \cdot Et_2O$ (0.60 mL) was added, and the mixture was stirred at rt for 1 hour. Workup consisted of adding 20 mL of CH_2Cl_2 and washing the mixture with saturated $NaHCO_3$ (2 × 25 mL), extracting with ethyl ether (3 × 25 mL) and drying the combined organic layers over anhydrous $MgSO_4$. The solution volume was reduced to approximately 10 mL. The resultant solution was passed through

a short pad (1.5 cm × 2.0 cm) of DOWEX 1 × 8-400 ion exchange resin, strongly basic anion and flushed with an additional 75 mL of ethyl ether. The solvent was removed under vacuum. Flash chromatography was performed using 50% ethyl acetate/hexanes to furnish **120** (279 mg, 60%) as a white solid: mp 67-69°C. IR (CCl_4) ν_{max} 3136 (m), 2956 (m), 1662 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.49 (1H, b s, H-2), 5.81 (1H, m, H-3'), 5.02 (2H, m, H-4'), 3.72 (1H, t, J = 5.6 Hz, H-4), 2.54 (1H, m, H-6), 2.35 (1H, m, H-6), 1.93 (2H, m, H-2'), 1.77 (2H, m, H-5), 1.73 (1H, m, H-1'), 1.57 (1H, m, H-1'), 1.20 (3H, s, H-1'"), 0.90 (9H, s, H-3", H-4" and H-5"), 0.10 (6H, s, H-1" and H-2"). ^{13}C NMR ($CDCl_3$): δ 171.4 (0, C-1), 138.4 (1, C-3'), 115.0 (2, C-4'), 72.3 (1, C-4), 58.4 (0, C-3), 36.2 (2, C-1'), 27.8 (2, C-6 and C-2'), 26.3 (3, C-1'"), 25.9 (3, C-3", C-4" and C-5"), 25.4 (2, C-5), 18.2 (0, C-6"), -3.9 (3, C-1" or C-2"), -4.9 (3, C-1" or C-2"). MS *m/z* (%): 297 (2, M^+), 256 (28), 242 (44), 240 (40), 198 (37), 115 (33), 111 (10), 110 (13), 101 (25), 99 (11), 98 (24), 96 (13), 82 (16), 75 (100), 74 (35), 73 (98), 59 (34), 58 (46), 57 (27), 55 (20), 43 (15), 42 (18), 41 (37), 39 (11), 29 (29), 27 (12). HRMS calcd for $C_{16}H_{31}NO_2Si$: 297.2122; found: 297.2115.

General Procedure for Electrophilic Cyclization. Compounds **87**, **88**, and **121**, were prepared based on the method of Knapp and co-workers.[38]

(6*R,9*R**)-1-Aza-9-(iodomethyl)-6-isobutyl-4,4-dimethylbicyclo[4.3.0]nonane 2,5-dione (87)**

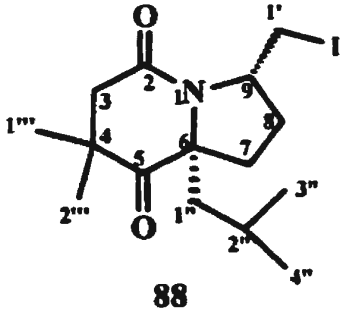


87

Triethylamine (0.21 mL, 2.9 mmol) and TMS-OTf (0.50 mL, 2.9 mmol) were added to a stirred solution of 77 (238 mg, 0.948 mmol) in pentane (1.4 mL) at 0°C. The solution was stirred for 20 min at rt, after which time the two layers were allowed to separate. The top layer was cannulated into a 10 mL round bottom flask, and the oily residue was washed with dry pentane (2 × 1 mL). The pentane extracts were concentrated under reduced pressure. The residue was cooled in an ice bath and iodine (0.53 g, 2.1 mmol) in THF (2.1 mL) was added. The reaction mixture was stirred for 10 minutes. The mixture was removed from the ice bath and quenched with saturated sodium sulfite (3.5 mL), and saturated sodium bicarbonate (3.5 mL). Workup consisted of extracting with ethyl acetate (3 × 15 mL), washing the combined organic layers with saturated sodium bicarbonate (25 mL) and drying over anhydrous $MgSO_4$. The solvent was removed under vacuum. Flash chromatography was performed using 30% ethyl acetate/hexanes to yield a mixture of **87** and **88** in a 4.8:1 ratio. (218.4 mg, 61%) as a beige solid. It was possible to isolate a small amount of the two diastereomers. The physical data for compound **87** is as follows: mp 83-85°C. IR (CCl_4) ν_{max} 1712 (s), 1654 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.25 (1H, m, H-9), 3.67 (1H, dd, J = 2.7, 9.7 Hz, H-1'), 3.43

(1H, dd, J = 8.4, 9.7 Hz, H-1'), 2.84 (1H, d, J = 16.6 Hz, H-3), 2.49 (1H, d, J = 16.6 Hz, H-3), 2.16 (2H, m, H-8) 1.98 (2H, m, H-7), 1.66 (3H, m, H-1" and H-2"), 1.25 (3H, s, H-1"'or 2"'), 1.22 (3H, s, H-1"' or 2"'), 0.95 (3H, d, J = 6.3 Hz, H-3" or H-4"), 0.87 (3H, d, J = 6.2 Hz, H-3" or H-4"). ^{13}C NMR ($CDCl_3$): δ 213.0 (0, C-5), 167.0 (0, C-2), 73.8 (0, C-6), 57.6 (1, C-9), 45.3 (2, C-1"), 44.9 (2, C-3), 42.5 (0, C-4), 31.2 (2, C-8), 28.0 (2, C-7), 27.8 (3, C-1"' or C-2"'), 26.0 (3, C-1"' or C-2"'), 24.8 (3, C-3" or C-4"), 24.6 (3, C-3" or C-4"), 24.1 (1, C-2"), 8.6 (2, C-1'). MS *m/z* (%): 349 (68, M^+ - CO), 320 (41), 306 (11), 292 (12), 266 (65), 265 (29), 250 (24), 223 (63), 222 (11), 178 (9), 138 (40), 97 (11), 96 (26), 95 (11), 83 (43), 82 (88), 80 (12), 67 (10), 58 (11), 57 (20), 56 (66), 55 (77), 54 (17), 53 (20), 43 (56), 42 (21), 41 (100), 40 (12), 39 (37), 29 (49), 28 (49), 27 (36).

(6*R,9*S**)-1-Aza-9-(iodomethyl)-6-isobutyl-4,4-dimethylbicyclo[4.3.0]nonane 2,5-dione (88)**

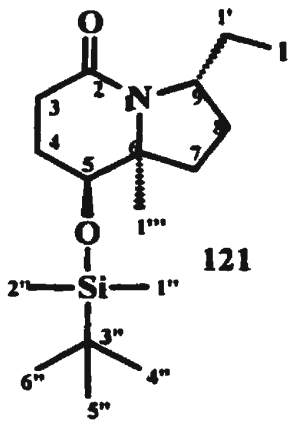


88

Beige solid: mp 75-77°C. IR (CCl_4) ν_{max} 1718 (s), 1639 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.36 (1H, m, H-9), 3.85 (1H, dd, J = 3.6, 9.1 Hz, H-1'), 3.06 (1H, dd, J = 9.1, 10.1 Hz, H-1'), 2.79 (1H, d, J = 15.7 Hz, H-3), 2.39 (1H, d, J = 15.7 Hz, H-3), 2.23 (1H, m, H-8), 2.08 (2H, m, H-7), 1.92 (2H, m, H-8 and H-1"), 1.61 (2H, m, H-2" and H-1"), 1.19 (3H, s, H-1"' or H-2"'), 1.12 (3H, s, H-1"' or H-2"'), 0.92 (3H, d, J = 6.3 Hz, H-3" or H-4"), 0.89 (3H, d, J = 6.3 Hz, H-3"or H-4"). ^{13}C NMR ($CDCl_3$): δ 213.5 (0, C-5), 167.0

(0, C-2), 74.3 (0, C-6), 60.1 (1, C-9), 47.8 (2, C-1"), 43.9 (2, C-3), 42.4 (0, C-4), 36.7 (2, C-7), 29.6 (2, C-8), 26.2 (3, C-1‴ or C-2‴), 24.9 (1, C-2"), 24.6 (3, C-4" or C-3"), 24.6 (3, C-3" or C-4"), 24.3 (3, C-1‴ or C-2‴), 9.9 (2, C-1'). MS *m/z* (%): 349 (52, M^+ - CO), 320 (11), 266 (55), 265 (24), 250 (21), 223 (55), 222 (10), 138 (34), 97 (9), 96 (22), 83 (30), 82 (81), 80 (11), 68 (10), 67 (10), 57 (19), 56 (62), 55 (72), 54 (17), 53 (19), 43 (31), 42 (20), 41 (100), 40 (11), 39 (34), 29 (46), 28 (30), 27 (33). HRMS calcd for $C_{15}H_{24}INO_2$: 349.0904 (M^+- CO); found: 349.0915.

(6*S*,5*S*,9*S*)-1-Aza-5-[(*tert*-butyldimethylsilyl)oxy]-9-(iodomethyl)-6-methyl-bicyclo[4.3.0]nonan-2-one (121)



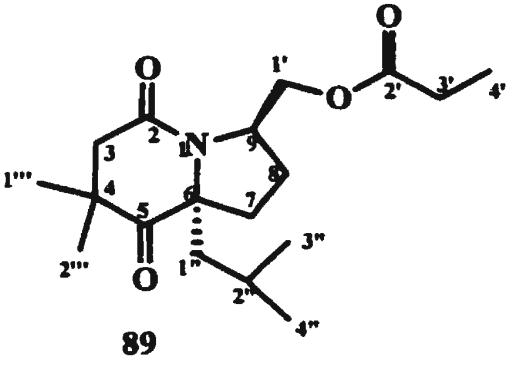
Triethylamine (0.18 mL, 1.3 mmol) and TMS-OTf (0.23 mL, 1.3 mmol) were added to a solution of **120** (174 mg, 0.584 mmol) in pentane (0.9 mL) at 0°C. The reaction mixture was stirred at rt for 30 minutes after which time the two layers were allowed to separate. The top layer was cannulated into a 10 mL round-bottom flask, and the oily residue was washed with dry pentane (2 × 1 mL). The pentane extracts were concentrated under reduced pressure. The residue was cooled in an ice bath, and a solution of iodine (0.33 g, 1.30 mmol) in THF (1.3 mL) was added. The mixture was stirred at this temperature for 10 minutes, removed from the ice bath and quenched with saturated sodium sulfite (2.2 mL),

followed by saturated sodium bicarbonate (2.2 mL). The reaction mixture was extracted with ethyl acetate (3 × 20 mL) and dried the combined organic layers over anhydrous $MgSO_4$. The volume of the solution was reduced under vacuum. Flash chromatography was performed using 30% ethyl acetate/hexanes to yield **121** (34.6 mg, 14%) and a fraction containing **121** and its isomer (39.8 mg, 16%) in a ratio of 4.2:1. Compound **121** was a beige solid: mp 128-129°C. IR (CCl_4) ν_{max} 2956 (m), 1648 (s) cm^{-1}. $[\alpha]_D^{24}$ = -6.5°, C = 3.51 mg/mL in MeOH. ^1H NMR ($CDCl_3$): δ 4.04 (1H, m, H-9), 3.82 (2H, t, J = 9.1 Hz, H-1'), 3.79 (1H, m, H-5), 3.23 (1H, t, J = 9.0 Hz, H-1'), 2.44 (1H, m, H-3), 2.32 (1H, m, H-3), 2.24-2.08 (3H, m, H-8, H-7 and H-4), 1.81 (1H, m, H-4), 1.74 (1H, m, H-8), 1.45 (1H, m, H-7), 1.26 (3H, s, H-1'''), 0.87 (9H, s, H-4", H-5" and H-6"), 0.08 (3H, s, H-2" or H-1"), 0.06 (3H, s, H-1" or H-2"). ^{13}C NMR ($CDCl_3$): δ 170.5 (0, C-2), 70.4 (1, C-5), 67.6 (0, C-6), 59.7 (1, C-9), 32.9 (2, C-7), 29.5 (2, C-8), 27.2 (3, C-1'''), 26.8 (2, C-3), 26.2 (3, C-4", C-5", and C-6"), 25.5 (2, C-4), 18.5 (0, C-3"), 12.5 (2, C-1'), -4.1 (3, C-1" or C-2"), -4.6 (3, C-1" or C-2"). MS *m/z* (%): 423 (6, M^+), 366 (19), 366 (100), 296 (21), 292 (33), 265 (24), 224 (31), 223 (16), 164 (10), 150 (11), 122 (13), 115 (44), 108 (10), 101 (32), 98 (33), 96 (30), 82 (12), 75 (45), 73 (58), 59 (27), 57 (21), 56 (11), 55 (24), 42 (15), 41 (36), 39 (11), 29 (23), 27 (10). HRMS calcd for $C_{16}H_{31}O_2INSi$: 423.1091; found: 423.1091.

General Procedure for the Nucleophilic Substitution using Cesium Propionate.

Compounds **89**, **90**, **122**, and **123** were prepared based on the method of Shieh and Prestwich.[39]

(6*R,9*R**)-1-Aza-9-(hydroxymethyl)-6-isobutyl-4,4-dimethyl-bicyclo[4.3.0]nonane-2,5-dione, propyl ester (89)**

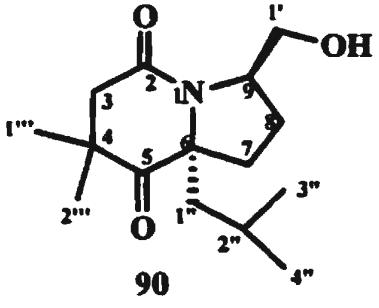


89

Cesium propionate (28.0 mg, 0.136 mmol) in DMF (1.4 mL) was added to a solution of **87** (48.0 mg, 0.127 mmol) in DMF (1.3 mL). The reaction mixture was stirred at rt for 2 hours, heated under reflux for 4 hours, and then stirred at rt overnight. Aqueous workup consisted of washing the organic layer with brine (25 mL) and extracting with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. Flash chromatography was performed using 30% ethyl acetate/hexanes. Further purification was required using 50 % acetone/hexanes to yield **89** (16.4 mg, 40%) and **90** (20.6 mg, 60%). Compound **89** was a pale yellow residue: IR (CCl_4) ν_{max} 2960 (m), 1740 (s), 1719 (s), 1662 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.53 (1H, dd, J = 4.5, 11.2 Hz, H-1'), 4.32 (2H, m, H-1' and H-9), 2.86 (1H, d, J = 16.5 Hz, H-3), 2.43 (1H, d, J = 16.5 Hz, H-3), 2.27 (2H, q, J = 7.3 Hz, H-3'), 2.13 (3H, m, H-8

and H-7), 1.84 (1H, m, H-7), 1.68 (3H, m, H-2" and H-1"), 1.23 (3H, s, H-1‴ or H-2‴), 1.17 (3H, s, H-1‴ or H-2‴), 1.09 (3H, t, J = 7.8 Hz, H-4'), 0.95 (3H, d, J = 6.2 Hz, H-4" or H-3"), 0.88 (3H, d, J = 6.1 Hz, H-3" or H-4"). ^{13}C NMR ($CDCl_3$): δ 213.6 (0, C-5), 174.2 (0, C-2'), 168.9 (0, C-2), 73.4 (0, C-6), 63.3 (2, C-1'), 56.0 (1, C-9), 45.7 (2, C-1"), 45.0 (2, C-3), 42.6 (0, C-4), 32.6 (2, C-8), 27.7 (2, C-3'), 26.9 (3, C-1‴ or C-2‴), 25.8 (3, C-1‴ or C-2‴), 25.7 (2, C-7), 24.9 (1, C-2"), 24.7 (3, C-4" or C-3"), 24.2 (3, C-4" or C-3"), 9.2 (3, C-4'). MS *m/z* (%): 295 (15, M^+-CO), 252 (13), 212 (65), 211 (26), 210 (48), 196 (23), 180 (15), 169 (21), 156 (12), 96 (15), 97 (29), 84 (11), 83 (30), 82 (75), 57 (66), 56 (37), 55 (44), 43 (12), 41 (64), 39 (19), 29 (100), 28 (13), 27 (31).

(6*R,9*R**)-1-Aza-9-(hydroxymethyl)-6-isobutyl-4,4-dimethylbicyclo[4.3.0]nonane-2,5-dione (90)**

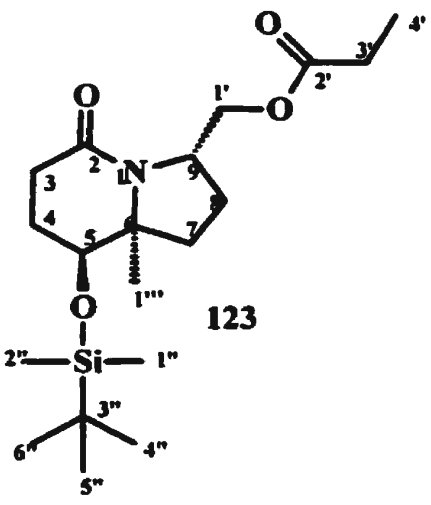


90

Beige solid: mp 80-82°C. IR (CCl_4) ν_{max} 3426 (bm), 2962 (m), 1721 (s), 1644 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.67 (1H, m, -OH), 4.16 (1H, m, H-9), 3.74 (2H, m, H-1'), 2.87 (1H, d, J = 16.5 Hz, H-3), 2.49 (1H, d, J = 16.5 Hz, H-3), 2.09 (2H, m, H-8), 1.64 (5H, m, H-7, H-1" and H-2"), 1.23 (3H, s, H-1‴ or 2‴), 1.19 (3H, s, H-2‴ or H-1‴), 0.95 (3H, d, J = 6.2 Hz, H-3" and H-4"), 0.88 (3H, d, J = 6.2 Hz, H-3" or H-4"). ^{13}C NMR ($CDCl_3$): δ 213.0 (0, C-5), 170.8 (0, C-2), 74.3 (0, C-6), 66.5 (2, C-1'), 62.2 (1, C-9), 45.7 (2, C-7 or C-1"), 44.8 (2, C-3), 42.0 (0, C-4), 32.7 (2, C-8), 26.9 (3,

C-1''' or C-2'''), 26.3 (2, C-7 or C-1''), 25.6 (3, C-1''' or C-2'''), 24.9 (1, C-2''), 24.7 (3, C-3'' or C-4''), 24.3 (3, C-3'' or C-4''). MS *m/z* (%): 249 (4, M^+- H_2O), 239 (24), 234 (14), 210 (27), 196 (13), 182 (14), 180 (30), 178 (32), 156 (62), 155 (24), 140 (22), 138 (14), 125 (10), 124 (23), 113 (39), 112 (16), 97 (10), 96 (19), 95 (27), 94 (10), 86 (12), 84 (13), 83 (77), 82 (97), 81 (12), 80 (12), 69 (16), 68 (18), 67 (15), 60 (12), 57 (31), 56 (49), 55 (77), 54 (15), 53 (18), 45 (22), 44 (41), 43 (64), 42 (28), 41 (100), 40 (12), 39 (34). HRMS calcd for $C_{15}H_{25}NO_3N$: 239.1833 (M^+-CO); found: 239.1855.

(6*S*,5*S*,9*S*)-1-Aza-5-[(*tert*-butyldimethylsilyl)oxy]-9-(hydroxymethyl)-6-methylbicyclo[4.3.0]nonan-2-one, propyl ester (123)

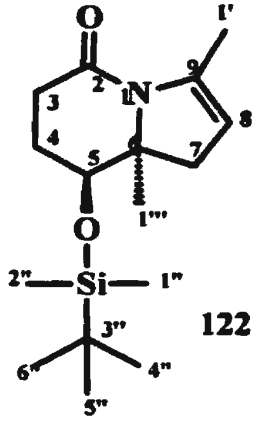


123

Cesium propionate (30 mg, 0.15 mmol) in DMF (0.70 mL) was added to a solution of **121** (28.3 mg, 0.0667 mmol) in DMF (0.63 mL). The mixture was stirred at rt for 14 hours, heated to reflux for 2 hours and then stirred at rt overnight. Aqueous workup consisted of washing the organic layer with brine (15 mL), then back-extracting the aqueous layer with CH_2Cl_2 (3 × 15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$. The volume of the solution was reduced under vacuum. Flash chromatography was performed using 30% ethyl acetate/hexanes to produce **123** (8.0 mg, 32%) and

122 (11.5 mg, 58%). Compound **123** was a beige solid: mp 71-74°C. IR (CCl_4) ν_{max} 2956 (m), 1742 (s), 1644 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.37-4.26 (3H, m, H-1' and H-9), 3.83 (1H, m, H-5), 2.45 (1H, m, H-3), 2.33 (3H, m, H-3', H-3), 2.22-2.08 (2H, m, H-4 and H-7), 2.02 (1H, m, H-8), 1.82 (2H, m, H-4 and H-8), 1.46 (1H, m, H-7), 1.21 (3H, s, H-1'"), 1.14 (3H, t, J = 7.4 Hz, H-4'), 0.87 (9H, s, H-4", H-5" and H-6"), 0.08 (3H, s, H-1" or H-2"), 0.07 (3H, s, H-1" or H-2"). ^{13}C NMR ($CDCl_3$): δ 174.5 (0, C-2'), 170.1 (0, C-2), 70.0 (1, C-5), 66.8 (0, C-6), 65.3 (2, C-1'), 57.2 (1, C-9), 33.0 (2, C-7), 27.8 (2, C-3'), 26.5 (2, C-3), 26.2 (3, C-1'"), 26.0 (3, C-4", C-5", C-6"), 25.3 (2, C-4), 24.5 (2, C-8), 18.3 (0, C-3"), 9.4 (2, C-4"), -4.3 (3, C-1" or C-2"), -4.8 (3, C-1" or C-2"). MS *m/z* (%): 369 (5, M^+), 313 (19), 312 (76), 295 (14), 283 (22), 282 (100), 256 (12), 239 (13), 238 (63), 211 (17), 198 (10), 183 (18), 182 (12), 170 (54), 169 (36), 164 (45), 162 (12), 154 (18), 150 (56), 137 (29), 136 (12), 131 (22), 126 (24), 122 (30), 116 (11), 115 (69), 114 (11), 112 (18), 110 (10), 109 (12), 108 (34), 101 (44), 97 (12), 96 (60), 95 (41), 94 (17), 85 (11), 83 (13), 82 (26), 81 (14), 75 (63), 74 (10), 73, (91), 69 (1), 59 (32), 57 (57), 56 (12), 55 (43), 43 (11), 42 (12), 41 (30), 29 (60), 28 (21), 27 (10). HRMS calcd for $C_{18}H_{35}O_4NSi$: 369.2333; found: 369.2326.

(6*S*,5*S*)-1-Aza-5-[(*tert*-butyldimethylsilyl)oxy]-6,9-dimethylbicyclo[4.3.0]non-8-en-2-one (122)

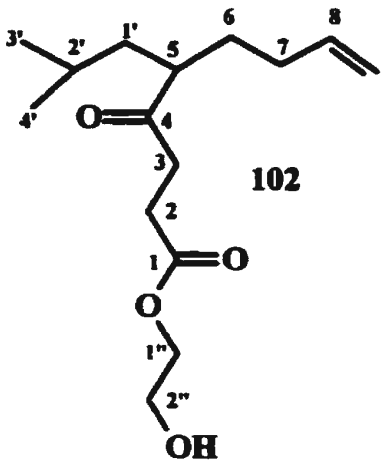


122

Beige solid: mp 74-76°C. IR (CCl_4) ν_{max} 2929 (m), 1670 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.76 (1H, n m, H-8), 3.84 (1H, t, *J* = 2.8 Hz, H-5), 2.93 (1H, m, H-4), 2.51 (1H, m, H-3), 2.34 (1H, m, H-3), 2.25 (3H, m, H-1'), 2.10 (1H, m, H-7), 1.83 (2H, m, H-7 and H-4), 1.21 (3H, s, H-1'''), 0.87 (9H, s, H-4", H-5" and H-6"), 0.08 (3H, s, H-1" or H-2"), 0.78 (3H, s, H-1" or H-2"). ^{13}C NMR ($CDCl_3$): δ 168.4 (0, C-2), 140.9 (0, C-9), 106.9 (1, C-8), 69.5 (1, C-5), 68.8 (0, C-6), 38.0 (2, C-4), 27.4 (2, C-7), 25.7 (3, C-1'''), 25.9 (3, C-4", C-5" and C-6"), 25.7 (2, C-3), 18.3 (0, C-3"), 17.3 (3, C-1'), -4.1 (3, C-1" or C-2"), -4.8 (3, C-1" or C-2"). MS *m/z* (%): 295 (29, M^+), 239 (17), 238 (80), 164 (16), 162 (15), 148 (28), 137 (23), 120 (11), 115 (71), 109 (25), 108 (24), 101 (40), 97 (18), 96 (99), 95 (100), 94 (25), 85 (11), 75 (53), 73 (64), 59 (47), 57 (17), 55 (11), 54 (11), 53 (10), 42 (12), 41 (28), 39 (12), 29 (21). HRMS calcd for $C_{16}H_{29}O_2NSi$: 295.1966; found: 295.1955.

General Procedure for the Formation of Reductive Succinoylation Products. Compounds **102** and **105** were produced as by-products using the method of Curran and co-workers.[42,43]

(±)-2-Hydroxyethyl-5-isobutyl-4-oxononanoate (102)

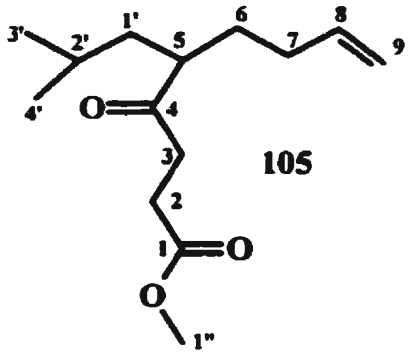


102

Compound **101** (188 mg, 1.02 mmol) was dissolved in CH_2Cl_2 (10.2 mL) and cooled to -78°C. $BF_3 \cdot Et_2O$ (1.45 mL, 11.4 mmol) was added dropwise over 2 hours, and, after ten minutes, **1** (304 mg, 1.32 mmol) was introduced slowly. The mixture stirred at -78°C for 3 hours and then warmed to 5°C slowly . After ten minutes, the reaction was diluted with Et_2O (20 mL), followed by H_2O (20 mL). The mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Flash chromatography was performed eluting with 20% ethyl acetate/hexanes to yield **102** (133 mg, 48%) as a yellow liquid: IR ν_{max} 3459 (b s), 2956 (m), 1737 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.76 (1H, m, H-8), 4.99 (2H, m, H-9), 4.24 (2H, m, H-1"), 3.82 (2H, m, H-2"), 2.79 (2H, t, J = 6.0 Hz, H-3), 2.60 (3H, m, H-2 and H-5), 2.02 (2H, m, H-7), 1.72 (2H, m, H-6), 1.50 (2H, m, H-2' and H-1'), 1.23 (1H, m, H-1'), 0.89 (6H, apparent t, J = 6.3 Hz, H-3' and H-4'). ^{13}C NMR ($CDCl_3$): δ 213.3 (0, C-4), 173.3 (0, C-1), 138.3(1, C-8), 115.4 (2, C-9), 66.4 (2, C-1"), 61.2 (2, C-2"), 49.3 (2, C-2), 41.1 (2, C-1'), 37.1 (2, C-3), 31.6 (2, C-7), 31.2 (2, C-6), 27.9 (1, C-5), 26.1(1, C-2'), 23.1 (3, C-3' or C-4'), 22.6 (3, C-3' or C-4'). MS *m/z* (%): 270 (1, M^+), 198 (11), 173 (24), 155 (57), 154 (13), 153 (12), 145 (16), 111 (97), 101

(100), 85 (12), 83 (22), 69 (52), 57 (19), 56 (13), 55 (45), 45 (26), 43 (33), 41 (36), 32 (12), 29 (19), 28 (47), 27 (13). HRMS calcd for $C_{15}H_{26}O_4$: 270.1829; found: 270.1803

Methyl (±)-5-isobutyl-4-oxononanoate (105)



105

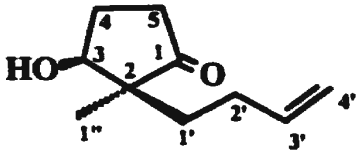
Compound **104** (356 mg, 1.91 mmol) was dissolved in CH_2Cl_2 (19 mL) followed by the addition of 5Å powdered Molecular Sieves (0.50 g). The reaction mixture was cooled to -78°C and BF_3•Et_2O (2.42 mL, 19.1 mmol) was added dropwise. After ten minutes, **1** (572 mg, 2.48 mmol) was introduced slowly. The reaction mixture was stirred at -78°C for 3 hours and allowed to warm slowly to 5°C . To the mixture was added with Et_2O (20 mL), and H_2O (20 mL). The aqueous layer was re-extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The volume of the solution was reduced under vacuum. Flash chromatography was performed eluting with 20% ethyl acetate/hexanes to yield **105** (223 mg, 49%) as a colorless liquid: IR ν_{max} 2955 (m), 1742 (s), 1713 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.76 (1H, m, H-8), 5.01 (2H, m, H-9), 3.68 (3H, s, H-1"), 2.76 (2H, t, J = 6.2 Hz, H-3), 2.61 (3H, m, H-2 and H-5), 2.02 (2H, m, H-7), 1.72 (1H, m, H-6), 1.49 (3H, m, H-6, H-2' and H-1'), 1.21 (1H, m, H-1'), 0.88 (6H, apparent t, J = 6.4 Hz, H-3' and H-4'). ^{13}C NMR ($CDCl_3$): δ 212.6 (0, C-4), 173.4

(0, C-1), 138.3 (1, C-8), 115.5 (2, C-9), 51.9 (3, C-1"), 49.4 (1, C-5), 41.2 (2, C-1'), 37.0 (2, C-3), 31.7 (2, C-7), 31.3 (2, C-6), 27.8 (2, C-2), 26.2 (1, C-2'), 23.1 (3, C-3' or C-4'), 22.7 (3, C-3' or C-4'). MS *m/z* (%): 186 (26), 143 (100), 115 (99), 111 (97), 87 (16), 83 (24), 69 (60), 67 (11), 59 (20), 57 (16), 55 (16), 43 (36), 41 (54), 39 (13), 29 (18), 27 (19). HRMS calcd for $C_{14}H_{24}O_3$: 240.1724; found: 240.1704.

General Procedure for Baker's Yeast Reduction

Compound **118** was prepared by a procedure based on that of Burnell and Zhu.[9]

(2*S*, 3*S*) 2-(3-Butenyl)-3-hydroxy-2-methylcyclopentanedione (118)



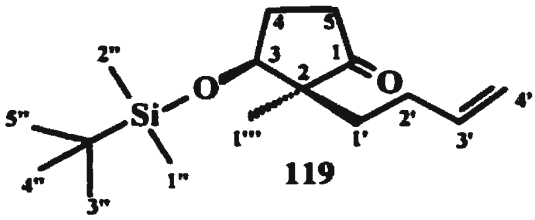
118

Fleischman's Traditional dry yeast (8.0 g) and sucrose (18.0 g) were added to deionized H_2O (100 mL). The mixture was agitated in a 32°C bath. After 10 minutes a solution of **100** (167 mg, 1.00 mmol) in 95% EtOH (3.0 mL) and 0.2% Triton X-100 (12 mL) was added. This suspension was agitated for an additional 48 hours. Ethyl ether (100 mL) was added and the mixture was allowed to stand for 20 hours. The ether layer was decanted, and the process was repeated three times with 100 mL of ethyl ether. The combined organic layers were washed with brine (150 mL) and dried over anhydrous $MgSO_4$. Flash chromatography was performed with 50% ethyl acetate/hexanes to furnish **118** (58.7 mg, 35%) a yellow liquid and starting material **100** (80.1 mg) thus the yield based on recovered starting material was 66%.

IR ν_{max} 3456 (b s), 2967 (m), 1729 (s) cm^{-1}. $[\alpha]^{24}_D$ = +62°, C = 0.95 mg/mL MeOH. ^1H NMR ($CDCl_3$): δ 5.85 (1H, m, H-3'), 5.01 (2H, m, H-4'), 4.13 (1H, t, *J* = 4.5 Hz, H-3), 2.47 (1H, m, H-5), 2.30 (1H, m, H-5), 2.24 - 2.13 (2H, m, H-4 and H-2'), 2.06 (1H, m, H-2'), 1.96 (1H, m, H-4), 1.63 (2H, t, *J* = 8.1 Hz, H-1'), 1.01 (3H, s, H-1"). ^{13}C NMR ($CDCl_3$): δ 220.6 (0, C-1), 138.8 (1, C-3'), 115.1 (2, C-4'), 77.6 (1, C-3), 53.2 (0, C-2), 34.1 (2, C-5), 29.5 (2, C-4), 28.3 (2, C-1'), 28.1 (2, C-2'), 19.4 (3, C-1"). MS *m/z* (%): 168 (1, M^+), 114 (100), 113 (54), 99 (31), 97 (27), 86 (15), 85 (30), 84 (30), 81 (37), 71 (15), 55 (19), 51 (12), 49 (48), 43 (39), 41 (36). HRMS calcd for $C_{10}H_{16}O_2$: 168.1149; found: 168.1146.

General Procedure for Protection of Alcohol. Compound **119** was prepared based on the procedure of Corey and Venkateswarlu.[47]

(2*S*, 3*S*) 2-(3-Butenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylcyclopentanone (119)

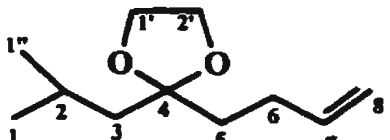


119

Imidazole (170 mg, 2.50 mmol), and then TBS-Cl (200 mg, 1.30 mmol) were added to a solution of **118** (189 mg, 1.12 mmol) in DMF (5.0 mL). The mixture was stirred for 24 hours at rt. H_2O (10 mL) was added, and the mixture was extracted with petroleum ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The volume of the solution was reduced under vacuum. Flash chromatography was performed using 20% ethyl acetate/hexanes to yield **119** (199

mg, 63%) as a yellow liquid. The yield for this reaction based on recovered starting material was 83%. IR ν_{max} 2956 (m), 1741 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.79 (1H, m, H-3'), 4.99 (2H, m, H-4'), 4.03 (1H, t, J = 6.3 Hz, H-3), 2.40 (1H, m, H-5), 2.23 (1H, m, H-5), 2.14-1.87 (4H, m, H-4 and H-2'), 1.66 (1H, m, H-1'), 1.51 (1H, m, H-1'), 0.98 (3H, s, H-1'''), 0.89 (9H, s, H-4", H-5", and H-6"), 0.10 (3H, s, H-1" or H-2"), 0.08 (3H, s, H-1" or H-2"). ^{13}C NMR ($CDCl_3$): δ 220.8 (0, C-1), 139.0 (1, C-3'), 114.5 (2, C-4'), 78.4 (1, C-3), 53.4 (0, C-2), 34.4 (2, C-5), 29.8 (2, C-1'), 28.6 (2, C-2' or C-4), 28.3 (2, C-4 or C-2'), 25.8 (3, C-4", C-5" and C-6"), 19.5 (3, C-1'''), 18.2 (0, C-3"), -4.1 (3, C-1" or C-2"), -4.6 (3, C-1" or C-2"). MS *m/z* (%): 241 (15), 225 (M^+ - *t*Bu, 17), 181 (10), 171 (12), 133 (24), 129 (28), 107 (25), 105 (11), 101 (33), 91 (11), 75 (100), 73 (80), 59 (18), 55 (10), 41 (21). HRMS calcd for $C_{16}H_{30}O_2Si$: 225.1310 (M^+ - ^{t}Bu); found: 225.1288.

2-Methyloct-7-en-4-one, ethylene acetal (101)

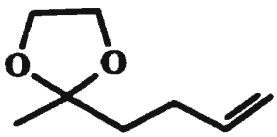


101

Ethylene glycol (3.20 g, 51.5 mmol) and **75** (1.43 g, 10.2 mmol) were dissolved in 75 mL of benzene. A small spatula-tip of *p*-TsOH was added, and the reaction mixture was heated to reflux for 2 days, with azeotropic removal of H_2O. Most of the benzene was removed by distillation and the residue was washed with saturated $NaHCO_3$ (2 × 50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield **101** (1.87 g, 98%) as a

colorless liquid: IR ν_{max} 2952 (m). ^{1}H NMR ($CDCl_3$): δ 5.84 (1H, m, H-7), 4.97 (2H, m, H-8), 3.93 (4H, s, H-1' and H-2'), 2.12 (2H, m, H-6), 1.74 (3H, m, H-2 and H-5), 1.52 (6H, d, J = 6.3 Hz, H-1 and H-1"). ^{13}C NMR ($CDCl_3$): δ 138.9 (1, C-7), 114.3 (2, C-8), 111.9 (0, C-4), 64.8 (2, C-1' and C-2'), 45.5 (2, C-3), 36.7 (2, C-5), 28.3 (2, C-6), 24.3 (1, C-2), 24.2 (3, C-1 and C-1"). MS *m/z* (%): 129 (77, M^+-C_4H_7), 127 (73), 85 (35), 57 (35), 55 (38), 45 (11), 43 (18), 41 (28), 39 (14), 32 (21), 29 (17), 28 (100), 27 (18). HRMS calcd for $C_{11}H_{20}O_2$: 129.0915 (M^+ - C_4H_7); found: 129.0889

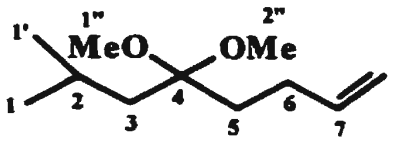
Hex-5-en-2-one, ethylene acetal (99)



99

Ethylene glycol (6.35 g, 102 mmol) was placed in 75 mL of benzene followed by allyl acetone (1.96 g, 20.0 mmol). A small spatula-tip of *p*-TsOH was added and the reaction mixture was heated to reflux for 2 days with azeotropic removal of H_2O. Most of the benzene was distilled, and the residue was washed with saturated $NaHCO_3$ (2 × 50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield **99** (2.52 g, 89%) as a colorless liquid: IR ν_{max} 2962 (m). ^{1}H NMR ($CDCl_3$): δ 5.84 (1H, m), 4.98 (2H, m), 3.95 (4H, m), 2.16 (2H, m), 1.74 (2H, m), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$): δ 138.7, 114.4, 110.0, 64.9, 38.5 , 28.5, 24.1. MS *m/z* (%): 127 (15, M^+-Me), 87 (100), 55 (22), 43 (93), 41 (14), 28 (40).

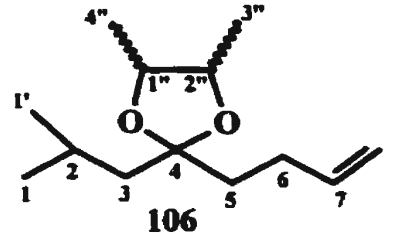
2-Methyloct-7-en-4-one, methyl acetal (104)



104

Based on a procedure by Wenkert and Goodwin,[48] trimethylorthoformate (1.90 mL, 17.4 mmol) was added to a solution of **75** (485 mg, 3.46 mmol) in MeOH (10 mL). A small spatula-tip of *p*-TsOH was added, and the mixture was heated to reflux for 17 hours. The mixture was cooled to rt and diethyl ether (50 mL) was added followed by a 1:1 mixture of 5% NaOH/saturated NaCl. The organic layer was washed with brine (50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum to yield **104** (423 mg, 66%) as a brown liquid: IR ν_{max} 2955 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.84 (1H, m, H-7), 4.99 (2H, m, H-8), 3.14 (6H, s, H-1" and H-2"), 2.01 (2H, m, H-6), 1.70 (3H, m, H-5 and H-2), 1.50 (2H, d, J = 6.3 Hz, H-3), 0.96 (6H, d, J = 6.7 Hz, H-1 and H-1'). ^{13}C NMR ($CDCl_3$): δ 138.4 (1, C-7), 114.5 (2, C-8), 103.5 (0, C-4), 47.6 (3, C-1" and C-2"), 40.5 (2, C-3), 31.9 (2, C-5), 28.3 (2, C-6), 23.9 (1, C-2), 23.7 (3, C-1 and C-1').

2-Methyl-oct-7-en-4-one, 2,3-butanediol acetal (106)



106

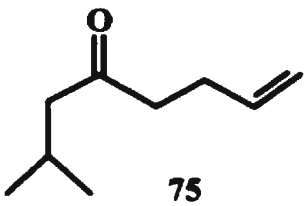
Compound **75** (1.22 g, 8.70 mmol) and technical grade (±) 2,3-butanediol (4.00 g, 44.4 mmol) were dissolved in benzene (35 mL). A small spatula-tip of *p*-TsOH was added, and the mixture was heated to

reflux for 4 days with azeotropic removal of H_2O. Most of the benzene was removed by distillation and the residue was washed with saturated $NaHCO_3$ (100 mL). The aqueous layer was back-extracted using CH_2Cl_2 (2 × 75 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The volume of the solution was reduced under vacuum. Flash chromatography was performed using 5% ethyl acetate/hexanes. There was some difficulty separating **75** from **106**, but a small amount of **106** was isolated (524 mg, 28%) as a colorless liquid: IR ν_{max} 2955 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.84 (2H, m, H-7), 4.98 (4H, m, H-8), 4.25 (2H, m, H-1", H-2" of *meso* acetal), 3.61 (2H, m, H-1", H-2" of *d/l* acetal), 2.19 - 2.07 (4H, m, H-6), 1.73 (6H, m, H-2 and H-5), 1.53 (4H, m, H-3), 1.23 (6H, d, J = 5.7 Hz, H-3", H-4" of *d/l* acetal), 1.13 (6H, t, J = 6.0 Hz, H-3", H-4" of *meso* acetal), 0.95 (6H, m, H-1 and H-1') . ^{13}C NMR ($CDCl_3$): δ 139.1, 139.0, 138.8 (1, C-7), 114.3 (2, C-8), 111.1, 110.6, 110.3 (0, C-4), 78.8, 78.5 (1, C-1" and C-2" of *d/l* acetal), 73.7, 73.5 (1, C-1" and C-2" of *meso* acetal), 47.3, 46.9, 45.4 (2, C-3), 38.2, 37.3, 36.5 (2, C-5), 29.1, 28.3, 28.2 (2, C-6), 24.8 (1, C-2), 24.6, 24.4, 24.3, 24.2, 24.1 (3, C-1 and C-1'), 17.2, 17.0 (3, C-3" and C-4" of *d/l* acetal), 16.0, 15.9 (3, C-3" and C-4" of *meso* acetal). MS *m/z* (%): 157 (64, $M^+ - C_4H_7$), 155 (58), 85 (64), 83 (40), 69 (10), 57 (85), 55 (100), 43 (23), 41 (38), 39 (12), 29 (29), 28 (30), 27 (16). HRMS calcd for $C_{13}H_{24}O_2$: 157.1228 (M^+-C_4H_7); found: 157.1208.

General Procedure for the Grignard reaction and Oxidation using PCC.

Compounds **45** and **75** were prepared based on the method of Newcomb and coworkers[49] with some modifications. Oxidation using PCC was performed based on the method of Corey and Suggs,[50] and the mechanical activation of the magnesium turnings was accomplished using the procedure of Baker and coworkers.[51]

2-Methyloct-7-en-4-one (75)

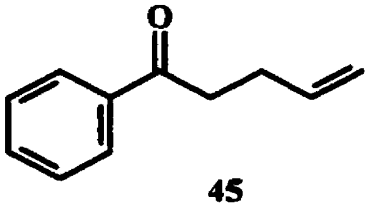


75

Magnesium turnings (1.46 g, 59.9 mmol) were stirred under an atmosphere of nitrogen for 24 hours. THF (40 mL) was added followed by a solution of 4-bromo-1-butene (4.23 g, 31.3 mmol) in THF (10 mL). The mixture was heated to reflux for 2.5 hours, cooled to rt and then in an ice/salt bath. A solution of isovaleraldehyde **73** (3.30 g, 38.3 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at rt overnight. The reaction mixture was poured into saturated NH_4Cl (100 mL). The aqueous layer was extracted with diethyl ether (4 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the volume was reduced under vacuum to yield the alcohol, which was immediately oxidized to the ketone. A solution of the alcohol (4.45 g, 38.3 mmol) in CH_2Cl_2 (10.5 mL) was added to a solution of PCC (10.7 g, 49.8 mmol) in CH_2Cl_2 (52.5 mL). The mixture was stirred at rt for 4.5 hours. The solution was decanted from the black precipitate. The precipitate was extracted

with diethyl ether (4 × 50 mL). The volume of the solution was reduced to 50 mL and the residue was flushed through a Florisil column containing activated charcoal to yield **75** (3.84 g, 88%) as a yellow liquid: IR ν_{max} 2957 (s), 1712 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.00 (1H, m), 5.81 (2H, m), 2.49 (2H, m), 2.31 (4H, m), 2.17 (1H, sep., J = 6.4 Hz), 0.93 (6H, s), 0.91 (3H, s,) . ^{13}C NMR ($CDCl_3$): δ 210.0, 137.1, 115.0, 51.8, 42.2, 27.6, 24.5, 22.5.

1-Phenylpent-4-en-1-one (45)

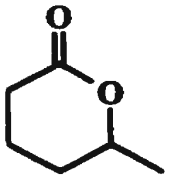


45

Magnesium turnings (1.06 g, 43.6 mmol) were stirred under an atmosphere of nitrogen for 24 hours. THF (30 mL) was added followed by a solution of 4-bromo-1-butene (4.90 g, 36.3 mmol) in THF (10 mL). The mixture was heated to reflux for 2.5 hours, cooled to rt and then in an ice/salt bath. A solution of benzaldehyde **42** (3.93 g, 37.0 mmol) in THF (10 mL) was added and the mixture was stirred at rt overnight. The reaction mixture was poured into saturated NH_4Cl (100 mL). The aqueous layer was extracted with diethyl ether (4 × 80 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the volume was reduced to yield the alcohol (5.50, 93%). A solution of the alcohol (5.25 g, 32.4 mmol) in CH_2Cl_2 (14 mL) was added to a solution of PCC (10.5 g, 48.6 mmol) in CH_2Cl_2 (65 mL). The mixture was stirred at rt for 4 hours, and then the solution was decanted from the black precipitate. The precipitate was extracted with diethyl ether (4 × 100 mL). The volume of the

solution was reduced under vacuum to 50 mL and the residue was flushed through a Florisil column containing activated charcoal to furnish **45** (4.70 g, 91%) as a yellow liquid: IR ν_{max} 2919 (m), 1667 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.96 (2H, m), 7.58-7.42 (3H, m), 5.89 (1H, m), 5.03 (2H, m), 3.01 (2H, t, J = 7.2), 2.50 (2H, m). ^{13}C NMR ($CDCl_3$): δ 199.3, 137.3, 136.9, 133.0, 128.6, 128.0, 115.3, 37.7, 28.1.

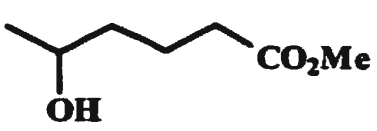
(±)-Hydroxyhexanoic Acid, δ-Lactone (32)



32

According to the procedure of Hernandez and coworkers,[31] a solution of *m*-CPBA (6.20 g of 57-86%) in CH_2Cl_2 (50 mL) was added to a solution of (±)-2-methylcyclopentanone (1.54 g, 15.7 mmoL) in CH_2Cl_2 (8 mL) The mixture was stirred at rt for 22 hours. The mixture was filtered to remove the white precipitate, and the filtrate was passed through a Florisil column. The solution was washed with saturated $NaHCO_3$ (2 × 50 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Flash chromatography was performed using 80% ethyl acetate/hexanes to yield **32** (1.56 g, 87%) as a colorless liquid: ^1H NMR ($CDCl_3$): δ 4.46 (1H, m), 2.59 (1H, m), 2.44 (1H, m), 1.91 (3H, m), 1.53 (1H, m), 1.38 (3H, d, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$): δ 171.9, 76.9, 29.4, 29.1, 21.6, 18.4.

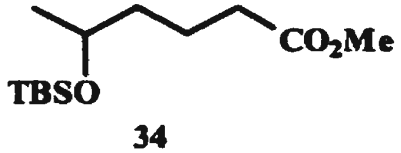
Methyl (±)-5-hydroxyhexanoate (33)



33

According to the method of Hernandez and co-oworkers,[31] a MeONa/MeOH solution, prepared from sodium (0.13 g, 5.7 mmol) in MeOH (7.7 mL) and cooled to -78°C, was cannulated into a solution of **32** (4.12 g, 36.1 mmol) in MeOH (28 mL), also cooled to -78°C. The reaction was warmed to 0°C and stirred at this temperature for 6 hours. Glacial acetic acid (0.39 mL) was added and stirring was continued for an additional 15 minutes. The solution was washed with saturated $NaHCO_3$ (2 × 100 mL). The aqueous layers were extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried using anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to yield **33** (4.81 g, 91%) as a colorless liquid. The physical data of **33** was identical to that reported by Hernandez and cooworkers.[31] ^{1}H NMR ($CDCl_3$): δ 3.80 (1H, m), 3.68 (3H, s), 2.35 (2H, t, J = 7.1 Hz), 1.72 (2H, m), 1.47 (2H, m); 1.19 (3H, d, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 174.4, 67.4, 51.6, 38.6; 33.9, 23.5, 21.2.

Methyl (±)-5-(*tert*-butyldimethylsilyl)oxyhexanoate (34)

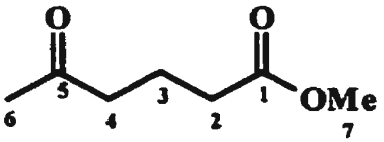


34

According to the procedure of Hernandez and co-oworkers,[31] a solution of TBS-Cl (1.97 g, 13.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of **33** (1.45 g, 9.91 mmol) and imidazole (1.77 g, 26.0 mmol) in CH_2Cl_2 (21 mL). The solution was stirred at rt overnight. The solution was washed with

saturated $NaHCO_3$ (2 × 50 mL) and brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Flash chromatography was performed using 5% ethyl acetate/hexanes to provide **34** (2.58 g, 87%), a colorless liquid. The physical data of **34** was identical to that reported by Hernandez and co-oworkers.[31] ^{1}H NMR ($CDCl_3$): δ 3.79 (1H, m), 3.67 (3H, s), 2.31 (2H, t, J = 7.3 Hz), 1.75-1.39 (4H, m), 1.12 (3H, d, J = 6.0 Hz), 0.88 (9H, s), 0.05 (6H, s). ^{13}C NMR ($CDCl_3$): δ 174.3, 68.4, 51.7, 39.2, 34.3, 26.1, 23.9, 21.5, 18.3, -4.2, -4.5.

Methyl 5-oxohexanoate (39)

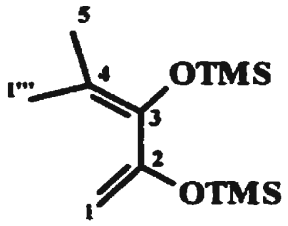


39

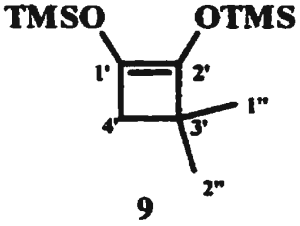
Compound **39** was produced based on the method of Corey and Suggs.[50] A solution of **33** (1.51 g, 10.3 mmol) in CH_2Cl_2 (4 mL) was added to a solution of PCC (2.92 g, 13.6 mmol) in CH_2Cl_2 (18 mL), and the mixture was stirred at rt overnight. The solution was decanted from the black precipitate, which was then extracted with ethyl ether (4 × 50 mL). The volume was reduced to 50 mL under vacuum and the residue was flushed through a Florisil column containing activated charcoal. Flash chromatography was performed using 50% ethyl acetate/hexanes to yield **39** (1.18 g, 82%) as a colorless liquid: ^{1}H NMR ($CDCl_3$): δ 3.67 (3H, s, H-7), 2.52 (2H, t, J = 7.4 Hz, H-2), 2.35 (2H, t, J = 7.5 Hz, H-4), 2.15 (3H, s, H-6), 1.90 (2H, m, H-3). ^{13}C NMR ($CDCl_3$): δ 208.1, 173.8, 51.7, 42.6, 33.1, 30.1, 19.0. MS *m/z* (%): 144 (1,

M^+), 112 (11), 74 (15), 55 (12), 43 (100).

4-Methyl-2,3-bis[(trimethylsilyl)oxy]-1,3-pentadiene (126)



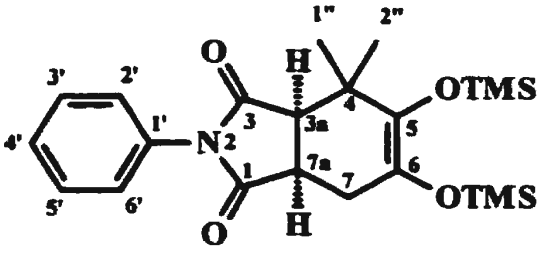
126



9

A solution of 2,2-dimethyl dimethylsuccinate (25.6 g, 146 mmol) in toluene (140 mL) and TMS-Cl (86.0 mL, 676 mmol) was placed in an addition funnel. This mixture was slowly added to a stirred and heated suspension of Na^0 (15.03 g, 654 mmol) in toluene (355 mL). After the addition was complete, the reaction was heated under reflux for 6 hours over the next 2 days. The mixture was suction-filtered and the filtrate was concentrated by simple distillation. The solution had to be re-distilled, since the product distilled along with toluene. The residue was vacuum distilled to yield a colorless liquid. Compounds **126** and **9** were present in a 1:2 ratio (28.8 g). ^{1}H NMR ($CDCl_3$): δ 4.40 (1H, s, H-1), 4.29 (1H, s, H-1), 1.96 (2H, s, H-4'), 1.77 (3H, s, H-1''' or H-5), 1.65 (3H, s, H-1''' or H-5), 1.12 (6H, s, H-1'' and H-2''), 0.21, 0.20, 0.19, 0.18, 0.17 (-OTMS of both **9** and **126**).

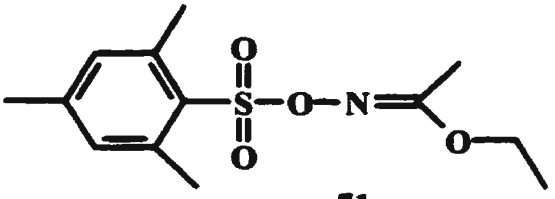
(3a*, 7a*) 5,6-bis[(trimethylsilyl)oxy]-4,4-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-*N*-Phenyl-1-*H*-isoindole (128)



128

N-Phenylmaleimide **127** (335 mg, 1.93 mmol) and a 1:2 mixture of **126** and **9** (1.04 g) were dissolved in benzene (25 mL). The mixture was heated under reflux for 4.5 hours and stirred at rt for 3 days. The volume of the mixture was reduced under vacuum and flash chromatography was performed eluting with 15% ethyl acetate/hexanes to provide **128** (6.0 mg) as a colorless residue: ^{1}H NMR ($CDCl_3$): δ 7.41 (3H, m, H-3', H-4', and H-5'), 7.22 (2H, m, H-2' and H-6'), 3.34 (1H, d, J = 9.6 Hz, H-3a or H-7a), 3.22 (1H, m, H-3a or H-7a), 2.92 (1H, m, H-7), 2.53 (1H, m, H-7), 1.66 (3H, s, H-1" or H-2") 1.64 (3H, s, H-1" or H-2"), 0.13 (9H, s, -OTMS), 0.10 (9H, s, -OTMS). MS *m/z* (%): 342 (14), 341 (M$^+$-OTMS, 45), 267 (20), 195 (11), 194 (50), 179 (38), 147 (20), 122 (17), 119 (12), 105 (20), 95 (20), 93 (14), 91 (22), 79 (11), 77 (29), 75 (47), 73 (100), 65 (13), 51 (11), 45 (18), 43 (50), 41 (13), 39 (15), 28 (19).

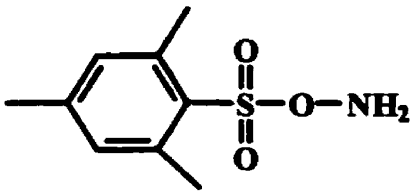
Ethyl *O*-(mesitylenesulfonyl)-acetohydroxamate (71)



71

Compound **72** and the intermediate **71** were prepared according to the method of Tamura and co-workers.[34] Mesitylene sulfonyl chloride **70** (13.5 g, 61.8 mmol) was added to a solution of ethyl acetohydroamate **69** (5.11 g, 49.6 mmol) and triethylamine (5.58 g, 55.1 mmol) in DMF (13 mL) in small portions over a period of 25 minutes with stirring and with cooling in an ice bath. Triethylamine (0.45 mL) was added to the mixture to keep the reaction mixture basic. Stirring was continued for an additional 20 minutes at 5-10°C, and then the mixture was poured into ice/water (30 mL). A white solid was collected and washed thoroughly with H_2O (75 mL). The solid was dissolved in diethyl ether (50 mL) and dried over anhydrous $MgSO_4$. The diethyl ether was removed under reduced pressure to yield a solid, which was then dissolved in petroleum ether with slight warming. The solution was filtered, and the filtrate was chilled in a dry ice acetone bath. The precipitate was collected and dried under vacuum to yield **71** (10.2 g, 76%) as a beige solid: ^{1}H NMR ($CDCl_3$): δ 6.97 (2H, s), 3.09 (2H, q, J = 7.2 Hz), 2.65 (6H, s), 2.32 (3H, s), 2.04 (3H, s), 1.19 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 169.4, 143.5, 140.9, 131.7, 130.5, 63.8, 23.0, 21.3, 15.1, 14.8.

***O*-Mesitylenesulfonylhydroxylamine (72)**



72

To a solution of **71** (1.66 g, 6.07 mmol) in dioxane (4.6 mL), 70% perchloric acid (0.6 mL) was added dropwise with stirring at 0°C. Stirring was continued for an additional 30 minutes. The mixture was poured into ice/water (25 mL) to yield a white solid, which was collected, washed with cold water (50 mL), then with cold petroleum ether (50 mL), and dried under vacuum to yield **72** (1.02 g, 78%) as a white solid: ^{1}H NMR ($CDCl_3$): δ 7.00 (2H, s), 5.19 (2H, bs), 2.67 (6H, s), 2.33 (3H, s). ^{13}C NMR ($CDCl_3$): δ 144.0, 141.1, 131.9, 129.2, 120.5, 22.9, 21.3.

References

1. (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961-963. (b) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759-1773. (c) Nakamura, E.; Kuwajima, I. *Organic Synthesis*; Wiley: New York, 1987; Vol. 65, pp 17-25.
2. (a) Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4326-4372. (b) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804-811. (c) Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311-1318.
3. Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1989**, *30*, 1021.
4. Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485-1491.
5. Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352-1355.
6. (a) Jenkins, T. J.; Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722-8729. (b) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708-5710.
7. Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1998**, 1755-1756.
8. Mariano, P. S.; Kavash, R. J.; Lin, X. *J. Org. Chem.* **1996**, *61*, 7335-7347.
9. (a) Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104-110.

(b) Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymm.* **1996**, *7*, 3295-3304.

10. Oppolzer, W.; Wylie, R. D. *Helv Chim. Acta* **1980**, *63*, 1198-1203.

11. (a) Parker, K. A.; Koziski, K. A; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181-2184. (b) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. France* **1993**, *130*, 447-449. (C) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921-9926.

12. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789-12854.

13. Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 124-1267.

14. Adang, A. E. P.; Hermkens, P. H. H.; Linders, J. T. M.; Ottenheijm, H. C. J.; van Staveren, C. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 63-78.

15. Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699-1720.

16. Kahn, M. *Synlett* **1993**, 821-826.

17. Olson, G. L.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 323-333.

18. Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334-4344.

19. Belvisi, L.; Bernardi, A.; Manzoni, L.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2563-2569.

20. (a) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147-6149. (b) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9437-9446.

21. Baldwin, J. E.; Hulme, C.; Schofield, C. J.; Edwards, A. J. *J. Chem. Soc., Chem. Commun.* **1993**, 935.

22. (a) Angiolini, M.; Arano, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2571-2581. (b) Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, *35*, 4091-4092.

23. (a) Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Valentina, M. *Tetrahedron Lett.* **1995**, *4*, 625-628. (b) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Sardone, N.; Angiolini, M.; Belvisi, L.; Maffioli, S.; Manzoni, L.; Scolastico, C. *Tetrahedron* **1998**, *54*, 5325-5336.

24. (a) Hanessian, S.; Ronan, B.; *Biorg. Med. Chem. Lett.* **1994**, *4*, 1397-1400. (b) Hanessian, S.; McNaughton-Smith, G. *Biorg. Med. Chem. Lett.* **1996**, *6*, 1567-1572.

25. Moeller, K. D.; Li, W. *J. Am. Chem. Soc.* **1996**, *118*, 10106-10112.

26. Kahn, M.; Devens, B. *Tetrahedron Lett.* **1986**, *27*, 4841-4844.

27. (a) Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647-650. (b) Nagai, U.; Sato, K. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1231-1234.

28. Khalil, C. M.; Ojala, W. H.; Pradham, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 628-637.

29. Wagner, J.; Kallen, J.; Ehrhardt, C.; Evenou, J-P.; Wagner, D. *J. Med. Chem.* **1998**, *41*, 3664-3674.

30. Clive, D. L. J.; Coltart, D. M.; Zhou, Y. *J. Org. Chem.* **1999**, *64*, 1447-1454.

31. Hernandez, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314-323.

32. Olah, G. A.; Fung, A. P. *Synthesis* **1979**, 537-538.

33. Bartman, W.; Beck, G.; Knolle, J.; Rupp, R. H. *Tetrahedron Let.* **1982**, *23*, 3647-3650.

34. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1-17.

35. Tamura, Y.; Fujiwara, H.; Sumoto, K.; Ikeda, M.; Kita, Y. *Synthesis* **1973**, 215-216.

36. Krow, G.; Szczepanski, S. *J. Org. Chem.* **1982**, *47*, 1153-1155.

37. Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933-4940.

38. (a) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802-4809. (b) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006-4014.

39. Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4321-4323.

40. (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063-1072.

(b) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11-16.

41. Hatanaka, N.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1981**, 344.

42. Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337-344.

43. Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345-352.

44. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1986-2012.

45. Bloomfield, J. J.; Nelke, J. M. *Org. Synth.* **1988**, *Coll. Vol. VI*, 167.

46. Budavari, S.(ed.); "Merck Index, 12th Edition", Merck Research Laboratories, Whitehouse Station, NJ, 1805, (1996).

47. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

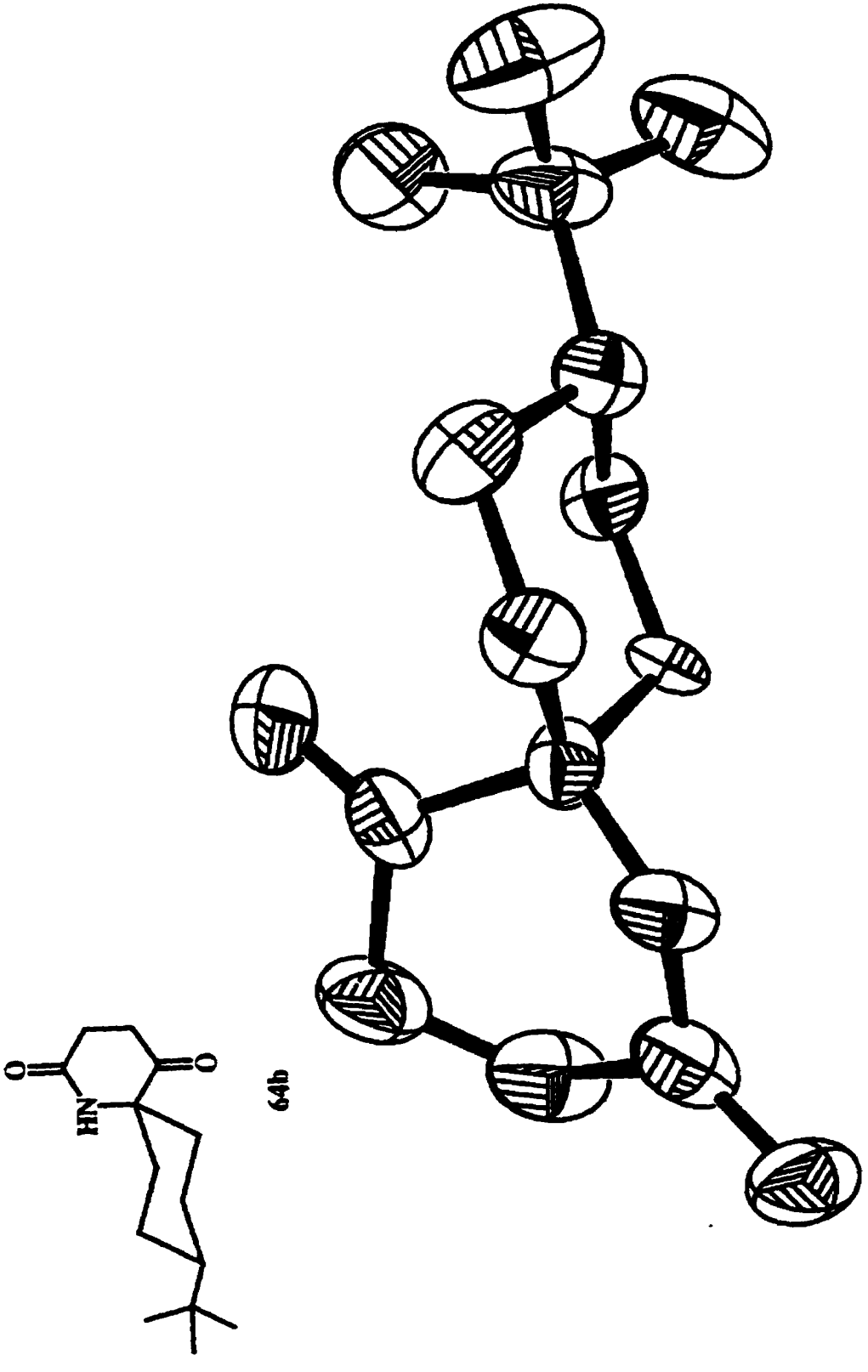
48. Werkert, E.; Goodwin, T. E. *Synth. Comm.* **1977**, *7*, 409.

49. Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329-2344.

50. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-2650.

51. Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, J. A.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698-703.

Appendix 1: X-ray structures



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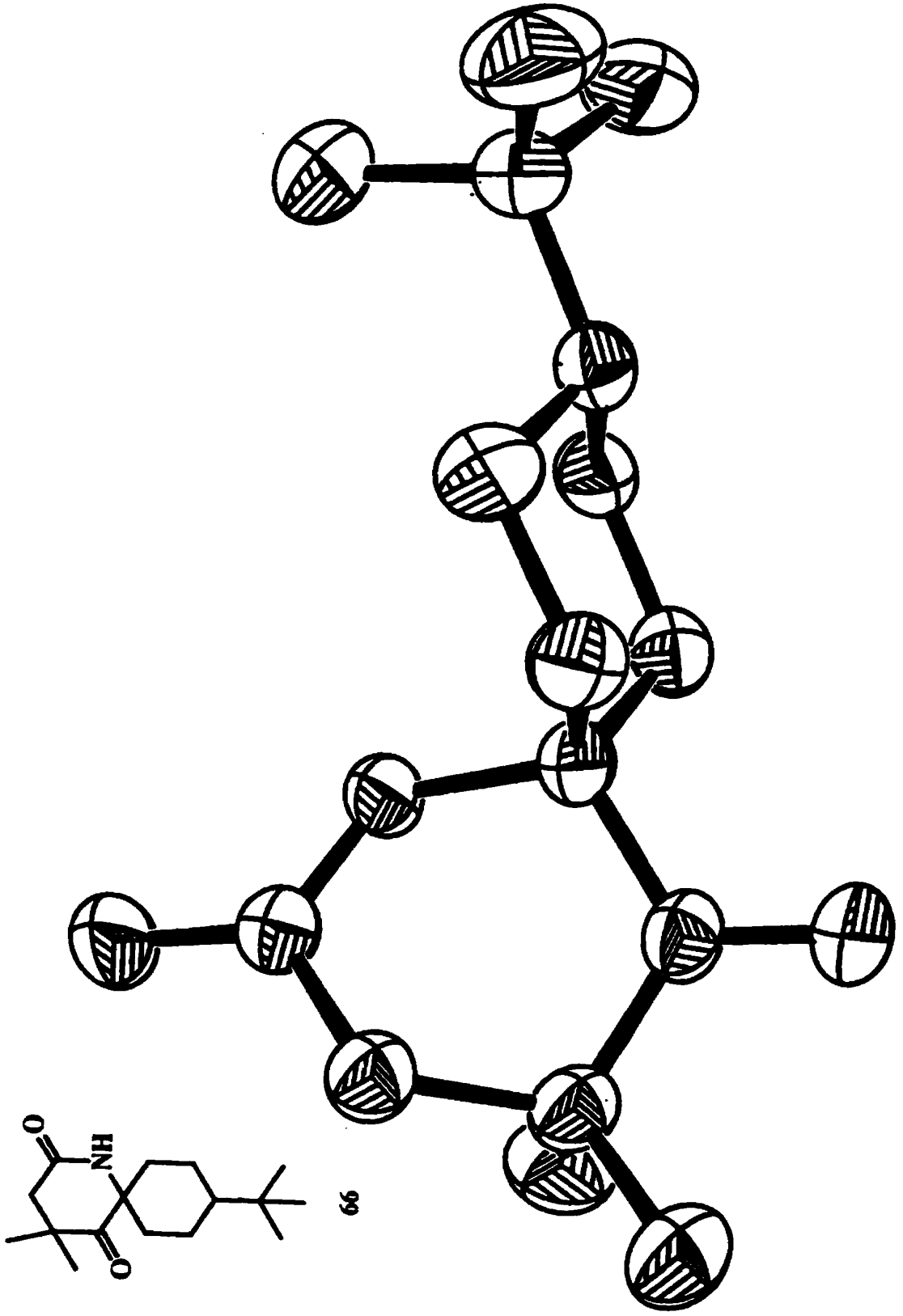
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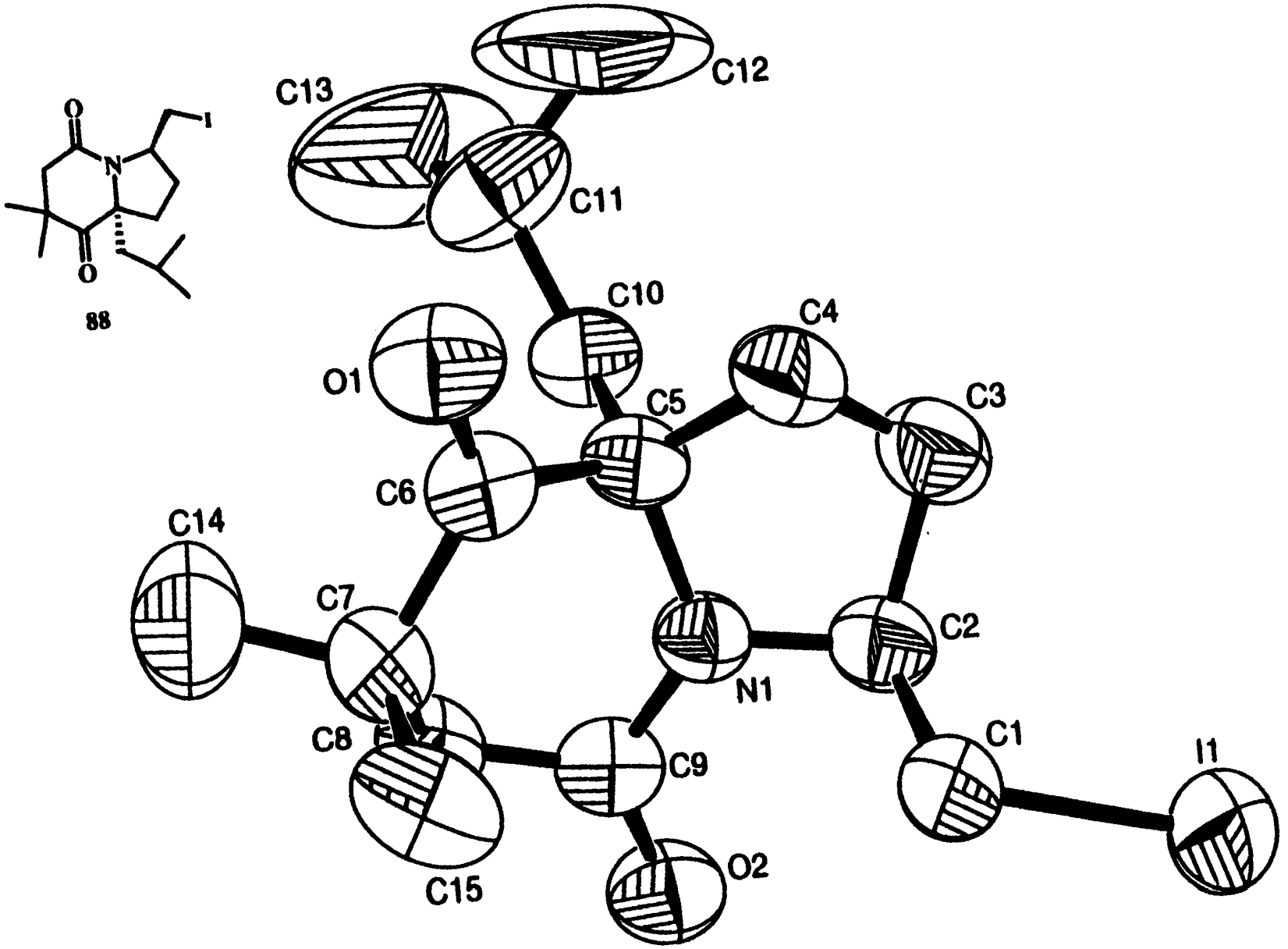
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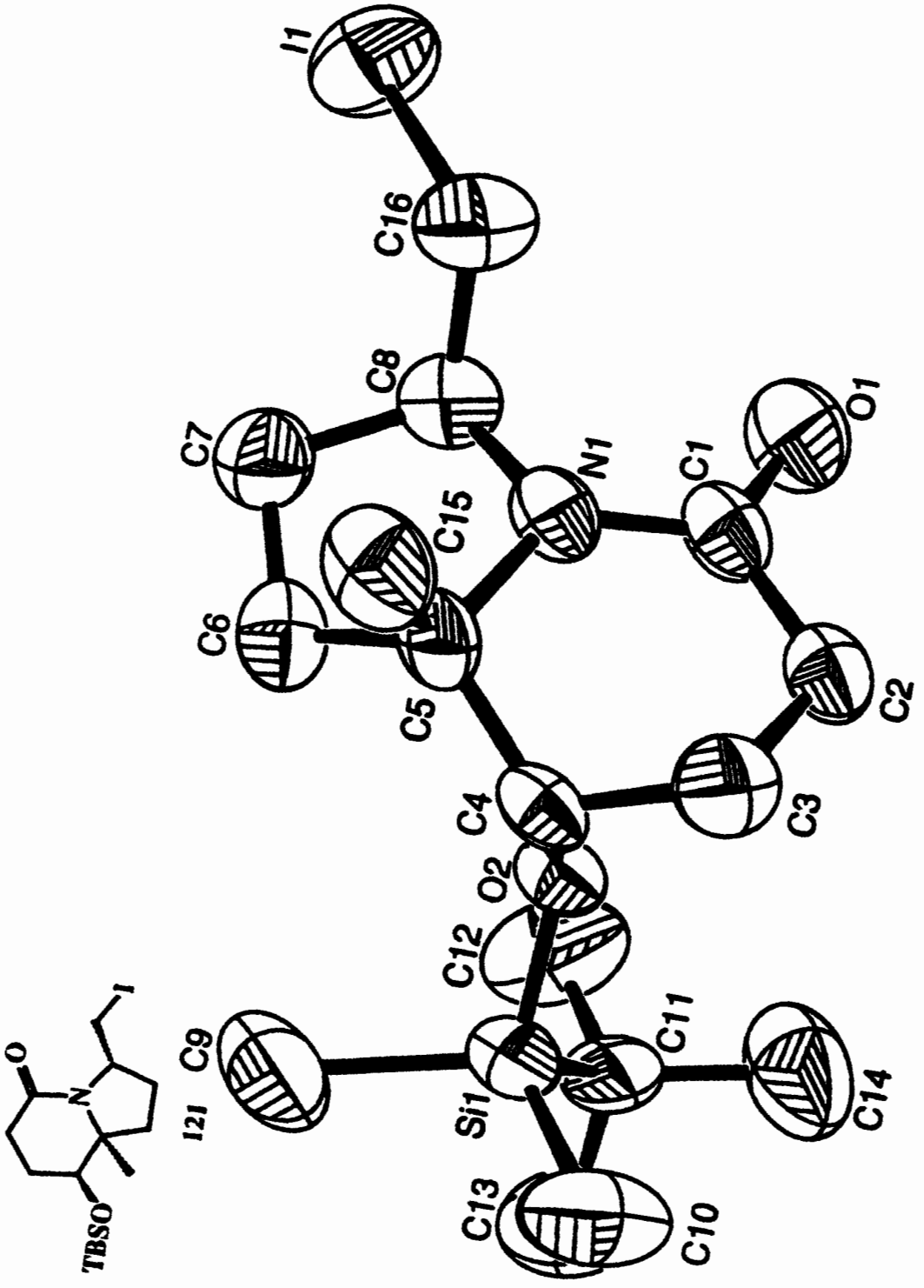
C15
O2

121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C3
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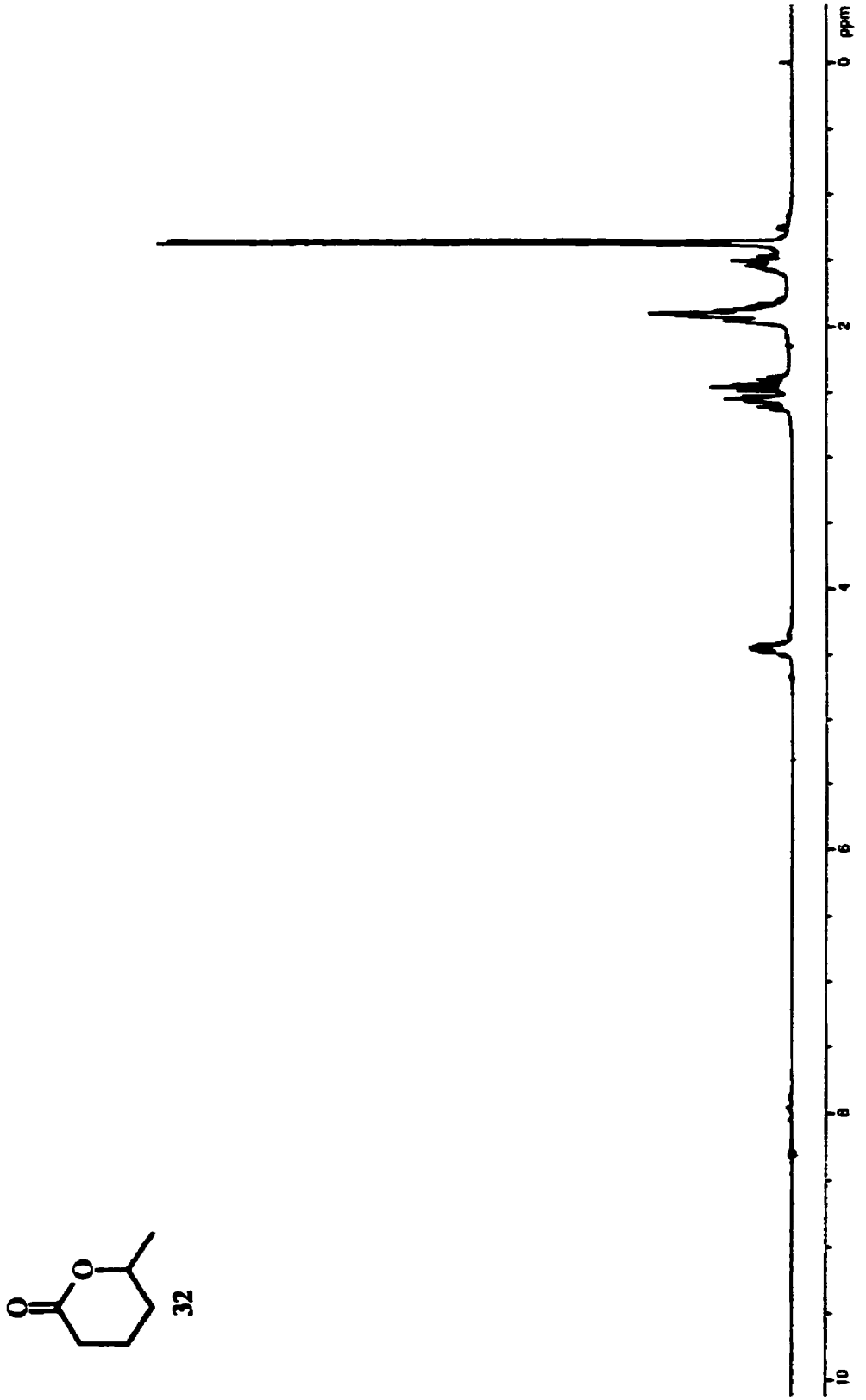
I
TBSO

Appendix 2: ^{1}H NMR Spectra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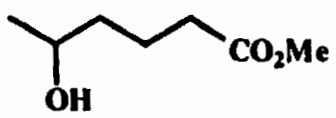
10



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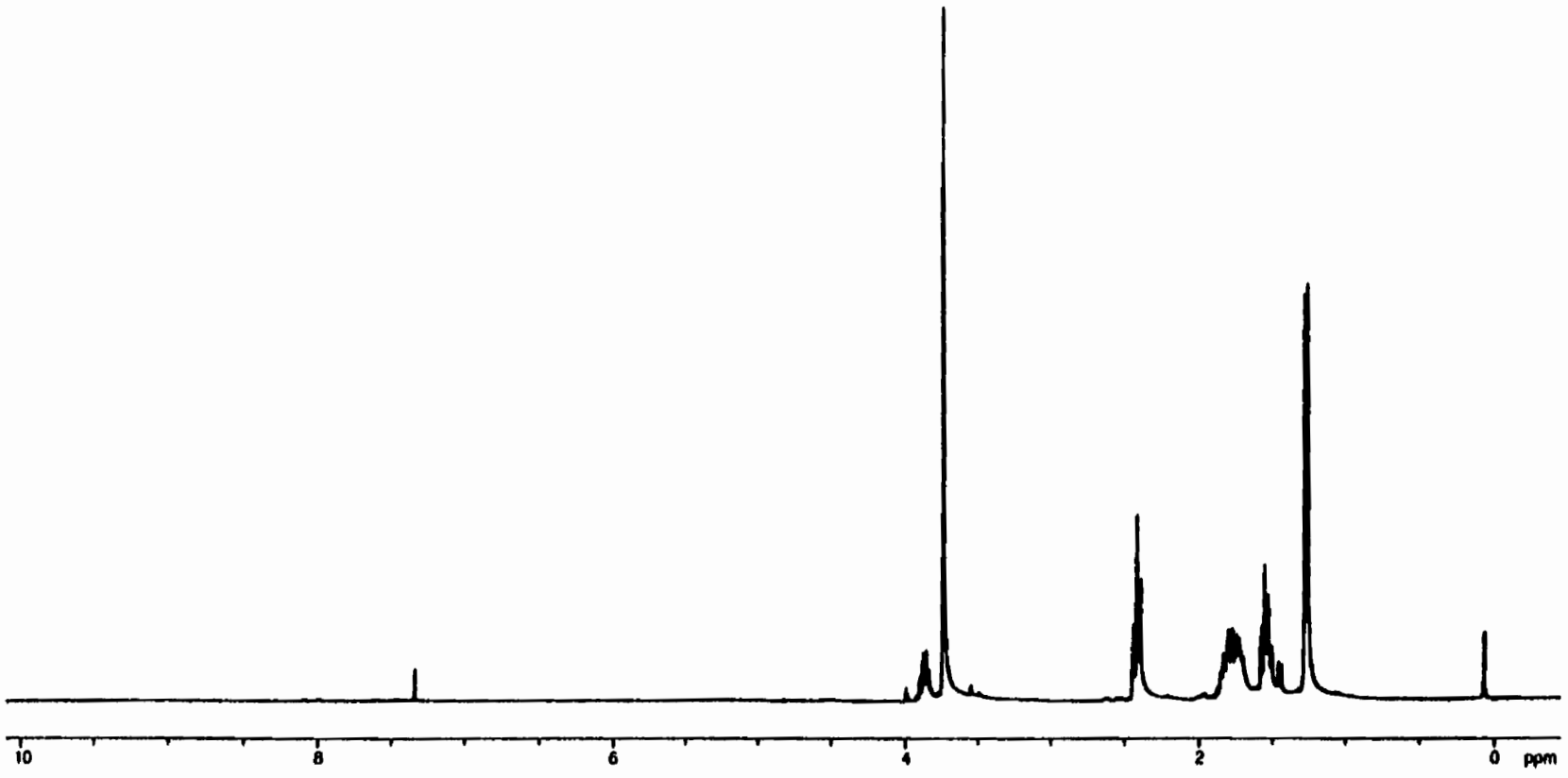

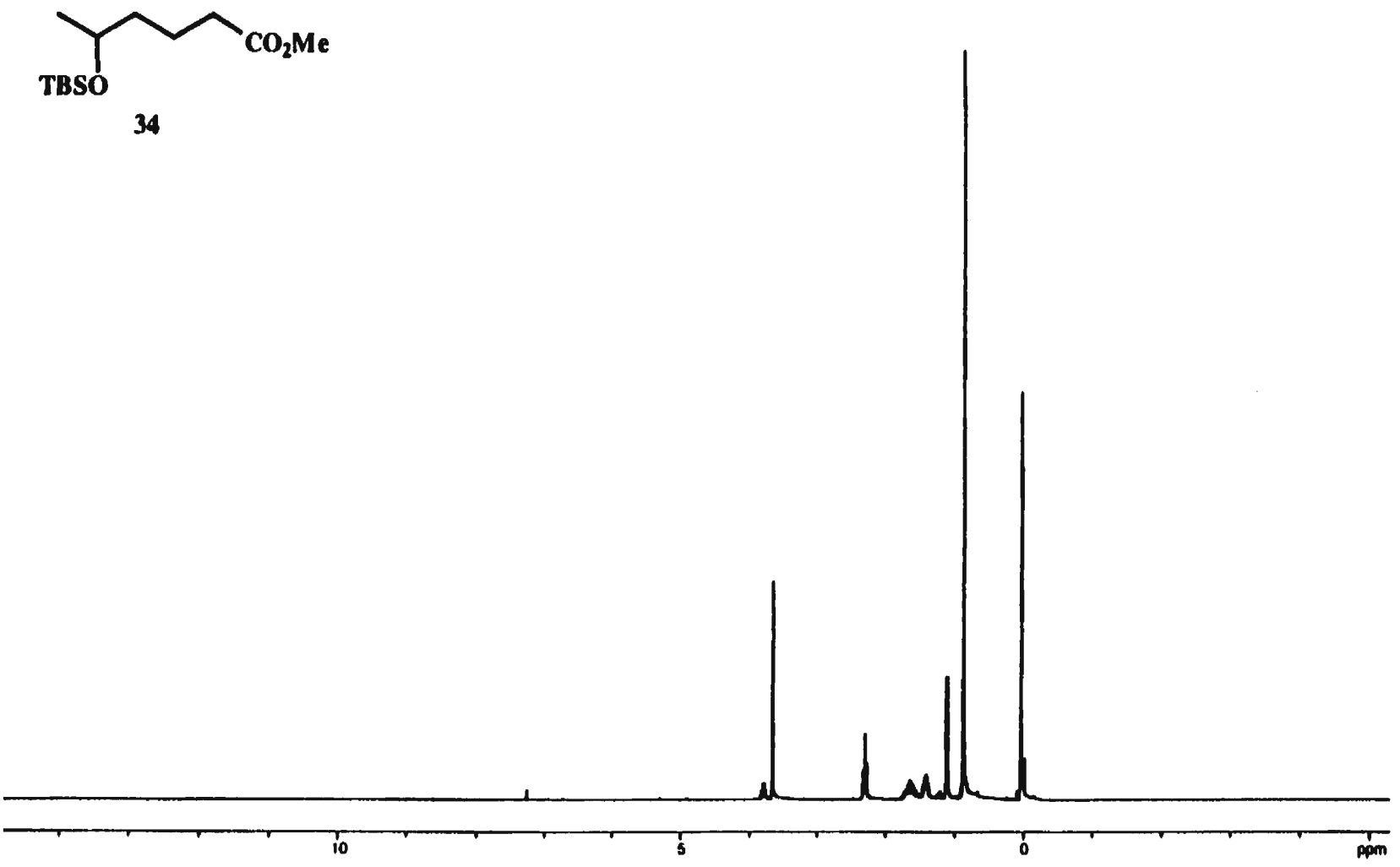
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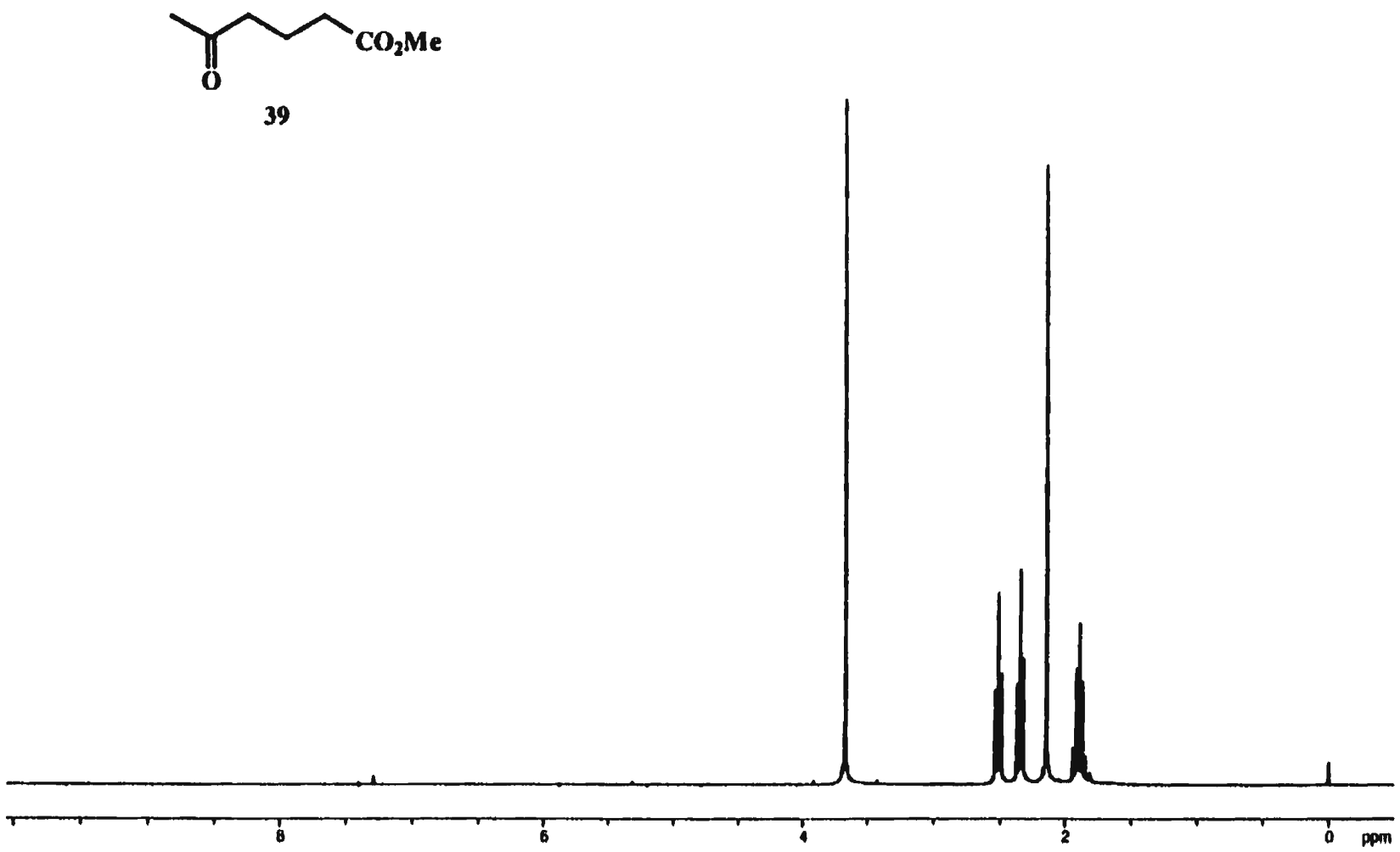
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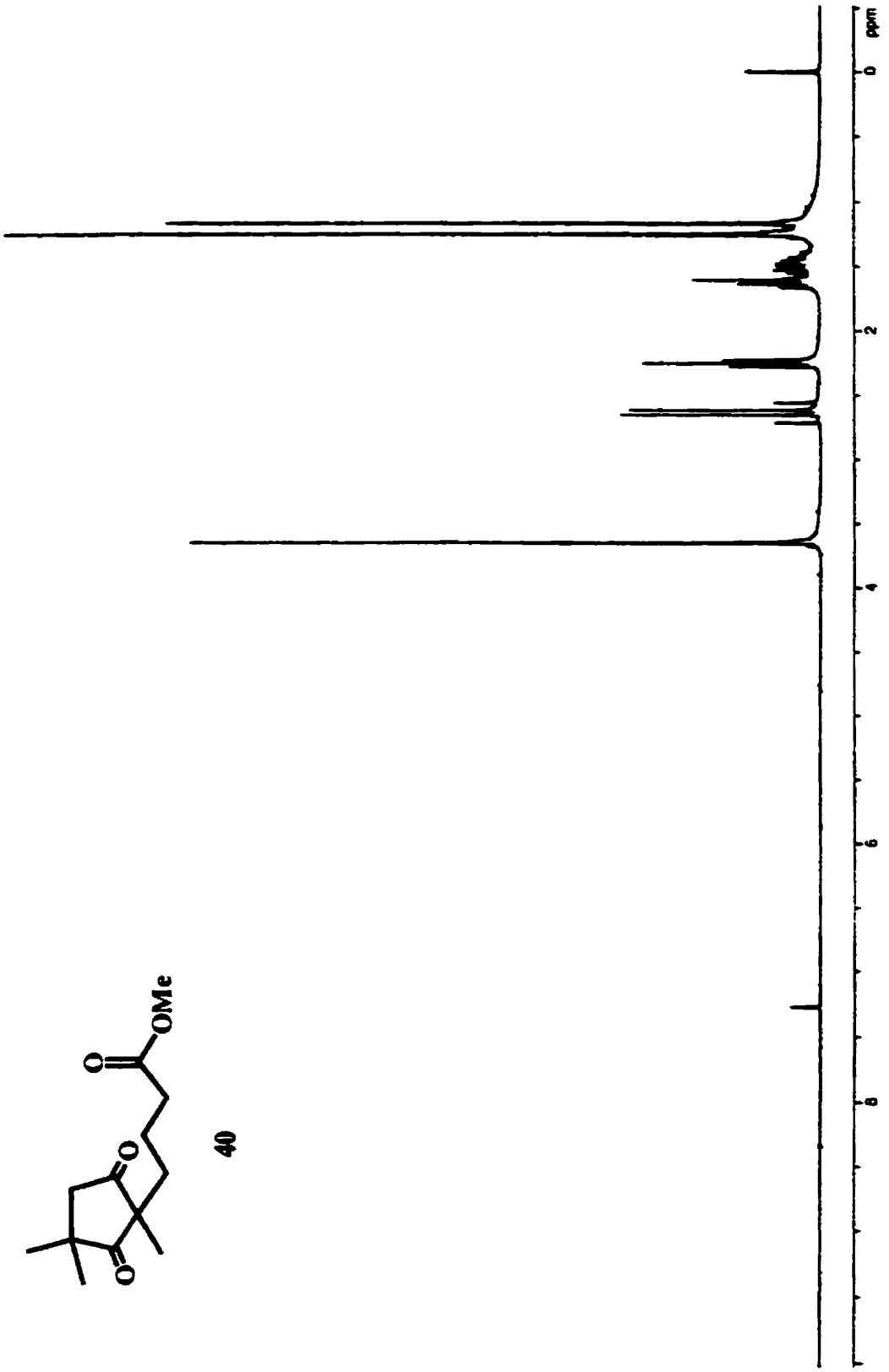

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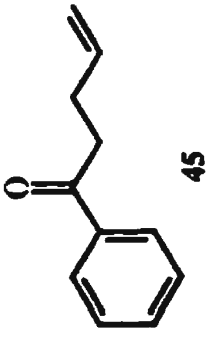

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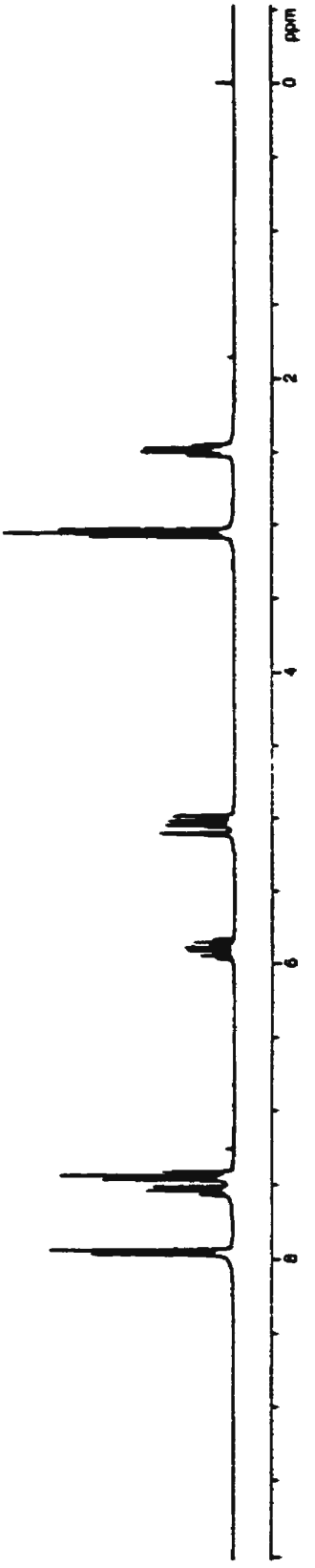

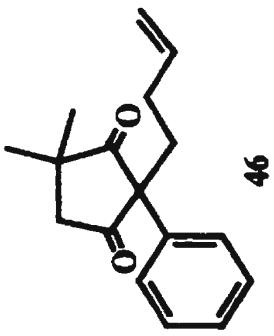

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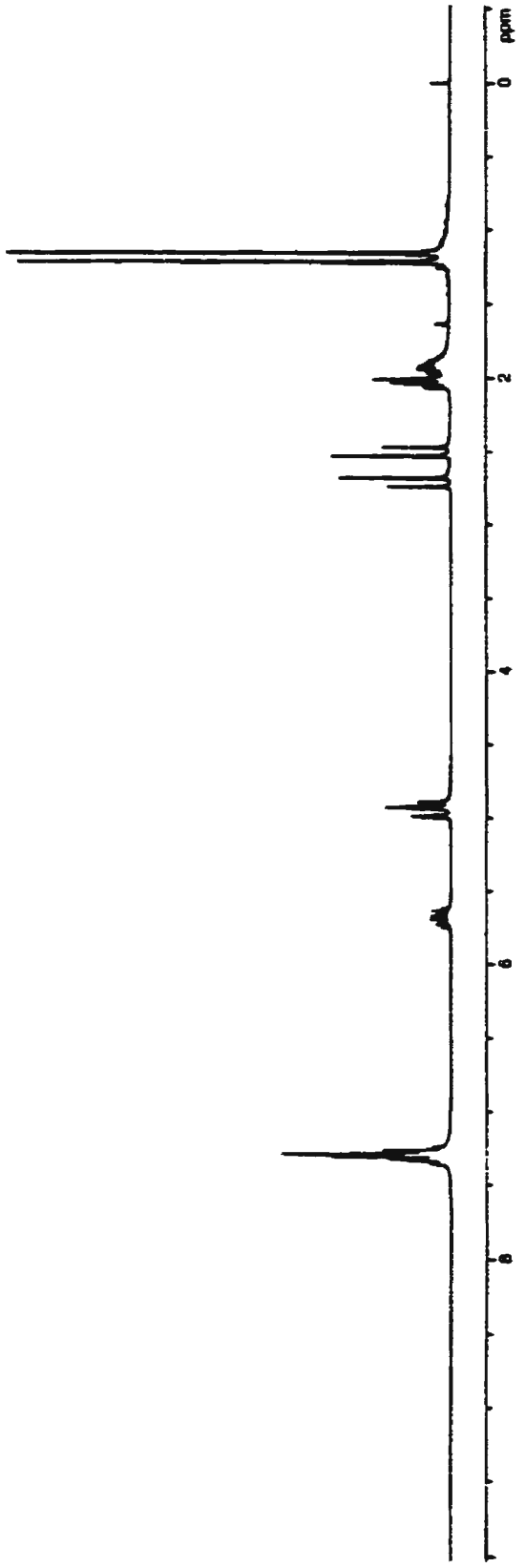

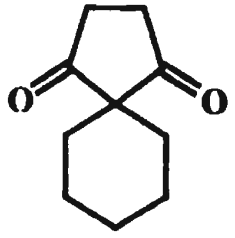

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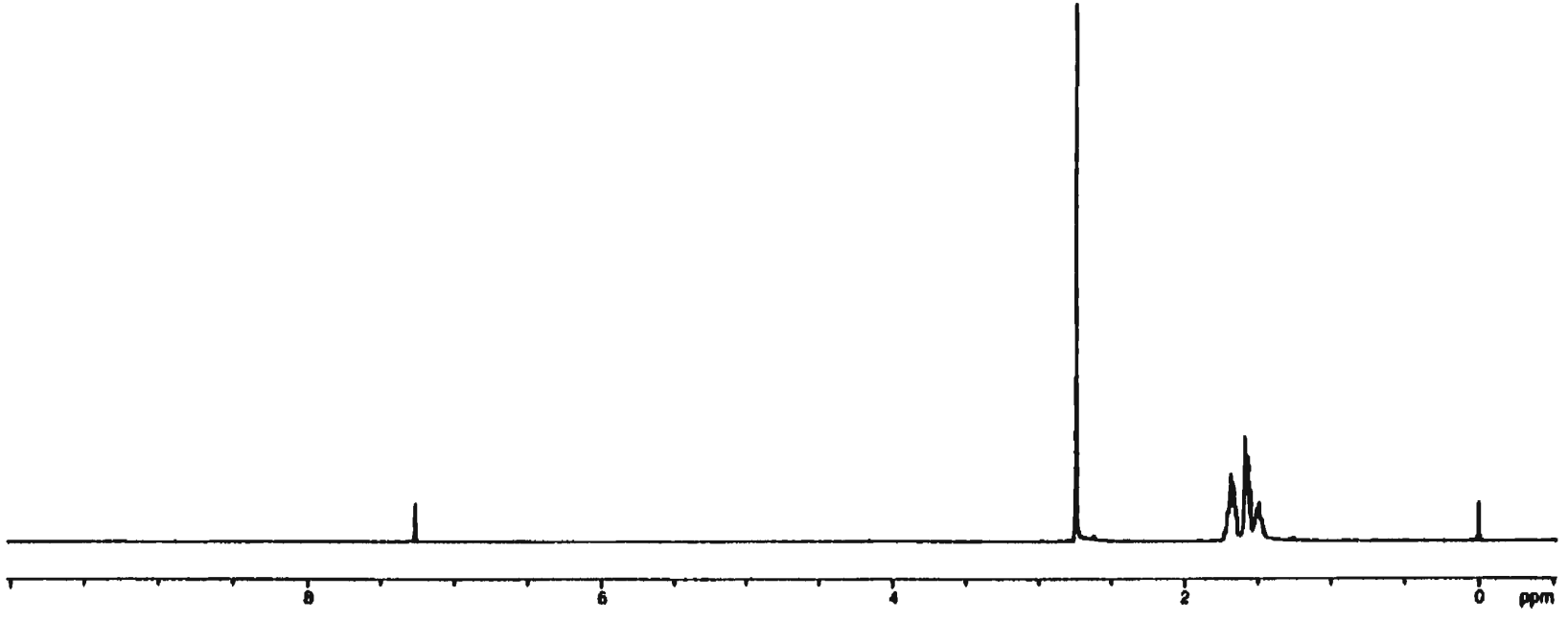

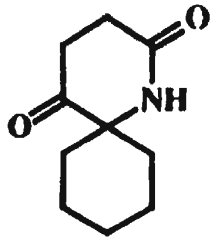

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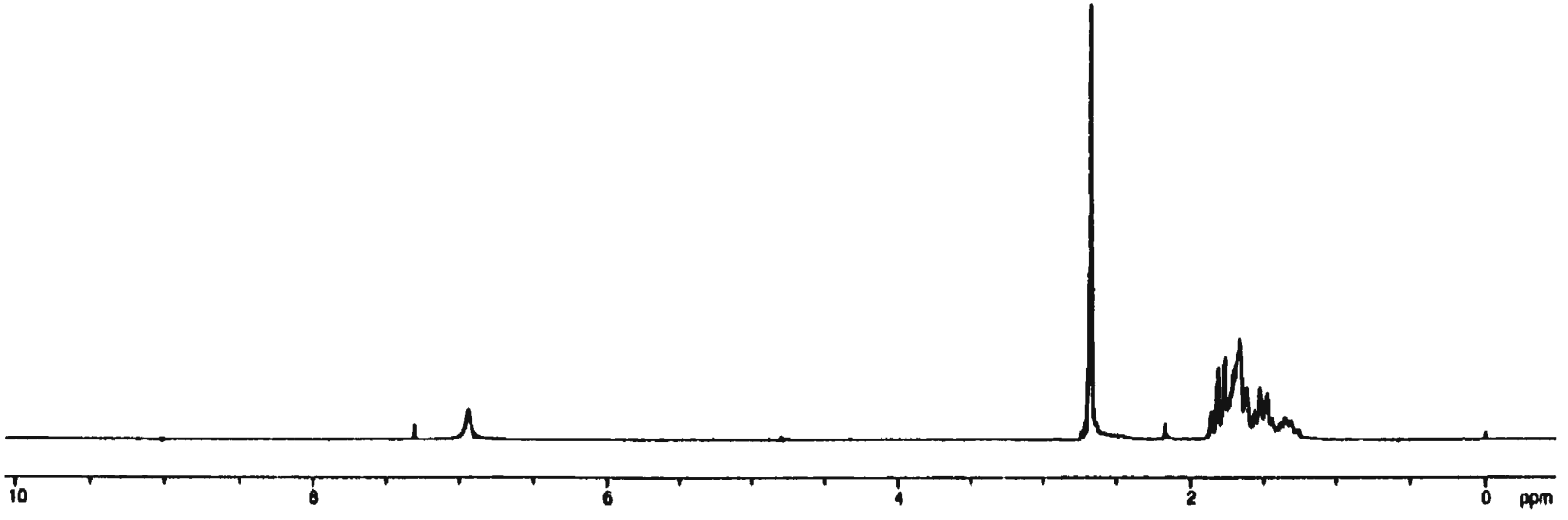

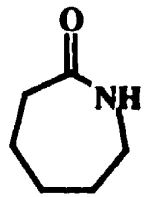

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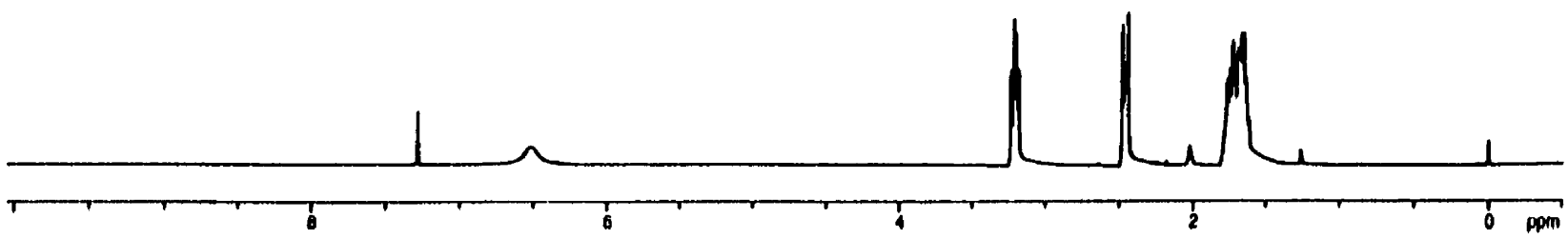

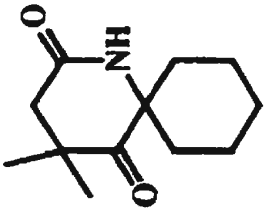

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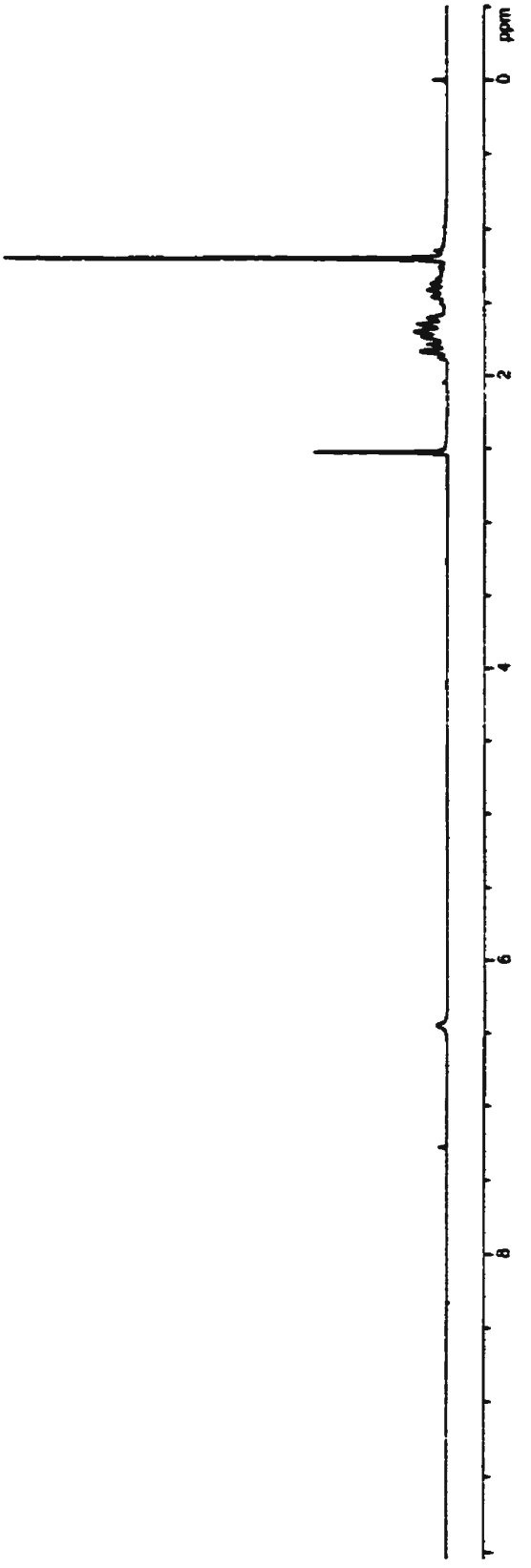

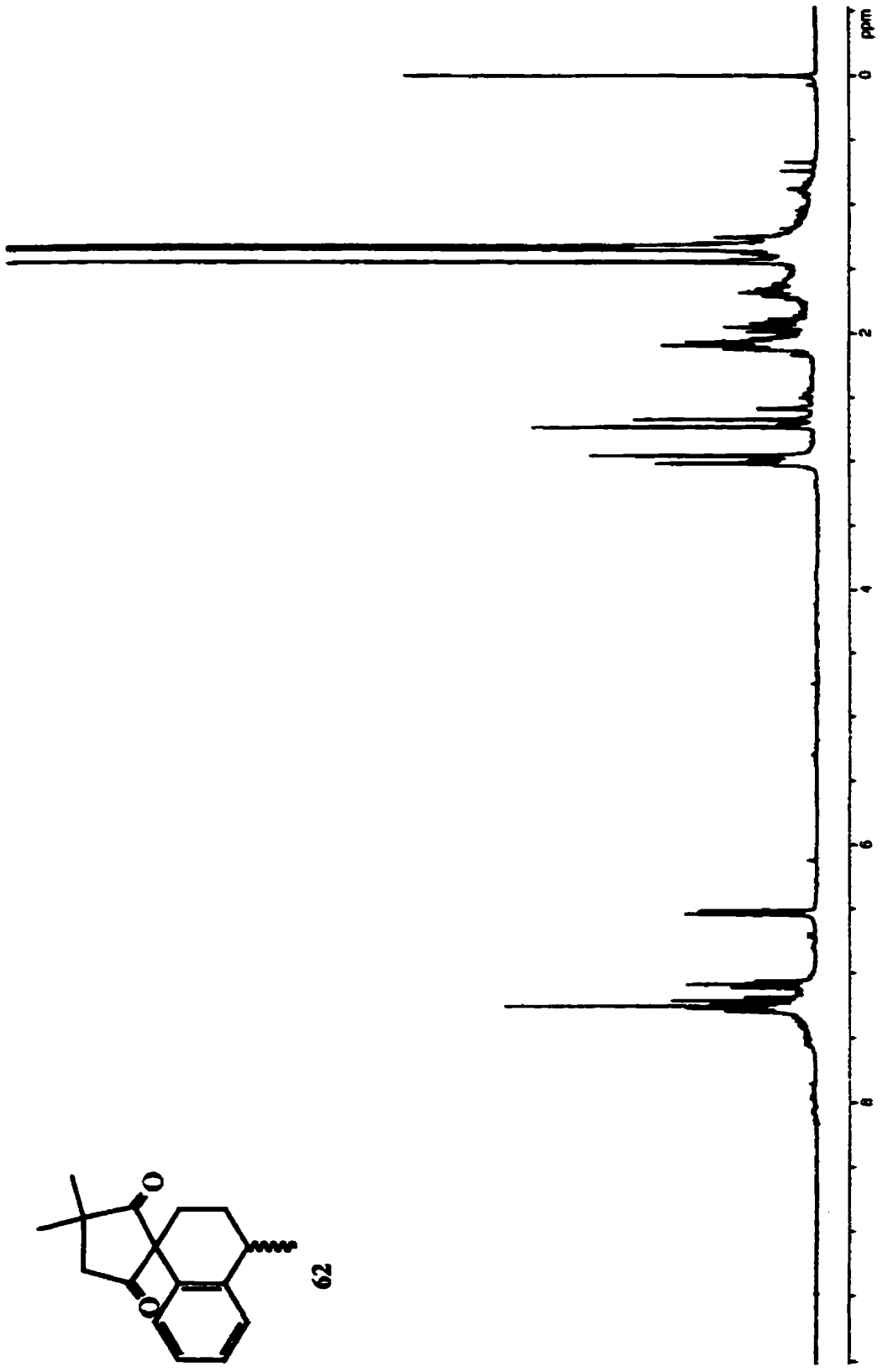

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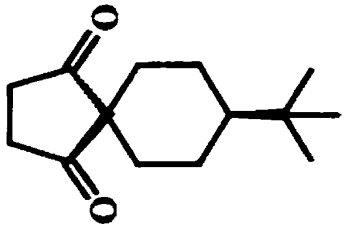

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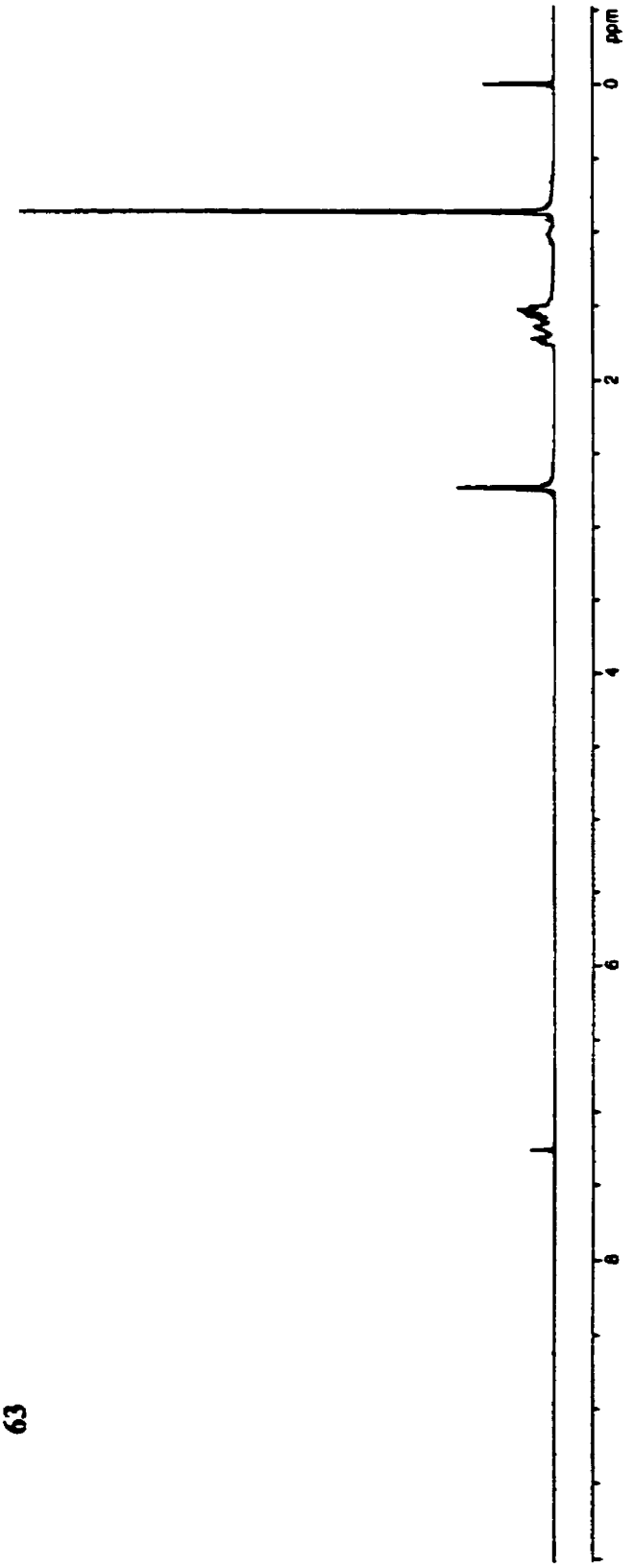

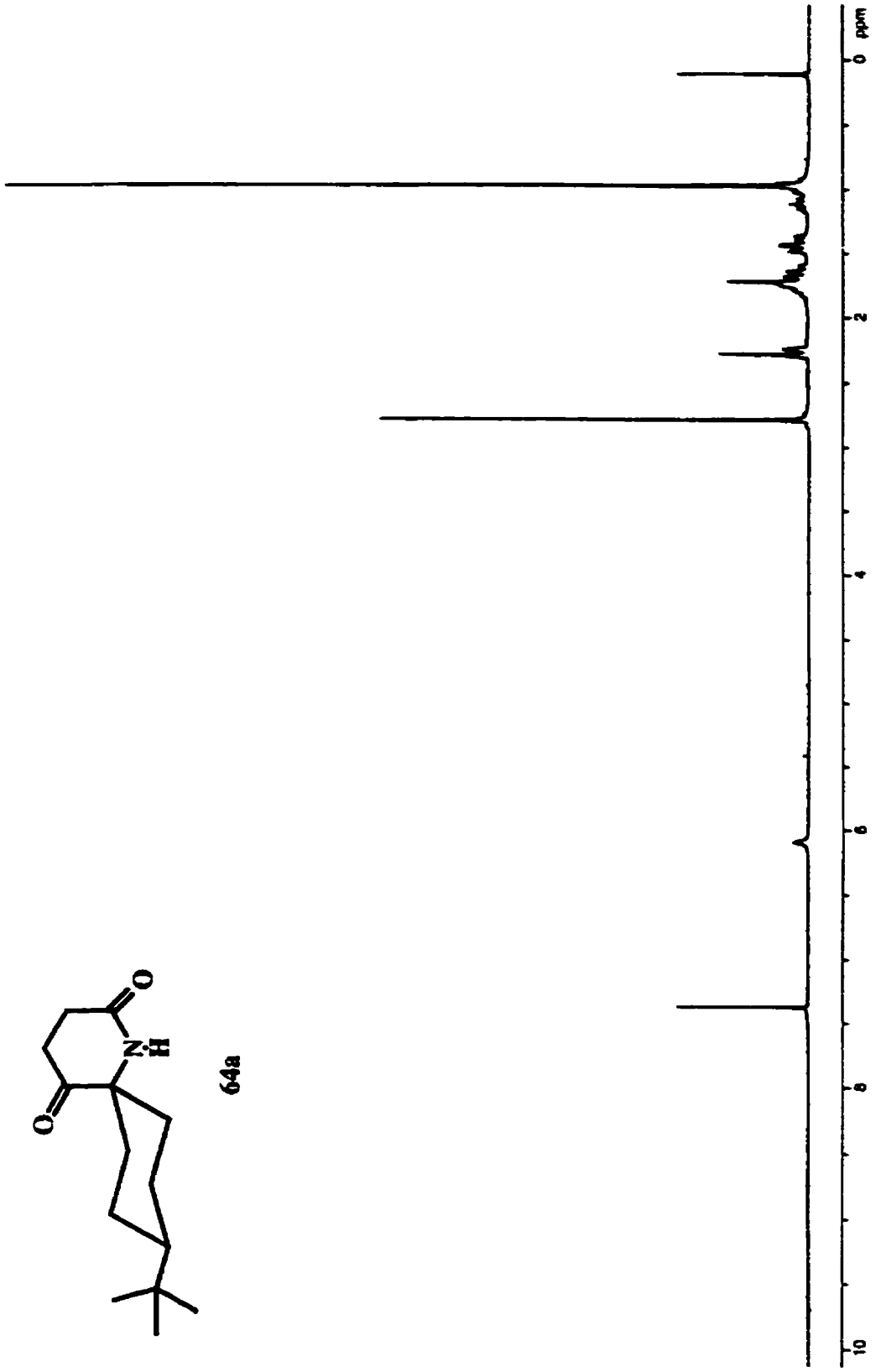

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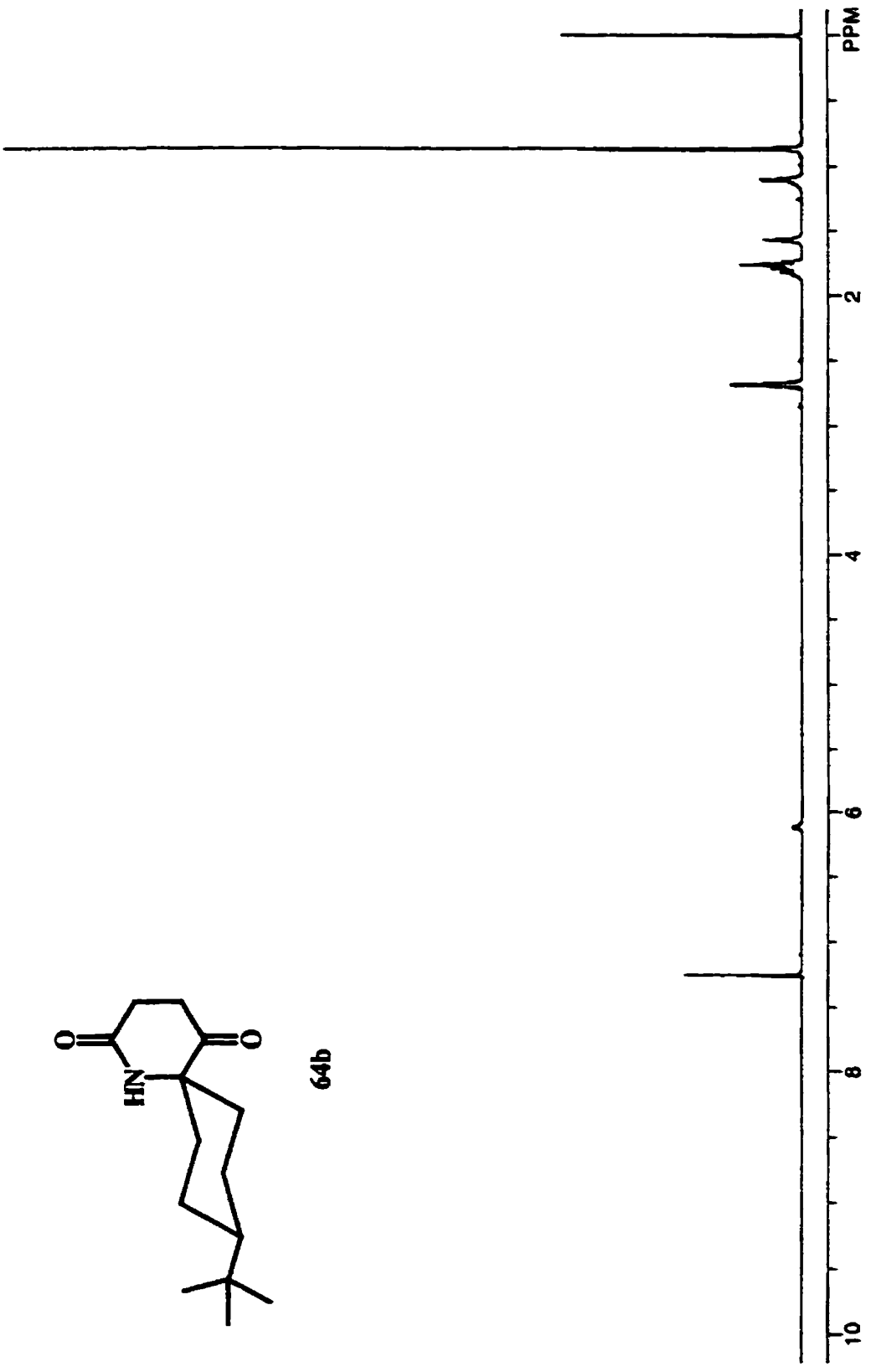

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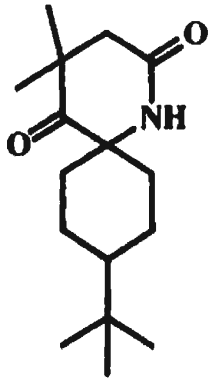

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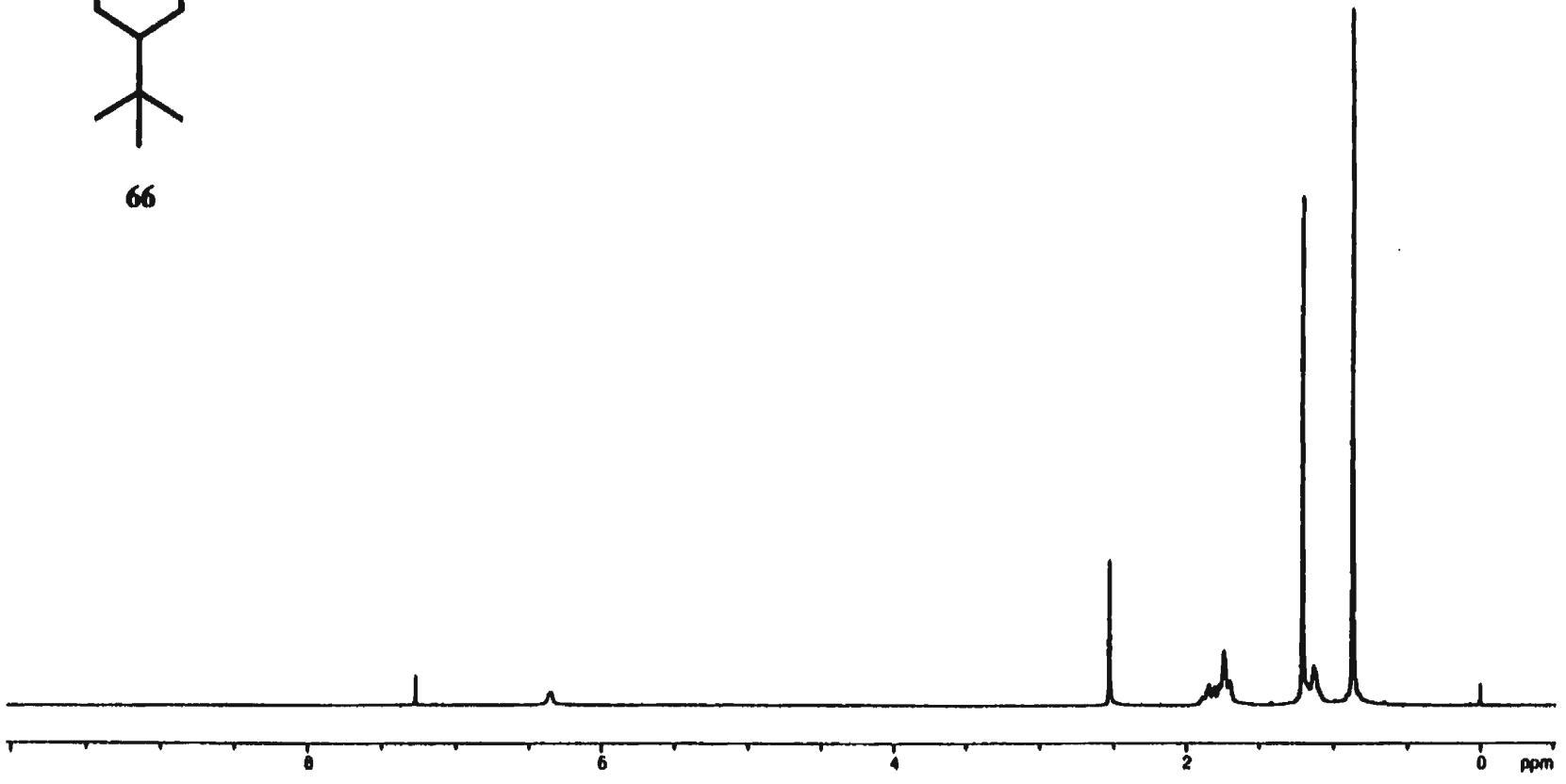

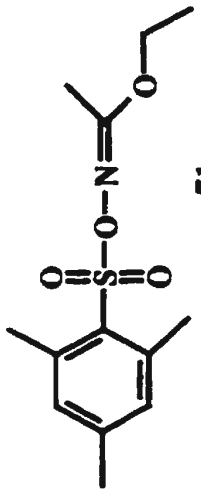

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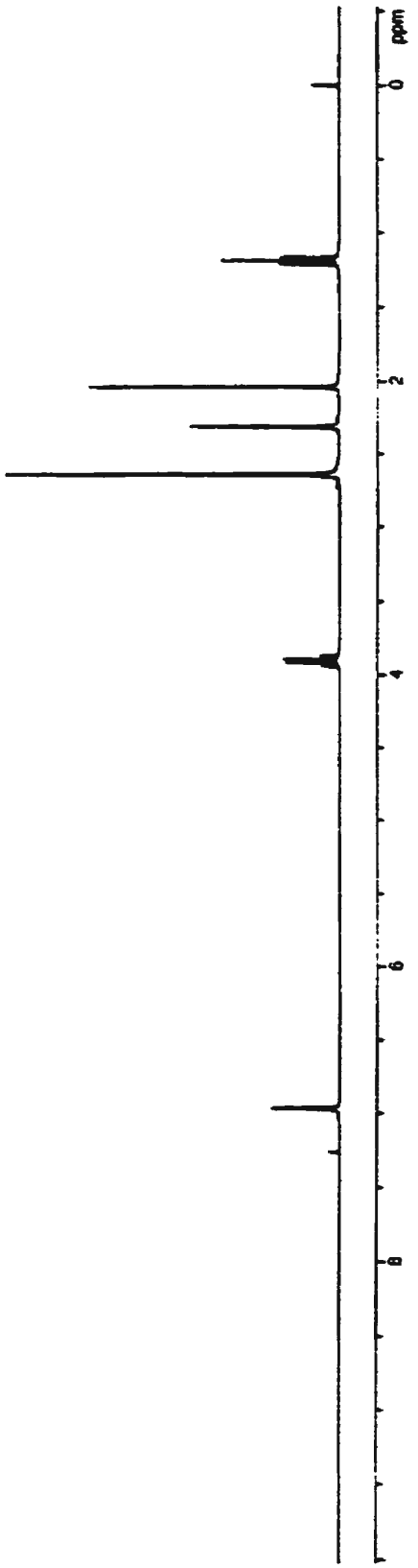

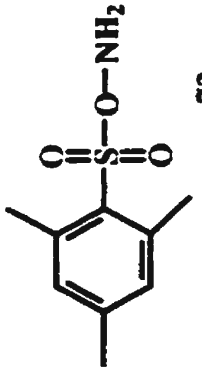

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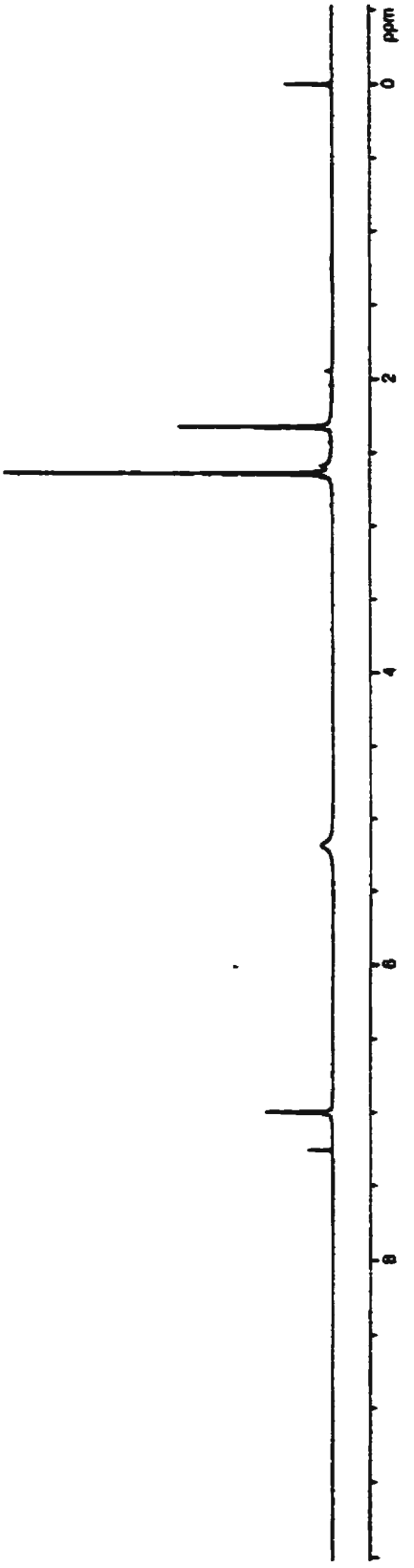

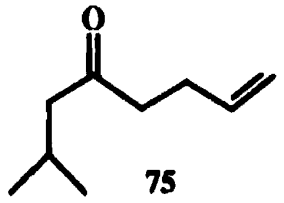

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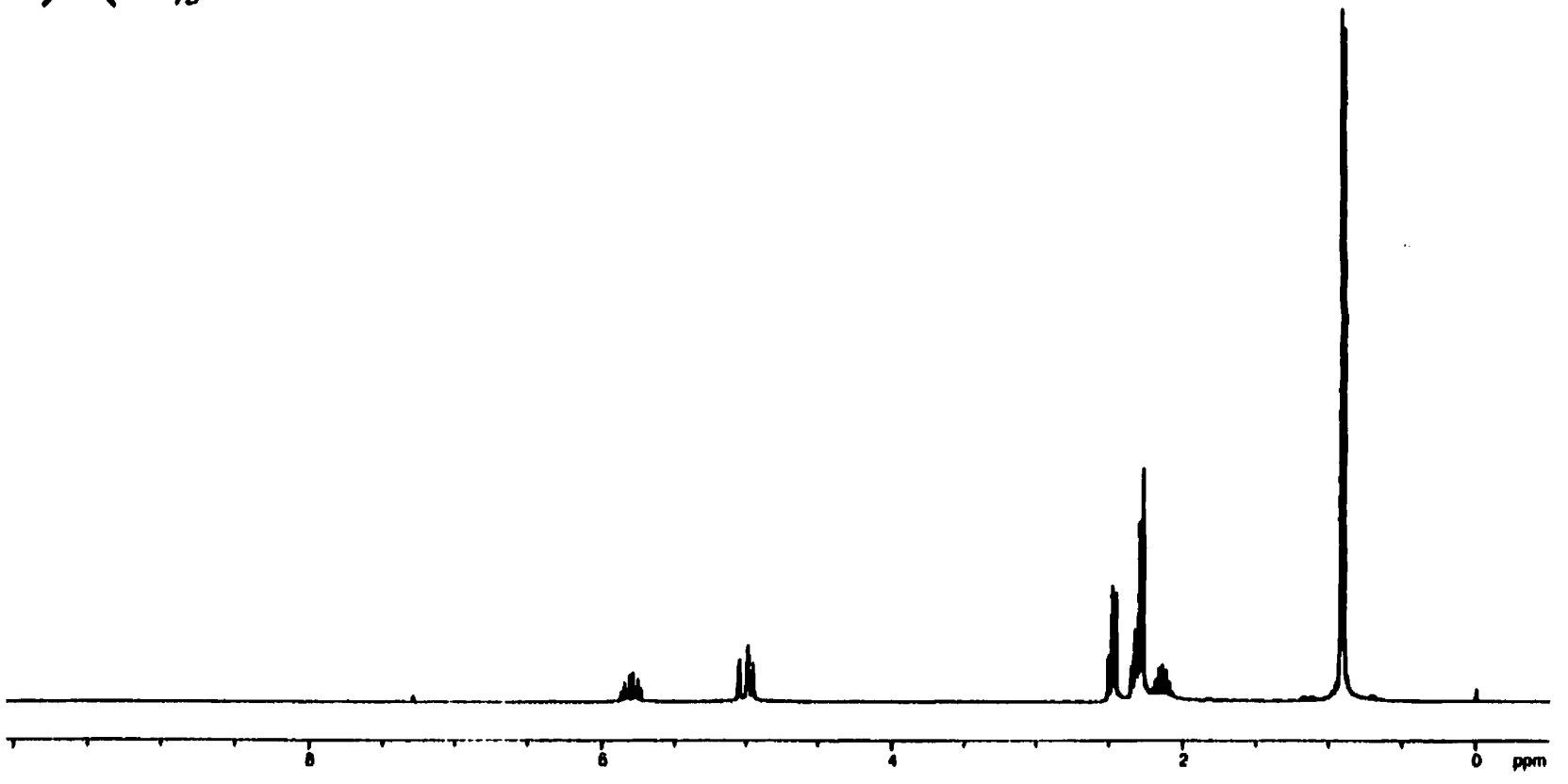

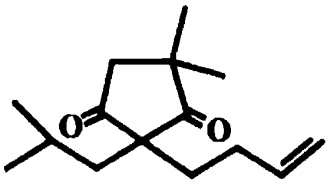

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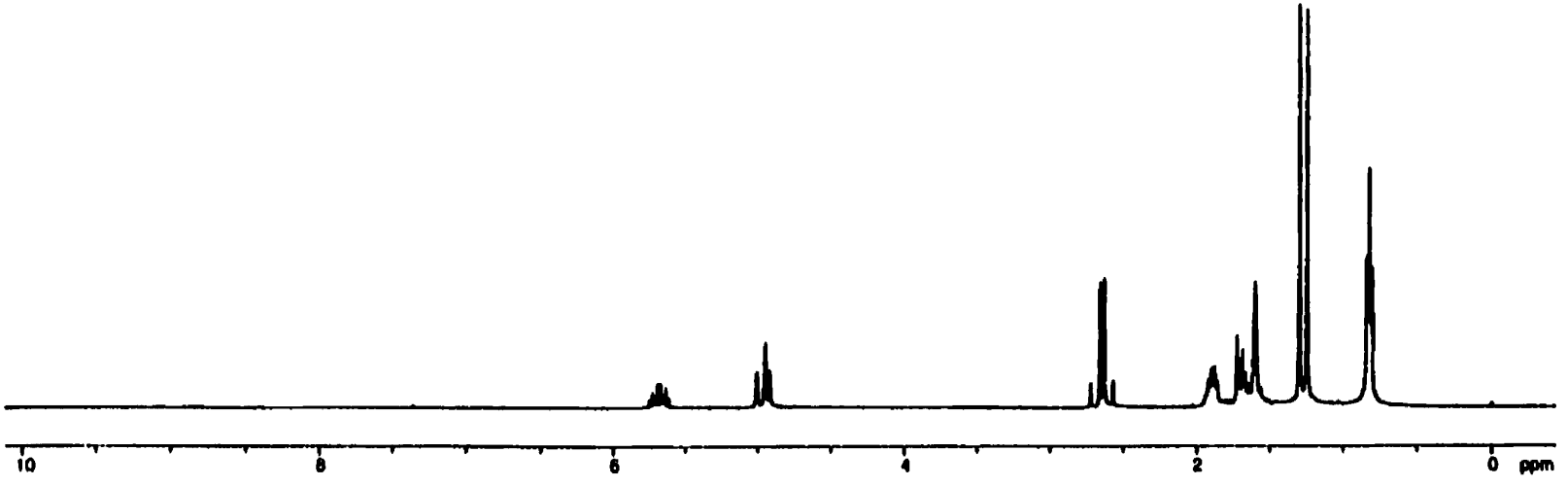

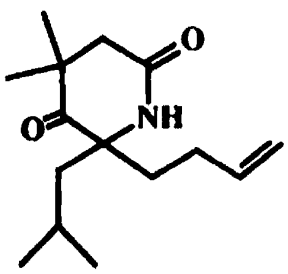

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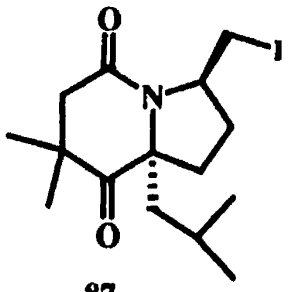

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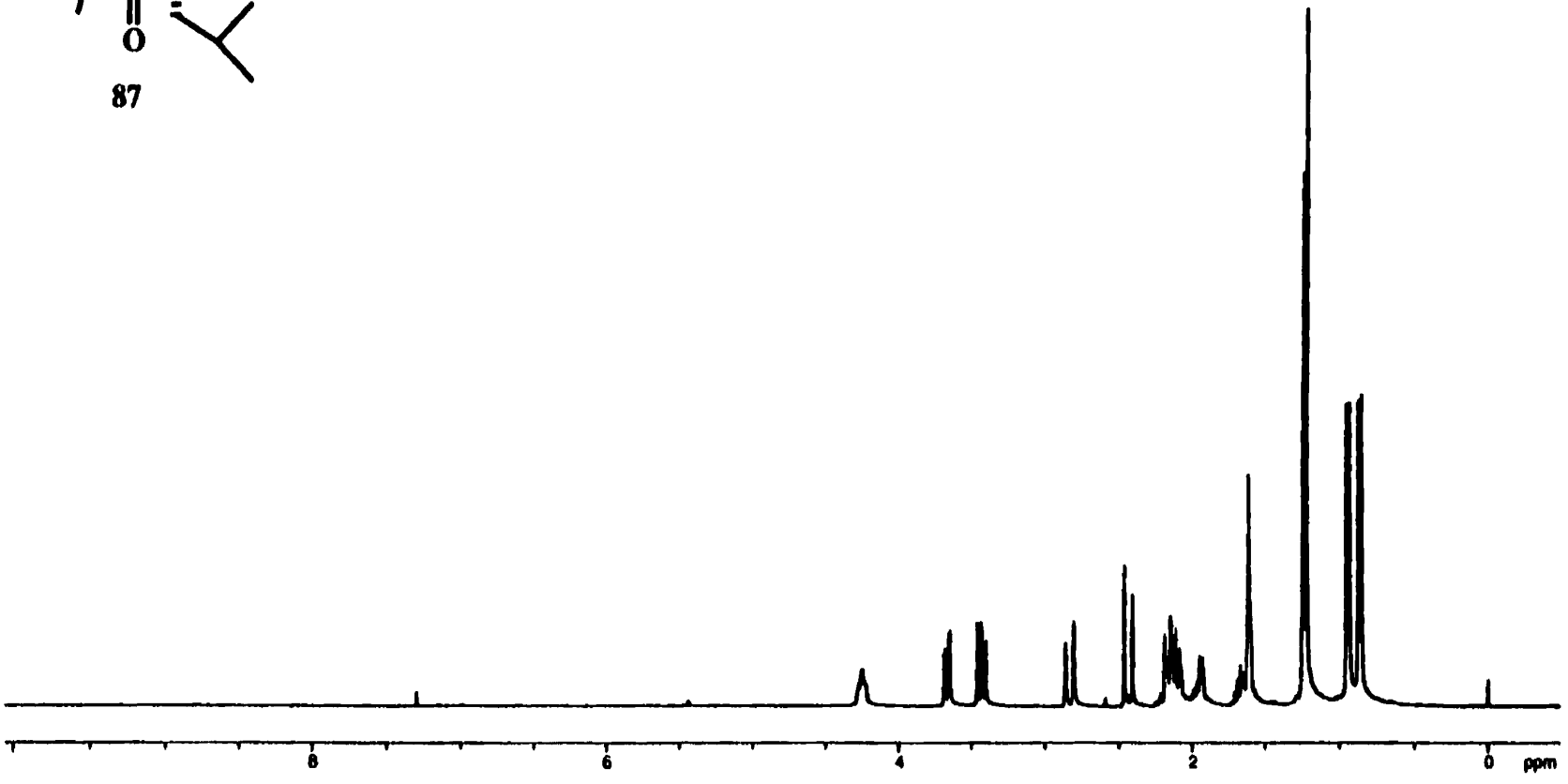

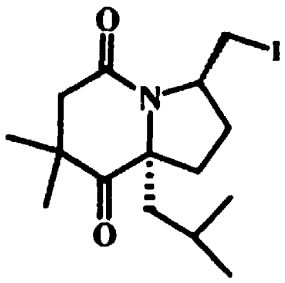

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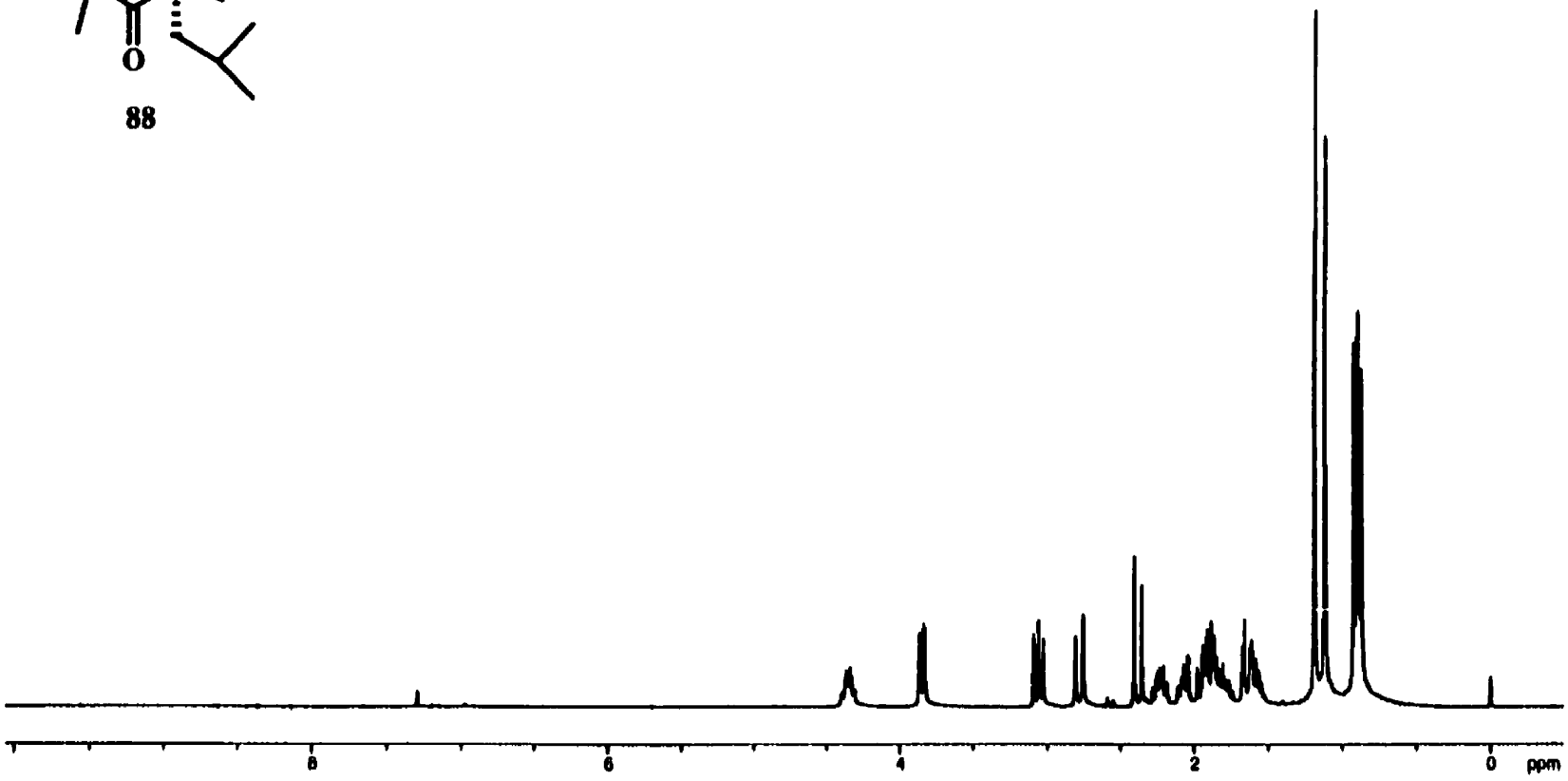

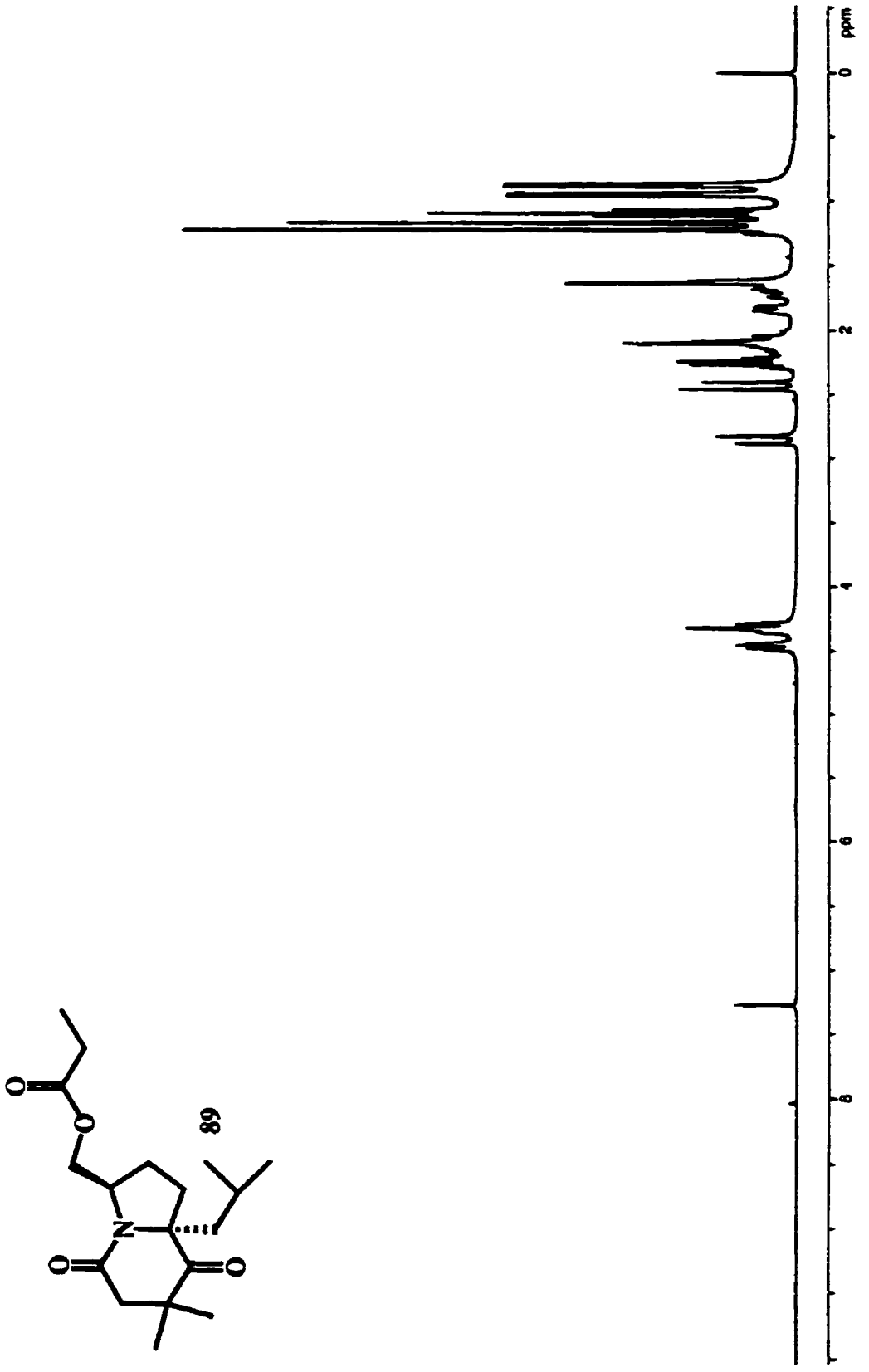
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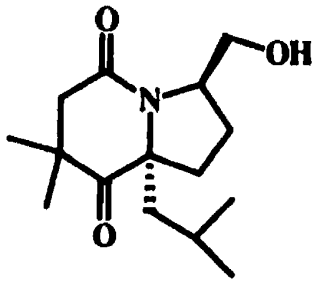

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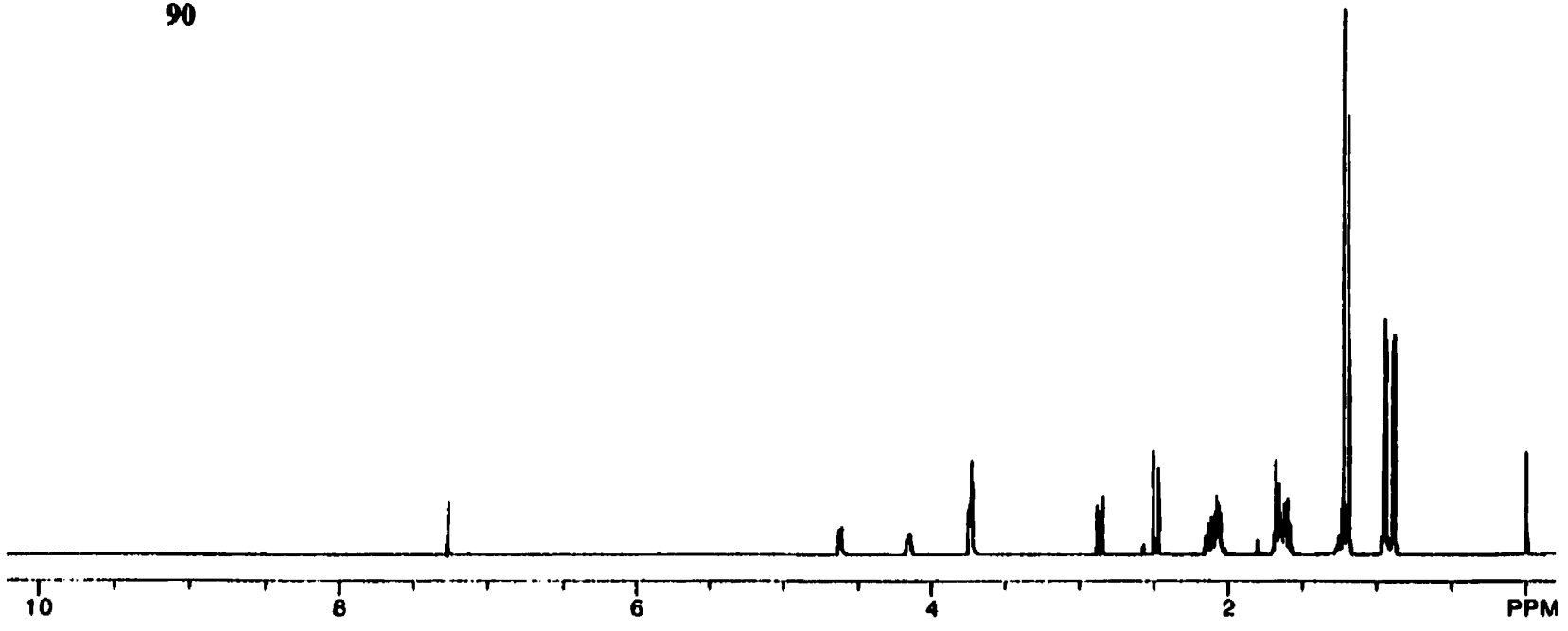

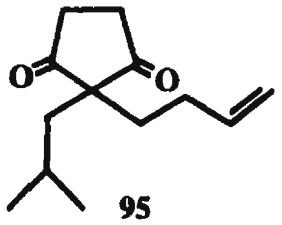

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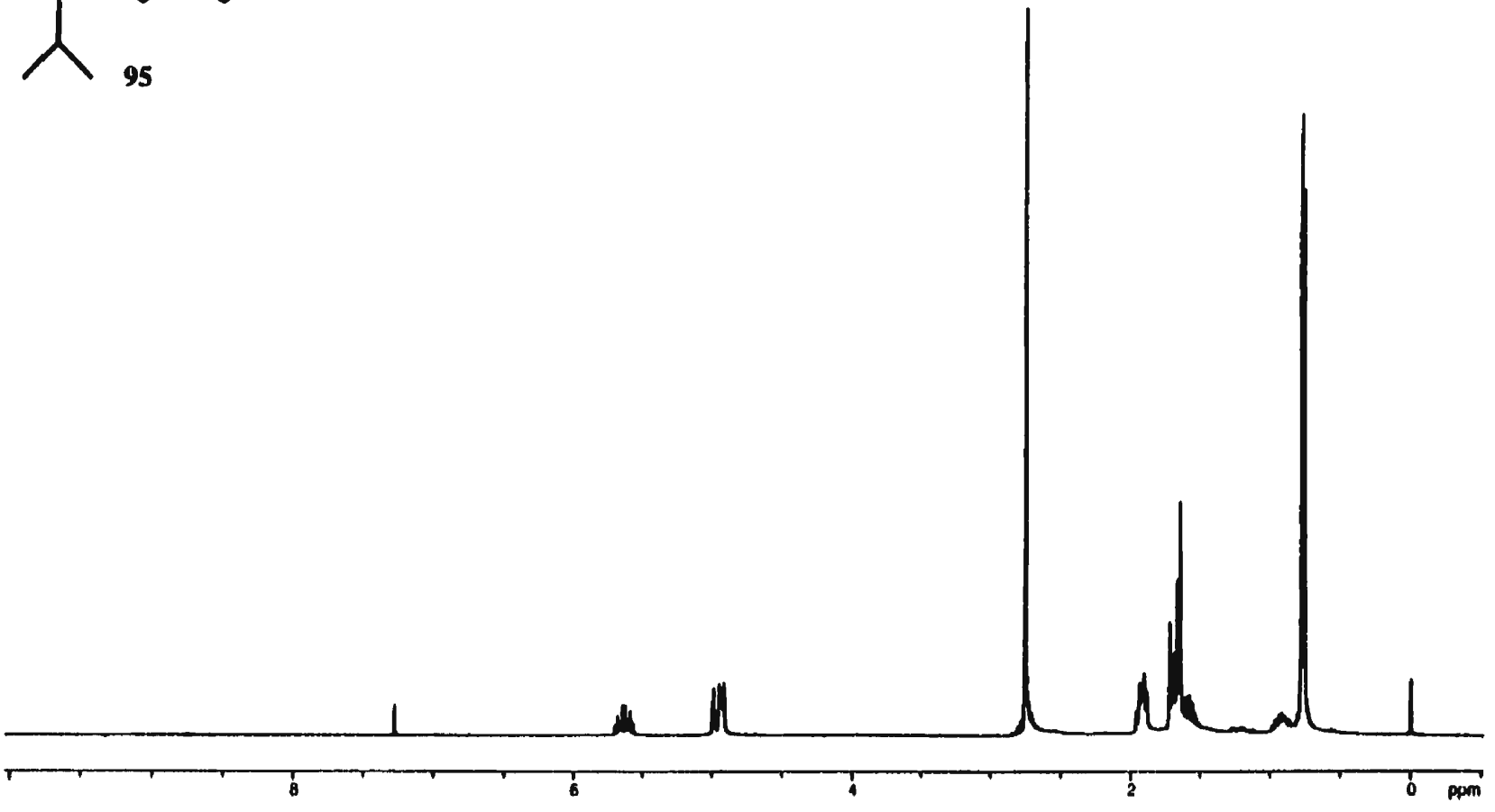

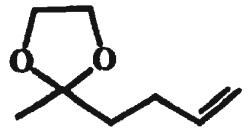

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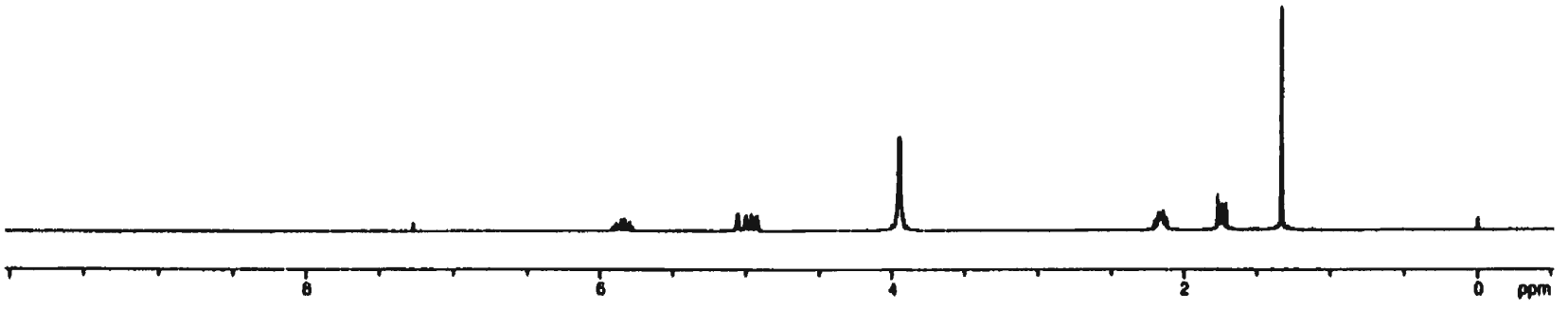

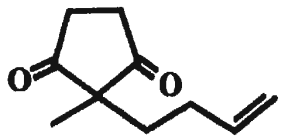

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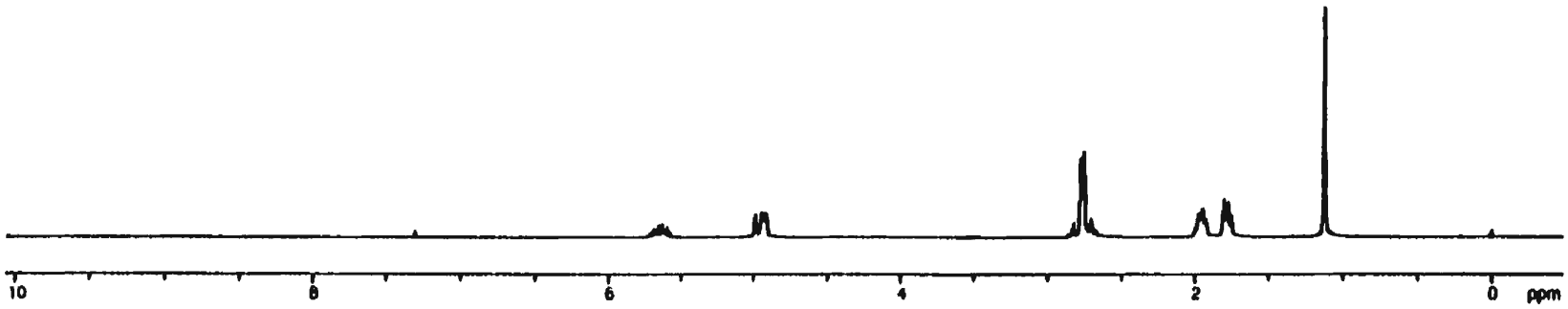

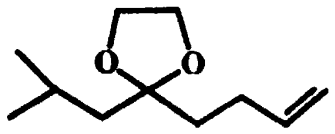

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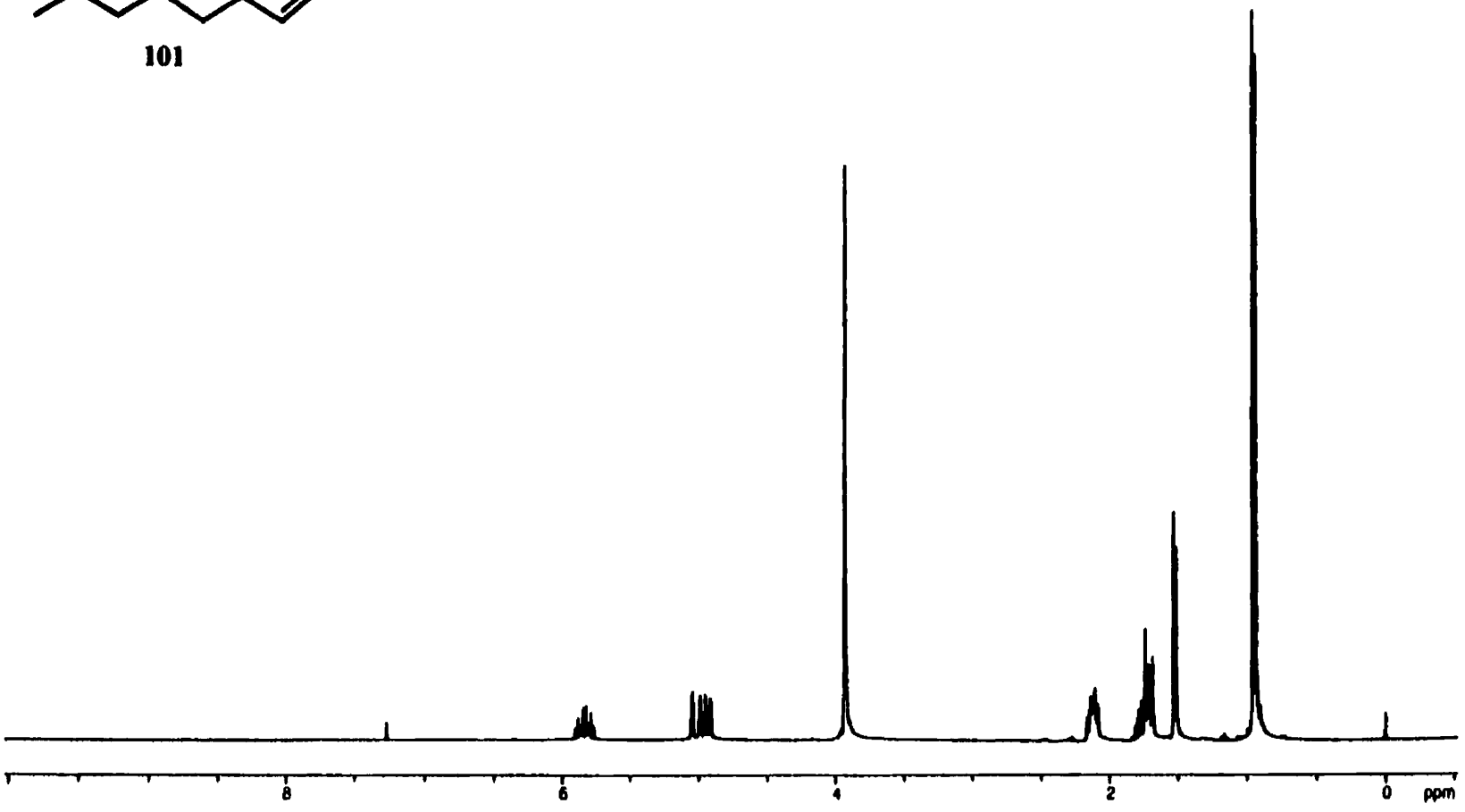

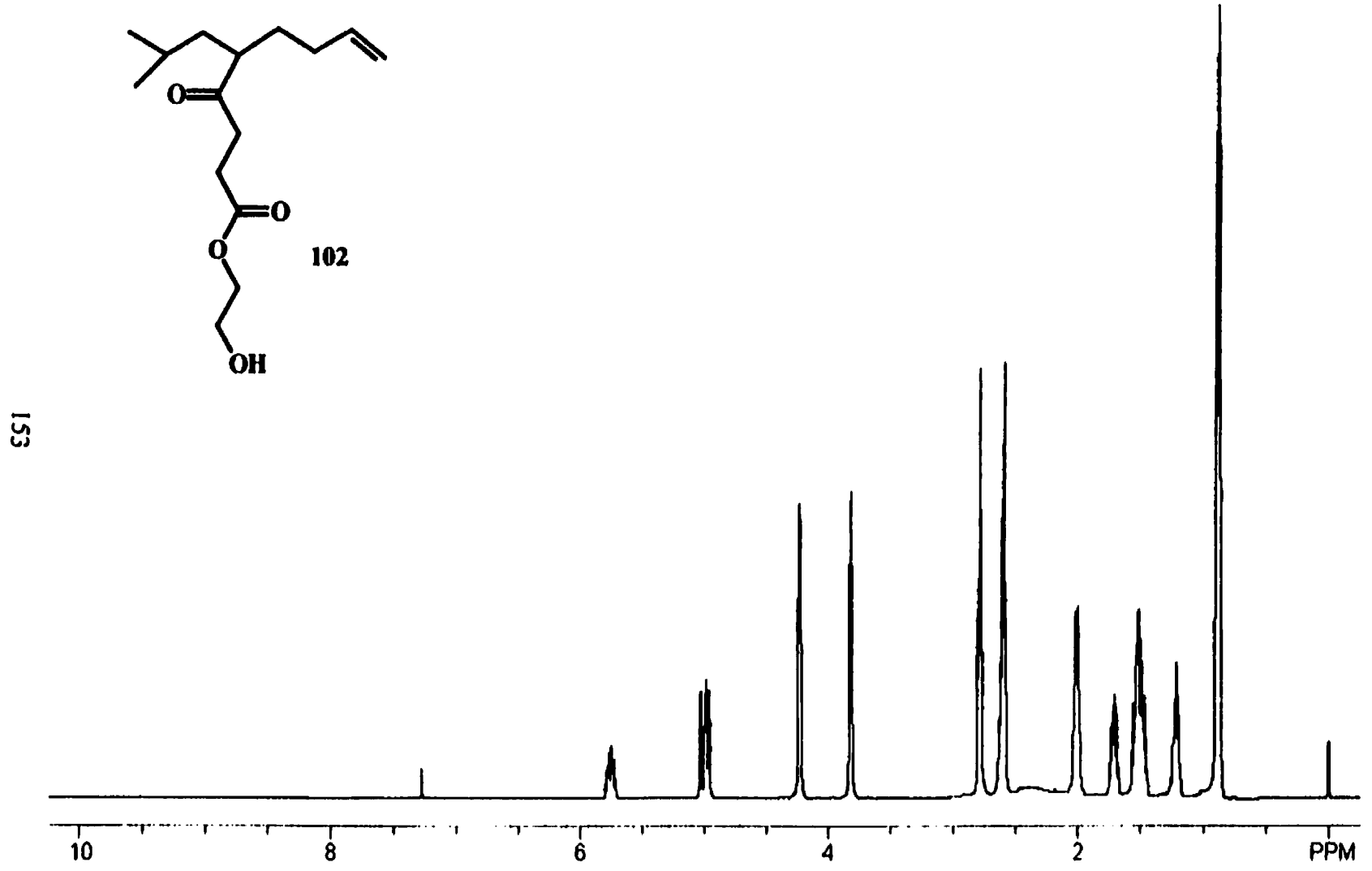
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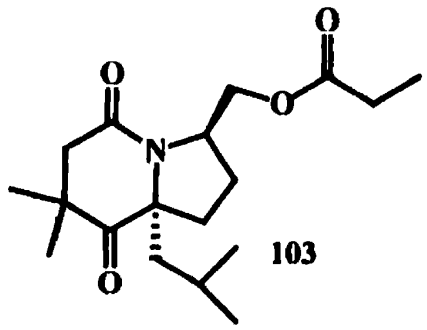

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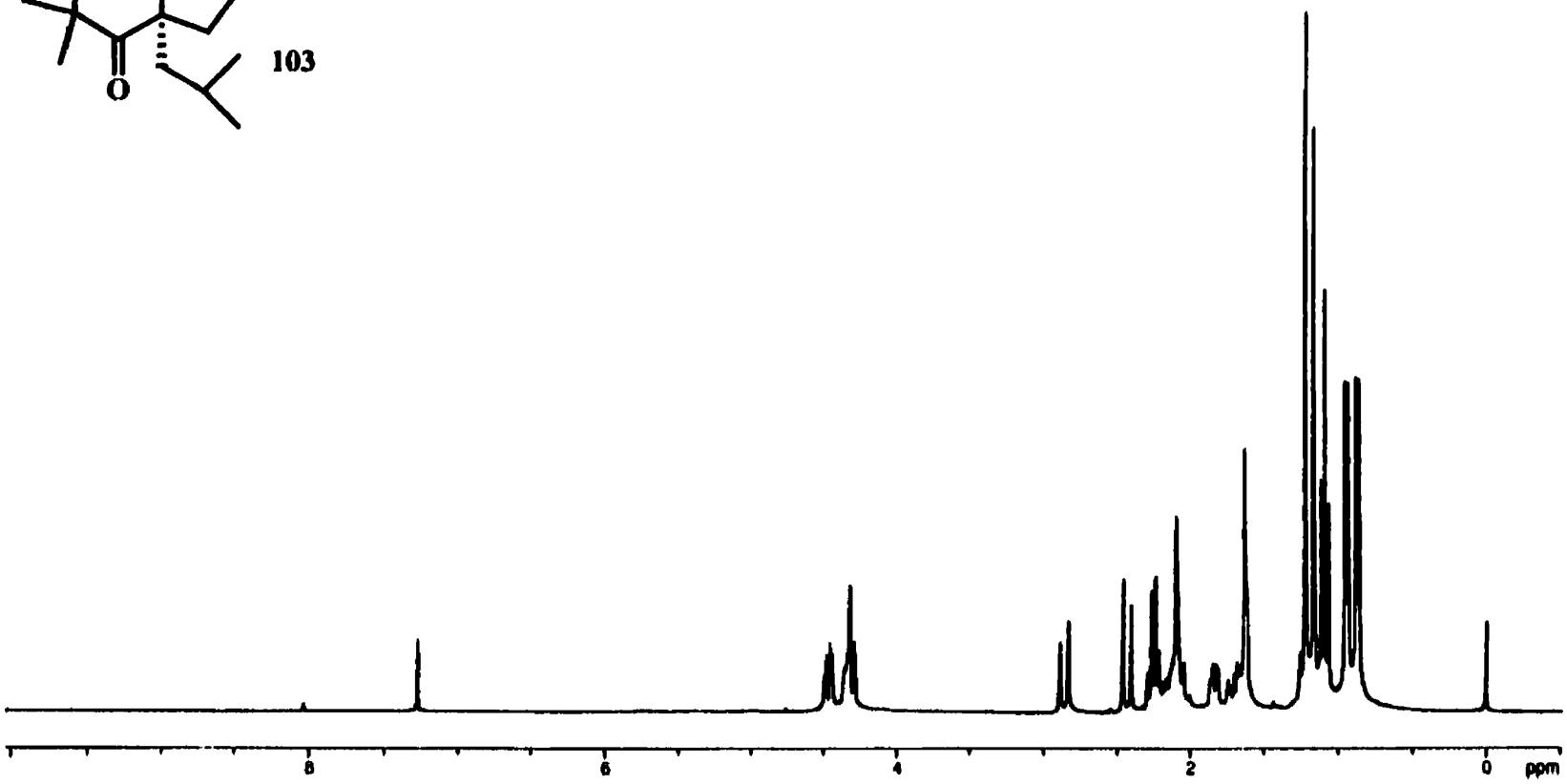

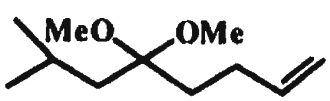

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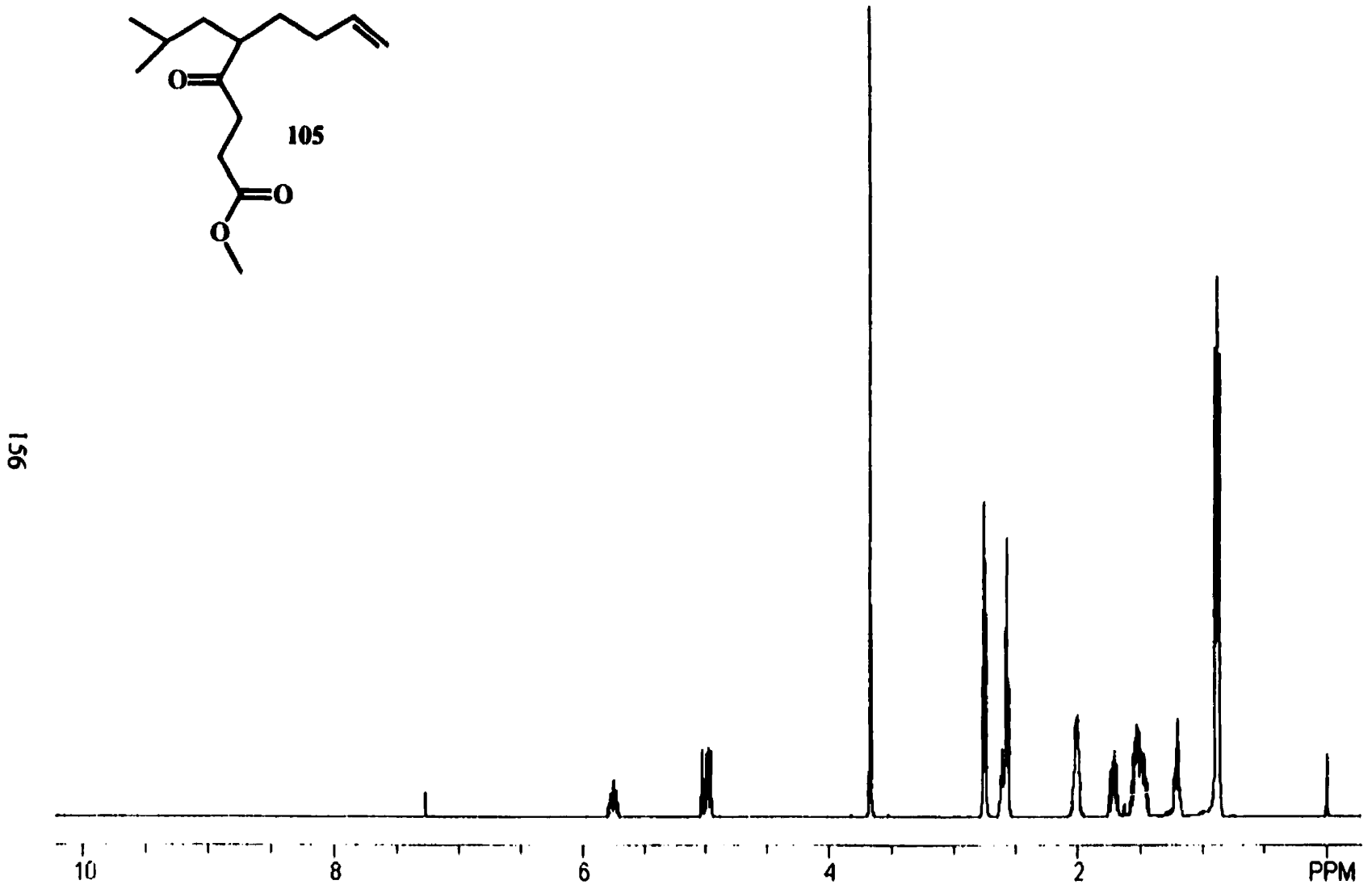
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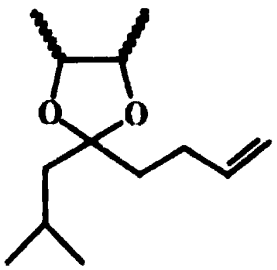

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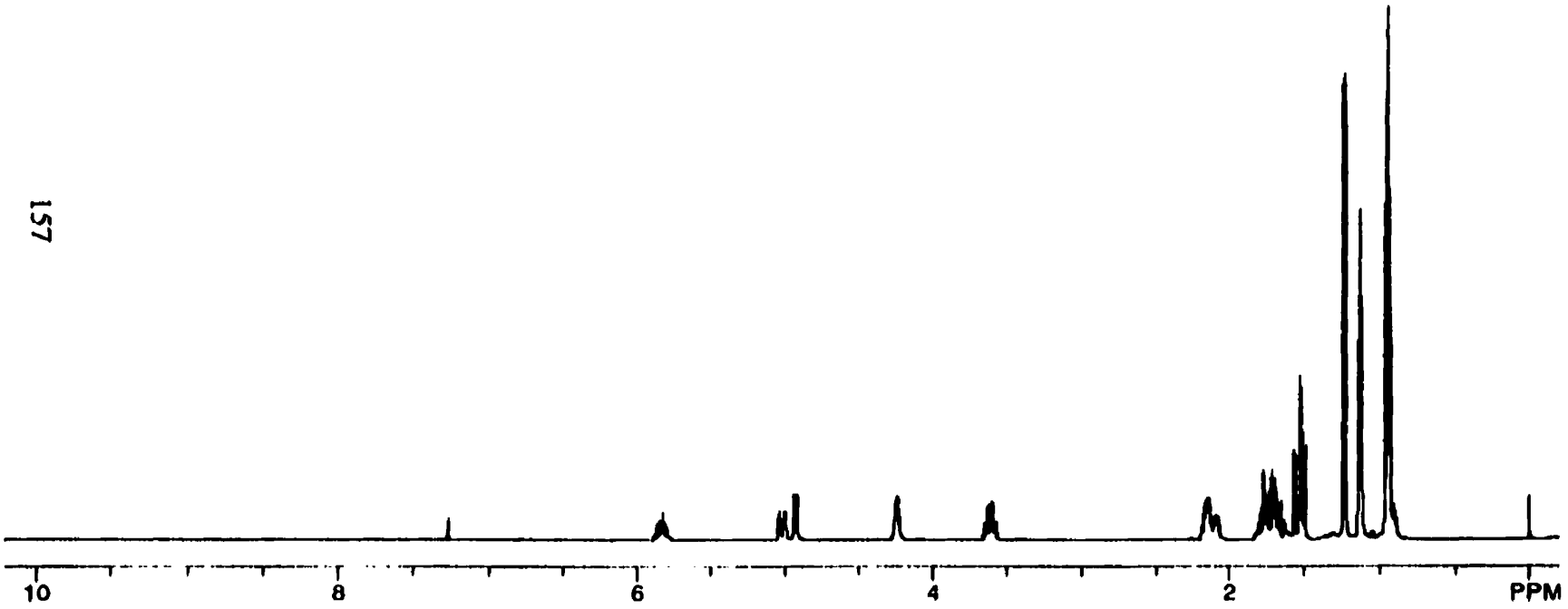
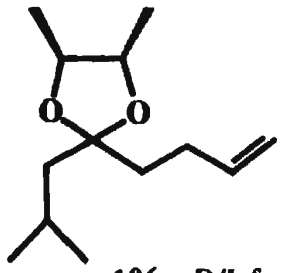
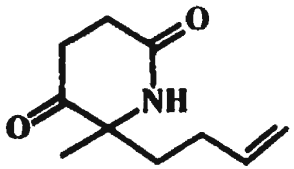




106a *D/L* form



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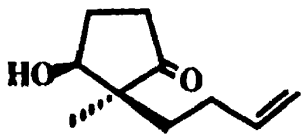

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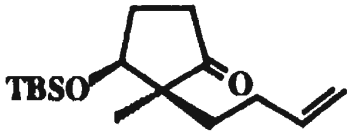

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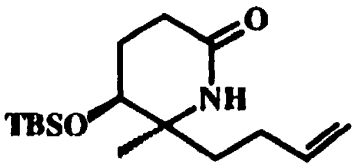

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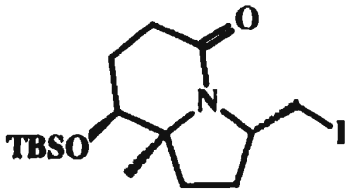

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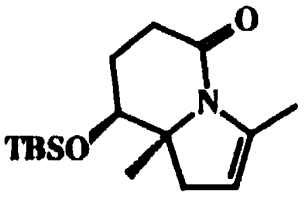

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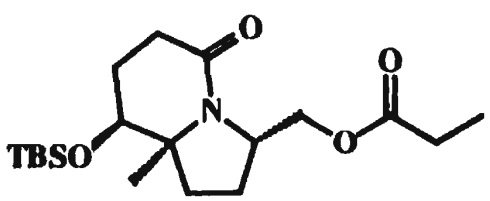

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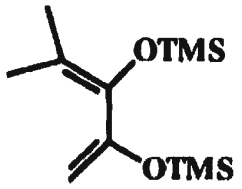

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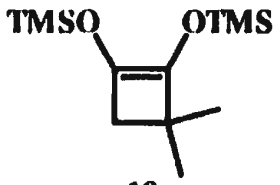

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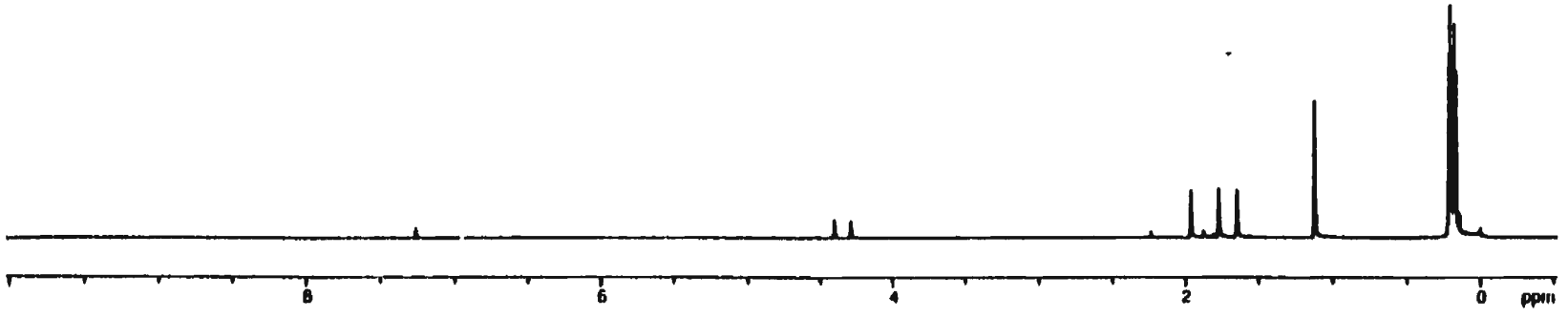

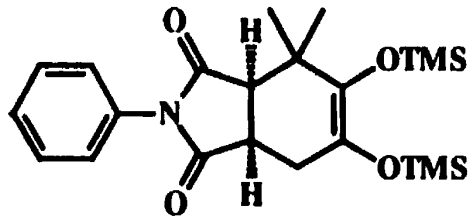

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