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**APPROACH TO THE SYNTHESIS OF SPIROIRIDAL-TYPE TRITERPENOIDS
VIA AN IRELAND-CLAISEN REARRANGEMENT**

By

PATRICK BEAULIEU

B.Sc. Université de Sherbrooke, 2000

A thesis submitted to the School of Graduate Studies and Research
In partial fulfillment of the requirements for the degree of
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ABSTRACT

The formation of carbon-carbon bonds in an asymmetric manner is a central goal of modern synthetic chemistry. Many methods have been developed to form a variety of linkages and substitutions, however the asymmetric formation of quaternary carbons of spirocycles is still a formidable challenge. These compounds represent special challenges because of the requirement of double ring formation together with the control of facial selectivity during the formation of a quaternary carbon centre. The present work demonstrates our efforts towards establishing a strategy based on the Ireland-Claisen rearrangement as the key step for the synthesis of the quaternary spiro-fused ring system such as those found in iridal triterpenoids. 28-Deacetylbelamcandal, a spiroiridal-type triterpenoid, is a representative compound found in iridaceous plants and shows important biological activities in tumor promotion. The synthesis of this compound has been planned from the methodology currently in progress in our group.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
HOAc	acetic acid
Bn	benzyl
br	broad
Bu	butyl
CI	chemical ionization
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	<i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
dr	diastereomeric ratio
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	electron impact
eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethyl alcohol

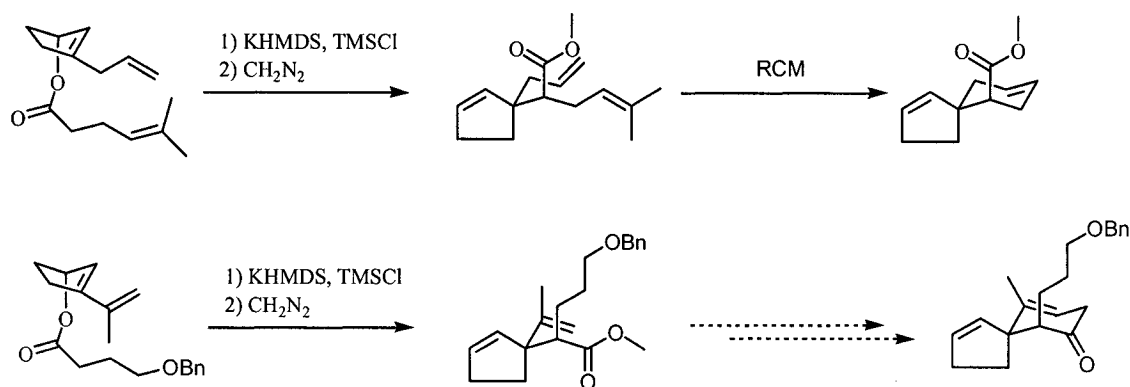
Et ₂ O	diethylether
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
Hz	hertz
IPA	isopropyl alcohol
IR	infrared spectrometry
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
m	multiplet
Me	methyl
MeOH	methanol
MHz	megahertz
mmol	millimoles
MS	mass spectrometry
NaHMDS	sodium hexamethyldisilazide
NBS	N-bromosuccinimide
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ph	phenyl
PPh ₃	triphenylphosphine

ppm	parts per million
PTSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
q	quartet
RCM	ring-closing metathesis
rt	room temperature
s	singlet
SM	starting material
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TBSCl	<i>t</i> -butyldimethylsilyl chloride
TBSOTf	<i>t</i> -butyldimethylsilyl trifluorosulfonate
<i>t</i> -BuLi	<i>t</i> -butyllithium
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluorosulfonate
TEA	triethylamine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluorosulfonate
TLC	thin layer chromatography

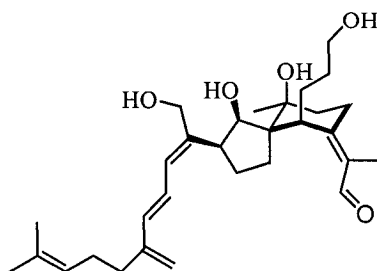
ABSTRACT

The formation of carbon-carbon bonds in an asymmetric manner is a central goal of modern synthetic chemistry. Many methods have been developed to form a variety of linkages and substitutions, however the asymmetric formation of quaternary carbons is still a formidable challenge. Spirocycles represent a special case of quaternary carbon with added synthetic difficulties found in many natural products. These compounds represent special challenges because of the requirement of double ring formation together with the control of facial selectivity during the formation of a quaternary carbon centre.

The present work demonstrates our efforts towards establishing a strategy based on the Ireland-Claisen rearrangement as the key step for the synthesis of the quaternary spiro-fused ring system such as those found in iridal triterpenoids.



28-Deacetylbelamcandal, a spiroiridal-type triterpenoid, is a representative compound found in iridaceous plants and shows important biological activities in tumor promotion. The synthesis of this compound has been planned from the methodology currently in progress in our group.



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« À mes parents, Andrée et Claude ainsi que mes sœurs Christine et Nancy »

CHAPTER 1

1.1 Introduction

The enzyme protein kinase C (PKC) is a calcium and phospholipids-dependent protein.¹ Its activation by the lipophilic second messenger *sn*-1,2-diacylglycerol (DAG) (**1**) allows PKC to phosphorylate serine and threonine containing proteins which are responsible for growth control and cellular differentiation (figure 1).²

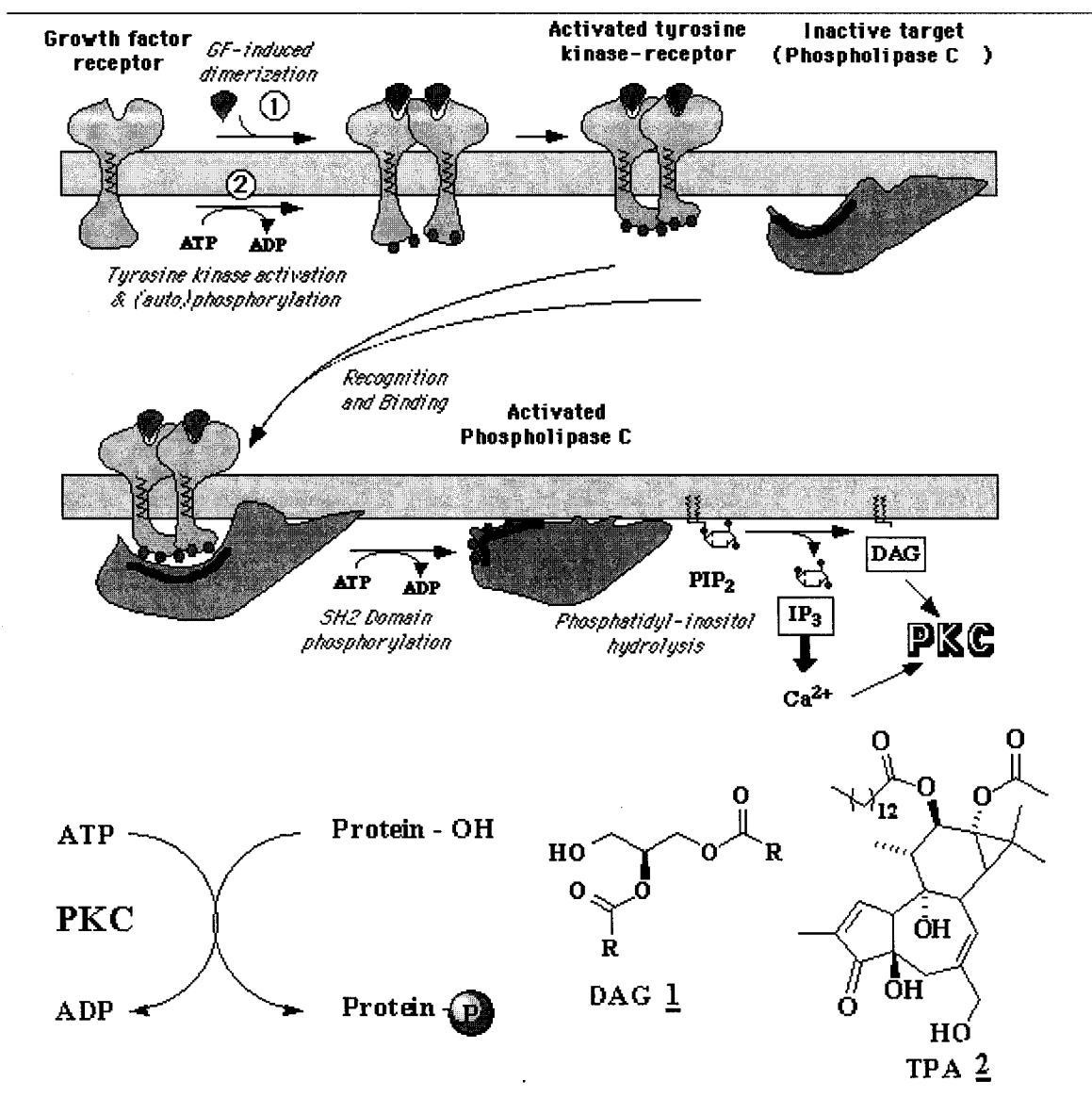


Figure 1. Protein Kinase C

The well known 12-*O*-tetradecanoylphorbol-13-acetate (TPA, **2**) is a ligand acting through the diacylglycerol signalling pathway and it is a potent tumor promoter. Upon treatment with a small dose of a carcinogen, TPA induces cancer cell proliferation by increasing the protein kinase C response. In the last decade, iridal-type triterpenoids (figure 2), isolated from iridaceous plants and rhizomes of *Belamcanda chinensis*, have gained wide interest in medicinal chemistry.³⁻⁶ More than forty isomers have been isolated so far and it is known that this class of compound exhibits important biological properties such as antiulcer and antimalarial activities. Even more interesting, it has been found recently that selected iridals have the property of binding to and activating protein kinase C in a similar fashion as do phorbol esters like 12-*O*-tetradecanoylphorbol-13-acetate.⁷⁻⁹ This makes iridal compounds potent tumor promoters in second stage carcinogenesis. Although the chemical structures of these compounds are significantly different from TPA, iridals such as 28-deacetylbelamcandal (**4**) and NSC 631939 (**5**) represent new leads in medicinal chemistry and cancer investigations.

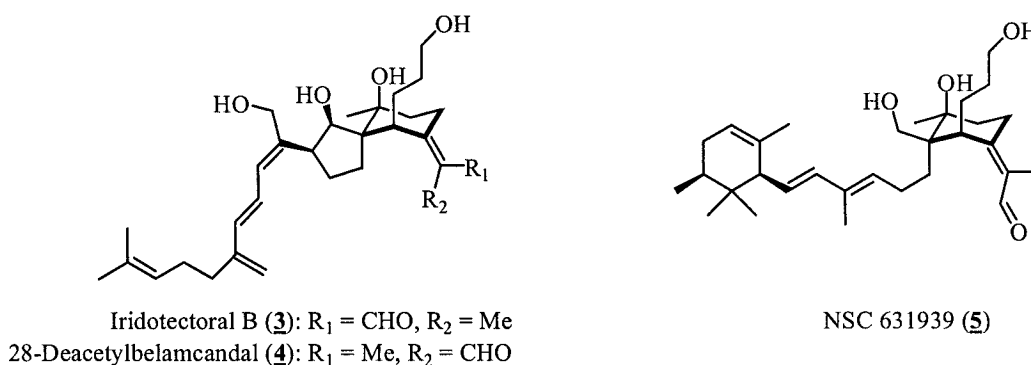
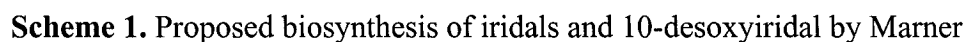
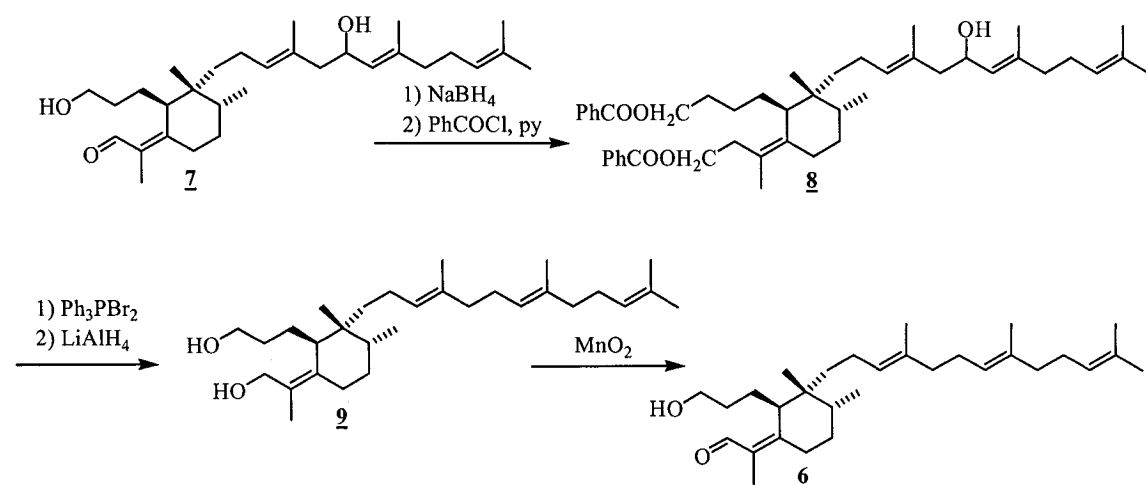


Figure 2. Iridal-type triterpenoids

The biosynthesis of iridal triterpenoids has been intensively investigated by Marner and co-workers.¹⁰ They proposed that 10-desoxyiridal (**6**) plays a central role in iridal biosynthesis after observing this key metabolite in cell cultures of *Iris pseudacorus* Linn (scheme 1).



These researchers showed that **6** could be prepared from the natural product **7** which in turn could be isolated from extracts of *I. sibirica*. The synthesis of **6** began with the reduction of the methylidene aldehyde group with sodium borohydride followed by selective protection of the two primary hydroxyl groups as benzoate esters (scheme 2). The secondary alcohol **8** was dehydrogenated in a two step sequence by converting the alcohol into a bromide and then reducing it with lithium aluminum hydride. In the same step, the two benzoate esters were removed to recover both primary alcohols. Finally, the remaining allylic hydroxyl moiety on **9** was selectively oxidized with manganese (IV) oxide to give **6**. With a reasonable amount of synthetic standard of 10-desoxyiridal, the Marner group was able to study the biosynthetic pathways of the iridals in cell culture extracts.



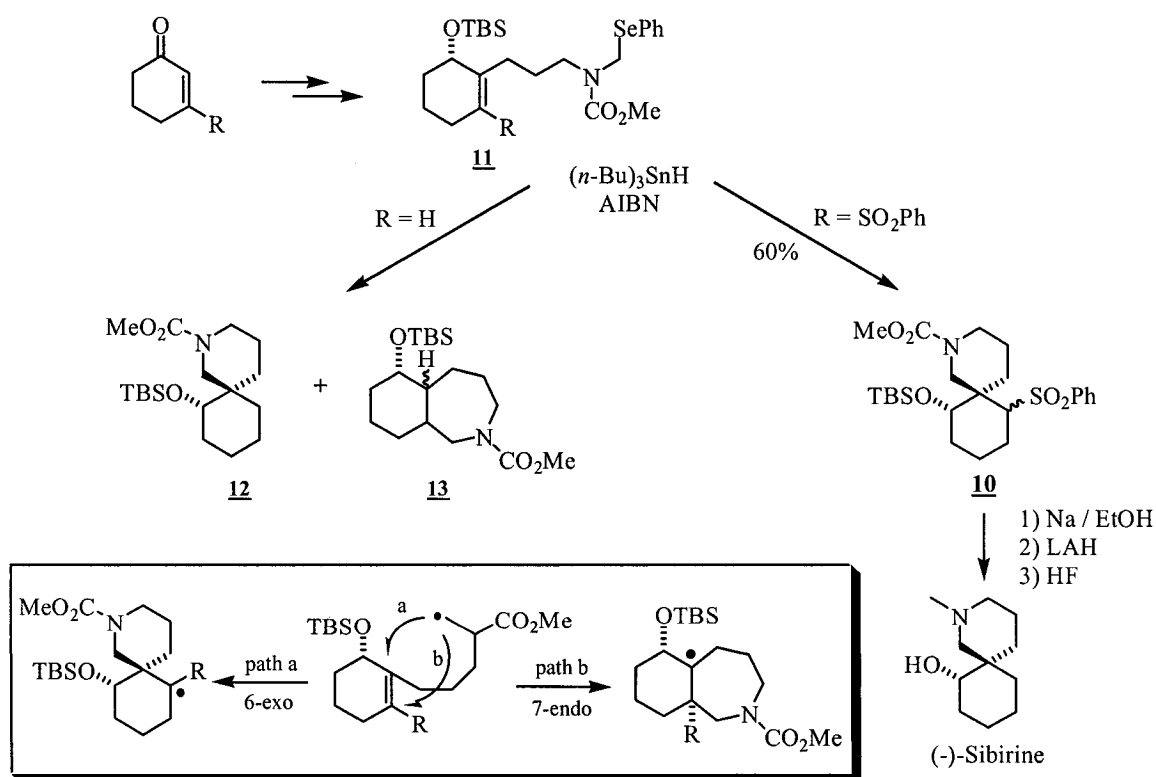
Scheme 2. Synthesis of 10-desoxyiridal used as synthetic standard

1.3 Novel methodologies for the synthesis of spirocyclic compounds

Spirocyclic compounds with a quaternary center ¹¹ at the spiro-fused ring are encountered in a wide variety of natural products such as spiroiridal-type triterpenoids. Syntheses of quaternary spiro-fused ring compounds have been well reviewed.¹² Newer approaches and novel methodologies were discovered recently in that field of study and are discussed in this section.

1.3.1 Intramolecular radical cyclization of (alkoxycarbonylamino)methyl

The alkaloid (-)-Sibirine was synthesized ¹³ by Koreeda *et al.* in 11% overall yield (scheme 3), by using an highly regio- and stereoselective (alkoxycarbonylamino)methyl radical cyclization. The generation of a radical α to a nitrogen atom could readily be

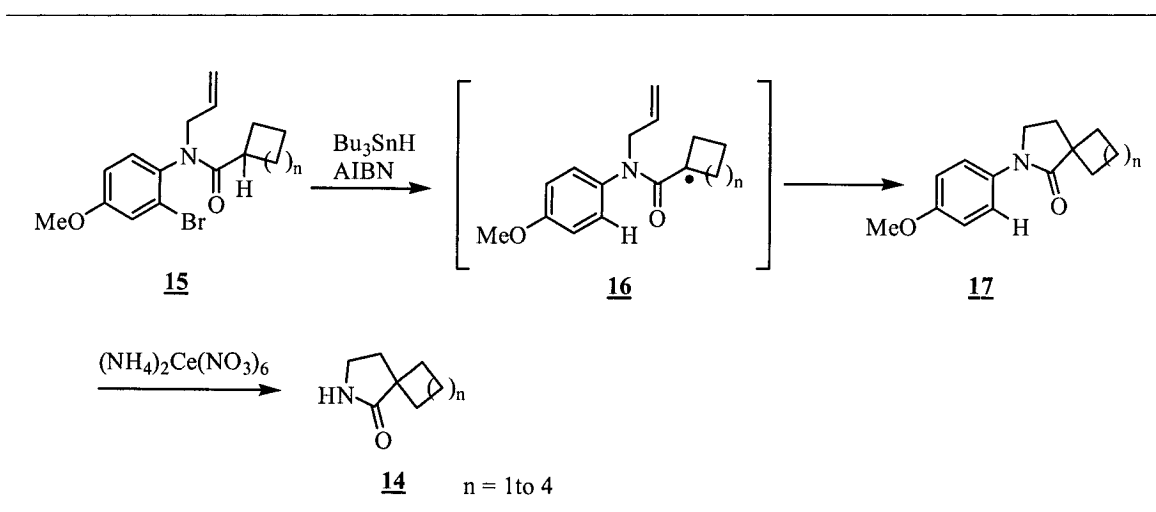


Scheme 3. Stereoselective (alkoxycarbonylamino)methyl radical cyclization

achieved due to the stabilizing interaction between the incipient radical and the nitrogen lone pair. Such stabilization could be further enhanced by an electron-withdrawing group attached to the nitrogen atom. Therefore, treatment of phenyl selenide **11** with tri(*n*-butyl)tin hydride in the presence of a catalytic amount of AIBN generated a radical which gave a mixture of products **12** and **13** when R = H. The formation of both products was explained by a competitive 6-exo and 7-endo cyclization modes which result in poor regioselectivity. By analysing the two possible reacting pathways, the 7-endo radical cyclization process could be suppressed by a careful choice of the R substituent. The easy removable sulfone group was chosen to control the regioselectivity of the reaction to give exclusively **10**. The sterically demanding sulfone disfavoured the approach of the alkyl side chain at the 7 position and stabilized the resulting radical formed after the spirocyclization. The stereoselectivity of the reaction was simply controlled by steric interactions imposed by the *t*-butyldimethylsilyloxy group which dictated the facial approach of the radical onto the alkene.

1.3.2 Tandem [1,5]-hydrogen atom abstraction/cyclization strategy

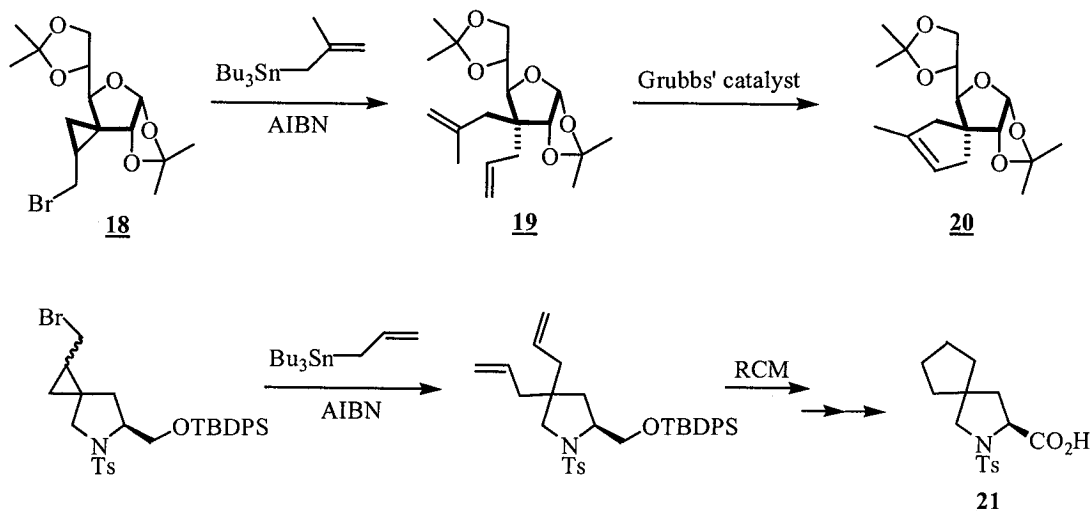
With the aim of synthesizing spirocyclic pyrrolidin-2-ones (**14**), Storey¹⁴ reported a novel tandem intramolecular hydrogen atom transfer reaction/cyclization methodology that produces spirocyclic compounds in high yield (scheme 4). Treatment of **15** under standard radical conditions generated an highly reactive aryl radical which underwent 1,5-hydrogen atom transfer to produce the tertiary radical **16**. The latter radical then took part in a 5-*exo trig* cyclization which gave spirocyclic products **17**. Removal of the *p*-methoxyphenyl protecting/radical translocating group with ceric ammonium nitrate gave the pyrrolidin-2-one system. The above strategy was successfully used to prepare spirocycles of 4- to 7-membered size rings.



Scheme 4. Synthesis of pyrrolidin-2-ones by Storey

1.3.3 Sequential ring-opening of (halomethyl)cyclopropanes/ring-closing metathesis

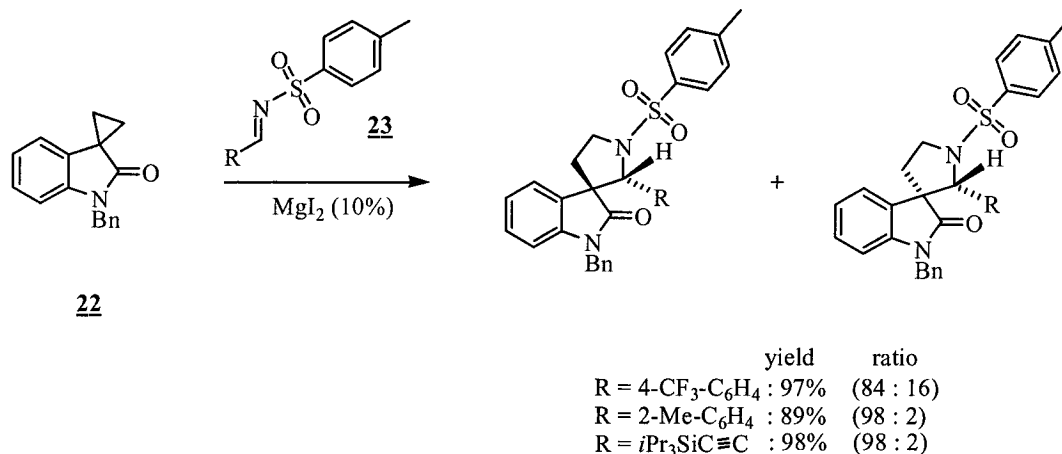
Stereocontrolled synthesis of *gem*-diallyl compounds could be done on xanthate derivatives from (bromomethyl)cyclopropanes to produce spirocycles with a quaternary chiral center (scheme 5).¹⁵ Reaction of spirocyclopropylmethyl bromide **18** with methallyltributyltin and AIBN gave rise to 3-deoxy-3-*C*-allyl-3-*C*-methallyl derivative **19** stereoselectively which was treated with first generation Grubbs' catalyst to provide in good yield spirocyclopentenyl product **20**. The versatile methodology was also applied with success in the synthesis of **21**, an interesting scaffold for the development of potent angiotensin converting enzyme.



Scheme 5. Ring opening of (bromomethyl)cyclopropanes

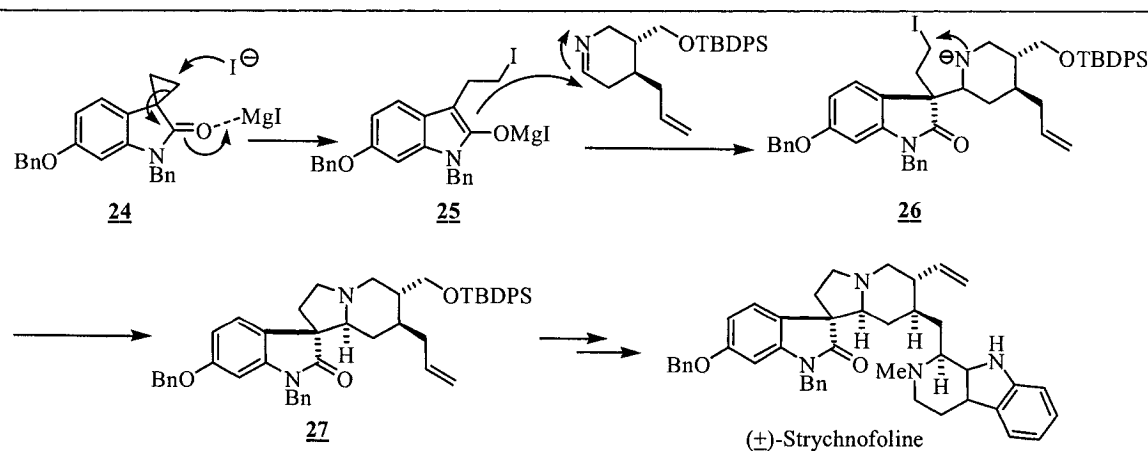
1.3.4 Ring expansion of cyclopropanes

Carreira *et al.* had recently developed a novel methodology for the synthesis of spiro[pyrrolidin-3,3'-oxindoles] via a catalyzed ring expansion reaction of cyclopropanes by aldimines.¹⁶ The process involves the reaction of an oxindole such as **22** with an aldimine of type **23** to furnish spirocyclic pyrrolidine-3,3'-oxindoles in excellent diastereoselectivity (scheme 6). The reaction was successful for both classes of electron-rich and electron-deficient aldimines and usually proceed at temperature below 80 °C.



Scheme 6. Ring expansion of cyclopropanes by aldimines

The proposed mechanistic pathway leading to the formation of the pyrrolidine ring is illustrated in scheme 7. It is believed that MgI_2 had a dual nucleophilic and electrophilic activity due to the critical role of the halide in the success of the reaction. Thus, treatment of **24** with a catalytic amount of MgI_2 might afford *in situ* the iodo enolate **25**. The resulting enolate could react with an imine to give the intermediate **26** which can in turn undergo alkylative intramolecular cyclization to provide product **27** that could be used for the total synthesis of (+)-Strychnofoline in 9 steps.

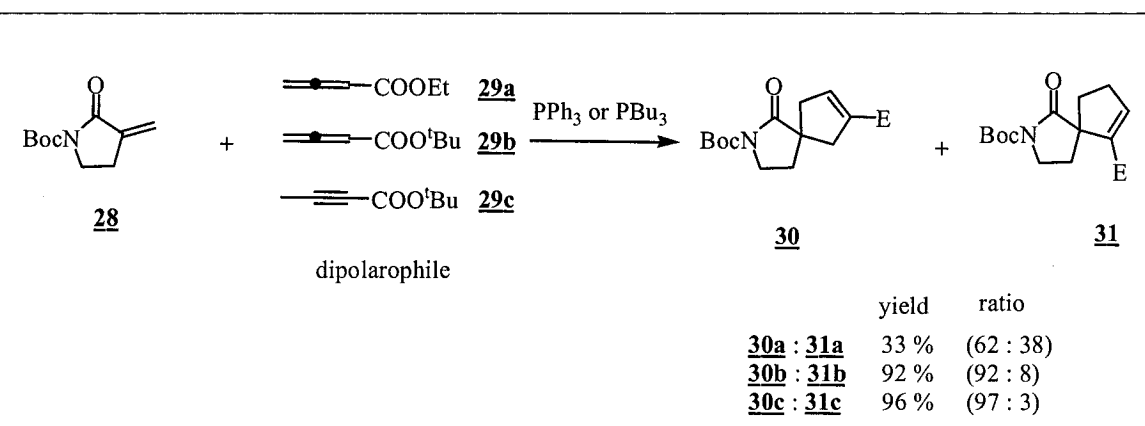


Scheme 7. Mechanistic pathway for MgI_2 catalyzed ring expansion of cyclopropanes

The relative stereochemistry of **27** has been suggested to result from thermodynamic consideration where the lactam carbonyl group is placed in a way to avoid unfavourable stereoelectronic interactions between the tertiary nitrogen and carbonyl lone pairs.

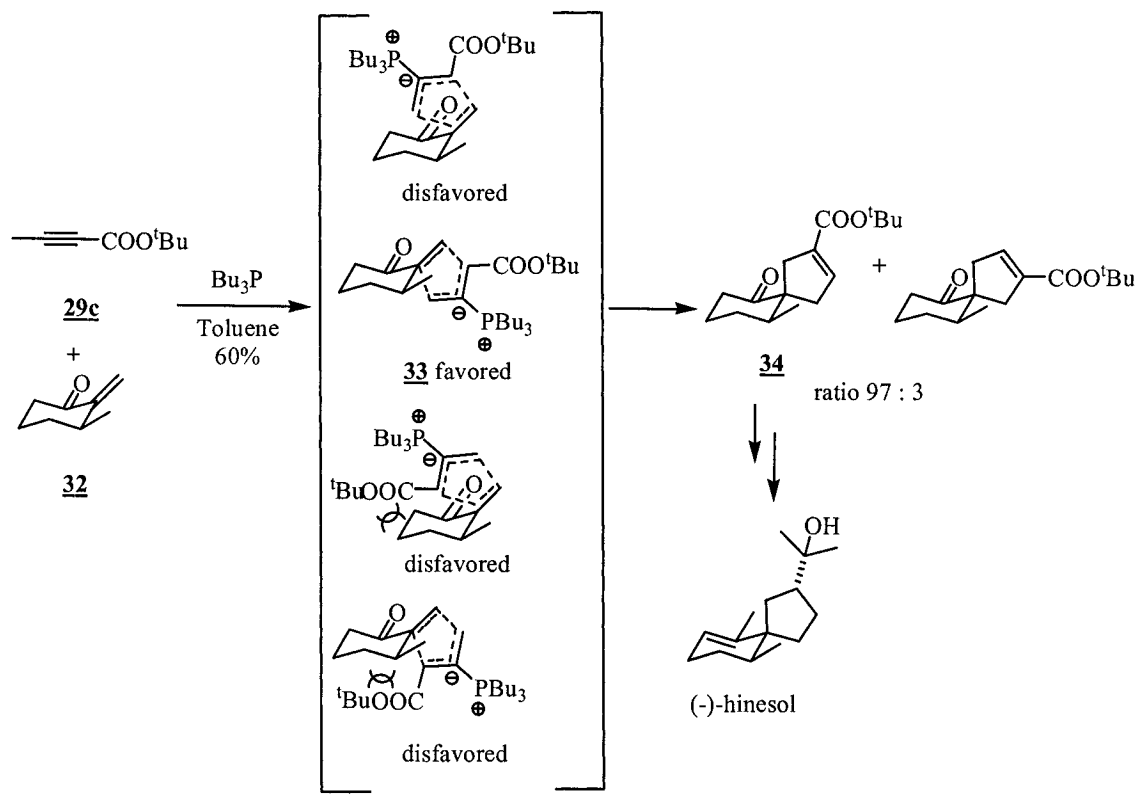
1.3.5 [3 + 2] sigmatropic cycloaddition

An highly regioselective [3 + 2] cycloaddition was developed by Lu and Du for the synthesis of spiro[4.n]alkanes.¹⁷ In this strategy, a phosphine ligand was reacted with an electron-deficient allene or alkyne such as **29** to produce a 1,3-dipole which then adds to an alkene such as **28** to give cyclopentane carbocycles **30** and **31** (scheme 8). Regioselectivity was improved when the dipolarophile bore a large *tert*-butyl group to give **30** and could be further improved by replacing the allene **29b** with the alkyne **29c**.



Scheme 8. Synthesis of spirocycles via phosphine-catalyzed [3 + 2] cycloaddition

The first total synthesis of (-)-Hinesol was recently accomplished with the aforementioned approach (scheme 9).¹⁸ Alkyne **29c** in the presence of tributylphosphine afforded a 1,3-dipole which was reacted with compound **32** via the less sterically hindered transition state **33** to give **34** in good yield and high diastereomeric ratio. Then, product **34** could be converted into (-)-Hinesol in five steps.

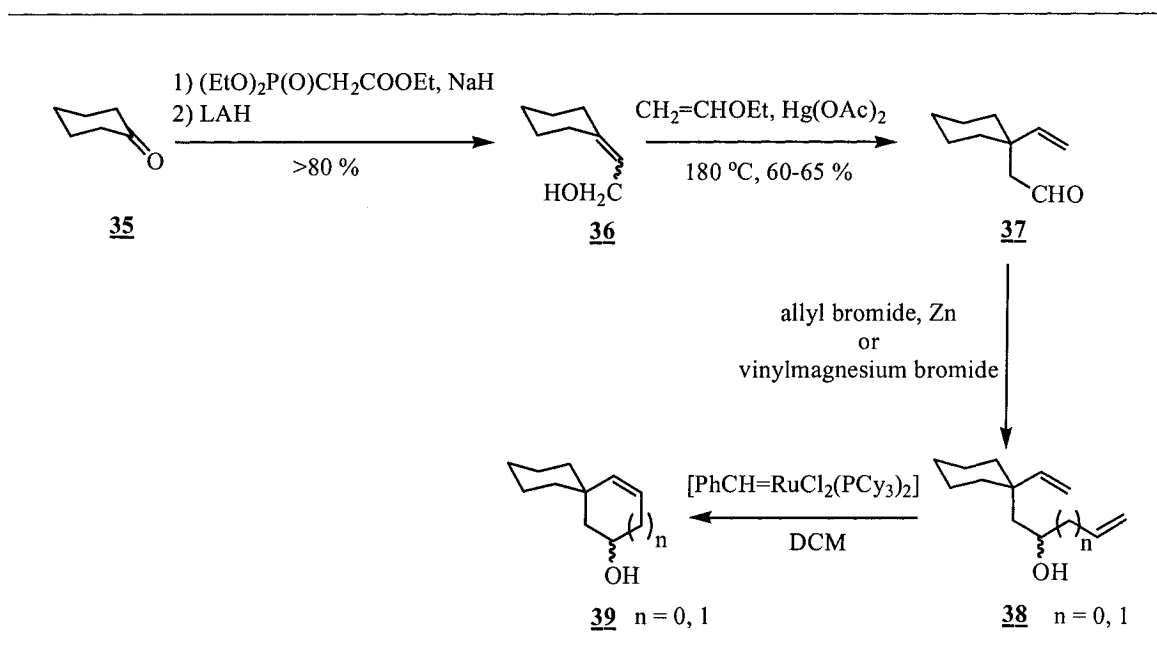


Scheme 9. First total synthesis of (-)-Hinesol by Lu in 2003

1.3.6 Claisen/ring-closing metathesis

An efficient approach to the synthesis of cyclopentanes and cyclohexanes was reported by Srikrishna based upon a Claisen/ring-closing metathesis (scheme 10). The methodology allows constructing rapidly spirocycle products from various cyclic ketones as starting materials.¹⁹ Allyl alcohol **36** were prepared from ketone **35** in a two step sequence via a Horner-Wadsworth-Emmons reaction followed by reduction of the resulting ester. Product **36** was then rearranged by a one pot Claisen protocol with ethyl vinyl ether to furnish in moderate yield **37**. The resulting aldehyde was alkylated with the desired nucleophile to give substrates such as **38** which were then submitted to ring-closing

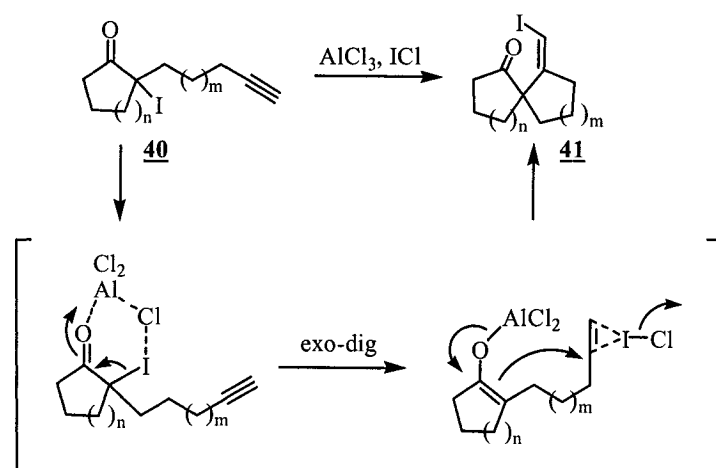
metathesis to afford in high yield spirocarbocycles **39**. The approach was used successfully in the racemic formal synthesis of sesquiterpenes like isoacorone and acorane.



Scheme 10. Claisen/ring-closing metathesis based approach to the synthesis of spirocyclic cyclopentanes and cyclohexanes

1.3.7 Iodo-carbocyclization of α -iodo cycloalkanones

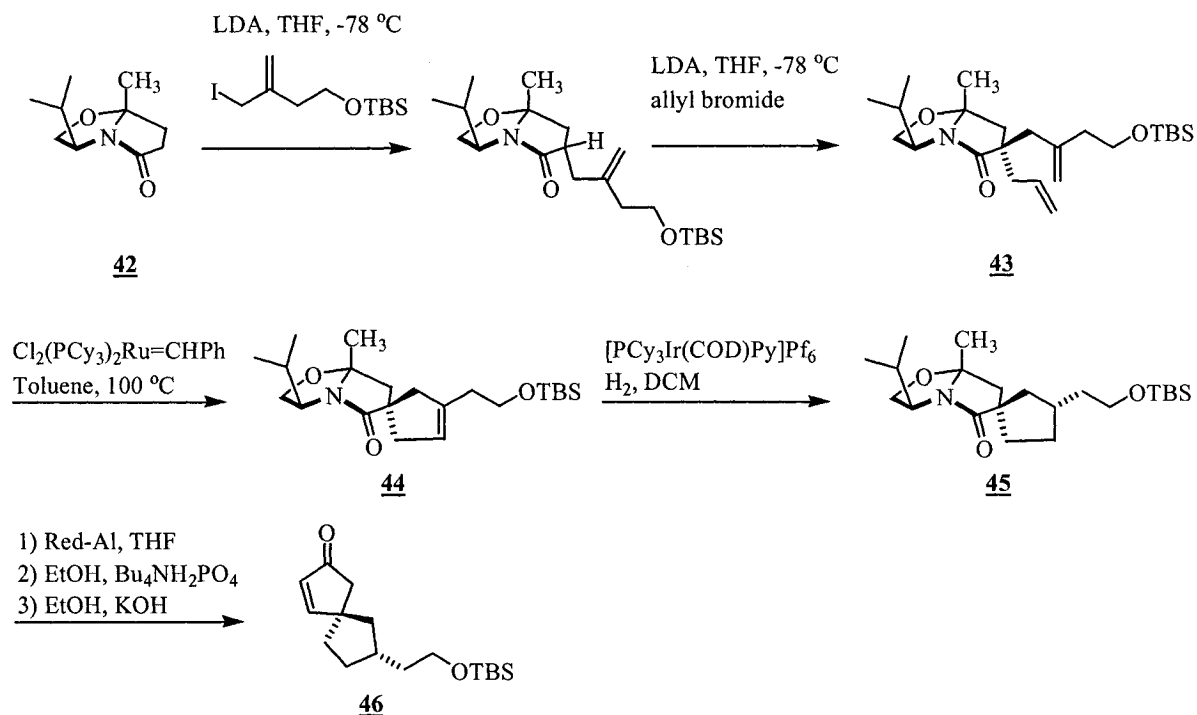
A new procedure was developed by Sha *et al.*²⁰ to produce in good yield spirocyclic ketones via an ionic iodo-carbocyclization of α -iodo cycloalkanones (scheme 11). The key step of the reaction involves the generation of an enolate from the α -iodo ketone **40** with a Lewis acid and simultaneous activation of the terminal acetylenic moiety with ICl to give spirocycle **41**. In all cases tried, the stereochemistry of the vinyl iodide moiety was assigned as *Z*. Performing the same reaction without the use of ICl resulted in a decrease in the yield of the reaction. The mechanism of the reaction is not yet fully understood but might involve transfer of I^+ to the acetylenic group with subsequent cyclization of the resulting enolate. The method is general and allows the preparation of spirocycles of various sizes in good to excellent yield without the use of toxic tin reagents.



Scheme 11. Syntheses of spirocyclic ketones via an ionic iodo-carbocyclization of α -iodo cycloalkanones

1.3.8 Meyers' bicyclic lactams

Meyers' bicyclic lactams ²¹ such as **42** have proved to be efficient tools for the construction of quaternary chiral centers (scheme 12). This strategy is based on the highly predictable chemistry that could be achieved on cyclic frameworks. Alkylation on this type of structure takes place from the concave face away from the isopropyl and methyl groups. A methodology developed by Meyers and co-workers uses **42** as a chiral template in combination with ring-closing metathesis to synthesize, in an asymmetric fashion, spirocyclic compounds.²² At this moment, this approach might be the most efficient and straightforward protocol to produce spirocyclic compounds with fused rings directly attached to four carbons.

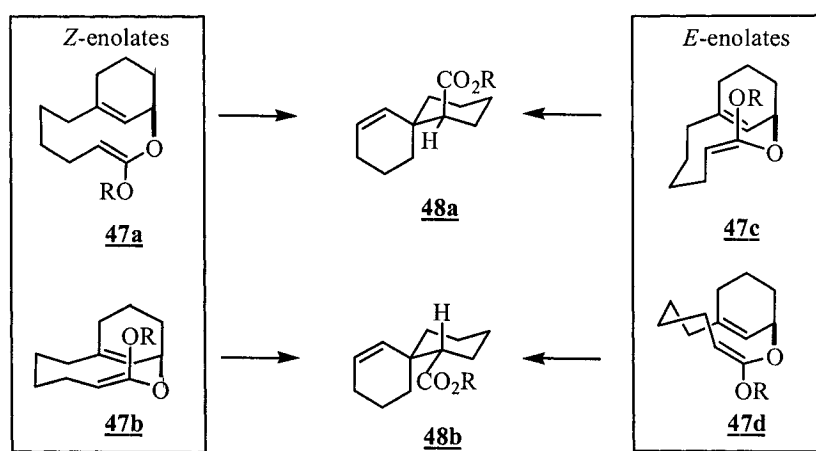


Scheme 12. Asymmetric synthesis of spirocyclic systems via dialkylation of Meyers' auxiliary followed by ring-closing metathesis

Bicyclic lactam **42** was doubly alkylated with the appropriate electrophiles to give **43** in 95 % diastereoselectivity and good yields. The reaction of **43** with the first generation Grubbs' catalyst in refluxing toluene afforded in 95 % yield product **44** that was stereoselectively reduced with Crabtree's iridium catalyst to **45**. The stereochemical outcome of the reduction was explained by a coordinating effect between the carbonyl oxygen electron lone pair and the catalyst to deliver the hydrogen to one face of the alkene. Finally, the lactam carbonyl of **45** was reduced to form a carbonolamine. Subsequent hydrolyzation with Bu₄NH₂PO₄ and submission of the resulting keto-aldehyde to an aldol cyclization with potassium hydroxide gave spirocarbocycle **46**. This strategy was also successfully applied to the asymmetric construction of spirocycles of different ring sizes.

1.6 Aim of this project

In the first part of the present work we surveyed the feasibility of using an Ireland-Claisen rearrangement mediated ring contraction of macrocyclic lactones such as **47** to give access to spirocyclic compounds **48** which can in turn be used for the synthesis of spiroiridal-type triterpenoids (scheme 13). Careful analysis of the four possible transition states suggests that **48a** might be the major diastereomer formed after the [3 + 3] sigmatropic rearrangement independently of the geometry of the resulting enolate. In the case of the generation of an *E*-enolate, we believe that transition state **47d** is disfavoured over **47c** due to severe transannular interactions between the 10-membered ring and the cyclohexenyl framework and also for conformational strain. The same conclusion was made with *Z*-enolates where transition state **47a** is favoured because **47b** suffers from transannular interactions between the silyloxy group of the ketene acetal and the six-membered ring. Therefore, to gain insight into this project, an efficient route to the synthesis of this unprecedented macrolactone was required.



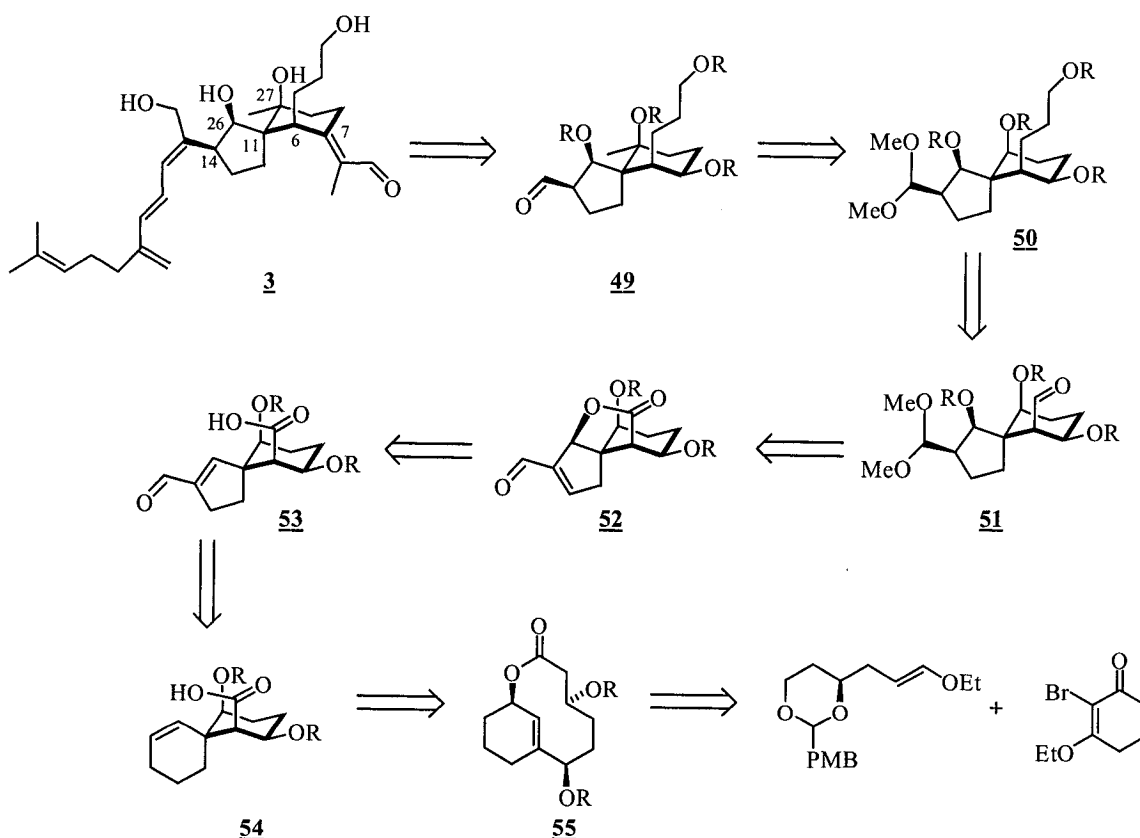
Scheme 13. Ireland-Claisen of 10-membered ring macrolactone

The second subject of this thesis shows the research progress in the development of a new strategy for the construction of spirocarbocycles with four carbons at the spiro-fused ring system using an Ireland-Claisen/ring-closing metathesis approach. The scope and the limitations of this methodology are also discussed for the synthesis of iridals.

CHAPTER 2

2.1 Introduction

The syntheses of spiroiridal-type triterpenoids represent a challenging endeavour for synthetic organic chemists. The most striking feature of this class of compounds is the presence of an asymmetric quaternary center surrounded by three stereogenic centers like those found in Iridotectoral B (**3**). The installation of such crowded chiral centers requires novel methods and good strategies. To the best of our knowledge, syntheses of iridals are unprecedented. Due to the recent interest in this class of products in medicinal chemistry, a systematic study towards their synthesis was undertaken. A retrosynthetic analysis of **3** is presented in scheme 14.



Scheme 14. Retrosynthetic analysis of Iridotectoral B

Disconnection of the unsaturated alkyl side chain in **3** and functional group interconversions gives aldehyde **49**. Introduction of the tertiary alcohol at C-27 could be achieved via a Wittig/epoxidation strategy or by nucleophilic addition of methyllithium to the corresponding ketone. Homologation of the side chain at C-6 might be done using a stabilized Wittig type reaction on aldehyde **51** to produce **50** after reduction. Product **51** was expected to be the major compound resulting from hydrogenation of lactone **52** or its parent structure, with a protected hydroxyl group at C-26, from the less hindered face of the alkene. Bromolactonization of **53** followed by DBU mediated elimination of the resulting bromide should give the lactone **52**. Ozonolysis of **54** and intramolecular aldol condensation of the resulting dialdehydes under basic condition should afford the α,β -unsaturated aldehyde **53**. Our key intermediate **54** might come from an Ireland-Claisen mediated ring contraction of macrolactone **55**.

2.2 Ireland-Claisen rearrangement

2.2.1 The transition state

The silyl ketene acetal variant of the Claisen rearrangement is a [3 + 3] suprafacial sigmatropic shift well described by frontier molecular theory. It was first introduced in 1972 by Ireland and co-workers²³ and has found wide application in synthetic organic chemistry due to the lower reaction temperature required for the pericyclic process.²⁴ This feature has allowed chemists to perform, in some cases, the modified Claisen rearrangement on thermally sensitive substrates. The relative activation energy for the rearrangement of silyl ketene acetals has been estimated to be approximately 9 kcal/mol lower than the parent Claisen rearrangement on allyl vinyl ether.²⁵ The pericyclic reaction has a strong preference to go through a chair-like transition state in which there are no severe steric interactions, as does the Cope rearrangement. One reasonable and accepted explanation for this result is realized from frontier orbital molecular theory in which the boat-like transition state suffers from unfavourable secondary orbital interactions between orbitals on atoms 2 and 5 (figure 3, **56**).²⁶ Thus, this conformational preference allows one to easily predict the stereochemistry of the final product from the starting material.

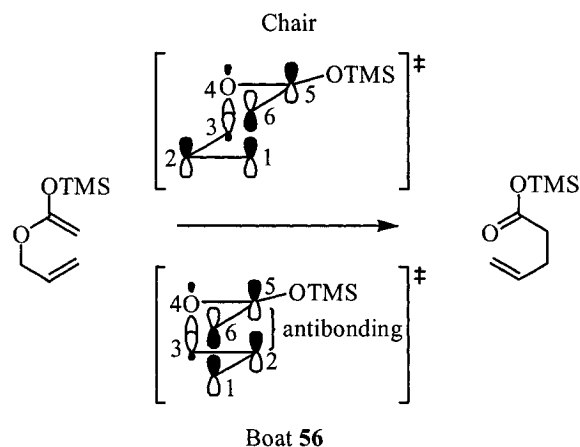
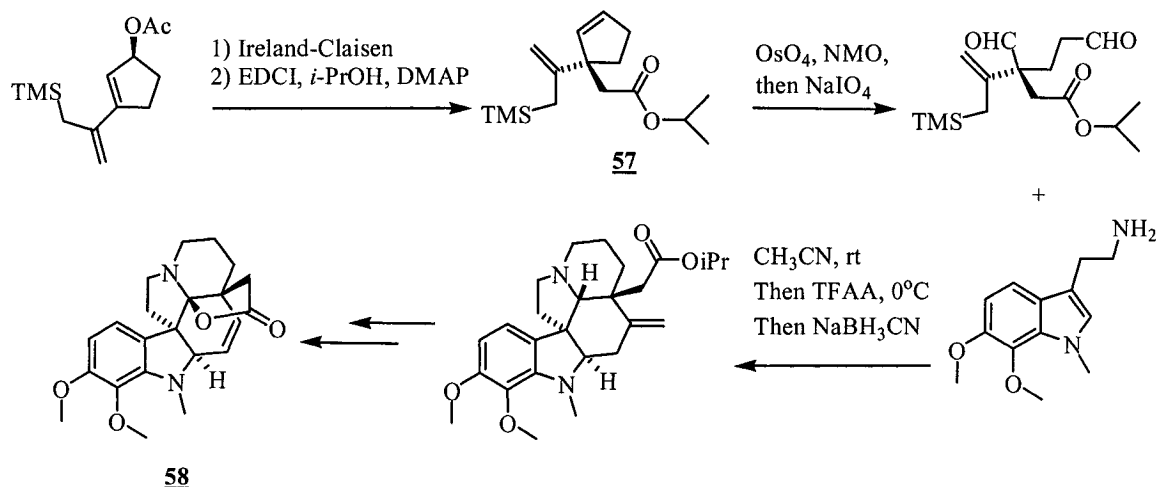


Figure 3. Chair and boat transition state in the Ireland-Claisen rearrangement

Cyclohexenyl esters and derivatives are well known substrates for [3 + 3] sigmatropic rearrangements. They are mainly used to control the stereochemistry of the rearrangement reaction via a ring template. A good example of this application was found in the remarkable enantioselective total synthesis of Aspidophytine (**58**) done by Corey and co-workers in 1999 (scheme 15).²⁷ They used a suprafacial Ireland-Claisen rearrangement on a five-membered ring template to install the key quaternary center on **57** which controlled all the subsequent stereochemical outcomes of the synthesis.



Scheme 15. Ireland-Claisen rearrangement in the enantioselective total synthesis of Aspidophytine by Corey

While the diastereoselectivity of the Ireland-Claisen is well controlled by a chair-like transition state in the acyclic rearrangement of silyl ketene acetals, the diastereoselectivity of the reaction on cyclic substrates is lower and more complicated to predict than the parent Cope or Claisen rearrangements. This arises from the fact that boat and chair-like transition states are now nearly equal in energy. Calculations done by the Houk group,²⁸ with Gaussian98 using the RB3LYP functional and the 6-31G basis set, have shown that three possible competing transition states could explain results obtained by Ireland²⁹ and Neier³⁰ (figures 4 and 5). The *syn* and the *anti* terms in figure 4 refer to chair and boat conformations with respect to the cyclohexenyl framework. Their calculations showed that the addition of a R₁ substituent leads to the preference for *syn*-chair (**59a**) and *anti*-chair (**59b** and **62c**) transition states. In the absence of a substituent at R₁, the *syn*-boat (**59c**) tends to be the lowest energy conformation for the rearrangement of *Z* silyl ketene acetals while the *anti*-boat (**59d**) is uncommon as the favoured transition state.

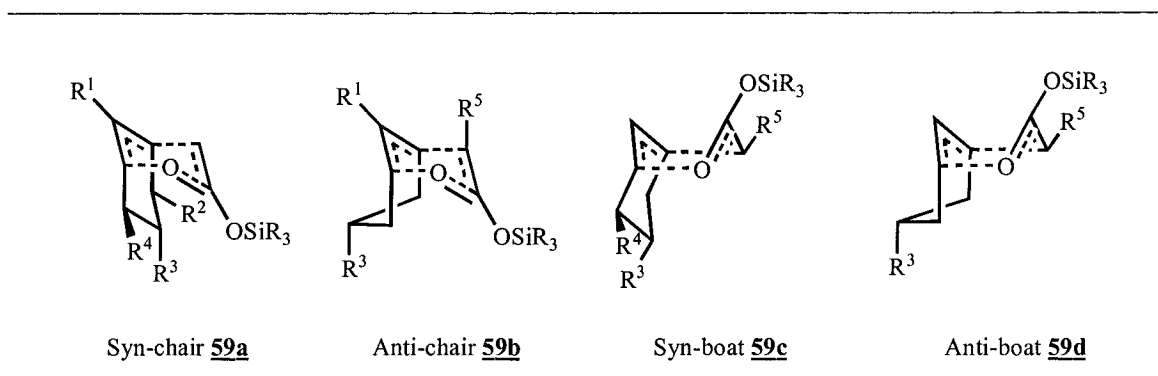


Figure 4. Idealized transition states according to the substitution patterns

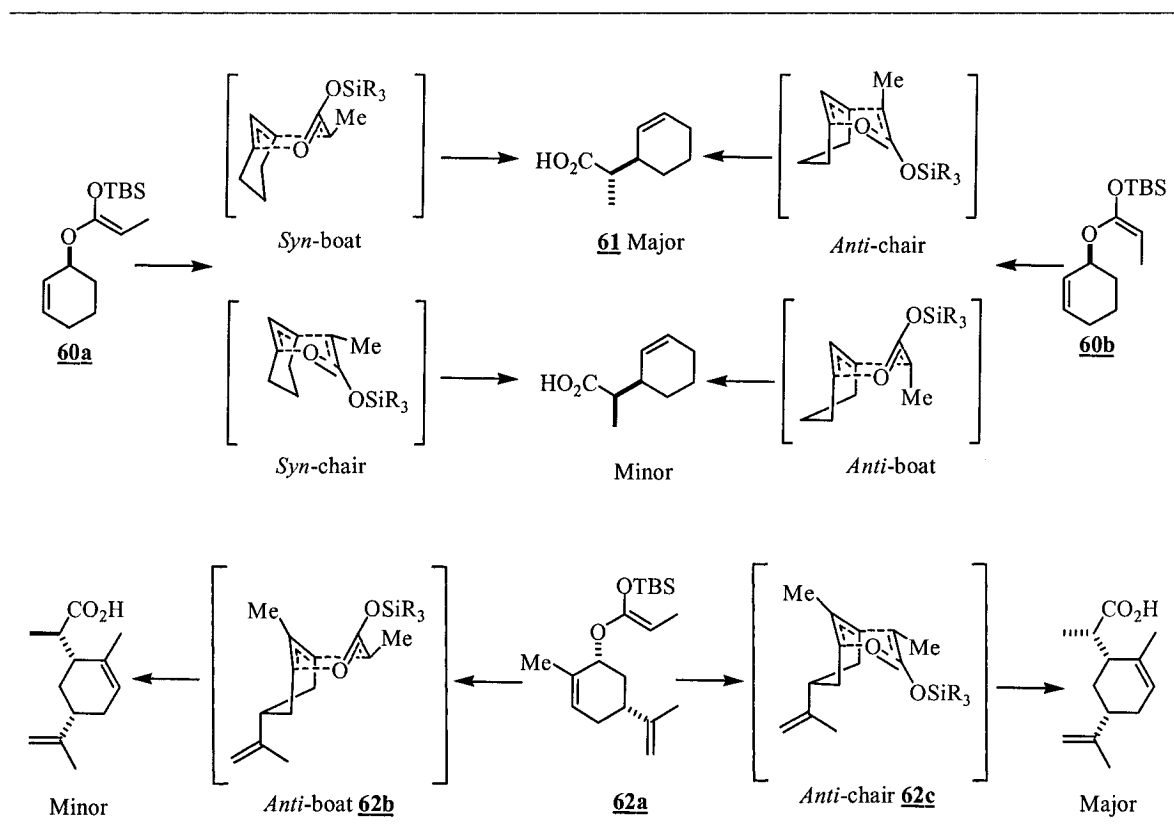


Figure 5. Proposed transition states of Ireland-Claisen rearrangements of cyclohexenyl esters by Houk according to computational results

Ireland-Claisen rearrangements of compounds such as **60a** and **60b** are known to proceed with low diastereoselectivity.^{31, 32} In the case of compound **60a**, a relative energy preference of 1.0 kcal/mol was estimated for the *syn*-boat over the *syn*-chair conformation. In comparison, the major transition state of compound **60b** had a relative energy preference of 1.4 kcal/mol for the *anti*-chair over the *anti*-boat conformation. The latter conformation was found to be the more favourable transition state to give the minor diastereomer of **60b**. This is in agreement with Ireland's results where compound **60a** was rearranged with a diastereomeric ratio of 2.6 : 1 while compound **60b** rearranged with a 5.3 : 1 ratio. It was important to note that the same diastereomer **61** was obtained for both silyl ketene acetals **60a** and **60b**.

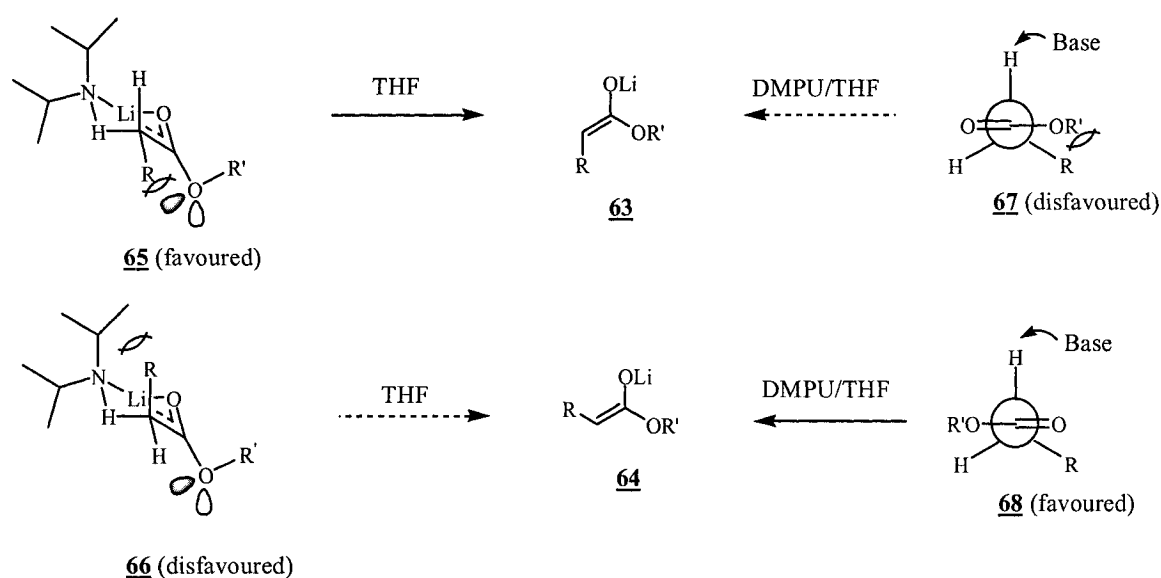
The diastereoselectivity was enhanced when a substituent (R₃) was *cis* to the *Z* silyl ketene acetals. That was illustrated by compounds such as **62a** that exhibits a 12.5 : 1 diastereomeric ratio after a [3 + 3] sigmatropic shift. The transition state **62c** was preferred over **62b** due to destabilizing interactions of the silyloxy group and the methyl substituent at R₁.

2.2.2 Solvent effects in the stereoselective formation of silyl ketene acetals

Stereoselective deprotonation of esters is an important part of the Ireland-Claisen rearrangement.^{33, 34} Deprotonation in THF with LDA leads only to the formation of the *E*-(O) enolate **63** whereas a mixture of THF and a dipolar solvent such as hexamethylphosphoramide (HMPA) or *N,N'*-dimethyl-*N,N'*-propyleneurea (DMPU) produces mostly the *Z*-(O) enolate **64** (scheme 16). DMPU gives better stereoselectivity in ester deprotonation than HMPA because the solvent ratio of DMPU/THF can be higher than the HMPA/THF system. At high concentration, HMPA has the tendency to freeze in THF when the reaction mixture is chilled to -78 °C or below.

The geometry of the ester enolate can be easily understood from consideration of a six-membered cyclic transition state. With a mixture of LDA in THF only, it is believed that deprotonation occurs through an early transition state in which the R substituent is placed pseudo-equatorial. In this case, the 1,3-diaxial interaction between one isopropyl group of the

amide base overrides the destabilizing $A_{1,3}$ strain between R and OR'. Steric interaction in **65** with the OR' of the Z ester is minimal since an oxygen lone pair is relatively small compared to the isopropyl group in **66**. In the case of deprotonation in a solvent system such as DMPU/THF, the greater solvation of the lithium cation makes the lithium oxygen bond much longer and weaker and makes the process proceed probably via a loose transition state. The 1,3-diaxial interaction between R and one of the isopropyl groups of the amide base diminishes and the conformation of the deprotonation is believed to go through a late transition state such as **68**. Conformation **67** is disfavoured in DMPU/THF due to the developing $A_{1,3}$ strain between R and the OR' group.

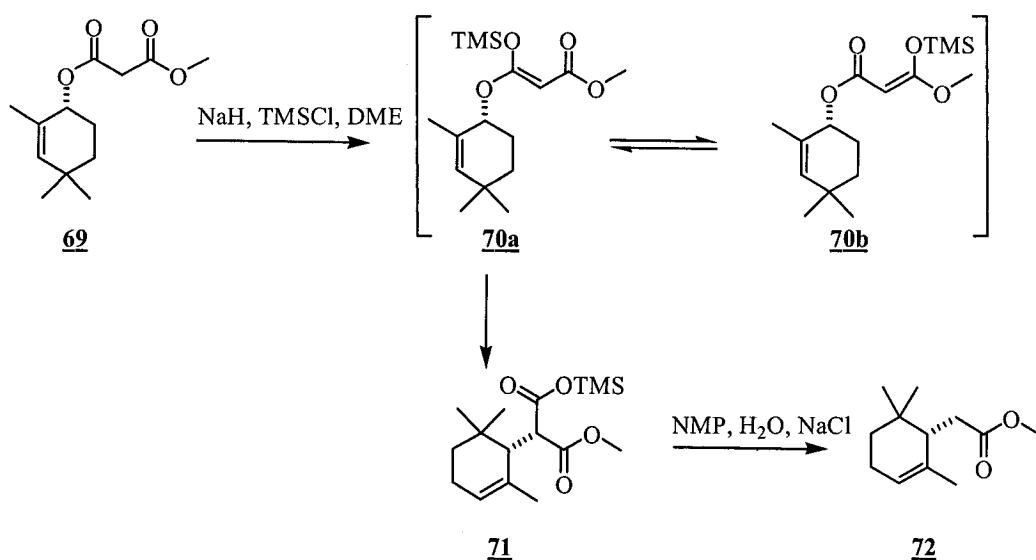


Scheme 16. Zimmerman-Traxler transition states of esters deprotonation

2.2.3 Variant of the Ireland-Claisen rearrangement

Lithium ester enolates are usually trapped with a silyl reagent before performing an Ireland-Claisen rearrangement. Ester enolate anions have limited use due to their instability at higher reaction temperatures compared to silyl ketene acetals for [3 + 3] shifts. The most often cited silyl reagent used is *tert*-butyldimethylchlorosilane (TBSCl). This compound is preferred to trimethylchlorosilane because C-silylation becomes competitive in some cases with TMSCl.²³

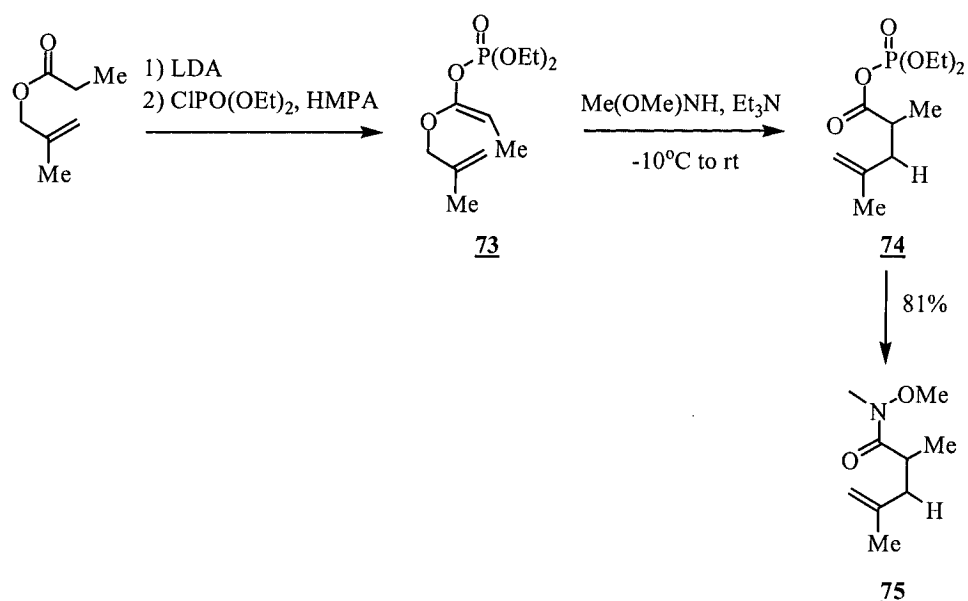
Ireland-Claisen rearrangements of ester acetates often suffer from low reaction yields under standard conditions. An interesting variation of the present pericyclic reaction is the use of malonate-derived allylic trimethylsilyl ketene acetals.³⁵ This methodology was developed by Fehr and Galindo for the synthesis of jasmonate derivatives (scheme 17).



Scheme 17. Claisen rearrangement of malonate-derived allylic trimethylsilyl ketene acetals

Compound **69** was deprotonated under mild conditions with sodium hydride and silylated with TMSCl to give an equilibrium mixture of intermediates **70a** and **70b**. Product **71** was isolated upon heating **70a** and **70b** and then converted to compound **72** after a desilylation/decarboxylation sequence in 72% overall yield. This methodology has an advantage over the Ireland-Claisen process due to better yields, and no harsh base was required because of the enhanced acidity of malonate protons. Also, the reaction is more practical than the Johnson-Claisen pericyclic reaction because the latter requires excess of orthoesters making industrial applications rather difficult.

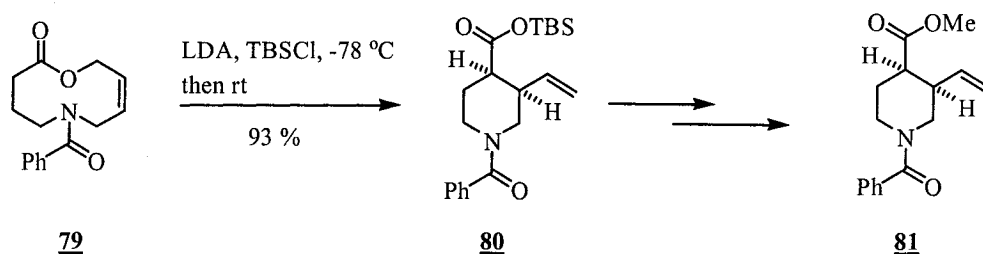
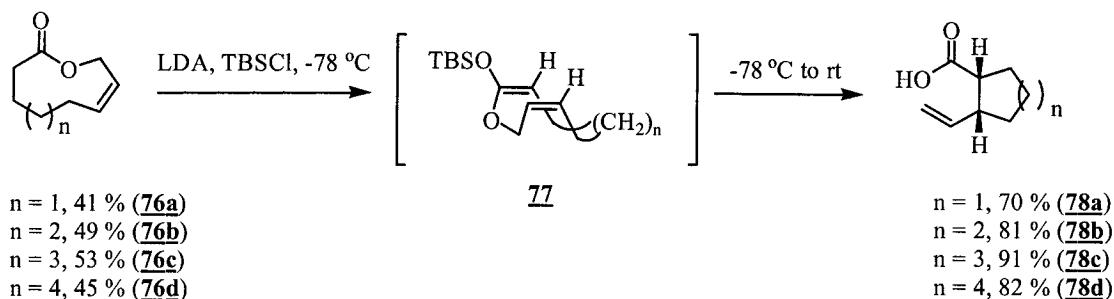
The Claisen rearrangement of enol phosphates³⁶ was also found to be an attractive modification of the usual Ireland-Claisen protocol. In this reaction, tert-butyldimethylsilylchloride was replaced by a phosphoryl chloride reagent to give a dialkoxyphosphinyl ketene acetal (scheme 18). The sigmatropic [3 + 3] rearrangement of **73** was reported by Funk to be easier than the trialkyl silyl counterpart, sometimes with an increase of diastereoselectivity. The acyl phosphate **74**, the product of the rearrangement reaction, is a versatile group that could be converted into a wide variety of carboxylic acid derivatives upon quenching with nucleophiles like MeOH, EtSH or Me(MeO)NH. The latter nucleophile gave rapid access to the versatile Weinreb amide **75**.



Scheme 18. Claisen Rearrangement of enol phosphates

2.2.4 Ireland-Claisen rearrangement mediated ring contraction of macrocyclic lactones

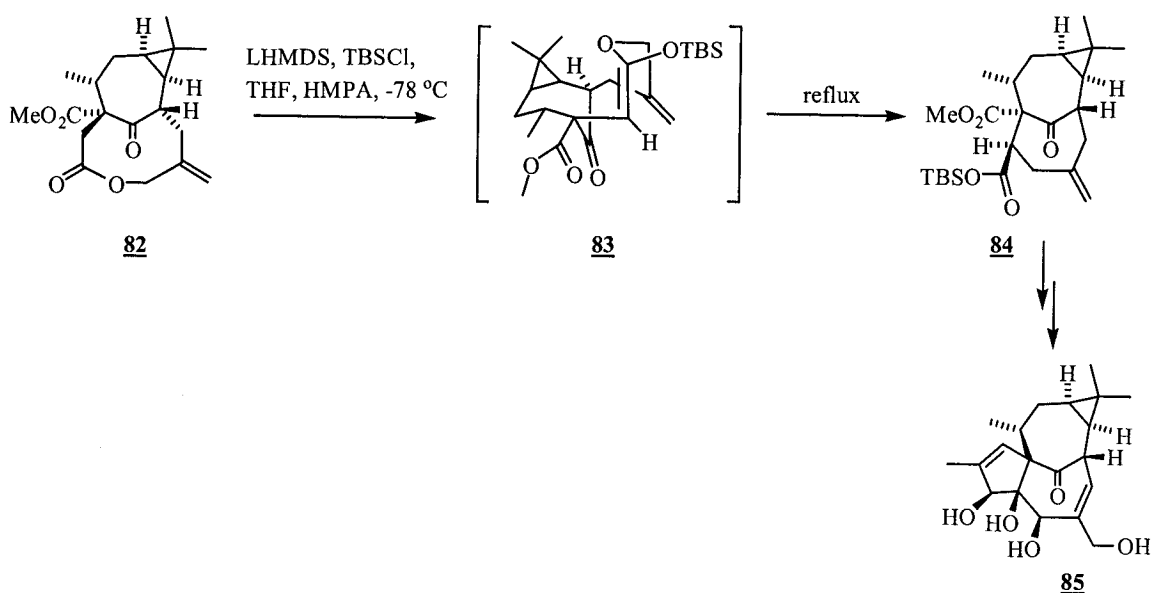
Pioneering work was done by the Funk group on alicyclic Ireland-Claisen rearrangements to synthesize complex carbocycles via ring-contraction strategies.³⁷⁻³⁹ During the course of their research,^{40, 41} they studied a wide range of different sized macrolactones as substrates for [3 + 3] sigmatropic rearrangements (scheme 19).



Scheme 19. Alicyclic Ireland-Claisen rearrangement of medium-sized ring macrolactones

Macrolactones such as **76** were prepared by conventional methods using the Mukaiyama protocol in 41 to 53 % yield. Those products were submitted to standard Ireland-Claisen procedures to form ketene acetals such as **77**. In all cases studied, the [3 + 3] sigmatropic rearrangement of **76** proceeded exclusively through a boat-like conformation to yield *cis*-disubstituted carbocycles such as **78**. The success of those alicyclic rearrangements was due to several factors: (i) the conformation of the medium-sized ring allows control of the geometry of the ester enolate; (ii) high asymmetric induction could be achieved through transannular interactions; (iii) the rigidity of the system imposes double bond proximity to facilitate the pericyclic rearrangement. This elegant strategy was applied successfully to the racemic synthesis of *N*-Benzoylmerquinene methyl ester (**81**), an important intermediate in quinine synthesis.⁴² Medium ring **79** was rearranged via an Ireland-Claisen procedure giving the exclusive formation of *cis*-3,4-disubstituted heterocycle **80**, presumably via a boat-like conformation. The power of the ring contraction of macrocyclic lactones through an Ireland-Claisen rearrangement was demonstrated in the synthesis of an advanced intermediate of the

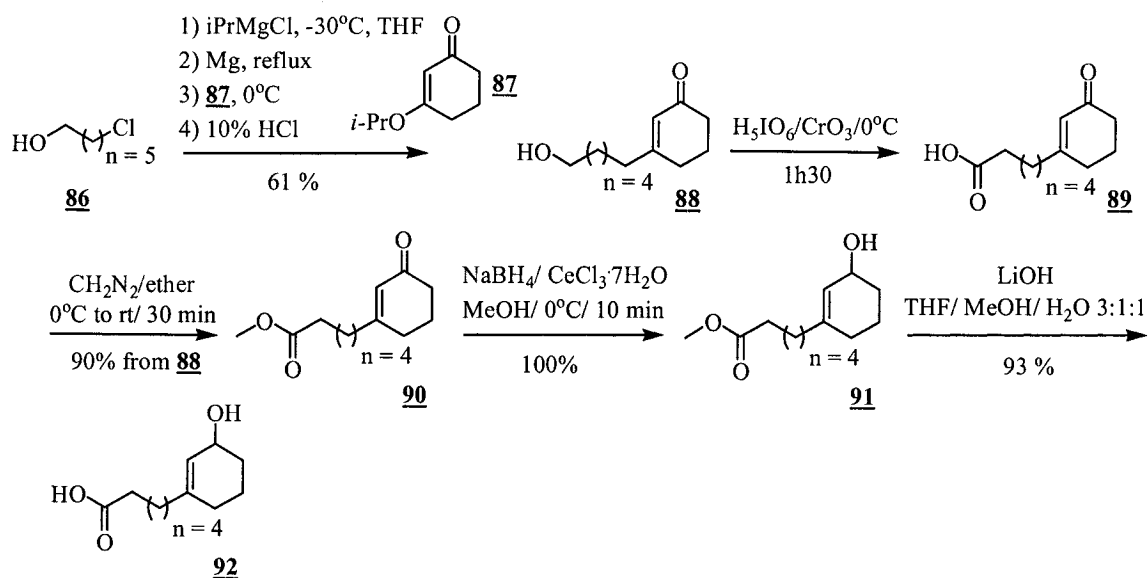
Ingenol (**85**) core (scheme 20).^{43, 44} In that strategy, developed by Funk, eleven-membered ring macrolactone **82** was submitted to a ring contraction via an Ireland-Claisen reaction to form rapidly the ingenane ring system **84** in 88 % yield and 19 : 1 diastereomeric ratio. One sigmatropic carbon of intermediate **83** is exocyclic to the macrocyclic ring and, therefore, a chair-like transition state was proposed to explain the stereochemical outcome of the reaction.



Scheme 20. Stereoselective construction of the Ingenane ring system via an Ireland-Claisen ring contraction

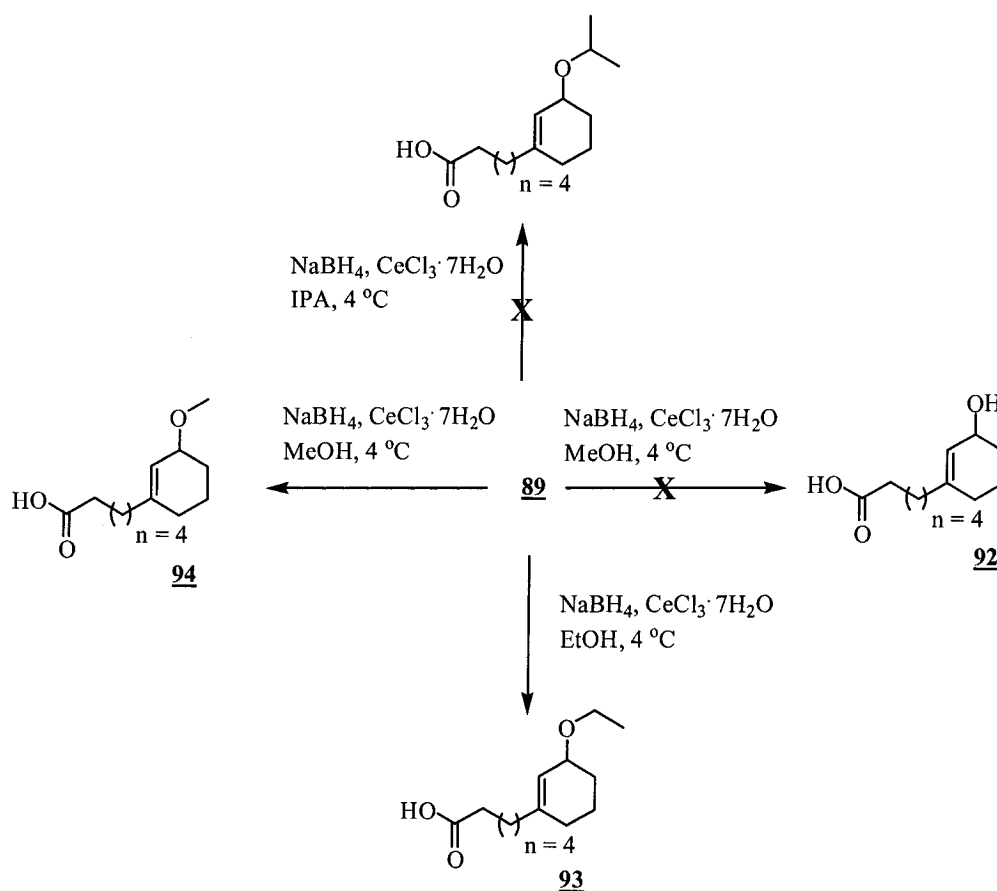
2.3 Synthesis of the macrolactone precursor

Before undertaking the synthesis of macrolactones such as **55**, an investigation with a simpler model was carried out (scheme 21).



Scheme 21. Synthesis of macrolactone precursor **92**

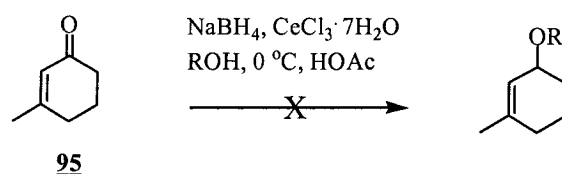
The synthesis of hydroxy acid **92** commenced with the preparation of the Normant Grignard⁴⁵ of **86**. Thus, 6-chlorohexan-1-ol was first reacted with isopropylmagnesium chloride to deprotonate the free hydroxyl group and then treated with solid magnesium under refluxing conditions to produce the corresponding Grignard of **86** which was titrated with salicylaldehyde phenylhydrazone⁴⁶ before use. The production of the Grignard was shown to be sluggish when it was performed in small quantity but worked better on 25 millimole scale or larger. With compound **88** in hand after alkylation of the known enone **87**, the free hydroxyl group on the side chain was quantitatively oxidized using a catalytic amount of chromium trioxide⁴⁷ and periodic acid as co-oxidant to give **89**. The latter oxidation worked very well if the solvent used for this reaction was distilled before use. Reduction of enone **89** with sodium borohydride and cerium chloride was initially investigated to give directly hydroxy acid **92** (scheme 22).



Scheme 22. Luche reduction of **89** in various alcoholic solvents

This type of reaction is known to be highly chemoselective.^{48, 49} However, when submitting **89** to the Luche procedure the expected hydroxy acid **92** was never isolated. Instead, alcoholysis of **89** with methanol or ethanol was observed to give, in high yield, **93** and **94** respectively. The same reaction in isopropanol was slow and only starting material was observed. Alcoholysis of cyclic allylic alcohols with cerium (IV) is well documented.⁵⁰⁻⁵³ The reaction usually proceeds in refluxing conditions in alcoholic solvent to give an alkyl ether. Therefore, it was really surprising to observe a one pot reduction/etherification at 4 °C. Replacing the alcoholic solvent for the non-nucleophilic THF was not suitable since Cerium (IV) is not soluble in that solvent.⁵⁴ A survey of this reaction using 3-methyl-2-cyclohexen-1-one (**95**) with an external source of organic acid in methanol or in ethanol to get an insight of

the reaction mechanism was fruitless (scheme 23). Those results suggest that the allylic alcohol **92** might be a highly unstable substrate due to the ease of the substitution.

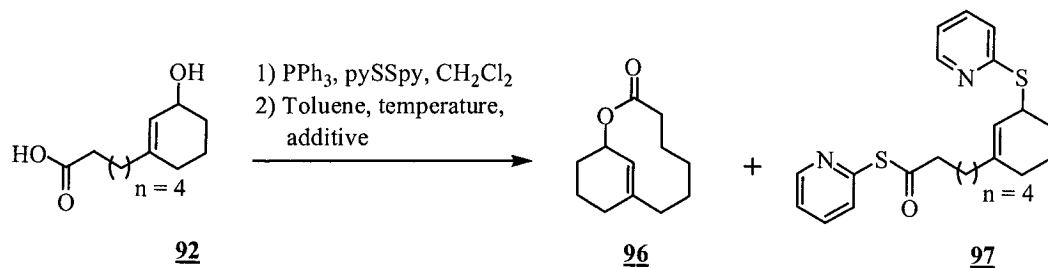


Scheme 23. Luche reduction of enones under acidic condition

To pursue our goal to synthesize macrolactones such as **55**, product **89** was therefore esterified with diazomethane before reducing the enone moiety. With **90** in hand, chemoselective reduction of the enone was achieved under Luche conditions to give in high yield the hydroxy ester **91** which was saponified under standard conditions to provide **92**. Compound **92** was found to be highly unstable and precise pH control was necessary to extract it from the reaction mixture. Thus, the basic lithium hydroxide solution was first neutralized with a 2M phosphonate buffer adjusted to pH= 4 and the mixture was then carefully acidified to pH= 3.5 with a 10 % HCl solution. At pH = 3, the formation of side products was observed and at pH lower than 2 only the product of elimination of the hydroxyl group was formed according to TLC results.

2.4 Macrolactonization

Different reaction conditions were screened for the macrolactonization of the hydroxyl acid **92**. The first reagent surveyed was 2,2'-dipyridyl disulfide (AldrithiolTM2).⁵⁵ The conditions used and results obtained are summarized in table 1.

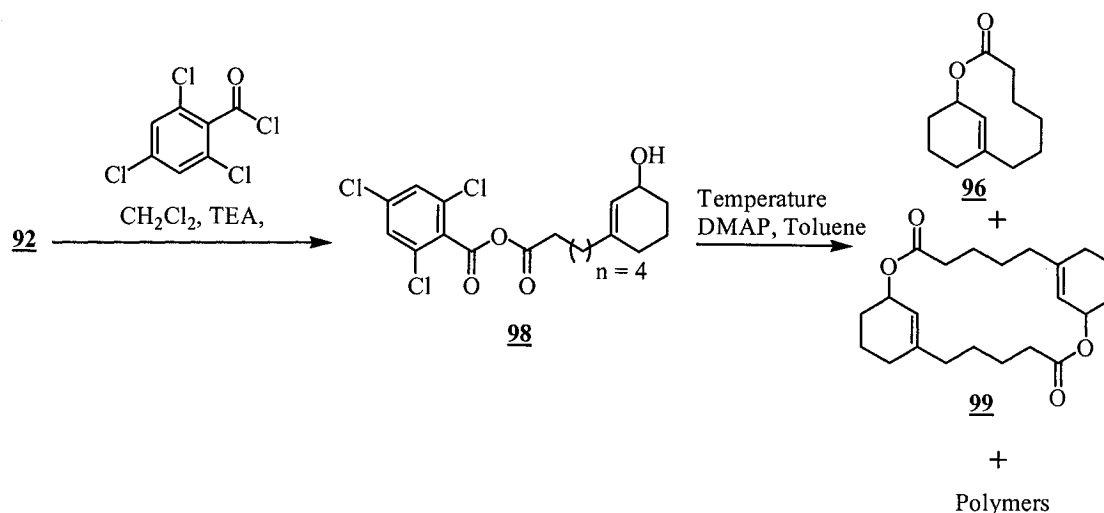


Entry	Temperature	Additive	Results
1	110 °C	15 mol% AgClO_4	Side product
2	110 °C	10 mol% AgClO_4	Side product
3	70 °C	-	Side product
4	110 °C	2 eq DMAP	Decomposition

Table 1. Macrolactonization with aldrithiolTM-2

Reaction of the 2-pyridinethiol ester of the parent carboxylic acid of **92** failed to give any macrolactonization products. The reaction was followed by TLC and it was observed that **92** was completely converted to the intermediate 2-pyridinethiol ester. The latter product was then heated in toluene in various conditions to give one compound after flash chromatography. Proton NMR demonstrated the addition of two pyridinethiol moieties on **92** and **97** was believed to be the product formed.

1,1'-carbonyldiimidazole⁵⁶ (CDI) and 2-chloro-1-methylpyridinium iodide⁵⁷⁻⁵⁹ are also known to be efficient reagents for macrolactonization. However, under those conditions substrate **92** was decomposed or no reaction occurred. The last reagent surveyed to accomplish the macrocyclization of **92** was 2,4,6-trichlorobenzoyl chloride.⁶⁰⁻⁶² The conditions and results obtained with the Yamaguchi reagent are summarized in table 2.



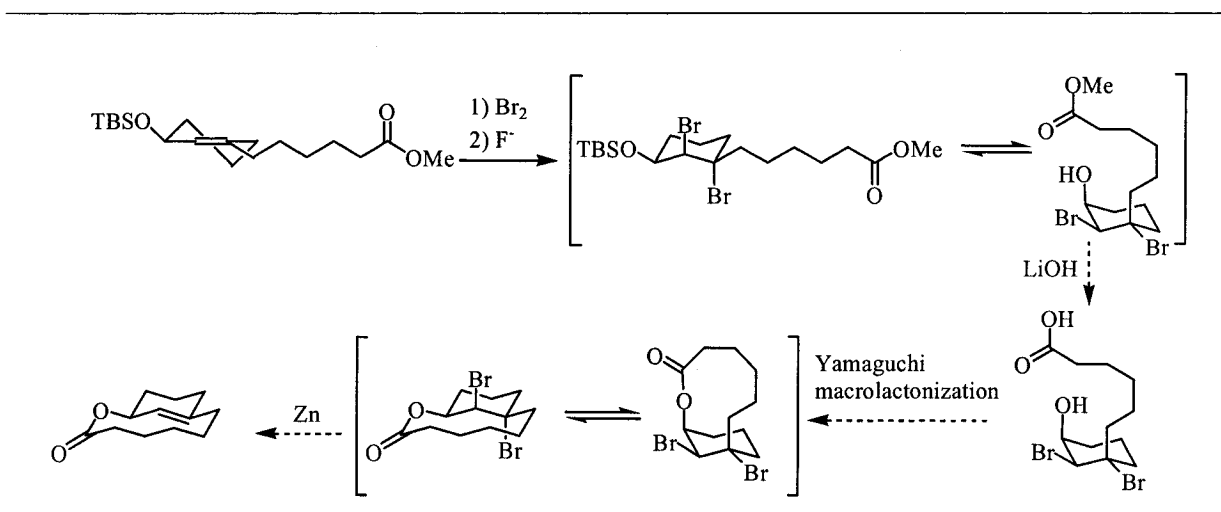
Entry	Temperature	Eq of DMAP	Rate of addition (final concentration)	Results (%)
1	0 °C	10	233 $\mu\text{mol/h}$ (2.7 mmol/L)	99 (50 %) + polymers
2	rt	10	88 $\mu\text{mol/h}$ (2.6 mmol/L)	99 (42 %) + polymers
3	70 °C	12	88 $\mu\text{mol/h}$ (2.2 mmol/L)	99 (40%) + polymers
4	110 °C	10	41 $\mu\text{mol/h}$ (0.9 mmol/L)	99 (37 %) + polymers
5	rt	3	22 $\mu\text{mol/h}$ (3.6 mmol/L)	99 (42 %) + polymers
6	rt	7	88 $\mu\text{mol/h}$ (3.3 mmol/L)	99 + polymers
7	rt	7	24 $\mu\text{mol/h}$ (3.1 mmol/L)	99 (58 %) + polymers

Table 2. Yamaguchi macrolactonization

Reaction of hydroxy acid **92** with the Yamaguchi reagent was quantitative as was demonstrated by TLC analysis of the crude reaction mixture to provide **98**. Then, the resulting mixed anhydride was added via a syringe pump at different rates and temperatures to a solution of DMAP in toluene. Close monitoring of the reaction indicated that dimer **99** was the sole product formed, contaminated with trace amounts of polymers of different molecular weights, for every condition tested. Even at very high dilution (entry 4), no trace of monomer **96** could be detected. The yield of **99** ranged from 37 % to 58 % and the amount of polymers was reduced when the reaction was performed at lower temperature. The structure of **99** was assigned according with the results of NMR, GC-MS and MS of the pure isolated product.

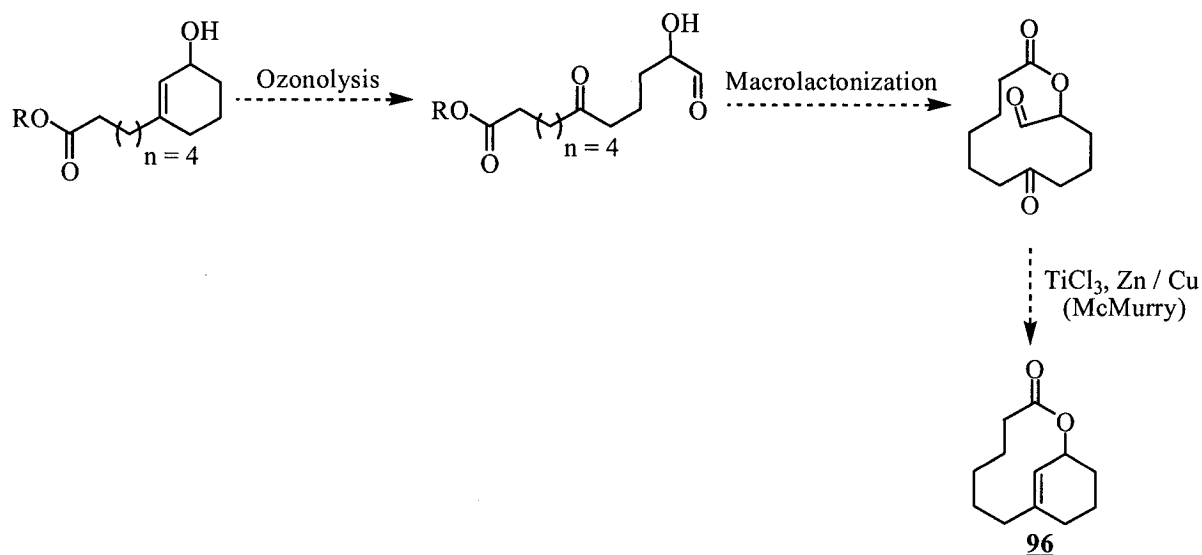
2.5 Conclusion and general remarks

Syntheses of macrolactones of sizes between 8 and 12-membered rings constitute a challenging task for organic chemists. Usually, to accomplish such macrolactonizations, the substrate must have a specific conformation that forces the carboxylic acid and the hydroxyl group to be close together. For example, the introduction of a *cis*-alkene on the carboxylic side chain of **92** should favor the macrocyclization by reducing the free entropy of it. This strategy is based on the Thorpe-Ingold effect, however the instability of the free allylic hydroxyl group on substrate **92** makes this methodology rather difficult to develop and optimize. In the aforementioned study, the alcohol group should adopt preferentially the equatorial position on the cyclohexenol framework. This conformation makes the cyclization very difficult. Therefore, a double bond precursor might be a solution to circumvent those difficulties (scheme 24).



Scheme 24. Alkene precursor for the macrolactonization methodology

An alternative approach to reach the 10-membered ring macrolactone comes from the ring contraction of a 12-membered ring macrolactone via ring-closing metathesis or the McMurry reaction (scheme 25). The formation of macrolactone **96** should be easier to achieve due to the absence of the six-membered framework which disfavoured the macrolactonization.

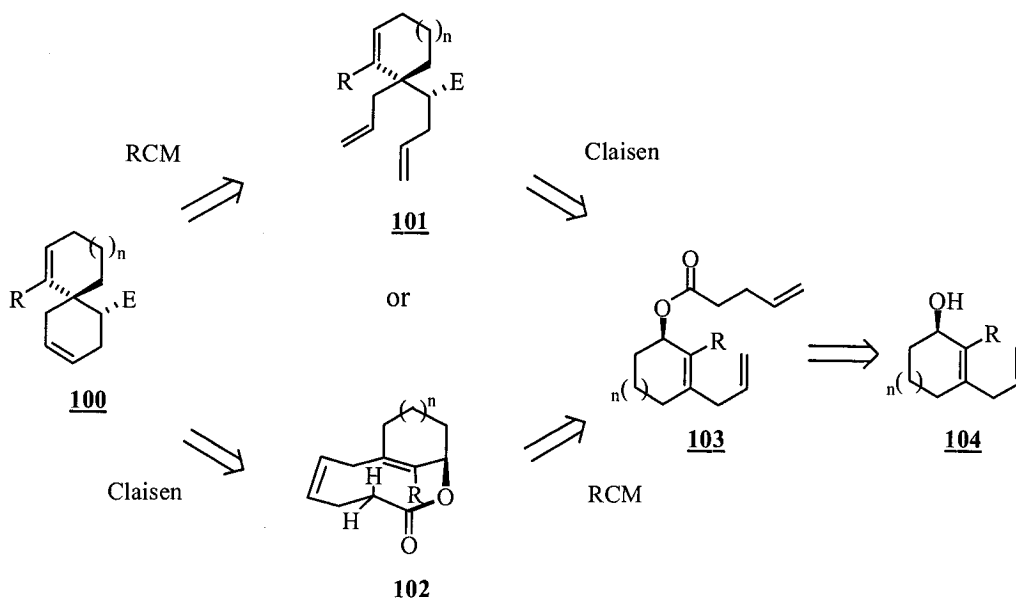


Scheme 25. Ring contraction of 12-membered ring macrolactone

CHAPTER 3

3.1 Introduction

The study presented in the following chapter will describe the research progress on the asymmetric synthesis of spirocyclic compounds via a sequential Ireland-Claisen/ring-closing metathesis approach that produces spirocyclic cyclopentanes and cyclohexanes. The formation of the quaternary center of the spiro-fused ring was envisaged to be set by an Ireland-Claisen rearrangement that controls the configuration of the quaternary center by virtue of suprafacial migration. The configuration of the quaternary carbon would be dictated by the configuration of the starting allylic alcohol such as **104** (scheme 26).



Scheme 26. Retrosynthesis analysis based on a sequential Ireland-Claisen/ring-closing metathesis strategy

When designing this strategy, we first expected to establish the configuration of the carbon α to the carbonyl group in the final product via a ring contraction of macrocyclic lactones of type **102**. The enantioselective synthesis of alcohol **104** could be achieved from reduction of the corresponding enone with the Corey-Bakshi-Shibata (CBS) reagent^{63, 64} or optically active N-methylephedrine⁶⁵ and provides stereochemical information to set the absolute configuration of the spiro center. Acylation of **104** would give esters such as **103**. With compounds **103** in hand, various conditions and approaches were tried to get macrolactones **102** via ring-closing metathesis. Unfortunately, compounds **103** have proved to be unreactive and did not afford any macrocyclic compounds with the use of ruthenium Grubbs catalyst (1st and 2nd generation) under various conditions. As an alternative route, compounds **103** were submitted to an Ireland-Claisen rearrangement to form **101** which underwent smoothly ring-closing metathesis to give **100**.

3.2 Ring-closing metathesis

3.2.1 Mechanism

The ruthenium-based catalyst, which exhibits an excellent tolerance towards a wide variety of functional groups, is actually the most useful and versatile reagent for metathesis reactions (figure 6).⁶⁶ Such transformations include ring-closing metathesis (RCM) and ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis polymerization (ADMET) and finally cross-metathesis reactions (CM).⁶⁷⁻⁶⁹

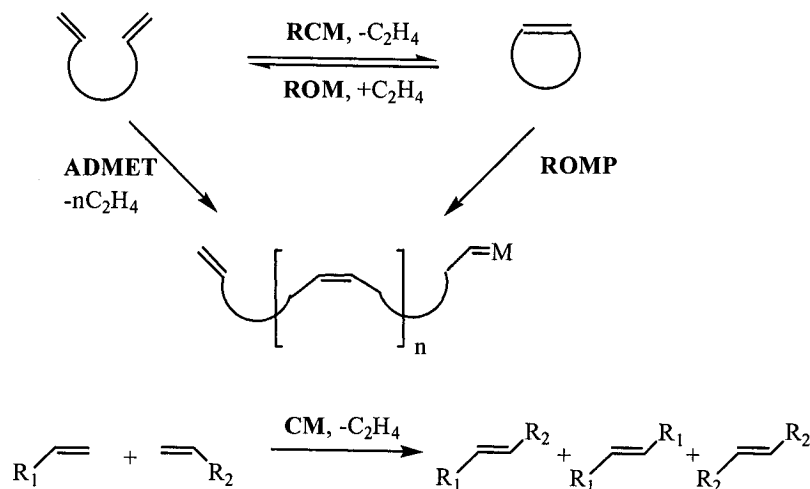
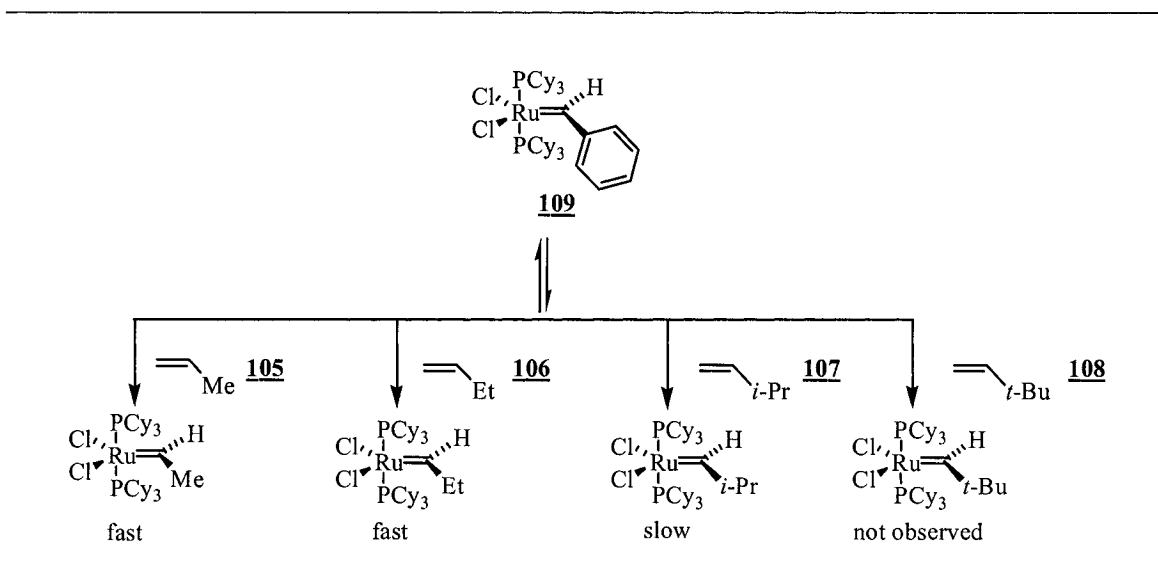


Figure 6. Metathesis reactions

The mechanism of metathesis reactions is believed to involve carbenes and metallacyclobutane complexes via a reversible series of [2 + 2] cycloadditions onto olefins. This widely accepted mechanism is known as the “Chauvin mechanism”. Among all metathesis reactions, ring-closing metathesis has emerged to be a powerful tool in the synthesis of natural products. It is a reversible reaction, usually under thermodynamic control, which can produce in principle an equilibrium mixture of alkenes. Therefore, to accomplish such transformations in a quantitative manner, the substrate must be chosen in a way to drive the reaction to the desired product. This is done when the catalyst reacts onto terminal alkenes to produce ethene or other volatile by-products thus increasing the entropy of the system.

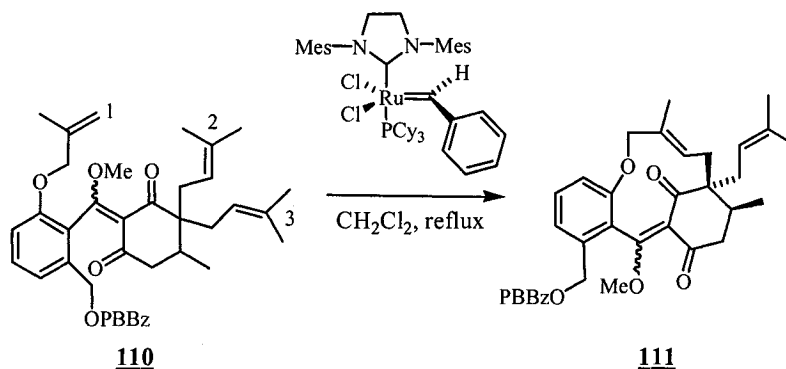
3.2.2 Alkylidene structure and reactivity

Kinetic studies done by Grubbs and co-workers have demonstrated that metathesis reactions are very sensitive towards the steric environment of the reacting center (scheme 27). When the terminal alkylidene moiety was bearing a small methyl (**105**) or ethyl (**106**) group, the insertion of the ruthenium catalyst (**109**) was fast and quantitative at room temperature.⁷⁰ However, when this terminal alkene was substituted with an isopropyl (**107**) group the reaction was slow and not complete and no reaction was observed within 12 h even with an excess of 3,3-dimethyl-1-butene (**108**).



Scheme 27. Influence of steric hindrance on catalyst insertion onto double bonds

Steric hindrance could be exploited with success to perform regioselective RCM when more than two alkenes could be involved in the reaction process. This is well illustrated in the total synthesis of Coleophomone B (**111**) by Nicolaou and co-workers (scheme 28).⁷¹ In the RCM reaction of **110**, alkenes 2 and 3 were not reacting together to give a 5-membered ring due to steric hindrance. However, the catalyst preferred to insert first onto alkene 1 and then, the resulting carbene reacted with alkene 2 to form an 11-membered ring which is usually more difficult to form than a cyclopentene derivative. Such preferences might be exploited for the synthesis spirocyclic compounds.

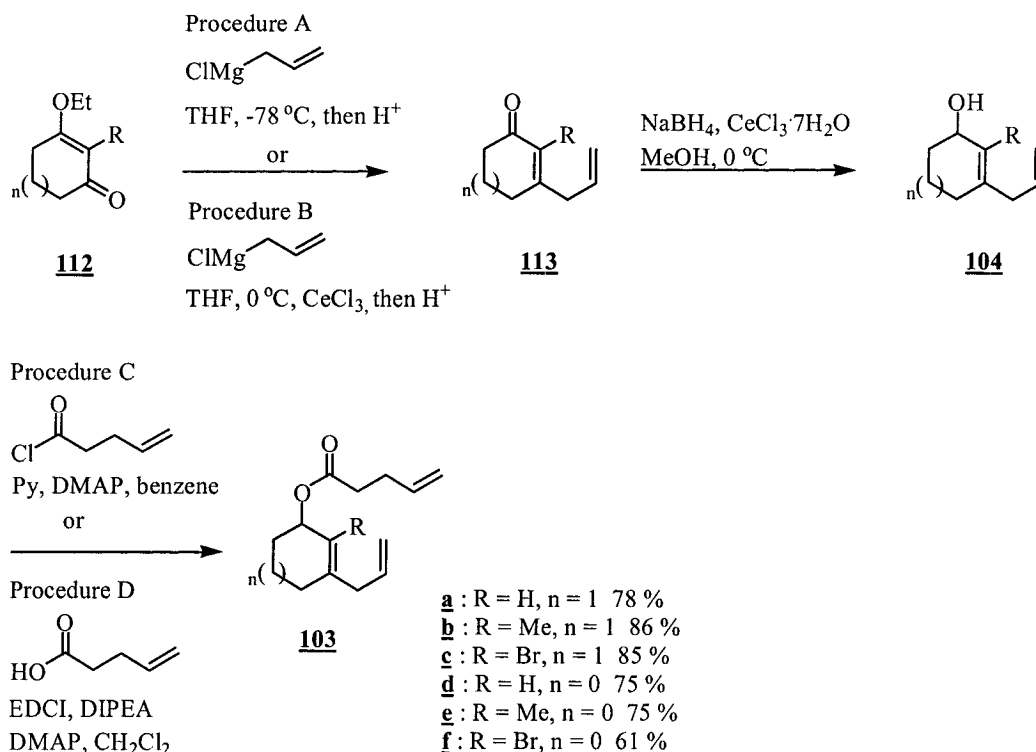


Scheme 28. Regioselective RCM in the synthesis of Coleophomone B

3.3. Results and discussion

3.3.1 Preparation of esters of type 103

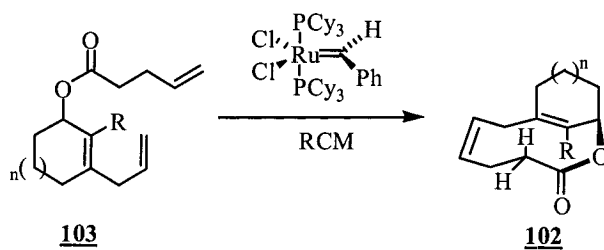
The esters required for this work were prepared as shown in scheme 29. Allylmagnesium chloride was added to known enol ethers 112 following procedure A when R = H or Me and procedure B in presence of cerium trichloride ²⁷ when R = Br. α,β -Unsaturated ketones 113 were isolated after mild acidic workup. Selective 1,2-reduction under Luche conditions resulted in the clean formation of the corresponding allylic alcohols 104 in almost quantitative yield. Acylation ^{72, 73} of the hydroxyl group was done under standard conditions with 4-pentenoyl chloride (procedure C) and catalytic amounts of DMAP or under coupling conditions (procedure D) when acid sensitive substrates like 103d, 103e and 103f were used. Those transformations proceeded extremely well and the required esters 103 were obtained in 61 to 86 % overall yield from the ketones 112.



Scheme 29. Ester precursors for RCM and Ireland-Claisen rearrangements

3.3.2 Medium-sized ring macrolactones via ring-closing metathesis

In order to synthesize macrolactones such as **102** or **96**, ring-closing metathesis was surveyed as a strategy to get the medium-sized ring. Therefore, **103a** and **103f** were chosen to study the RCM under various reaction conditions. The results obtained are listed in table 3. As shown in table 3, all attempts were fruitless to get the desired 10-membered ring product **102**. Changing solvent conditions and catalyst loading gave always the same results. In all cases tried, the starting material was recovered with traces of by-products seen by NMR. The reactions were conducted with high dilution techniques and no cross metathesis compounds and double bond isomerization were observed in ^{13}C NMR.



Entry	Substrate	Loading (catalyst)	Temperature	Solvent (additive)	Results
1	<u>103a</u>	5 mol %	Reflux 3 h	CH ₂ Cl ₂	SM recovered
2	<u>103a</u>	5 mol %	Reflux 12 h	CH ₂ Cl ₂	SM recovered
3	<u>103a</u>	5 mol %	Reflux 36 h	Benzene	SM recovered
4	<u>103a</u>	14 mol %	Reflux 2 h	CH ₂ Cl ₂ (Ti[OCH(CH ₃) ₂] ₄)	SM recovered
5	<u>103f</u>	14 mol %	Reflux 5 h	CH ₂ Cl ₂	SM recovered

Table 3. 10-Membered macrolactone by olefin metathesis

In the system studied, the ruthenium catalyst could be inactivated by complexing the ester moiety to form a stable six-membered ring complex 114 (figure 7). Lewis acids had been reported to break chelates between ruthenium catalysts 109.⁷⁴ Therefore, it was thought that titanium(IV) isopropoxide used in catalytic amounts should help the RCM reaction in the present system. Unfortunately, the use of such catalyst also failed to give any products (table 3, entry 4). It was clear that RCM reactions on substrates such as 103 would be very challenging as a result of the inherent ring strain.

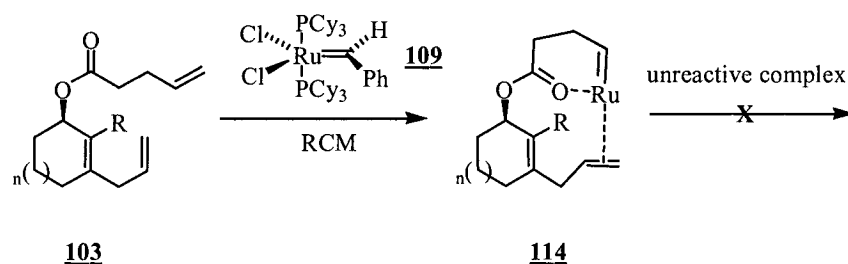


Figure 7. Possible six-membered ring complex of Grubbs catalyst with esters

3.3.3 Ring-closing metathesis on silyl ketene acetal templates

The formation of 8- to 11-membered rings is particularly difficult. This fact was observed in the unsuccessful macrolactonization of compound **92** where only dimers were isolated and in the ring-closing metathesis of compounds such as **103** that experience too much strain to afford macrolactone **102**. Therefore, we planned to use ketene acetals such as **115a** and **116** (figure 8) as potential candidates for ring-closing metathesis. These were chosen for these factors : (i) introduction of a double bond should reduce the free entropy of the alkyl side chain; (ii) it eliminates any possible coordination of the carbonyl of the ester moiety and the ruthenium catalyst to shut down the catalytic cycle; (iii) with proper geometry of the enolate, the alkyl side chain should point inwards to favour the RCM process; (iv) the R_2 group should be large enough to avoid any reaction of the ruthenium catalyst with the new enolate formed; (v) the R_2 group must be easily removable or transformed into other functional groups.

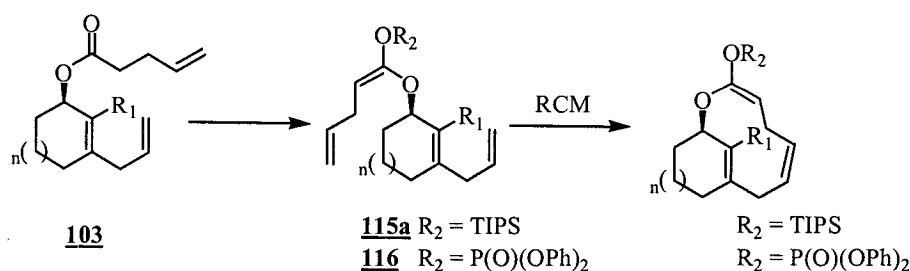
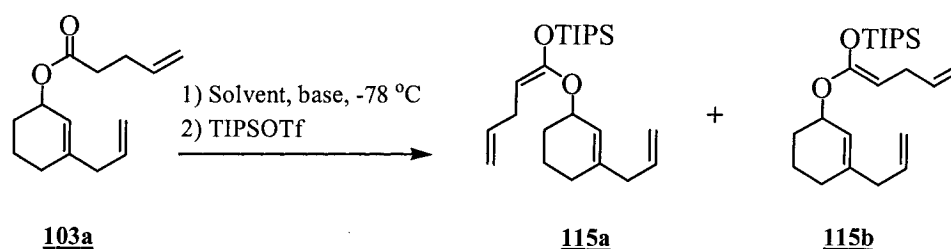


Figure 8. Ring-closing metathesis based upon silyl ketene acetal strategy

Ring-closing metatheses of enol silanes⁷⁵, enol phosphates and phosphate ketene acetals⁷⁶ are well preceded. However, to the best of our knowledge, there is no example of silyl and phosphate ketene acetals used as template for the formation of macrolactones.

Before undertaking the present study, it was required to know if ketene acetals such as **115** could be generated in high yield and good diastereoselectivity. Therefore, ester **103a** was chosen due to its ease of preparation and submitted to various deprotonation conditions. The resulting enolates were trapped with TIPSOTf to measure the diastereomeric ratio of the enolates formed by ¹H NMR (300 MHz). The results obtained are summarized in table 4.



Entry	Solvent	Base	Results	115a : 115b
1	Toluene	KHMDS	Quantitative	12 : 1
2	Toluene	NaHMDS	Not clean	-
3	Ether	KHMDS	Quantitative	23 : 1
4	THF	KHMDS	Not clean	-
5	Ether/23% HMPA	LDA	SM recovered	-
6	THF/23% HMPA	LDA	Moderate conversion	1 : 4
7	Toluene/23% HMPA	KHMDS	Not clean	-

Table 4. Stereoselective generation of ester enolates

The choice of base and solvent was critical to achieve complete conversion of ester **103a** into the *E* enolate **115a**. Deprotonation with KHMDS in ether was the optimal condition surveyed (entry 3) and the reaction was very clean. THF and HMPA were not suitable solvents due to their propensity to react with TIPSOTf (entry 4 and 7). Therefore, enolates generated in THF/HMPA were trapped with TBSCl (entry 6) to give in moderate yield **115b** in a 4 : 1 ratio. Attempts to identify the enolate structure by NOE measurement were fruitless. Therefore, the geometry of the major silyl ketene acetal was assigned by ^{13}C NMR (300 MHz). The chemical shift of the carbon of *E* enolates such as **115a** is known to be downfield to the carbon of *Z* enolates such as **115b** which is more shielded (figure 9).²⁹

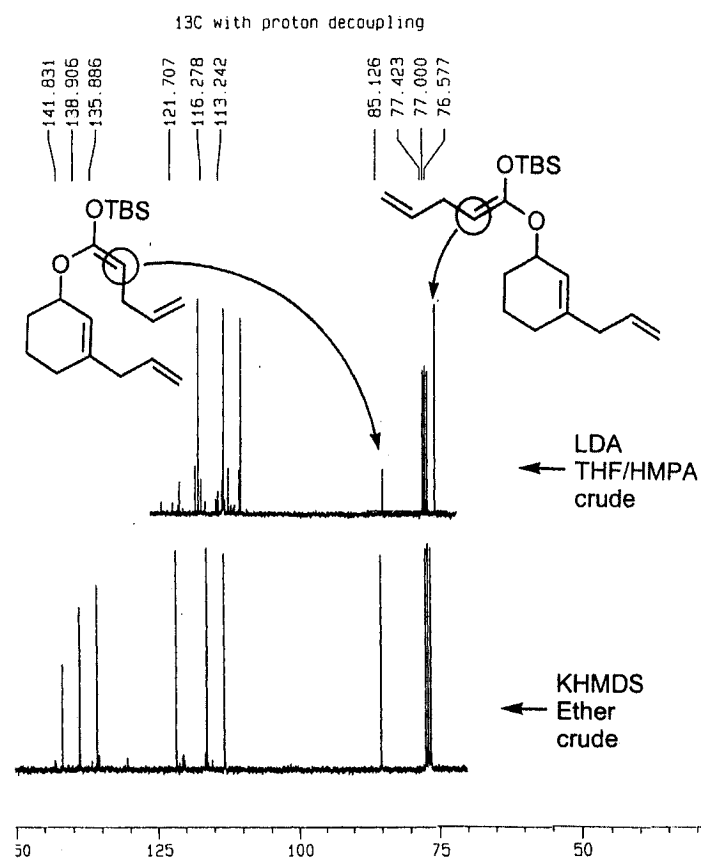
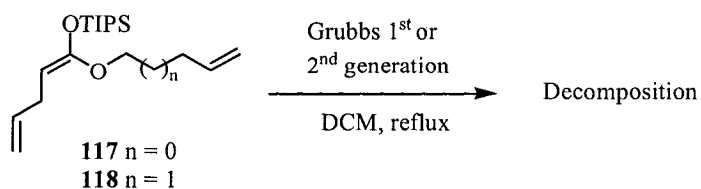


Figure 9. ^{13}C NMR of silyl ketene acetals

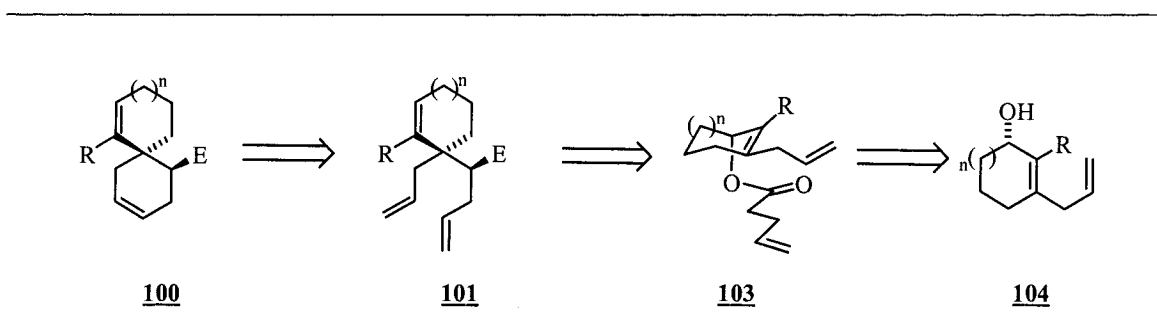
With good conditions to generate the *E* ester enolate from substrate **103a**, ring-closing metathesis on substrate **115a** was investigated. When submitting the latter *E* silyl ketene acetal to metathesis reactions with second generation Grubbs catalyst, one major product, with contamination, was observed by TLC. However, the NMR of the crude reaction mixture demonstrated that the new product formed was an acid as evidenced by the characteristic chemical shift of the carboxylic acid proton. Thus, it was concluded that the silyl ketene acetal was unstable under metathesis conditions and the substrate was not appropriate for this kind of reaction. Also, due to the ring strain of the macrocycle compound, forcing conditions were required for cyclization. It was found later that substrates such as **103a** were sensitive towards Lewis acids such as TiCl_4 and triflates giving elimination of the ester moiety. Therefore, it is reasonable to expect that the derived silyl ketene acetal of **103a** should be even more unstable and this could explain the isolation of a carboxylic acid in the reaction mixture. The enolate **116** was also tested as a substrate for ring-closing metathesis. Its reaction with second generation Grubbs catalyst gave one product following TLC analysis. Unfortunately, the exact structure of the final compound was not assigned since it decomposed on silica gel even with the use of triethylamine as buffer. To be sure that the present methodology was not limited by the choice of our substrate, simpler molecules were also synthesized. **117** and **118** were deprotonated with KHMDS in ether and the resulting enolates trapped in high yield with TIPSOTf or $\text{ClP}(\text{O})(\text{OPh})_2$ ⁷⁷ and submitted to RCM reactions (scheme 30). One major product was observed by TLC that was less polar than the starting material and again, traces of carboxylic acid by-products were seen by ^1H NMR. Therefore, to pursue that methodology, different silyl and phosphate reagents with different stereoelectronic properties must be screen to favor the reaction.



Scheme 30. Ring-closing metathesis of silyl ketene acetals

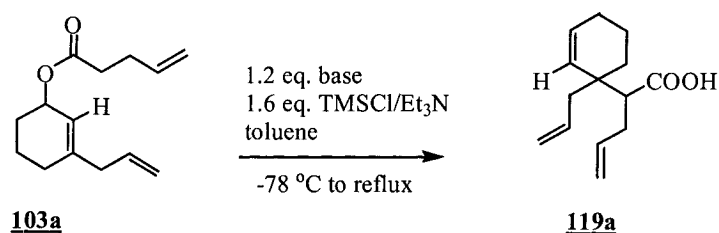
3.3.4 Synthesis of spirocyclic cyclopentanes and cyclohexanes

With the unsuccessful outcome to get any 10-membered ring macrolactones of type **96** or **102**, we planned to control the stereochemistry of the carbon α to the ester on the basis of the geometry established during the enolate stage, together with a chair-like transition state on **103** (scheme 31). In considering this latter method, we were aware of the fact that related endocyclic Ireland-Claisen rearrangements were reported with considerable variation in yields and diastereoselectivities.^{31, 34} We therefore needed to find conditions that would improve the reliability and efficiency of this transformation to make the process practical. Final cyclization to give the spiro system would employ olefin metathesis to give **100**. We expected that the endocyclic olefin formed from the rearrangement would not react in the metathesis reaction because of the steric encumbrance of the neighboring quaternary centre. This hypothesis was supported by the results of Grubbs and co-workers which showed that the insertion of the ruthenium catalyst was not observed at room temperature on olefins bearing a *t*-butyl group (chapter 3, scheme 27).



Scheme 31. Sequential Ireland-Claisen/ring-closing metathesis

Considerable difficulties arose with the enolization of **103a**. Application of standard conditions³³ gave the desired product **119a** in modest yield and variable recoveries. Therefore, optimization of the rearrangement was necessary. After considerable experimentation, we found that the counter ion of the amide base was critical and KHMDS was essential to realize synthetically useful yields (table 5, entry 4).⁷⁸

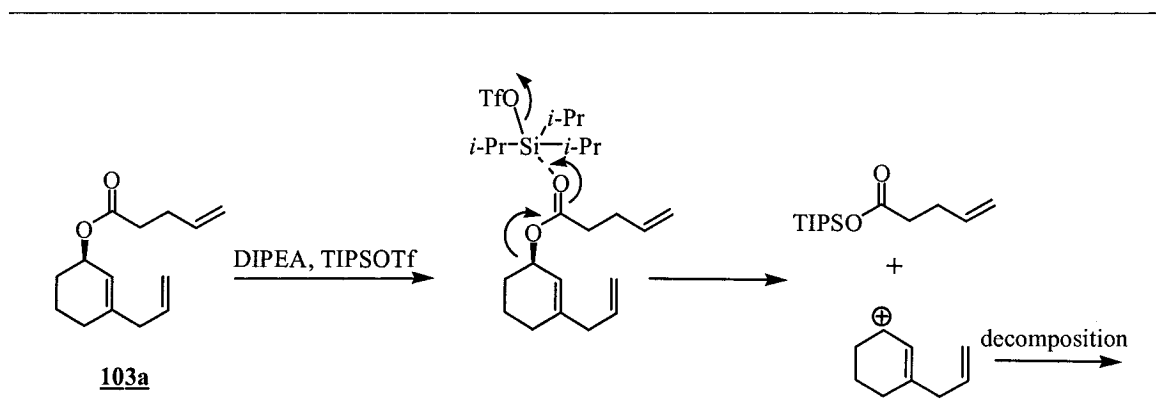


Entry	Base	Yield (%)	dr ^a
1	LDA	0	-
2	LiHMDS	12	2.1:1
3	NaHMDS	44	1.4:1
4	KHMDS	76	3:2
5	DIPEA/TIPSOTf	0	-

^a Estimate on 300 MHz ¹H NMR

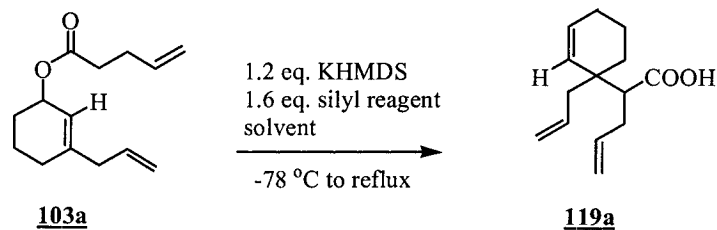
Table 5. Effect of base on the Ireland-Claisen rearrangement of **103a**

The use of LDA, LiHMDS or NaHMDS gave significantly decreased recoveries with a mixture of starting material and by-products (entries 1- 3). Attempts to form the silyl ketene acetal using silyl triflates and Hunig's base resulted in decomposition due to the sensitive nature of **103a** to strong Lewis acid (entry 5). In that case, the silyl ester derivative of 4-pentenoic acid was isolated as the sole product in quantitative yield following proton and carbon NMR (scheme 32). Replacing Hunig's base by stronger KHMDS gave better results even in the presence of triflates (see table 6, p. 61).



Scheme 32. Decomposition pathway of **103a** with Lewis acid

Toluene was superior to THF or THF/HMPA as rearrangement solvent. However, selectivities were slightly higher when THF or ether were used as solvents for deprotonation. These were removed *in vacuo* to complete the rearrangement in refluxing toluene (table 6, entries 1-3). It is also worthy of note that deprotonation occurred rapidly and better conversion was achieved when the silyl reagent was added after a short period of time (usually within 10 minutes). Among the silyl reagents used, TMSCl with TEA gave best yields and reproducibility. Surprisingly, the most often reported TBSCl gave no product at all and often, only starting material was recovered when it was used (table 6, entries 9 and 10). That may be a consequence of the difficulty of trapping the enolate formed. HMPA was therefore required when TBSCl was used to get in moderate yield any silyl ketene acetals (entry 8). THF and HMPA must be avoided when TIPSOTf or any triflates are used (entry 6 and 11). Lithium salts were reported to increase the *E/Z* ratio in ketone enolization by the formation of mixed aggregates with the amide base thus influencing the transition state of deprotonation.^{79, 80} In our case, the addition of lithium salts gave a small increase in yield with the loss of diastereoselectivity during the rearrangement (entry 2). The selectivity after rearrangement was slightly increased when deprotonation was done at elevated temperatures, however the yield was lower due, maybe, to Claisen cross condensation (entry 4 and 5).



Entry	Solvent	Trapping reagent	Yield (%)	dr
1	THF ^a	TMSCl/Et ₃ N	47	4.5:1
2	THF ^{a, b}	TMSCl/Et ₃ N	52	2.3:1
3	Ether ^a	TMSCl/Et ₃ N	79	2:1
4	Toluene	TMSCl/Et ₃ N	76	3:2
5	Toluene ^c	TMSCl/Et ₃ N	49	3.5:1
6	Toluene/HMPA	TIPSOTf	0	-
7	THF/HMPA ^d	TMSCl/Et ₃ N	44	4:1
8	THF/HMPA ^d	TBSCl	38	4:1
9	THF ^d	TBSCl	0	-
10	Toluene	TBSCl	0	-
11	THF	TIPSOTf	0	-
12	Toluene ^c	TIPSOTf	79	1.9:1
13	Toluene	ClPO(OCH ₂ CCl ₃) ₂	0	-

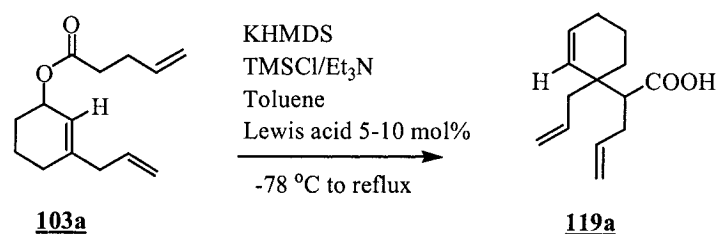
^a Solvent for silyl ketene acetal formation. Rearrangement performed in toluene.

^b 0.4 eq of LiCl was added before base. ^c KHMDS was added at 0 °C.

^d LDA was used as base. ^e Yield after deprotection of the TIPS ester with aqueous HF in CH₃CN.

Table 6. Effect of solvent and silyl reagents on the Ireland-Claisen rearrangement of **103a**

Rearrangement of dialkoxyposphinyl ketene acetals³⁶ derived from **103a** was unsuccessful (entry 13). Finally, we expected that the size of the silyl group could in principle destabilize one transition state in favour of the boat-like transition state on substrate **103a**. Although the yield of reaction was as good as with TMSCl, we observed only a small increase in diastereoselectivity when the bulky TIPSOTf was used (entry 4 compare to entry 12). The result suggests that the transition state could be biased by an anti-chair conformation like **59b** (chapter 2, figure 4). The TIPS silyl ketene acetal proved to be stable toward flash chromatography which allowed us to purify the intermediate, in quantitative yield, if warranted. Brief exposure to HF in acetonitrile was necessary in those cases after the pericyclic process in order to obtain the desired carboxylic acids. We also observed that TIPSOTf, even if it is a very bulky protecting group, seemed to speed up the rate of the rearrangement compared to TMSCl. Due to the Lewis acid nature of TIPSOTf, we therefore investigated the addition of various Lewis acids to facilitate the reaction.

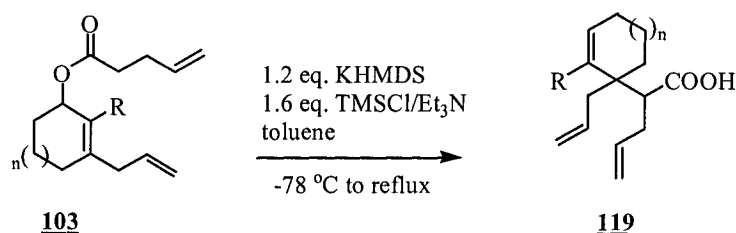


Entry	Lewis acid	Yield (%)	dr
1	none	75	3:2
2	TiCl ₄	47	1.9:1
3	BF ₃ ·Et ₂ O	64	3:1
4	Ti(Oi-Pr) ₄	48	4.5:1
5	ZnCl ₂	57	1.7:1
6	AlCl ₃	51	3.5:1
7	TIPSOTf	79	1.9:1

Table 7. Effect of Lewis acids on the Ireland-Claisen rearrangement of **103a**

Lewis acids had been reported recently to improve Ireland-Claisen processes on acyclic substrates (table 7).⁸¹ The use of other Lewis acids afforded slight improvements in selectivity but gave lower overall yields (table 7, entries 2-6). TiCl_4 was published to be the best Lewis acid as catalyst for Ireland-Claisen rearrangements on acyclic substrates to give very high diastereoselectivity. In our case, it was found that TiCl_4 was too harsh and decomposed the substrate instead of having a full catalytic effect. Among the Lewis acids used, $\text{BF}_3\cdot\text{OEt}_2$ and AlCl_3 offered the best compromise between yield and diastereoselectivity.

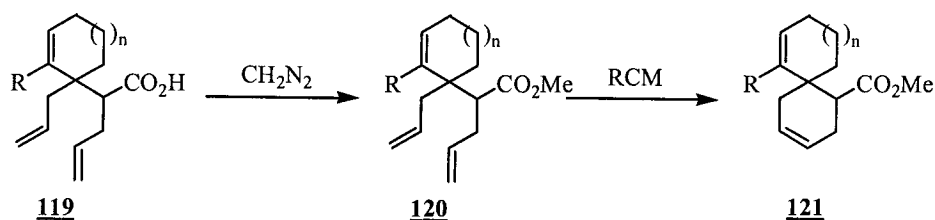
Having now good conditions for rearrangement with the use of KHMDS and TMSCl in toluene, we were able to rearrange substrates **103** to obtain acids **119** and verify the effect of the R group on yield and diastereoselectivity. As was expected, rearrangements on five and six membered rings when R = H could be achieved in good yields but with low diastereoselectivities (table 8, entries 1 and 4).



Entry	Substrate	Yield (%)	dr
1	103a R = H, n = 1	76	3:2
2	103b R = Me, n = 1	51	1.6:1
3	103c R = Br, n = 1	47	1.9:1
4	103d R = H, n = 0	74	1.3:1
5	103e R = Me, n = 0	0	-
6	103f R = Br, n = 0	41	4.6:1

Table 8. Influence of substrate structures on the Ireland-Claisen rearrangement

Then, it was planned to change the R group into a bromo substituent for the following reason: (i) this group was required for the enantioselective reduction of enones **113** into **104**, (ii) it is easy removable and offers also possibilities for further transformation, (iii) it was also expected that it could destabilize the boat-like transition state and therefore improve diastereoselectivity. When R = Br, the diastereoselectivity on the five-membered ring series was 3.5 times higher than when R = H. It had however little effect on 2-cyclohexenol derivatives (entries 3 and 6). The rearrangement of **103d** and **103e** proved to be challenging. The former must be reacted immediately after its isolation and the latter was notably unstable and quickly decomposed under the mild acidic conditions required for the isolation of the product. Lower yields were observed when R was a methyl or a bromide group. That might be the consequence of adding steric effects during the sigmatropic shift. With substrates **119a-d** and **119f** in hand we then explored the feasibility of using RCM to synthesize various spirocyclic cores after treating **119** with an excess of diazomethane (table 9).

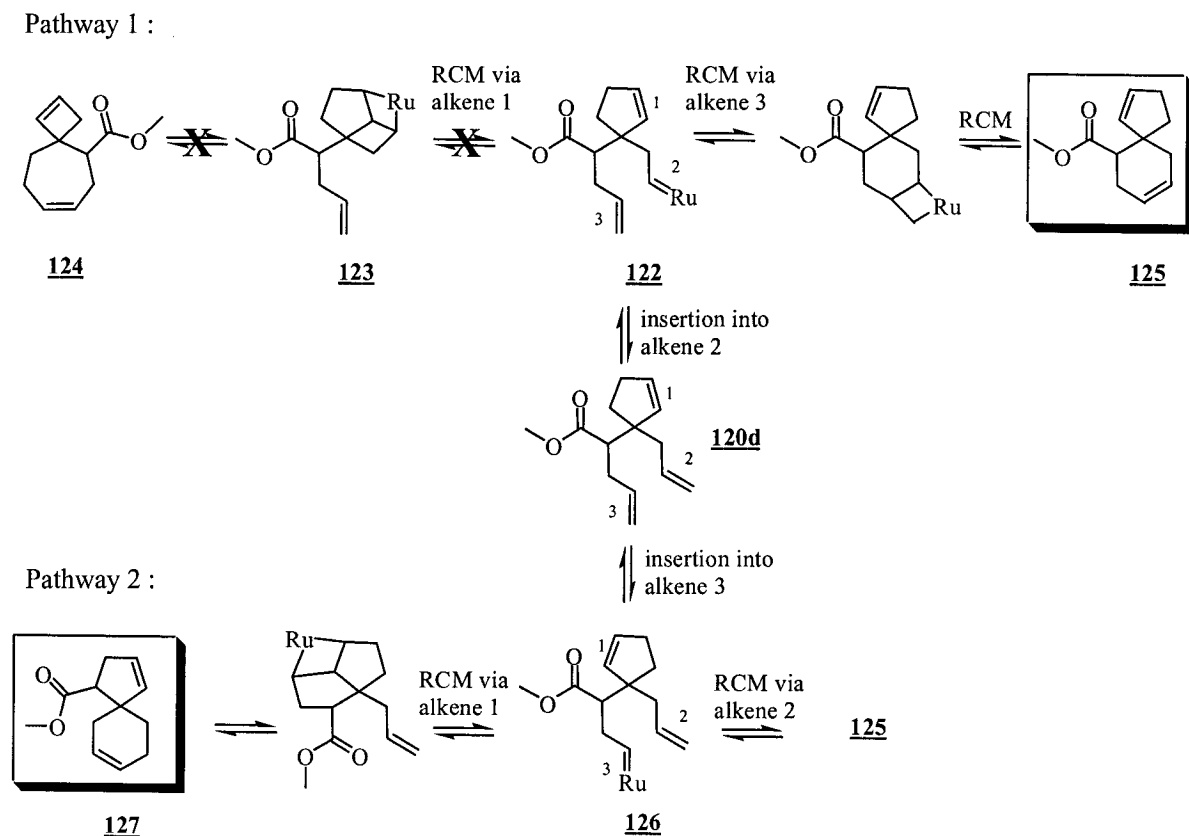


Entry	Substrate	Catalyst loading (mol %)	Yield (%)
1	120a R = H, n = 1	7	97
2	120b R = Me, n = 1	7	91
3	120c R = Br, n = 1	10	82
4	120d R = H, n = 0	5	-
5	120f R = Br, n = 0	5	96

RCM was performed at room temperature in DCM or benzene without any notable difference in yield

Table 9. Ring-closing metathesis of **120**

The metathesis reactions proceed extremely rapidly and cleanly giving the desired products **121** in 82 to 97 % yields. In all cases except **120d** the endocyclic olefins of the starting materials were untouched and we observed the formation of the desired spirocycle only. Compound **120d** however gave a mixture of two products resulting from opening of the five-membered ring with first or second generation Grubbs catalysts (scheme 33).

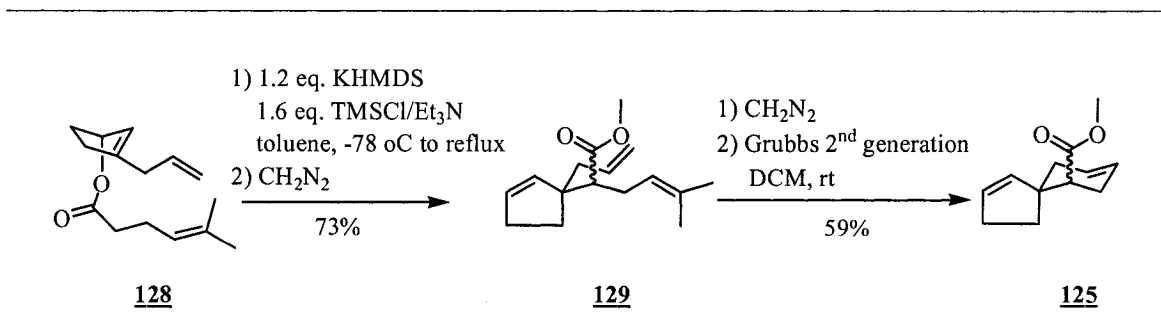


Scheme 33. Possible reaction pathways of **120d** during RCM

Compound **120d** could react with the ruthenium catalyst via the terminal alkene 2 to produce carbene **122** which could produce products **124** or **125**. The former compound was never isolated because the production of metallacyclobutane **123** must involve the formation of a highly strain cyclobutane ring. However, the ruthenium catalyst could also insert into alkene 3. In that case, the intermediate **126** could afford the desired compound **125** or **127** via its reaction with alkene 1 to produce a tandem ring-opening/ring-closing metathesis. This result

was presumably a consequence of increased ring strain in the five-membered ring system or the carbene **126** was suffering less from steric hindrance due to the intramolecular process to give **127**. This result was somewhat unexpected⁸² due to the excellent regioselectivity observed for the other substrates. As metathesis is an equilibrium process, we tried to control the selectivity of the reaction by using very short reaction times to maintain some kinetic control. Therefore, NMR experiments were performed to determine how rapidly the equilibration was occurring. It was found that the ring-closing metathesis on **120d** was too fast at room temperature (< 2 minutes) to permit monitoring the reaction by NMR.⁸³ Therefore, a reaction was performed at -78°C and quenched after 10 minutes with a 10% HCl solution. NMR of the crude mixture after extraction and isolation showed that after 64 % of conversion, the ratio **125:127** remained unchanged. Finally, substrate **120f**, possessing a more sterically demanding endocyclic double bond, did not suffer ring-opening metathesis under the conditions employed, and gave the desired product only.

In the goal of producing products such as **125**, compound **128** was synthesized according to the same procedure for compound **103**, submitted to an Ireland-Claisen rearrangement, esterified to give **129** and the latter successfully cyclized via ring-closing metathesis (scheme 34). In that strategy, the ruthenium catalyst preferred to insert first into the less sterically demanding exocyclic double bond and as it was demonstrated in the previous scheme 33, the ring-closing metathesis was completed via the pathway 1 to give exclusively product **125**.



Scheme 34. Regioselective ring-closing metathesis

To the best of our knowledge, there is no example of RCM with TIPS esters. We therefore explored that possibility. We observed that the use of TIPS esters in the metathesis reaction with substrate **120** produced side products that proved to be difficult to characterize. Thus, we concluded it was more convenient to do the rearrangement with TMSCl to avoid the extra step necessary to cleave the stable TIPS ester.

3.3.5 Diastereoselectivity of the Ireland-Claisen rearrangement

It is well known that the RS,SR isomer is the favored product of rearrangement of both geometric silyl ketene acetals **60a** and **60b** (chapter 2, figure 5). Therefore, assuming that the *Z* enolate **130** and the *E* enolate **131** rearrange respectively through boat-like and chair-like transition states to afford the same RS,SR isomer, we believed that the major product after the Ireland-Claisen rearrangement of substrate **103a** would be the epimer **134** no matter which conditions were used for deprotonation (figure 10).^{29, 31} Higher energy transition states **132** and **133** obtained after the rotation of the silyl ketene acetal around the carbon-oxygen bond will give the minor epimer **135**.

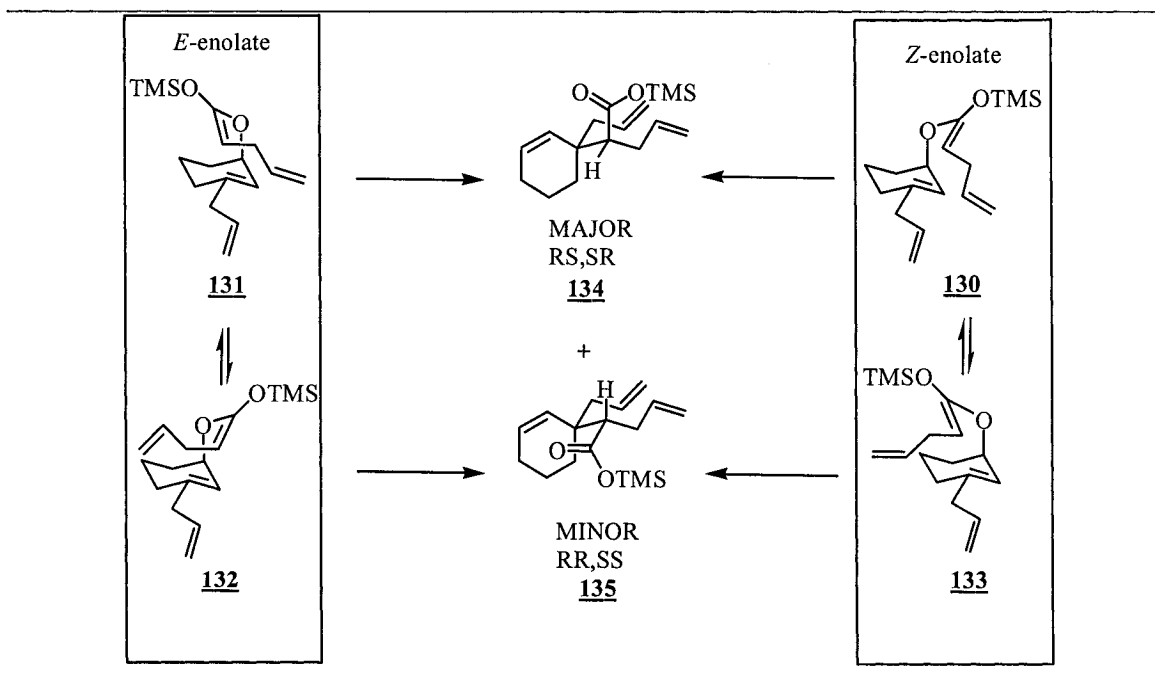
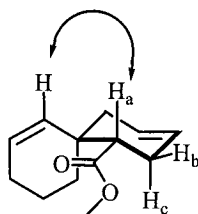


Figure 10. Diastereoselectivity observed in the Ireland-Claisen rearrangement of cyclohexenyl ester derivatives

Also, after careful NMR analysis, we have been able to conclude that the same isomer was obtained independently of the Lewis acid used as catalyst. The final structure of the major epimer **134** was confirmed indirectly by NOE interactions observed in the resulting spirocyclic compound of the minor epimer **135** after its ring-closing metathesis (figure 11).

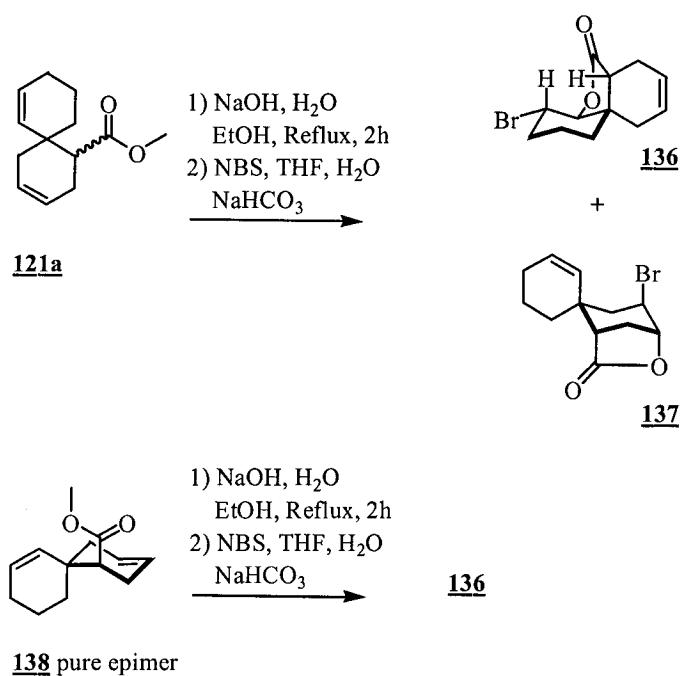


- H_a was assigned by HMQC and DEPT 135
 - $J_{ab} = 5.4$ Hz
 - $J_{ac} = 9.9$ Hz
-

Figure 11. Key NOE interaction observed in the spirocycle product derived from **135**

The proton α to the ester in the spectrum of the minor spirocyclic epimer showed couplings of 9.9 Hz and 5.4 Hz. These results suggest that the ester moiety is pseudo-equatorial. Therefore, a possible structure which explains the NOE interaction between H_a and one hydrogen on one alkene is the spirocycle product derived from **135**. The same observations and conclusion were made with the RCM product **121b**.

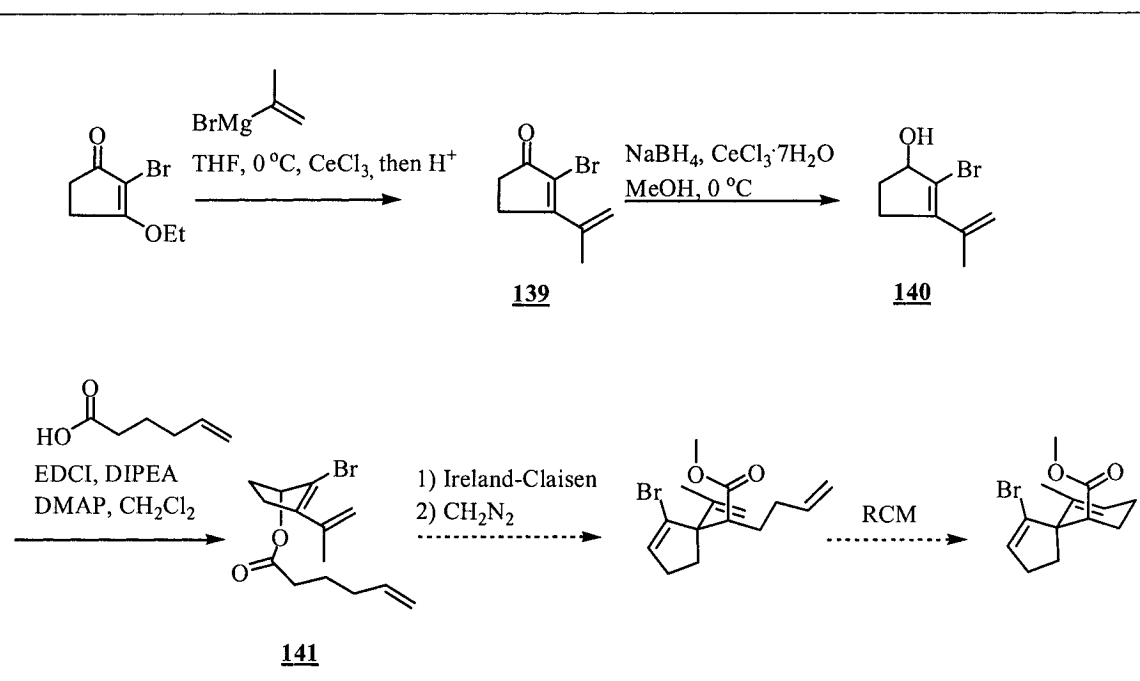
The mixture of diastereomers of **121a** was saponified in refluxing ethanol with an aqueous solution of sodium hydroxide and the resulting carboxylic acid was treated with N-bromosuccinimide to produce a mixture of bromolactone **136** and **137** (scheme 35). To ensure that compound **121a** did not epimerize during the saponification reaction, the major epimer **138** was isolated and submitted under the same reaction conditions as described above to give exclusively product **136**. From those results, we were able to confirm again that **134** was the major diastereomer obtained after the Ireland-Claisen rearrangement of **103a** using NOE interactions and we also demonstrated that the bromolactonization could be regioselective.



Scheme 35. Regioselective bromolactonization

3.3.6 Towards spirovetivanes

Ireland-Claisen rearrangements were tried on more complex substrates such as **141** (scheme 36), that product might potentially give access to spirovetivane⁸⁴ cores. Unfortunately, as it is seen in table 8, rearrangements on compounds where a bromo substituent was involved in the sigmatropic shift were too demanding and afforded only partial conversion to the desired product.



Scheme 36. Towards spirovetivanes syntheses

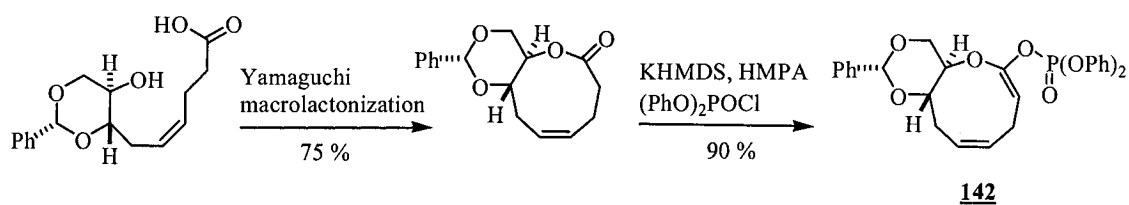
3.3.7 Conclusion and general remarks

The sequential Ireland-Claisen/ring-closing metathesis approach constitutes a rapid and simple method for the construction of spirocyclic compounds. The stereochemistry at the spiro-fused ring could be set by a suprafacial sigmatropic rearrangement on a cyclic framework. The aforementioned study also demonstrated that the ring-closing metathesis proceeded in excellent yield and could be highly regioselective by modifying the steric encumbrance of the reacting alkenes.

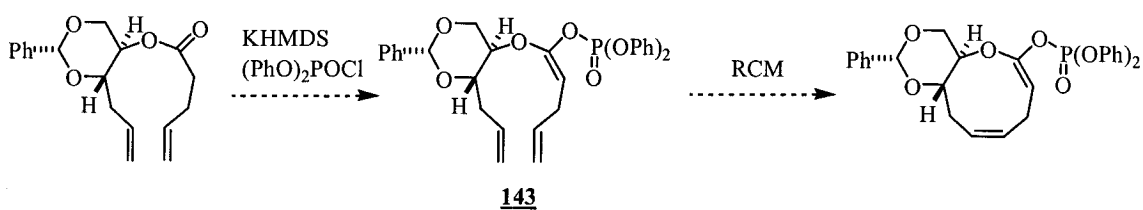
Ring-closing metathesis of silyl ketene acetals or ketene acetal phosphates for the synthesis of medium-sized rings had never been used to the best of our knowledge. The development of such strategies could potentially become an alternative route to macrocycles when macrolactonizations fail. With the proper geometry of the ester enolate, the ketene acetal phosphate side chain like in **143** should point inwards the system to favour the RCM

process (scheme 37). Application of such methodology might be useful in the synthesis of large cyclic ether rings such as **142**.⁷⁷

Nicolaou's macrolactonization approach



Ring-closing metathesis approach

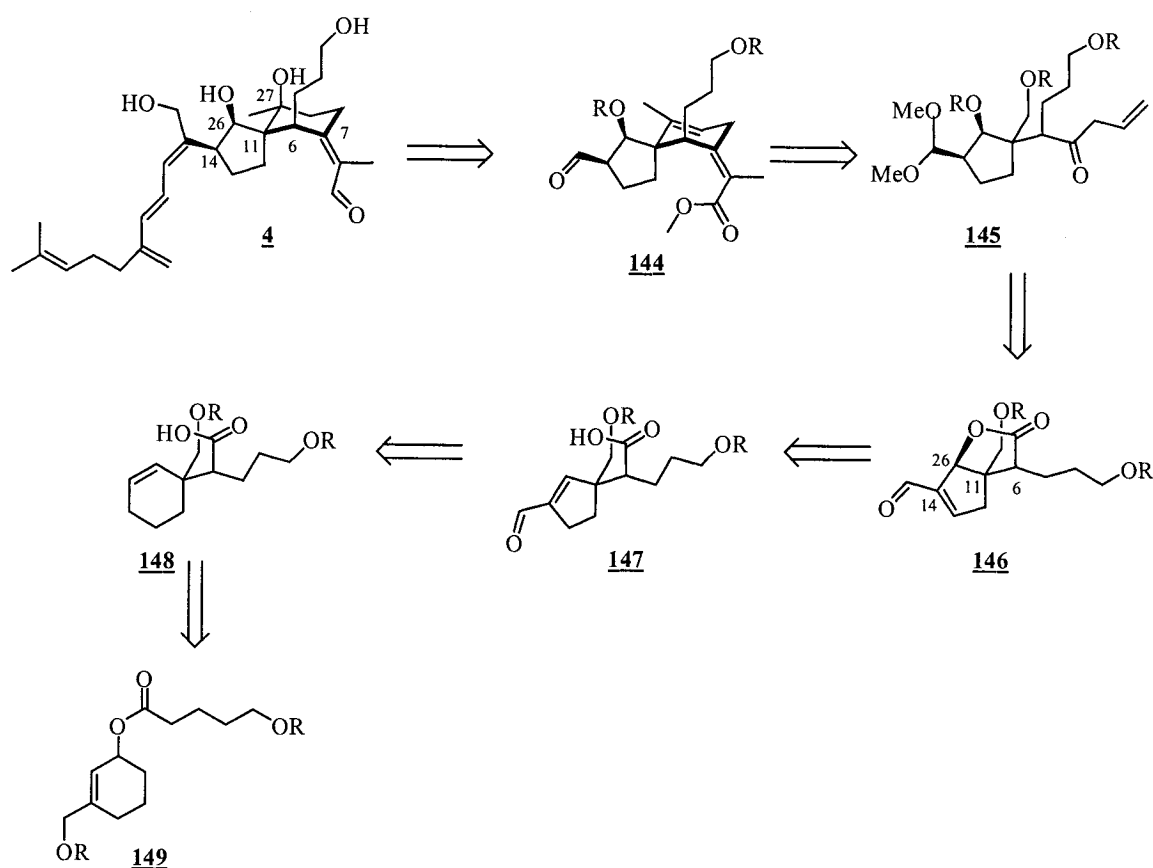


Scheme 37. Novel ring-closing metathesis of silyl ketene acetal phosphates

CHAPTER 4

4.1 Introduction

Attempts towards the synthesis of the core of spiro-iridal products will be discussed in the present chapter using an Ireland-Claisen rearrangement and ring-closing metathesis as key steps. The following work has been inspired from the retrosynthetic analysis of 28-deacetylbelamcandal (**4**) shown below (scheme 38) and previously on page 29.



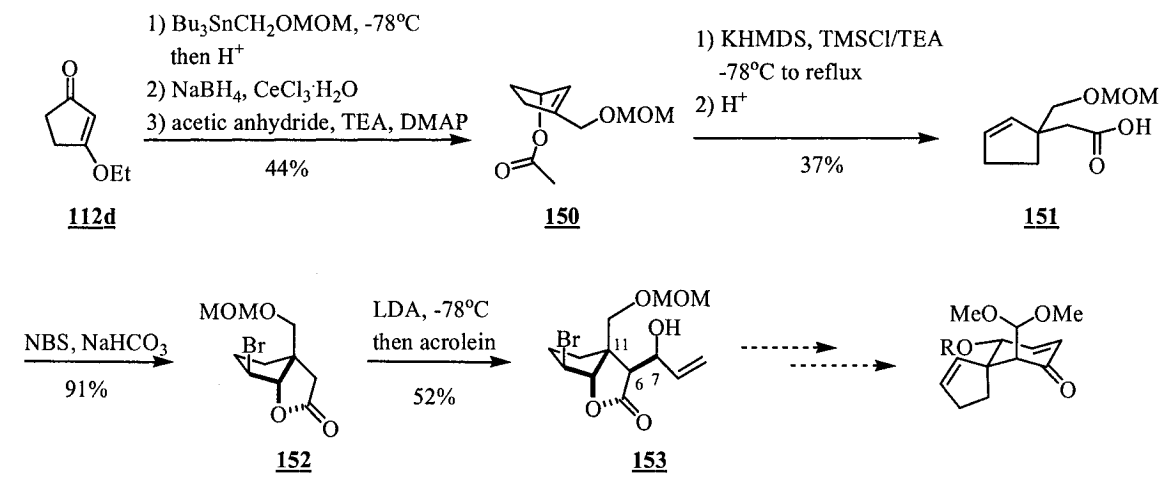
Scheme 38. Retrosynthetic analysis of 28-deacetylbelamcandal based upon an Ireland-Claisen and ring-closing metathesis strategy

The unsaturated alkyl side chain of **4** could be placed using a Wittig type olefination on related structures of **144**. Introduction of the tertiary alcohol at C-27 might be done via an epoxidation strategy or by selective oxymercuration of the more electron-rich double bond. The formation of the six-membered ring could be achieved by ring-closing metathesis after proper functionalization of **145** with terminal alkenes to produce **144**. Stereoselective hydrogenation of **146** and opening the resulting saturated lactone with *N,O*-dimethylhydroxylamine⁸⁵ should install the C-26 hydroxyl moiety with the requisite stereochemistry. Alkylation of the resulting Weinreb amide⁸⁶ would allow the introduction of one terminal alkene required for RCM. The bicyclic lactone **146** should be easily synthesized from an Ireland-Claisen rearrangement on **149** and subsequent ozonolysis/aldol methodology. In the aforementioned retrosynthesis, **146** or related structures are key substrates to reach the completion of the synthesis of **4**. Also, it is required to verify if the stereochemistry at the C-6 carbon could be fixed with high diastereoselectivity from the Ireland-Claisen rearrangement or by epimerization on lactone **146**.

4.2 Results and discussion

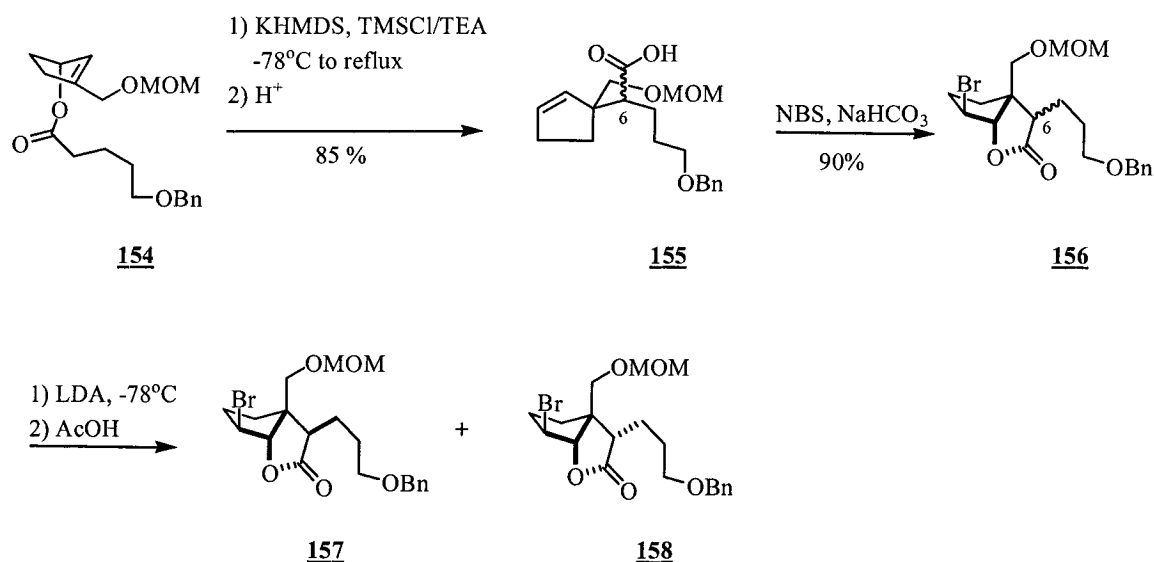
4.2.1 The cyclopentenyl esters series

Rearrangements of cyclopentenyl esters were first surveyed for the construction of related bicyclic lactones of type **146** since they give rapid access to 5,5-bicyclic templates (scheme 39). Therefore, alkylation of enone **112d** with [(methoxymethoxy)methyl]tributylstannane⁸⁷ followed by Luche reduction of the resulting enone gave a secondary alcohol which was acylated under standard conditions to give the cyclopentenyl ester **150**. Ireland-Claisen rearrangement of the silyl ketene acetal of **150** afforded in low yield the desired carboxylic acid **151** which was treated with *N*-bromosuccinimide to provide the bicyclic lactone **152**. Attempts to optimize the yield of the pericyclic reaction were fruitless. It was found later that ester acetates are not good substrates for Ireland-Claisen rearrangements since they usually rearrange in low yield.



Scheme 39. Stereoselective alkylation of bicyclic lactones

It was planned that alkylation of the lactone enolate of **152** should proceed from the less sterically congested exo face as opposed to Meyer's bicyclic lactams which are known to alkylate from the endo face.²¹ Therefore, treatment of **152** with LDA and subsequent addition of acrolein gave surprisingly the product **153** as a single diastereomer in moderate yield with trace of elimination product. Indeed, in one single step, the stereochemistry at C-6 and C-7 was fixed. The exact origin of the stereoselective installation of the secondary alcohol at C-7 remains unclear and its final configuration is not yet defined. However, we think that **153** might be the anti-aldol product resulting from the condensation of the ester onto acrolein via a Zimmerman-Traxler transition state. Finally, protection of the secondary alcohol as a silyl ether was unsuccessful under standard conditions with TBSCl and imidazole. At this stage, it was concluded that ester **150** was not a suitable substrate for pursuing the following strategy due to the difficulty arising from the scale up of compound **151**. Therefore, it was decided to install at the beginning of the synthesis the exo alkyl chain at the C-6 position with an Ireland-Claisen on a substrate such as **154** (scheme 40).

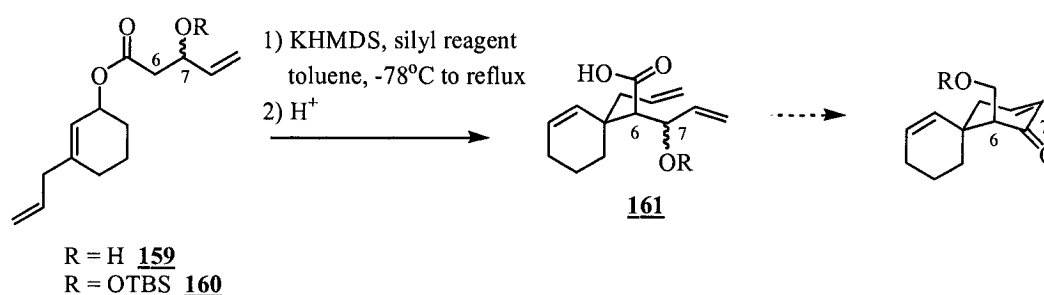


Scheme 40. Kinetically controlled protonation

Cyclopentenyl ester **154** was rearranged in high yield under modified Ireland-Claisen protocol to afford the carboxylic acid **155** in a 1.2 : 1 diastereomeric ratio. Acid **155** was reacted with NBS to give the bromolactone **156** in 77 % overall yield as a mixture of diastereomers. It was expected that we could correct the absolute stereochemistry at C-6 by kinetic protonation from the less sterically congested exo face. Such a strategy for stereocontrol has been employed in number of similar systems.³¹ Therefore, it was expected that treating **156** with LDA and quenching the enolate with a source of protons should provide compound **158** as the major epimer. Unfortunately, it was observed that the kinetic protonation on bicyclic lactone **156** afforded **157** in slight excess instead of **158**, accompanied by an important amount of by-products resulting from the reaction of the alkyl bromide. The latter alkyl bromide was however necessary to recover the masked double bond by treating the bromolactone with zinc or related reagents. In the aim to find a solution to that problem, it was decided to replace the bromolactonization step by a phenylselenolactonization,⁸⁹ where the resulting phenylselenenyl substituent should be stable towards elimination with LDA. Unfortunately, this strategy has not been pursued yet.

4.2.2 The cyclohexenyl ester series

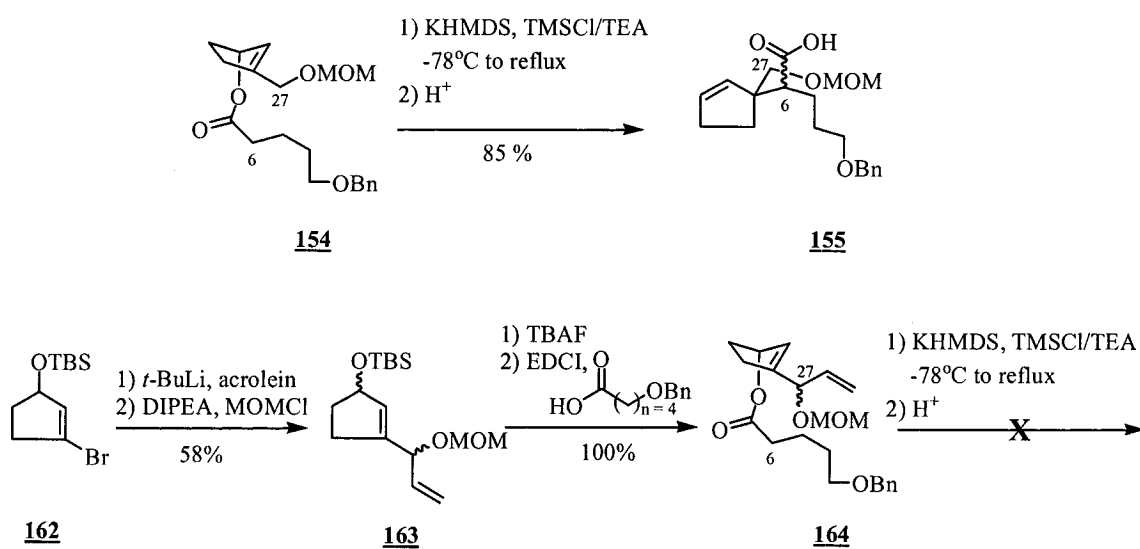
The syntheses of cyclohexenyl esters were found to be much easier than their cyclopentenyl ester counterparts. Also, the stability of the former products and the low cost of the starting materials for their preparation make them suitable substrates for pursuing the present study. Initially, it was explored to place at the beginning of the synthesis an hydroxyl group at C-7 (scheme 38, **4**) since it was required for the installation of the methyldene aldehyde functionality. Thus, compounds **159** and **160** were chosen as substrates for the Ireland-Claisen rearrangement (table 10). β -hydroxy esters are well known in acyclic dianionic Claisen rearrangements⁹⁰ and they are usually used because the stereochemistry of the ester deprotonation is well controlled through a cyclic six-membered ring transition state to afford in high yield Z (O)-enolates. In our case, we wanted to verify if the C-7 hydroxyl or silyloxy group could influence the chair/boat-like transition state in favor of one conformation.



Entry	Substrate	KHMDS	Silyl reagent	Results
1	159	2.6 eq	Me ₂ SiCl ₂	No reaction
2	159	2.3 eq	TMSCl	No reaction
3	160	1.3 eq	TMSCl	No reaction

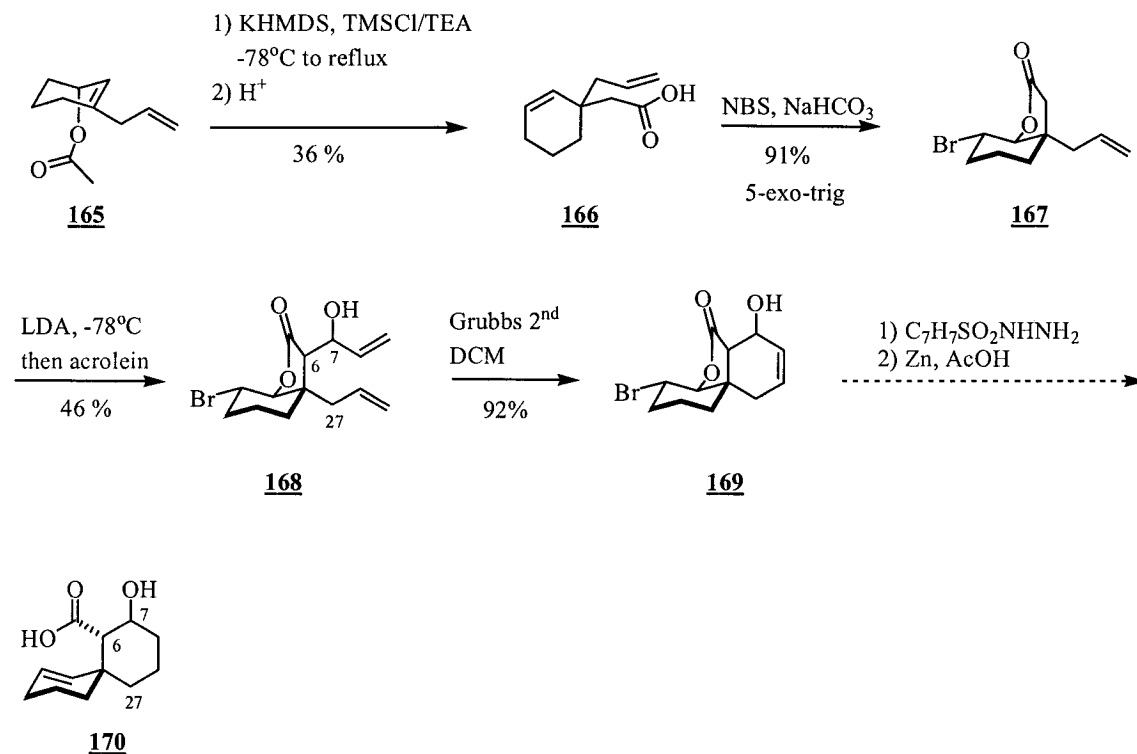
Table 10. Claisen of β -hydroxy esters

Therefore, **159** and **160** were submitted under various deprotonation protocols and conditions and then refluxed to promote the [3 + 3] rearrangement. Unfortunately, production of **161** arising from the Claisen rearrangement was not observed. This lack of reactivity was probably due to added steric congestion during the sigmatropic rearrangement. Later, it was found that the Ireland-Claisen was also sensitive to steric hindrance at C-27 on similar systems (scheme 41). While substrate **154** rearranged in excellent yield, ester **164** did not afford any Ireland-Claisen product after refluxing overnight.



Scheme 41. Consequence of added steric hindrance on the Ireland-Claisen rearrangement

Based on our success to install properly the right configuration at C-6 and C-7 in one aldol process (scheme 39, structure **153**), it was decided to explore that reaction on a six-membered ring template. Cyclohexenyl ester **165** was prepared under standard conditions and submitted to an Ireland-Claisen rearrangement to provide in low yield **166** (scheme 42). Regioselective 5-*exo-trig* bromolactonization afforded in high yield the bromolactone **167** which was stereoselectively alkylated via its ester enolate with acrolein to give **168** as a single diastereomer (probably the anti-aldol product).



Scheme 42. Synthesis of tricyclic lactones via ring-closing metathesis

The only detectable by-product of the reaction resulted from the elimination of the alkyl bromide group as suggested by the observation of new olefinic protons by NMR. β -Hydroxy lactone **168** was successfully cyclized via ring-closing metathesis to give in excellent yield the tricyclic lactone **169**. From this product, it was planned to reduce the remaining double bond and recover the masked alkene after a reverse bromolactonization to afford product such as **170**. By looking the structure of **170**, we can see that only carbon C-27 needs to be functionalized from the present strategy to reach an advanced template for the synthesis of the core of spiroiridal-type triterpenoids in an asymmetric fashion.

4.3 Conclusion

The study presented in the last chapter demonstrated our efforts towards the synthesis of spiroiridal cores. It was shown that the success of the Ireland-Claisen rearrangement is highly structural dependent. Also, we have found that the alkylation of bicyclic lactones such as **152** and **167** could afford in one single step two new stereogenic centers with defined stereochemistry. Such results gave new possibilities and new routes towards the synthesis of iridals. Finally, it was recommended to pursue this survey via the cyclohexenyl ester series since they are more stable than their cyclopentenyl homologues and less expensive to synthesize.

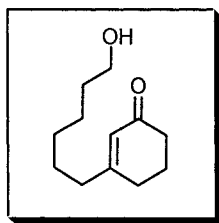
CHAPTER 5

5.1 Experimental

5.1.1 General

All reactions were performed under nitrogen atmosphere with oven-dried glasswares. All anhydrous solvents were distilled prior to use: ether and tetrahydrofuran (THF) over sodium/benzophenone ketyl; toluene, benzene, hexamethylphosphoramide (HMPA) and dichloromethane (DCM) were distilled over calcium hydride. Trimethylsilylchloride (TMSCl), diisopropylamine (DIPA) and triethylamine (TEA) were distilled over calcium hydride prior to use. All other starting materials and reagents were obtained commercially and used as such. Column chromatographies were performed with silica gel 60 (230-400 mesh, Merck). ^1H NMR and ^{13}C NMR were recorded on Bruker AMX instruments at 300 MHz and 75 MHz, respectively, except where noted. Chemical shifts are reported in ppm δ units relative to chloroform (7.26 ppm for ^1H NMR and 77.0 ppm for decoupled ^{13}C NMR) as internal standard. Melting points are uncorrected. IR spectra were recorded with a Bomen Michaelson 100 FTIR instrument. Low-resolution and high-resolution mass spectra were recorded at The University of Ottawa Mass Spectrum Center.

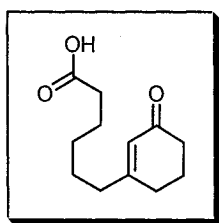
5.1.2 Procedures and characterizations of compounds relative to chapter 2



Compound 88: 3-(6-Hydroxyhexyl)-2-cyclohexen-1-one

To a solution of 6-chlorohexanol (3.437 g, 25.2 mmol) in 35 mL of THF was added slowly, keeping internal temperature below $-30\text{ }^{\circ}\text{C}$ during the addition, a solution of 1.8 M of $i\text{PrMgCl}$ in THF (14.0 mL, 25.2 mmol) under nitrogen. After 30 min of stirring, the solution was allowed to warm up slowly to room temperature. Magnesium (0.990 g, 40.7 mmol) was quickly added and the resulting mixture put under reflux. Two portions of dibromoethane (0.043 mL, 0.5 mmol) were added in one hour interval. After 3 h of refluxing, the reaction mixture was cooled at $30\text{ }^{\circ}\text{C}$. The Grignard

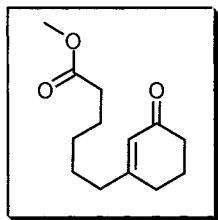
was titrated at 0.45 M with salicylaldehyde phenylhydrazone. To known enone **87**⁹¹ (2.80 g, 18.2 mmol), dissolved in 30.0 mL of THF, was added dropwise at room temperature to the previous prepared Grignard reagent (40.0 mL, 18.0 mmol). The solution was then refluxed for 90 min. The green-black mixture was cooled at room temperature and quenched with 10% HCl. The resulting yellow solution was extracted with ether (3x100 ml). The combined organic was washed with a saturated aqueous solution of sodium bicarbonate and brine. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to obtain 4.49 g of red-orange crude material. The crude product was purified on silica gel eluting with 20% to 40% of EtOAc in hexanes. 2.18 g (61%) of product **88** was obtained as an orange oil. IR (film) 3431 (br), 2929, 2859, 1660, 1622 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 5.87 (s, 1H), 3.64 (t, J = 6.0 Hz, 2H), 2.39-2.17 (m, 6H), 2.04-1.92 (m, 2H), 1.55-1.34 (m, 9H); ¹³C NMR (50 MHz, CDCl₃) δ 200.1(s), 166.9(s), 125.4(d), 62.5(t), 37.8(t), 37.1(t), 32.4(t), 29.5(t), 28.9(t), 26.7(t), 25.4(t), 22.5(t); MS (EI) 196, 123, 110, 95, 82, 67, 55, 41; HRMS (EI) calcd for C₁₂H₂₀O₂: 196.14633, found 196.14580.



Compound **89: 6-(3-Oxo-1-cyclohexenyl)hexanoic acid**

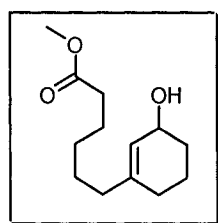
Compound **89** was synthesized following a modified procedure.⁴⁷ A solution of H₅IO₆/CrO₃ in wet acetonitrile was prepared as follow. H₅IO₆ (20.0 g, 87.7 mmol) and CrO₃ (0.040 g, 0.40 mmol) were dissolved in 200.0 mL of wet acetonitrile. To a solution of enone **88** (7.80 g, 39.7 mmol) in 50.0 ml of wet acetonitrile was added over 1 h the previous prepared solution of H₅IO₆/CrO₃ at 0 °C. A white-yellow precipitate was formed. The resulting mixture was aged at 0 °C for 30 min more after the addition was completed. A solution of 5% HCl was added until all precipitates had dissolved and the product was quickly extracted with ether (3x 125 mL). The organic layer was washed with 1:1 brine/water twice, with a solution of 2.0 g of NaHSO₃ diluted in 25 mL of water and then brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to afford 7.953 g (95%) of crude carboxylic acid as a yellow oil. IR (film) 3500-2350 (COOH), 1738, 1713, 1667, 1635, 1422, 1255, 1197 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 5.87 (s, 1H), 2.40-2.18 (m, 8H), 2.04-1.92 (m, 2H), 1.73-1.32 (m, 6H); ¹³C NMR (50 MHz, CDCl₃) δ 200.3(s), 179.3(s), 166.6(s), 125.6(d), 37.7(t), 37.2(t), 33.8(t), 29.6(t), 28.6(t),

26.4(t), 24.3(t), 22.6(t); MS (EI) 210, 123, 110, 95, 82, 67, 53, 41; HRMS (EI) calcd for $C_{12}H_{18}O_3$: 210.12560, found 210.12652.



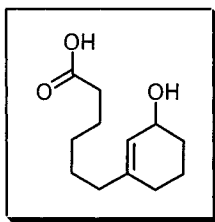
Compound 90: 6-(3-Oxo-1-cyclohexenyl)hexanoic acid methyl ester

The resulting crude product 89 was dissolved in 100.0 mL of ether and esterified with an excess of diazomethane at 0 °C. The organic solvent was carefully removed *in vacuo* and the crude product was purified on silica gel eluting with 5% to 25% EtOAc in hexanes to obtain 7.633 g (86%) of 90 as a yellow oil. IR (film) 2939, 2865, 1737, 1669, 1625, 1436, 1254, 1191 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 1H), 3.62 (s, 3H), 2.34-2.14 (m, 8H), 2.00-1.88 (m, 2H), 1.68-1.21 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.9(s), 173.9(s), 166.2(s), 125.6(d), 51.4(q), 37.7(t), 37.3(t), 33.8(t), 29.5(t), 28.6(t), 26.4(t), 24.6(t), 22.6(t); MS (EI) 224, 193, 165, 123, 110, 95, 82, 67, 41; HRMS (EI) calcd for $C_{13}H_{20}O_3$: 224.14125, found 224.14099.



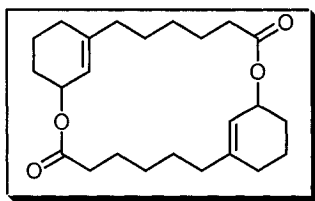
Compound 91: 6-(3-Hydroxy-1-cyclohexenyl)hexanoic acid methyl ester

To a solution of enone 90 (2.015 g, 8.99 mmol) and $CeCl_3$ heptahydrate (3.683 g, 9.88 mmol) in 25.0 mL of MeOH was added at 0 °C $NaBH_4$ (0.428 g, 11.3 mmol) in small portions over 5 min. After stirring 30 min, 20.0 mL of a saturated aqueous solution of ammonium chloride was added. The reaction mixture was stirred during 5 min and water was added until all salts formed had dissolved. The product was extracted with ether (3x 100 mL). The combined organic layers were washed with water (3x 50.0 mL) and brine, dried over $MgSO_4$ and evaporated under reduced pressure to give 2.030 g (100%) of 91 as a yellow oil. IR (film) 3390 (br), 2933, 2860, 1739, 1437, 1361, 1260, 1197, 1172, 1063, 1018 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 5.44 (br s, 1H), 4.13 (br s, 1H), 3.62 (s, 3H), 2.26 (t, $J = 7.0$ Hz, 2H), 1.95-1.87 (m, 4H), 1.75-1.47 (m, 7H), 1.42-1.16 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2(s), 141.9(s), 123.8(d), 65.7(d), 51.4(q), 37.1(t), 33.8(t), 31.8(t), 28.6(t), 28.3(t), 26.9(t), 24.6(t), 19.1(t); MS (EI) 208.



Compound 92: 6-(3-hydroxy-1-cyclohexenyl)hexanoic acid

Ester 91 (0.737 g, 3.26 mmol) was dissolved in a mixture of THF/MeOH/H₂O (6.0 mL/ 2.0 mL/ 2.0 mL) and cooled with an ice bath. LiOH monohydrate (0.226 g, 5.39 mmol) was added and the resulting solution was allowed to warm up slowly at room temperature and stirred 17 h. 10.0 mL of water and 20.0 mL of a 2M buffer of H₃PO₄ adjusted at pH 3.5 with NaOH were added. The pH of the resulting solution was carefully adjusted with 10% HCl at pH 3.5 with a pH meter. The solution was extracted with ether (5x) and the combined organic phases were washed with water (2x) and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to obtain 0.673 g (97%) of 92 as a colorless oil. IR (film) 3709-2350 (COOH), 1712, 1417, 1273 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 6.57 (br s, COOH), 5.48 (s, 1H), 4.20 (br s, 1H), 2.33 (t, J = 7.4 Hz, 2H), 2.00-1.83 (m, 4H), 1.78-1.50 (m, 7H), 1.47-1.24 (m, 4H); ¹³C NMR (50 MHz, CDCl₃) δ 179.2(s), 142.2(s), 123.6(d), 65.9(d), 37.1(t), 33.9(t), 31.7(t), 28.4(t), 28.3(t), 26.8(t), 24.4(t), 19.0(t); MS (EI) 194, 107, 97, 79.

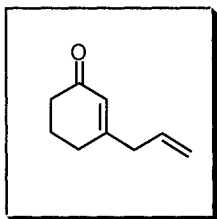


Compound 99: 2,14-Dioxatricyclo[19.1^{1,21}.1^{9,13}]hexacos-9(26), 21(25)-diene-3,15-dione

To a solution of hydroxy acid 92 (0.081 g, 0.384 mmol) in 17.0 mL of THF were added DIPEA (250 μL, 1.44 mmol) and 2,4,6-trichlorobenzoyl chloride (200 μL, 1.28 mmol). The reaction mixture was stirred 24 h under N₂ at room temperature and then added over 17 h with a syringe pump (24 μmol/h) to a solution of DMAP (0.373 g, 3.05 mmol) in 500.0 mL of toluene. The solution was kept stirring 5 h more after the addition was completed. The solution was concentrated to one third volume and 500.0 mL of EtOAc was added. The solution was washed with a saturated aqueous solution of sodium bicarbonate, water, brine and dried over MgSO₄ and filtered. The organic layer was concentrated *in vacuo* and the crude product was purified on silica gel with 2% EtOAc in hexanes to give 0.040 g (54%) of 99 as a colorless oil. ¹H NMR (200 MHz, CDCl₃) δ 5.42-5.34 (m, 2H), 5.33-5.19 (m, 2H), 2.37-2.21 (m, 4H), 2.17-1.17 (m, 28H); ¹³C NMR (50 MHz, CDCl₃) δ 173.7(s), 173.5(s), 143.5(s), 143.3(s), 120.6(d), 120.4(d), 68.9(d), 68.6(d), 36.9(t), 36.6(t), 34.2(t), 34.1(t),

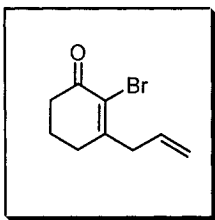
28.3(t), 28.2(t), 27.6(t), 27.5(t), 27.3(t), 27.0(t), 25.7(2C, t), 24.6(t), 24.5(t), 19.5(t), 19.4(t); MS (ci/iso) 389, 294, 224, 211, 195, 177.

5.1.3 Procedures and characterizations of compounds relative to chapter 3



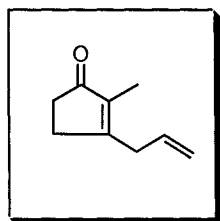
Compound **113a**: 3-Allylcyclohex-2-enone

Isopropoxy-cyclohex-2-enone (10.05 g, 65.2 mmol) was dissolved in THF (100 mL) and the resulting solution chilled to -78 °C. A 2M solution of allylmagnesium chloride (40.0 mL, 80.0 mmol) was added dropwise over 30 min and the reaction mixture was allowed to warm slowly to room temperature. After 1h of stirring at room temperature, ether was added (200 mL) and the solution quenched with 10% HCl (100 mL). The resulting mixture was extracted with ether (3 x 100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (75 mL), water (50 mL), brine (50.0 mL) and dried over MgSO₄ to afford the desired enone **113a**. IR (film) 2942, 1667, 1638 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.90 (t, J = 1.3 Hz, 1H), 5.79 (ddt, J = 16.8, 10.3, 6.8 Hz, 1H), 5.18-5.09 (m, 2H), 2.94 (d, J = 6.8 Hz, 2H), 2.36 (t, J = 6.7 Hz, 2H), 2.29 (t, J = 6.0 Hz, 2H), 2.04-1.93 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 199.8(s), 164.1(s), 133.2(d), 126.3(d), 118.3(t), 42.2(t), 37.3(t), 29.4(t), 22.6(t); MS (EI) 136, 108, 79; HRMS (EI) *m/z* (M⁺) calcd for C₉H₁₂O: 136.08882, found 136.08924.



Compound 113c: 3-Allyl-2-bromocyclohex-2-enone

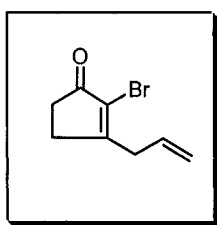
Anhydrous CeCl_3 (Aldrich, 99%+, 1.59 g, 6.45 mmol) was quickly ground to a fine powder in a mortar and placed in a 100 mL flask equipped with a stirring bar. The flask was immersed in an oil bath and heated gradually to 140-145 °C under reduced pressure. The CeCl_3 was then stirred under those conditions for 4 h. The flask was cooled to room temperature under a stream of nitrogen. THF (30 mL) was added slowly with vigorous stirring and ice-bath cooling. The ice-bath was then removed and the white milky suspension was stirred at room temperature 12 h. A solution of 2-bromo-3-ethoxycyclohex-2-enone (1.209 g, 5.55 mmol) in THF (20 mL) was added and the resulting mixture was stirred at room temperature for 3 h. A solution of allylmagnesium chloride (2M, 3.4 mL, 6.8 mmol) in THF was added dropwise at 0 °C over 15 minutes using a syringe pump. After 20 minutes of stirring, the reaction mixture was quenched with 10 mL of a saturated aqueous solution of NH_4Cl . 10 mL of 10% HCl was added to dissolve all salts formed. The resulting solution was extracted with ether (4 x 50 mL). The combined organic extracts were washed with water (3 x 20 mL) and brine, dried with MgSO_4 and filtered. The filtrate was concentrated under reduced pressure to obtain a crude material that was subjected to flash chromatography (15% EtOAc in hexanes) to give the desired product **113c** as a colorless oil (1.136 g, 95%). IR (film) 3080, 2950, 1686, 1598 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.79 (ddt, $J = 17, 10, 6.7$ Hz, 1H) 5.23-5.15 (m, 2H), 3.25 (d, $J = 6.7$ Hz, 2H), 2.62-2.57 (m, 2H), 2.50 (t, $J = 6.0$, 2H), 2.04-1.95 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 191.2(s), 160.9(s), 131.5(d), 123.1(s), 118.3(t), 43.4(t), 37.8(t), 32.1(t), 21.9(t); MS (EI) 214, 186, 162, 135, 107, 91, 79; HRMS (EI) m/z (M^+) calcd for $\text{C}_9\text{H}_{11}\text{BrO}$ 213.99933, found 214.00155.



Compound 113e: 3-Allyl-2-methylcyclopent-2-enone

To a solution of 3-Isopropoxy-2-methyl-cyclopent-2-enone (1.093 g, 7.09 mmol) in THF (40 mL) was added a 2M solution of allylmagnesium chloride (5.0 mL, 10.0 mmol) via a syringe pump over 15 minutes at -78 °C. After stirring for 25 minutes, the reaction mixture was allowed to warm slowly to 0 °C over 15 minutes and then quenched with 10 mL of 10% HCl. The aqueous phase was

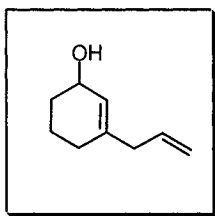
extracted with ether (3x) and the combined organic extracts were washed with water and a saturated aqueous solution of sodium bicarbonate, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Flash chromatography (30 % of EtOAc in hexanes) gave the desired enone **113e** as a colorless oil (0.878 g, 91%). IR (film) 3080, 2921, 1694, 1650, 1442, 1337 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.87-5.73 (m, 1H), 5.15-5.14 (m, 1H), 5.11-5.09 (m, 1H), 3.16 (d, $J = 6.6$ Hz, 2H), 2.51-2.50 (m, 2H), 2.37 (t, $J = 3.9$ Hz, 2H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 210.1(s), 170.6(s), 136.6(s), 132.7(d), 117.5(t), 35.7(t), 34.1(t), 29.3(t), 7.9(q); MS (EI) 136, 121, 93, 79; HRMS (EI) m/z (M^+) calcd for $\text{C}_9\text{H}_{12}\text{O}$ 136.08882, found 136.08723.



Compound 113f: 3-Allyl-2-bromocyclopent-2-enone

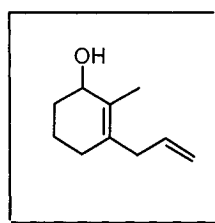
Anhydrous CeCl_3 (Aldrich, 99%+, 1.118 g, 4.54 mmol) was quickly ground to a fine powder then placed in a 100 mL flask equipped with a stirring bar. The flask was immersed in an oil bath and heated gradually to 140-145 $^\circ\text{C}$ under reduced pressure. The CeCl_3 was stirred under those conditions for 4 h. The flask was cooled to room temperature under a stream of nitrogen before 30.0 mL of THF was added slowly with vigorous stirring and ice-bath cooling. The ice-bath was removed and the white milky suspension was stirred at room temperature for 8 h. A solution of 2-bromo-3-ethoxycyclopent-2-enone⁹² (0.869 g, 4.26 mmol) in THF (15 mL) was added and the resulting suspension stirred at room temperature for 11 h. A 2M solution of allylmagnesium chloride (2.5 mL, 5.0 mmol) in THF was then introduced dropwise at 0 $^\circ\text{C}$ and the resulting mixture allowed to warm up slowly to room temperature. After 10 minutes of stirring, the reaction was quenched with 10 mL of a saturated aqueous solution of ammonium chloride and 15 mL of 10% HCl was added to dissolve all salts formed. The resulting solution was extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with water (2 x 20 mL), brine (20.0 mL), dried with MgSO_4 and filtered. The filtrate was concentrated under reduced pressure to obtain a red oil. Flash chromatography (15% EtOAc in hexanes) gave compound **113f** (630 mg, 74%) as a yellowish oil. IR (film) 3081, 3010, 2979, 2925, 1726, 1613 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.78 (ddt, $J = 16.7, 9.2, 6.8$ Hz, 1H), 5.19 (d, $J = 9.2$ Hz, 1H), 5.15 (s, 1H), 3.26 (d, $J = 6.8$ Hz, 2H), 2.63 (t, $J = 5.6$ Hz, 2H), 2.51 (t, $J =$

5.6 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.5(s), 174.1(s), 131.0(d), 123.1(s), 118.9(t), 37.1(t), 33.1(t), 30.2(t); MS (EI) 200, 189, 119, 91, 79.



Compound 104a: 3-Allylcyclohex-2-enol

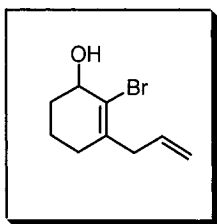
The crude material 113a so obtained (9.67g) was dissolved in MeOH (250 mL) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (24.78 g, 66.5 mmol) was introduced. The solution was cooled to 0 °C and sodium borohydride (1.75 g, 46.3 mmol) was introduced in small portions over 5 min. CAUTION: gas evolution. The solution was stirred for 15 minutes and then quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL). The resulting mixture was concentrated under reduced pressure to one third volume and water was added until all salts had dissolved. The solution was extracted with ether (3 x 150 mL). The combined organic extracts were washed with water (3 x 75.0 mL), brine, dried over MgSO_4 and filtered to give 104a. IR (film) 3342, 3077, 2936, 1667, 1637; ^1H NMR (200 MHz, CDCl_3) δ 5.88-5.68 (m, 1H), 5.54-5.50 (m, 1H), 5.09-5.04 (m, 1H), 5.00-4.99 (m, 1H), 4.19 (br s, 1H), 2.70 (d, $J = 7.0$ Hz, 2H), 1.96-1.51 (m, 7H); ^{13}C NMR (50 MHz, CDCl_3) δ 140.7(s), 135.9(d), 124.7(d), 116.3(t), 65.9(d), 41.9(d), 31.8(d), 28.4(d), 19.1(d); MS (EI) 137, 105, 97, 91, 79; HRMS (EI) m/z ($\text{M}^+ - 1$) Calcd for $\text{C}_9\text{H}_{14}\text{O}$: 137.09664, found 137.09376.



Compound 104b: 3-Allyl-2-methylcyclohex-2-enol

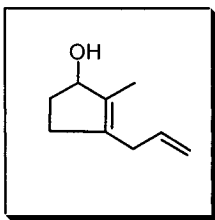
3-Ethoxy-2-methyl-cyclohex-2-enone (3.54 g, 23.0 mmol) was dissolved in THF (100 mL) and the resulting solution cooled to 0 °C. A solution of 2M allylmagnesium chloride (15.0 mL, 30.0 mmol) was added via a syringe pump over 30 minutes and the resulting mixture was then stirred for 2 h. Ether was added (150 mL) and the solution was quenched with 50 mL of 10% HCl. The resulting mixture was extracted with ether (3 x 100 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (50 mL), water (25 mL), brine (25 mL) and dried over MgSO_4 , filtered and concentrated *in vacuo* to give the desired enone as a yellowish oil. The crude product so obtained (3.60 g) was dissolved in MeOH (100.0 mL) to which was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (9.56 g, 25.7 mmol). The solution was cooled to 0 °C and

sodium borohydride (0.609 g, 16.1 mmol) was introduced in small portions over 5 min CAUTION: gas evolution. The solution was stirred for 15 min and then quenched with 20 mL of a saturated aqueous solution of NH_4Cl . The resulting mixture was concentrated under reduced pressure to one third volume. Water (20 mL) was introduced until all the salts had dissolved. The solution was extracted with ether (3x 100 mL). The combined organic extracts were washed with water (3 x 50 mL), brine, dried over MgSO_4 and filtered to give the desired (3.39 g, 97%) material after removal of solvent *in vacuo*. IR (film) 3331 br, 3077, 2929, 1822, 1669, 1637 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.72 (ddt, $J = 16.7, 9.9, 6.2$ Hz, 1H), 5.02-4.94 (m, 2H), 3.95 (br s, 1H), 2.73 (d, $J = 6.2$ Hz, 2H), 2.00-1.86 (m, 2H), 1.74-1.51 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.5(d), 132.7(s), 129.1(s), 115.0(t), 69.6(d), 37.9(t), 32.1(t), 29.7(t), 18.3(t), 16.0(q); MS (ci/iso) 151, 135, 119, 111, 105, 91.



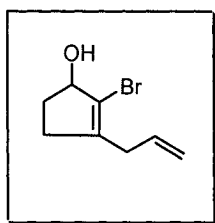
Compound 104c: 3-Allyl-2-bromocyclohex-2-enol

The product 113c (1.112 g, 5.20 mmol) was dissolved in MeOH (15.0 mL) to which was introduced $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2.00 g, 5.37 mmol). The solution was chilled using an ice bath and sodium borohydride (0.138 g, 3.65 mmol) was carefully added CAUTION: gas evolution. The reaction mixture was stirred for 15 minutes and then quenched with 10 mL of a saturated aqueous solution of ammonium chloride. Water was added until all salts had dissolved. The solution was extracted with ether (4 x 50 mL). The combined organic extracts were washed with water (3 x 25 mL), brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude material as colorless oil that was used as such. IR (film) 3377, 3078, 2940, 1650, 1636 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.75 (ddt, $J = 17, 10, 6.7$ Hz, 1H), 5.13-5.04 (m, 2H), 4.28 (br, t, $J = 4.4$, 1H), 2.95 (d, $J = 6.6$ Hz, 2H), 2.23-2.01 (m, 3H), 1.91-1.58 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 138.5(s), 133.5(d), 123.6(s), 116.6(t), 71.1(d), 41.6(t), 31.9(t), 31.2(t), 18.3(t); MS (ci/iso) 217, 199, 175, 137, 119, 109, 93.



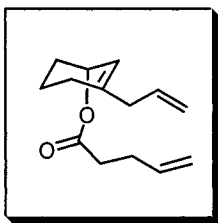
Compound 104e: 3-Allyl-2-methylcyclopent-2-enol

The enone 113e (0.808 g, 5.94 mmol) was dissolved in MeOH (15 mL) containing $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2.60 g, 6.98 mmol). The solution was cooled with an ice bath while sodium borohydride (0.185 g, 4.89 mmol) was introduced. The solution was stirred for 15 minutes then quenched with 20 mL of a saturated aqueous solution of ammonium chloride. Water was added until all salts had dissolved. The solution was extracted with ether (3 x 50 mL). The combined organic extracts were washed with water (3 x 25 mL), brine, dried over MgSO_4 and filtered. The crude material 104e (671 mg) was obtained as a colorless oil after evaporation of methanol *in vacuo*. IR (film) 3333 (br), 3078, 2916, 2850, 1690, 1637, 1434 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.82-5.68 (m, 1H), 5.05-4.97 (m, 2H), 4.61 (br, s, 1H), 2.83 (d, $J = 6.5$, 2H), 2.43-2.17 (m, 3H), 1.69 (s, 3H), 1.66-1.57 (m, 1H), 1.40 (d, $J = 3.8$, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.3(s), 135.4(d), 134.2(s), 115.4(t), 81.5(d), 33.4(t), 32.9(t), 32.6(t), 11.0(q); MS (EI) 138, 123, 105, 97, 91, 79; HRMS (EI) m/z (M^+) calcd for $\text{C}_9\text{H}_{14}\text{O}$ 138.10477, found 138.10671.



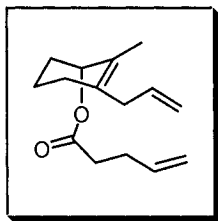
Compound 104f: 3-Allyl-2-bromocyclopent-2-enol

Enone 113f (0.630 g, 3.15 mmol) was dissolved in MeOH (20 mL) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.283 g, 3.44 mmol) added. The solution was cooled with an ice bath and sodium borohydride (0.081 g, 2.14 mmol) added in small portions. The solution was stirred for 15 minutes then quenched with 20 mL of a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with ether (3 x 75 mL). The combined organic phases were washed with water (3x 50 mL), brine, dried over MgSO_4 and filtered. Removal of solvent *in vacuo* afforded 104f as a yellowish oil (553 mg, 87%). IR (film) 3344 (br), 3079, 2975, 2914, 2849, 1653, 1638 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.80-5.67 (m, 1H), 5.12-5.04 (m, 2H), 4.73-4.70 (m, 1H), 2.93 (d, $J = 6.7$ Hz, 2H), 2.49-2.14 (m, 4H), 1.89-1.78 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.8(s), 133.2(d), 120.7(s), 116.8(t), 79.8(d), 34.7(t), 32.1(t), 31.0(t); MS (EI) 200, 187, 162, 143, 131, 121, 105, 91, 78; HRMS (EI) m/z (M^+) calcd for $\text{C}_8\text{H}_{11}\text{BrO}$ 201.9993, found 201.9844.



Compound 103a: (3-Allylcyclohex-2-enyl)-4-pentenoate

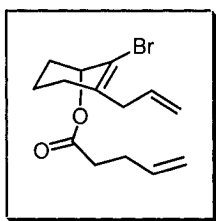
The crude material 104a obtained after concentration *in vacuo* was dissolved in dry benzene (250 mL). Pyridine (50.0 mL, 618 mmol) and DMAP (0.310 g, 2.54 mmol) were added and the resulting mixture stirred until all materials had dissolved. A solution of 4-pentenoyl chloride (9.47 g, 79.9 mmol) diluted in benzene (50 mL) was added dropwise via an addition funnel over 30 minutes. After the addition was complete, the reaction mixture was stirred for 3 h, quenched by the introduction of a saturated bicarbonate solution then extracted with EtOAc (3 x 125 mL). The combined organic extracts were washed with a 5% HCl solution, a saturated aqueous solution of NaHCO₃, water and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Flash chromatography (4% EtOAc in hexanes) afforded the desired product 103a as a colorless oil (11.1 g, 78% for 3 steps). IR (film) 1727, 1668, 1640 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.72 (m, 2H), 5.48-5.46 (m, 1H), 5.32-5.24 (m, 1H), 5.07-4.95 (m, 4H), 2.72 (d, J = 6.9 Hz, 2H), 2.39-2.35 (m, 4H), 1.99-1.92 (m, 2H), 1.80-1.61 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 172.8(s), 142.9(s), 136.7(d), 135.6(d), 120.5(d), 116.5(t), 115.4(t), 68.6(d), 42.0(t), 33.8(t), 29.0(t), 28.3(t), 28.2(t), 19.1(t); MS (ci/iso) 179, 161, 147, 137, 121, 105.



Compound 103b: (3-Allyl-2-methylcyclohex-2-enyl)-4-pentenoate

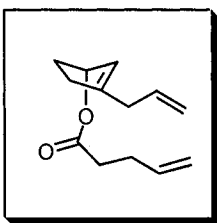
104b (2.06 g, 13.5 mmol) was dissolved in dry benzene (40 mL) containing pyridine (15.0 mL, 185 mmol) and DMAP (0.120 g, 0.982 mmol). A solution of 4-pentenoyl chloride (2.24 g, 18.9 mmol) diluted in benzene (15 mL) was added dropwise via an addition funnel over 30 minutes. After the addition was complete, the reaction mixture was stirred for 1 h, quenched with a saturated aqueous solution of NaHCO₃ solution and extracted with EtOAc (3x 100 mL). The combined organic extracts were washed with a solution of 5% HCl, a saturated solution of NaHCO₃, water and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (5% EtOAc in hexanes) afforded the desired material 103b (2.83 g, 86% for 3 steps) as a colorless oil. IR (film) 3079, 2977, 2937, 2866, 1731, 1638 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.64 (m, 2H), 5.20-5.19 (m, 1H), 5.06-4.95 (m, 4H), 2.75 (d, J = 6.4, 2H), 2.42-2.31 (m, 4H), 2.03-1.88 (m, 2H),

1.79-1.50 (m, 7H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.9(s), 136.6(d), 135.1(s), 135.0(d), 125.5(s), 115.3(t), 115.1(t), 72.0(d), 37.9(t), 33.8(t), 29.5(t), 29.0(t), 28.9(t), 18.6(t), 15.7(q); MS (EI) 234, 193, 134, 119, 91, 77, 55, 41; HRMS (EI) m/z (M^+) calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: 234.16198, found 234.15760.



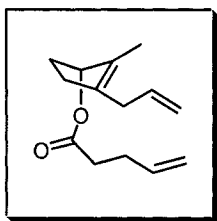
Compound 103c: (3-Allyl-2-bromocyclohex-2-enyl)-4-pentenoate

The crude alcohol 104c (1.057 g, 4.89 mmol) was dissolved in dichloromethane (40 mL). Diisopropylethylamine (2.5 mL, 14.6 mmol), a catalytic amount (15 mg) of DMAP, 4-pentenoic acid (0.979 g, 9.78 mmol) and EDCI (1.50 g, 7.83 mmol) were added in that order. After 14 h of stirring, the resulting mixture was diluted in EtOAc (125 mL) and washed with a saturated aqueous solution of NaHCO_3 (2 x 25 mL) and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. Flash chromatography (10% ether in hexanes) afforded ester 103c (1.312 g, 90 % for 2 steps) as a colorless oil. IR (film) 3079, 2945, 1737, 1638 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.91-5.69 (m, 2H), 5.50 (t, J = 3.8 Hz, 1H), 5.14-4.99 (m, 4H), 2.99 (d, J = 6.7, 2H), 2.50-2.39 (m, 4H), 2.26-2.02 (m, 2H), 1.90-1.84 (m, 2H), 1.72-1.66 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.4(s), 141.4(s), 136.6(d), 133.4(d), 117.6(s), 116.8(t), 115.5(t), 72.7(d), 41.6(t), 33.7(t), 30.9(t), 30.2(t), 28.9(t), 18.1(t); MS (ci/iso) 299, 255, 237, 219, 199, 173, 159, 137, 119.



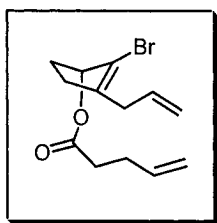
Compound 103d: (3-Allylcyclopent-2-enyl)-4-pentenoate

A solution of 3-Ethoxy-cyclopent-2-enone (0.631 g, 5.00 mmol) in THF (50 mL) was cooled to -78 °C and treated with a 2M solution of allylmagnesium chloride (7.0 mL, 14.0 mmol) over 20 minutes. The resulting mixture was stirred for 45 minutes, treated with 10 mL of a saturated aqueous solution of ammonium chloride and 10 mL of 10% HCl then allowed to warm up to room temperature. The resulting mixture was extracted with ether and the combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate, water and brine. The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo* to obtain a yellowish oil. The crude product so obtained was dissolved in MeOH (15 mL) and CeCl₃·7H₂O (2.00 g, 5.37 mmol) was introduced. The solution was cooled to 0 °C before sodium borohydride (0.130 g, 3.44 mmol) was added in one portion. The solution was stirred for 15 minutes then quenched by the addition of 10 mL of a saturated aqueous solution of ammonium chloride. Water (approx. 10 mL) was added until all salts had dissolved. The solution was extracted with ether (3 x 50 mL) and the combined organic extracts were washed with water, brine, dried over MgSO₄ and filtered. Concentration under reduced pressure gave a yellowish oil which was diluted in 30.0 mL of dichloromethane. A catalytic amount (1 crystal) of 4-dimethylaminopyridine (DMAP), 4-pentenoic acid (1.00 g, 10.0 mmol) and EDCI (1.25 g, 6.52 mmol) were added in that order with stirring. After 20 h, the resulting mixture was diluted with 100 mL of EtOAc then washed with a saturated aqueous solution of sodium bicarbonate (2x 25 mL), water, and brine. The organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. Flash chromatography (5% ether in hexanes) afforded the unstable ester **103d** (778 mg, 75% for 3 steps) as a colorless oil which must be used immediately after its isolation. IR (film) 3079, 2978, 2922, 2851, 1731, 1641 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.89-5.77 (m, 2H), 5.68-5.66 (m, 1H), 5.48 (d, J = 1.6 Hz, 1H), 5.11-4.97 (m, 4H), 2.89-2.86 (m, 2H), 2.45-1.79 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0(s), 150.6(s), 136.7(d), 134.9(d), 123.3(d), 116.4(t), 115.3(t), 80.8(d), 35.7(t), 33.7(t), 33.4(t), 30.4(t), 28.9(t); MS (EI) 107, 91.



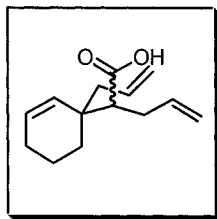
Compound 103e: (3-Allyl-2-methylcyclopent-2-enyl)-4-pentenoate

The product 103e was synthesized following the same procedure as for product 103d from 104e. Flash chromatography (3% ether in hexanes with 5% of triethylamine) afforded 103e as an unstable colorless oil (217 mg, 75% for 3 steps). IR (film) 3079, 2919, 2853, 1732, 1639 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.88-5.67 (m, 2H), 5.64-5.62 (m, 1H), 5.08-5.05 (m, 1H), 5.02-4.98 (m, 3H), 2.85 (d, $J = 6.1$, 2H), 2.45-2.18 (m, 7H), 1.71-1.61 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.2(s), 140.1(s), 136.7(d), 135.0(d), 130.5(s), 115.6(t), 115.4(t), 83.9(d), 33.8(t), 33.3(t), 33.2(t), 29.4(t), 29.0(t), 11.2(q); MS (EI) 220, 120, 105, 91, 77.



Compound 103f: (3-Allyl-2-bromocyclopent-2-enyl)-4-pentenoate

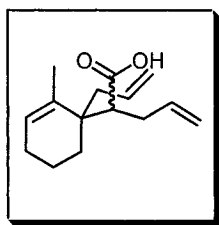
Compound 103f was synthesized following the same procedure as for product 103d from 104f. Flash chromatography (7 % ether in hexanes) afforded compound 103f as a colorless oil (700 mg, 61% for 3 steps). IR (film) 3080, 2979, 2920, 2851, 1737, 1640 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.90-5.68 (m, 3H), 5.14-4.99 (m, 4H), 2.98 (d, $J = 6.7$ Hz, 2H), 2.51-2.24 (m, 7H), 1.88-1.78 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.7(s), 146.1(s), 136.6(d), 133.0(d), 117.1(t), 115.5(t), 115.3(s), 81.8(d), 34.8(d), 33.7(d), 32.4(d), 29.3(d), 28.9(d); MS (EI) 283, 219, 201, 187, 173, 121, 105.



Compound 119a: 2-(1-Allylcyclohex-2-enyl)-4-pentenoic acid

Ester 103a (0.660 g, 3.00 mmol) was dissolved in toluene (7.0 mL) and the resulting solution cooled to $-78\text{ }^{\circ}\text{C}$. To this mixture was added KHMDS (7.0 mL, 0.5M in toluene, 3.5 mmol) dropwise over 5 min. The resulting yellow solution was stirred for 10 minutes before a mixture of TMSCl (0.61 mL, 4.81 mmol) with Et_3N (0.84 mL, 6.03 mmol) in toluene (3.0 mL) was added via a canula. The solution was allowed to warm up slowly with stirring to room temperature and then brought to reflux. After refluxing for 15 h, the reaction mixture was cooled to room temperature and 20.0 mL of 10% HCl added. The mixture was stirred for 10 minutes then

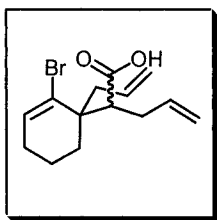
extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure to give a yellowish oil. Flash chromatography on silica gel (7% EtOAc in hexanes with 1% AcOH) afforded Ireland-Claisen product **119a** (0.50 g, 75%) as a colorless oil as a 3 : 2 mixture of diastereomers. IR (film) 3700-2300 (COOH), 1703, 1640 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 10.1 (br s, COOH), 5.89-5.62 (m, 3H), 5.34 (d, $J = 10.2$ Hz, 1H), 5.10-4.98 (m, 4H), 2.57-2.19 (m, 5H), 1.95-1.93 (m, 2H), 1.79-1.53 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ major: 180.82(s), 135.86(d), 134.37(d), 132.16(d), 128.93(d), 117.99(t), 116.56(t), 52.92(d), 43.17(t), 39.81(s), 32.06(t), 29.19(t), 24.62(t), 18.94(t); minor: 180.78(s), 135.77(d), 134.67(d), 131.79(d), 128.36(d), 117.80(t), 116.68(t), 52.83(d), 42.62(t), 39.36(s), 31.14(t), 29.53(t), 24.62(t), 18.72(t); MS (ci/iso) 221, 203, 179, 175, 161, 133, 121.



Compound 119b: 2-(1-Allyl-2-methylcyclohex-2-enyl)-4-pentenoic acid

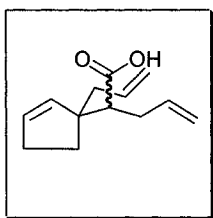
Ester **103b** (0.242 g, 1.03 mmol) was dissolved in 7.0 mL of toluene and cooled at -78°C under a stream of nitrogen. KHMDS (2.30 mL, 0.5M in toluene, 1.15 mmol) was added dropwise over 2 min. The resulting solution was stirred 15 min and a mixture of TMSCl (0.20 mL, 1.58 mmol) with Et_3N (0.275 mL, 2.00 mmol) diluted in 3.0 mL of toluene added via canula. The solution was allowed to warm up slowly at room temperature and then brought to reflux. After stirring 15 h, the reaction mixture was cooled a room temperature and 20.0 mL of 10% HCl added. The mixture was stirred for 10 min and extracted with dichloromethane (4x 50.0 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure to give a yellowish oil. Flash chromatography on silica gel (10% EtOAc in hexanes with 2% AcOH) afforded 123 mg (51%) of Ireland-Claisen product **119b** as a colorless oil and a mixture of 1.6:1 of diastereomers. IR (film) 3700-2200 (br), 3077, 2938, 1704, 1641 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.80-5.60 (m, 3H), 5.13-4.97 (m, 4H), 2.71-2.61 (m, 1H), 2.50-2.02 (m, 5H), 1.91-1.46 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.17(s), 180.53(s), 136.10(d), 135.86(d), 135.67(s), 135.64(d), 135.54(d), 134.52(s), 128.91(d), 127.81(d), 116.77(t), 116.72(t), 116.65(t), 116.36(t), 53.40(d), 52.73(d), 43.76(t), 43.38(t), 42.87(s), 42.82(s), 32.93(t), 30.95(t), 29.58(t), 29.12(t), 25.25(t), 25.13(t), 19.94(2C, t),

19.53(q), 18.83(q); MS (EI) 234, 193, 175, 147, 135, 105, 93, 79; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{22}O_2$ 234.16198, found 234.18284.



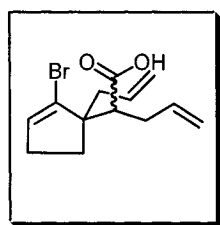
Compound 119c: 2-(1-Allyl-2-bromocyclohex-2-enyl)-4-pentenoic acid

To a solution of ester **103c** (0.155 g, 0.52 mmol) in toluene (7.0 mL) at -78 °C was added KHMDS (1.2 mL, 0.5M in toluene, 0.60 mmol) dropwise over 2 minutes. The resulting yellow solution was stirred for 15 minutes before adding a mixture of TMSCl (0.1 mL, 0.788 mmol) and Et_3N (0.14 mL, 1.0 mmol) in toluene (3.0 mL) via canula. The resulting solution was allowed to warm up to room temperature and then refluxed for 12 h. The reaction mixture was cooled to room temperature and 20 mL of 10% HCl was added. The mixture was stirred for 10 minutes and then extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (10 % EtOAc in hexanes with 2% AcOH) afforded Ireland-Claisen product **119c** as a yellowish oil (62 mg, 40 %) as a 2:1 mixture of diastereomers. IR (film) 3555-2200, 3077, 2938, 1704, 1640 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 6.38 (t, J = 4.4 Hz, 0.7H), 6.29 (t, J = 4.4 Hz, 0.3H), 5.89-5.69 (m, 2H), 5.13-5.01 (m, 4H), 2.93-2.86 (m, 1H), 2.61 (dd, J = 14.3, 5.8 Hz, 0.7H), 2.51 (dd, J = 13.6, 5.8 Hz, 0.3H) 2.45-1.93 (m, 7H), 1.80-1.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.72(s), 179.10(s), 135.52(d), 135.46(d), 135.33(d), 134.54(d), 134.48(d), 130.04(s), 129.77(s), 117.99(t), 117.85(t), 117.19(t), 116.94(t), 53.53(d), 53.27(d), 45.75(s), 45.39(s), 44.26(t), 43.40(t), 33.02(t), 30.91(t), 29.87(t), 29.40(t), 27.56(t), 27.39(t), 19.68(t), 19.27(t); MS (EI) 299, 281, 257, 233, 219, 201, 177, 159, 149, 119, 105.



Compound 119d: 2-(1-Allylcyclopent-2-enyl)-4-pentenoic acid

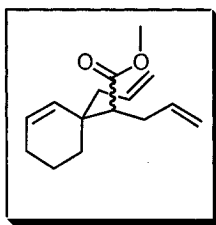
Ester **103d** (0.193 g, 0.936 mmol) was dissolved in 8.0 mL of toluene and cooled at -78 °C under a stream of nitrogen. KHMDS (2.0 mL, 0.5M in toluene, 1.05 mmol) was added dropwise. The resulting solution was stirred 15 min and was added TMSCl (0.19 mL, 1.5 mmol). The solution was allowed to warm up slowly at room temperature and then refluxed 13 h. The reaction mixture was cooled a room temperature and 20.0 mL of 10% HCl added. The mixture was stirred for 10 min and extracted with dichloromethane (4x 50.0 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (2% EtOAc in hexanes with 1% AcOH) afforded 142 mg (74 %) of Ireland-Claisen product **119d** as a mixture of 1.3 : 1 of diastereomers. IR (film) 3600-2300 (COOH), 2952, 1705, 1639; ¹H NMR (300 MHz, CDCl₃) δ 5.83-5.65 (m, 3.5H), 5.44-5.41 (m, 0.5H), 5.09-4.98 (m, 4H), 2.55 (dd, J = 11.5, 3.4 Hz, 1H), 2.40-1.90 (m, 7H), 1.77-1.60 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 181.11(s), 181.03(s), 135.72(d), 135.63(d), 135.30(d), 134.86(d), 134.71(d), 134.69(d), 131.85(d), 131.48(d), 117.73(t), 117.69(t), 116.64(t), 116.56(t), 54.54(s), 54.32(s), 53.33(d), 52.48(d), 43.15(t), 43.04(t), 32.50(t), 32.41(t), 32.15(t), 32.09(t), 31.09(t), 30.15(t); MS (ci/iso) 207, 107.



Compound 119f: 2-(1-Allyl-2-bromocyclopent-2-enyl)-4-pentenoic acid

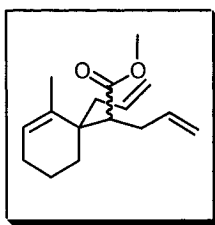
Ester **103f** (0.142 g, 0.50 mmol) was dissolved in toluene (7.0 mL) and the resulting solution was cooled to -78 °C under a stream of nitrogen. KHMDS (1.2 mL, 0.5M in toluene, 0.60 mmol) was then added dropwise. The resulting solution was stirred for 15 minutes before a mixture of TMSCl (0.10 mL, 0.79 mmol) and Et₃N (0.14 mL, 1.0 mmol) diluted in 3.0 mL of toluene was added via canula. The solution was allowed to warm up slowly to room temperature and then refluxed 7 h. The reaction mixture was cooled to room temperature and 20 mL of 10% HCl was added. The mixture was stirred for 10 minutes then extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give 137 mg of crude product. Flash chromatography afforded Ireland-Claisen product **119f** as a colorless oil (58 mg, 41%) and a mixture of 4.6:1 of diastereomers. IR

(film) 3500-2300 (br), 3077, 2926, 2853, 1706, 1641 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.99 (t, $J = 2.5\text{Hz}$, 0.82H), 5.89 (t, $J = 2.5\text{ Hz}$, 0.18H), 5.83-5.60 (m, 2H), 5.14-5.00 (m, 4H), 2.72 (dd, $J = 8.7, 6.2\text{ Hz}$, 0.82H), 2.67-2.61 (m, 0.18H), 2.48-2.00 (m, 7H), 1.85-1.76 (m, 1H); major diastereomer ^{13}C NMR (75 MHz, CDCl_3) δ 179.1(s), 135.0(d), 133.6(d), 133.2(d), 126.7(s), 118.7(t), 117.3(t), 56.5(s), 52.0(d), 41.2(t), 31.6(t), 30.9(t), 26.4(t); MS (ci/iso) 285, 267, 245, 221, 205, 187, 159, 117.



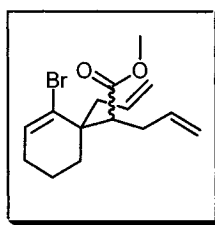
Compound 120a: 2-(1-Allylcyclohex-2-enyl)-4-pentenoic acid methyl ester

Acid 119a (0.107 g, 0.486 mmol) was dissolved in ether, reacted with an excess of diazomethane and stirred for 30 min. The solution was concentrated under reduced pressure to obtain 0.107 g of 120a in quantitative yield as a yellowish oil and a mixture of 3 : 2 of diastereomers: IR (film) 3077, 3016, 2937, 2838, 1740, 1640, 1436, 1360, 1159 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.87-5.59 (m, 3H), 5.32-5.28 (m, 0.7H), 5.07-4.94 (m, 4.3H), 3.64 and 3.60 (2s, 3H), 2.57-2.17 (m, 5H), 1.95-1.89 (m, 2H), 1.78-1.44 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.68(2C, s), 136.19(d), 136.14(d), 134.82(d), 134.58(d), 132.42(d), 132.05(d), 128.68(d), 128.01(d), 117.67(t), 117.60(t), 116.35(t), 116.26(t), 52.99(q), 52.76(q), 51.00(d), 50.92(d), 43.19(t), 42.66(t), 39.91(s), 39.44(s), 32.25(t), 31.28(t), 29.57(t), 29.18(t), 24.65(t), 18.94(t), 18.72(t); MS (ci/iso) 235, 203, 193, 175, 161, 149, 133.



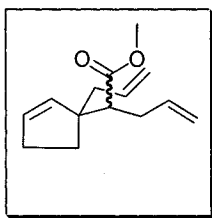
Compound 120b: 2-(1-Allyl-2-methylcyclohex-2-enyl)-4-pentenoic acid methyl ester

Treatment of 119b with an excess of diazomethane in ether gave 120b as mixture of 1.6:1 of diastereomers in quantitative yield. IR (film) 3077, 2947, 1734, 1640, 1436, 1355, 1158 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.72-5.65 (m, 3H), 5.08-4.93 (m, 4H), 3.66 and 3.57 (2s, 3H), 2.70-2.60 (m, 1H), 2.50-1.79 (m, 7H), 1.73-1.47 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.03(s), 174.40(s), 136.40(d), 136.25(d), 136.04(s), 135.71(d), 135.68(d), 134.79(s), 128.66(d), 127.35(d), 116.60(t), 116.51(t), 116.43(t), 116.10(t), 53.50, 52.61, 51.15, 50.90, 43.77(t), 43.35(t), 42.96(s), 42.67(s), 33.16(t), 31.16(t), 29.71(t), 28.97(t), 25.27(t), 25.15(t), 19.96(t), 19.88(t), 19.49(q), 18.81(q); MS (ci/iso) 249, 207, 189, 175, 147, 135, 119, 105.



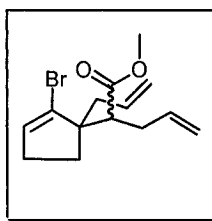
Compound 120c: 2-(1-Allyl-2-bromocyclohex-2-enyl)-4-pentenoic acid methyl ester

Acid 119c was dissolved in ether and treated with an excess of diazomethane. The solution was concentrated under reduced pressure to obtain ester 120c as a yellowish oil in quantitative yield as a 1.9 : 1 mixture of diastereomers. IR (film) 3078, 2948, 1734, 1640 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.35 (t, $J = 4.3$ Hz, 0.7H), 6.25 (t, $J = 4.3$ Hz, 0.3H), 5.88-5.63 (m, 2H), 5.14-4.96 (m, 4H), 3.66 (s, 2.1H), 3.62 (s, 0.9H), 2.90-2.85 (m, 1H), 2.56 (dd, $J = 14.3, 5.6$ Hz, 0.7H), 2.45 (dd, $J = 9.9, 5.6$ Hz, 0.3H), 2.40-2.34 (m, 1H), 2.28-2.10 (m, 2H), 2.02-1.87 (m, 3H), 1.76-1.59 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.31(s), 174.96(s), 135.79(d), 135.67(d), 135.21(d), 134.69(d), 134.56(d), 134.07(d), 130.41(s), 130.15(s), 117.77(t), 117.71(t), 116.81(t), 116.64(t), 53.44(d), 53.35(d), 51.29(q), 51.07(q), 45.85(s), 45.38(s), 44.22(t), 43.47(t), 33.23(t), 31.15(t), 29.97(t), 29.27(t), 27.59(t), 27.41(t), 19.69(t), 19.23(t); MS (ci/iso) 313, 299, 271, 253, 233, 213, 201, 173, 159, 121, 105, 91.



Compound 120d: 2-(1-Allylcyclopent-2-enyl)-4-pentenoic acid methyl ester

Treatment of 119d with an excess of diazomethane in ether gave 120d as mixture of 1.3:1 of diastereomers in quantitative yield. IR (film) 3077, 2950, 1735, 1641, 1437, 1193, 1168 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.78-5.64 (m, 3.5H), 5.40-5.37 (m, 0.5H), 5.05-4.94 (m, 4H), 3.65 (s, 1.7H), 3.61 (s, 1.3H), 2.59-2.52 (m, 1H), 2.40-1.88 (m, 7H), 1.66-1.57 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.98(s), 174.87(s), 136.04(d), 135.99(d), 135.48(d), 135.09(d), 134.88(d), 134.85(d), 131.64(d), 131.18(d), 117.52(t), 117.43(t), 116.30(t), 116.24(t), 54.71(s), 54.46(s), 53.16(d), 52.47(d), 51.07(q), 50.96(q), 43.17(t), 43.09(t), 32.58(t), 32.50(t), 32.20(t), 32.11(t), 30.99(t), 30.06(t); MS (EI) 179, 119, 107, 91, 79.

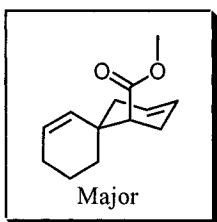


Compound 120f: 2-(1-Allyl-2-bromocyclopent-2-enyl)-4-pentenoic acid methyl ester

Treatment of 119f with an excess of diazomethane gave 120f in quantitative yield as a mixture of 4.6:1 of diastereomers. IR (film) 3077, 2980, 2948, 2852, 1735, 1436, 1194, 1167 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.97 (t, J = 2.5 Hz, 0.2H), 5.86 (t, J = 2.5 Hz, 0.8H), 5.78-5.61 (m, 2H), 5.15-4.97 (m, 4H), 3.67 (s, 0.6H), 3.59 (s, 2.4H), 2.72 (dd, J = 10.5, 4.3 Hz, 0.8H), 2.67 (dd, J = 11.8, 3.1 Hz, 0.2H), 2.52-2.06 (m, 7H) 1.93-1.74 (m, 1H); major diastereomer ^{13}C NMR (75 MHz, CDCl_3) δ 174.0(s), 135.4(d), 133.7(d), 132.9(d), 127.0(s), 118.5(t), 116.9(t), 56.5(s), 52.1, 51.0, 41.3(t), 31.8(t), 30.8(t), 26.5(t); MS (ci/iso) 299, 257, 219, 206, 187, 177, 159, 145, 117, 105.

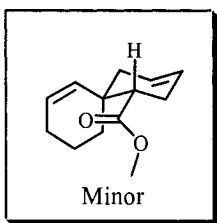
Compound 121a: Spiro[5.5]undeca-3,7-diene-1-carboxylic acid methyl ester

Ester **120a** (93 mg, 0.397 mmol) was dissolved in benzene (40.0 mL). This solution was sparged with nitrogen for 15 min and Grubbs' catalyst (23 mg, 27.9 μ mol) added. After stirring for 3 h at room temperature, the solvent was removed under reduced pressure to obtain a black oil. The crude product was purified on silica gel (3% ether in hexanes) to give **121a** (75 mg, 91%) as a mixture of diastereomers: IR (film) 3025, 2926, 1737 cm^{-1} ; Major



diastereomer: ^1H NMR (300 MHz, CDCl_3) δ 5.74 (dt, $J = 9.9, 3.1$ Hz, 1H), 5.68 (br s, 1H), 5.64 (br s, 2H), 3.65 (s, 3H), 2.54-2.49 (m, 1H), 2.43-2.17 (m, 3H), 1.97-1.90 (m, 3H), 1.71-1.48 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.22(s), 131.26(d), 127.56(d), 125.31(d), 123.62(d), 51.25(q), 48.22(d), 37.82(t), 34.73(s), 34.55(t), 25.90(t), 25.16(t),

18.71(t). MS (EI) 206, 174, 152, 91, 79; HRMS (EI) m/z (M^+) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: 206.13068,

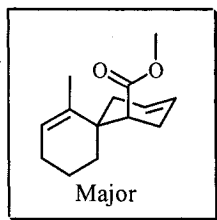


found 206.13153. Minor diastereomer: ^1H NMR (300 MHz, CDCl_3) δ 5.70-5.63 (m, 2H), 5.61-5.56 (m, 1H), 5.46 (ddd, $J = 10.1, 3.1, 2.0$ Hz, 1H), 3.60 (s, 3H), 2.57 (dd, $J = 9.9, 5.4$ Hz, 1H), 2.41-2.30 (m, 1H), 2.19-2.06 (m, 2H), 1.94-1.83 (m, 3H), 1.76-1.48 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.88(s), 134.45(d), 127.03(d), 125.16(d), 124.66(d), 51.02(q),

47.78(d), 36.39(t), 35.54(s), 26.22(d), 25.09(d), 25.02(d), 18.73(d).

Compound 121b: 7-Methylspiro[5.5]undeca-3,7-diene-1-carboxylic acid methyl ester

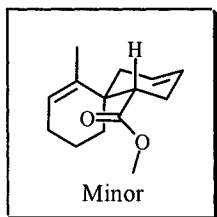
Ester **120b** (181 mg, 0.773 mmol) was dissolved in 30.0 mL of CH_2Cl_2 . The solution was sparged with nitrogen for 15 min and Grubbs' catalyst added (44 mg, 53.5 μ mol). The resulting solution was refluxed 16 h under N_2 and then the solvent was evaporated under reduced pressure to obtain a black oil. The crude product was purified on silica gel with 0%



to 5% of ether in hexanes to give 155 mg (91%) of **121b** as a mixture of diastereomers. The mixture of diastereomers was flashed again with 0% to 2% of ether in hexanes to isolate both diastereomers as pure products. IR (film) 3026, 2923, 1746, 1660, 1435, 1364, 1172 cm^{-1} ; MS (EI) 220, 166, 138, 119, 93; Major diastereomer: ^1H NMR (300 MHz, CDCl_3) δ

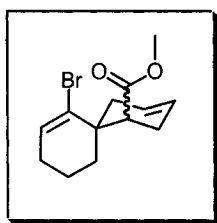
5.79-5.75 (m, 1H), 5.62-5.52 (m, 1H), 5.47 (br s, 1H), 3.64 (s, 3H), 2.72-2.63 (m, 2H), 2.34-

2.27 (m, 1H), 2.17-2.11 (m, 1H), 2.00 (br s, 2H), 1.87-1.80 (m, 1H), 1.75-1.58 (m, 6H), 1.38-1.26 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.35(s), 138.49(s), 126.34(d), 125.30(d),



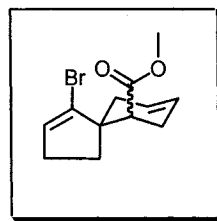
122.47(d), 51.46, 45.21, 37.28(t), 34.65(t), 33.37(t), 26.61(t), 25.40(t), 20.89(q), 17.97(t). Minor diastereomer: ^1H NMR (300 MHz, CDCl_3) δ 5.70-5.65 (m, 1H), 5.62-5.55 (m, 1H), 5.52 (m, 1H), 3.62 (s, 3H), 2.88 (dd, J = 11.8, 5.0, 1H), 2.45-2.31 (m, 1H), 2.27-2.12 (m, 2H), 1.95-1.84 (m, 4H), 1.72-1.67 (m, 4H), 1.63-1.39 (m, 2H); ^{13}C NMR (75 MHz,

CDCl_3) δ 174.90(s), 137.60(s), 125.76(d), 125.74(d), 124.60(d), 51.15, 45.08, 38.69(t), 33.89(t), 25.74(t), 25.63(t), 25.52(t), 18.88(t), 18.79(q). HRMS (EI) m/z (M^+) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$ 220.14633, found 220.14435.



Compound 121c: 7-Bromospiro[5.5]undeca-3,7-diene-1-carboxylic acid methyl ester

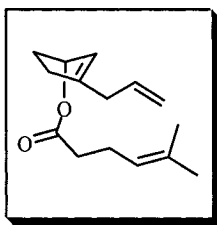
Ester **120c** (45 mg, 0.146 mmol) was dissolved in CH_2Cl_2 (50.0 mL) and the resulting solution was sparged with nitrogen for 15 minutes. After adding Grubbs' catalyst (12 mg, 15 μmol) the solution was stirred for 3 h at room temperature then stripped of solvent to obtain a black oil. The product was purified by flash chromatography (5 % of ether in hexanes) to obtain the major diastereomer of **121c** (33 mg, 82 %). IR (film) 3028, 2944, 1737, 1436, 1204, 1163 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.22 (t, J = 3.7 Hz, 1H), 5.78-5.74 (m, 1H), 5.62-5.58 (m, 1H), 3.68 (s, 3H), 3.04-2.98 (m, 1H), 2.75 (d, J = 6.8 Hz, 1H), 2.29-2.03 (m, 5H), 1.76-1.42 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.0(s), 133.1(d), 130.6(s), 125.4(d), 122.0(d), 51.9, 44.5, 40.4(s), 34.9 ($2\times\text{CH}_2$), 28.2(t), 26.3(t), 17.6(t); MS (EI) 205, 173, 151, 131, 91; HRMS (EI) m/z (M^+) calcd for $\text{C}_{13}\text{H}_{17}\text{BrO}_2$ 284.04119, found 284.04129.



Compound 121f: 1-Bromospiro[4.5]deca-1,8-diene-6-carboxylic acid methyl ester

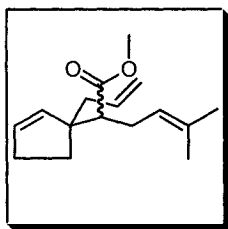
Ester **120f** (30 mg, 0.101 mmol) was dissolved in 10.0 mL of CH_2Cl_2 . Nitrogen was sparged through the solution for 15 minutes and then Grubbs' catalyst was added (4 mg, 12 μmol). The resulting solution was refluxed 5 h under nitrogen and then stripped of solvent to obtain a black oil. The crude

product was purified by flash chromatography (3% ether in hexanes) to recover the major diastereomer of **121f** (26 mg, 95%). IR (film) 3028, 2948, 2926, 2850, 1733, 1162 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.88 (t, $J = 2.5$ Hz, 1H), 5.71-5.62 (m, 2H), 3.63 (s, 3H), 2.84 (dd, $J = 10.8, 6.3$ Hz, 1H), 2.51-2.26 (m, 6H) 1.80-1.66 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.6(s), 131.4(d), 128.8(s), 125.1(d), 124.9(d), 52.2(s), 51.3, 44.1, 36.5(t), 29.7(t), 28.3(t), 26.5(t); MS (ci/iso) 271, 239, 211, 191, 171, 131, 117, 105.



Compound 128: (3-Allylcyclopent-2-enyl)-5-methyl-4-hexenoate

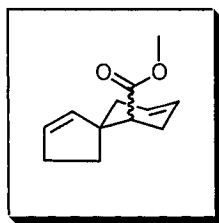
The crude alcohol **104d** (0.530 g, 4.89 mmol) was dissolved in dichloromethane (40 mL). Diisopropylethylamine (1.5 mL, 8.61 mmol), a catalytic amount (15 mg) of DMAP, 5-methyl-hex-4-enoic acid⁹³ (0.747 g, 5.83 mmol) and EDCI (1.27 g, 6.62 mmol) were added in that order. After 14 h of stirring, the resulting mixture was diluted in EtOAc (125 mL) and washed with a saturated aqueous solution of NaHCO_3 (2 x 25 mL) and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. Flash chromatography (3% ether in hexanes with 2% of Et_3N) afforded ester **128** (0.604 g, 59 %) as a colorless oil. IR (film) 3078, 2957, 1730, 1640; ^1H NMR (300 MHz, CDCl_3) δ 5.89-5.70 (m, 1H), 5.63 (br s, 1H), 5.46 (m, 1H), 5.07-5.01 (m, 3H), 2.84 (br s, 2H), 2.46-2.15 (m, 7H), 1.84-1.76 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3(s), 150.4(s), 134.9(d), 132.7(s), 123.3(d), 122.4(d), 116.4(t), 80.6(d), 35.7(t), 34.6(t), 33.4(t), 30.3(t), 25.6(q), 23.6(t), 17.6(q); MS (ci/iso) 107, 91.



Compound 129: 2-(1-Allylcyclopent-2-enyl)-5-methyl-4-hexenoic acid methyl ester

Ester 128 (0.604 g, 2.58 mmol) was dissolved in toluene (7.0 mL) and the resulting solution cooled to -78 °C. To this mixture was added KHMDS (6.0 mL, 0.46M in toluene, 2.8 mmol) dropwise over 2 min.

The resulting yellow solution was stirred for 10 minutes before a mixture of TMSCl (0.46 mL, 3.6 mmol) with Et₃N (0.72 mL, 5.2 mmol) in toluene (5.0 mL) was added via canula. The solution was allowed to warm up slowly with stirring to room temperature and then brought to reflux. After refluxing for 15 h, the reaction mixture was cooled to room temperature and 20.0 mL of 10% HCl added. The mixture was stirred for 10 minutes then extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give a yellowish oil. Flash chromatography on silica gel (7% EtOAc in hexanes with 1% AcOH) afforded Ireland-Claisen product (0.442 g, 73%) as a colorless oil. Treatment of the pure acid in ether with diazomethane gave ester 129 as a colorless oil. IR (film) 3077, 2955, 1733, 1194, 1172; Mixture of diastereomers ¹H NMR (300 MHz, CDCl₃) δ 5.76-5.67 (m, 2H), 5.64-5.61 (m, 0.53H), 5.39-5.36 (m, 0.47H), 5.03-4.93 (m, 3H), 3.61 (s, 1.6H), 3.57 (s, 1.4H), 2.47-2.40 (m, 1H), 2.32-1.92 (m, 7H), 1.67-1.54 (m, 7H); mixture of diastereomers ¹³C NMR (75 MHz, CDCl₃) δ 175.30(s), 175.17(s), 135.60(d), 135.22(2C, d), 134.90(d), 133.18(2C, s), 131.31(d), 130.90(d), 121.54(d), 121.50(d), 117.35(t), 117.27(t), 54.64(s), 54.41(s), 53.63(d), 52.97(d), 50.97(q), 50.85(q), 43.13(t), 43.02(t), 32.43(t), 32.05(t), 30.93(t), 30.11(t), 26.52(t), 26.70(t), 25.70(2C, q), 17.58(2C, q); MS (EI) 248, 207, 139, 107; HRMS (EI) *m/z* (M⁺) calcd for C₁₆H₂₄O₂ 248.17763, found 248.18039.

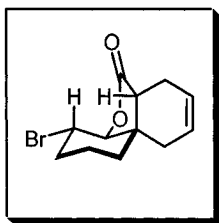


Compound 125: Spiro[4.5]deca-1,8-diene-6-carboxylic acid methyl ester

Ester 129 (96 mg, 0.387 mmol) was dissolved in 30.0 mL of CH₂Cl₂. Nitrogen was sparged through the solution for 15 minutes and then 2nd generation Grubbs' catalyst was added (31 mg, 36 μmol). The resulting

solution was stirred 30 min under nitrogen and then stripped of solvent to obtain a black oil. The crude product was purified by flash chromatography (3% ether in hexanes) to give 125

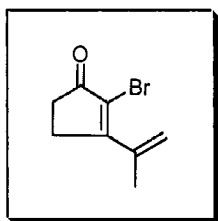
as a mixture of diastereomers (42 mg, 56%). IR (film) 3024, 2927, 1734; ^1H NMR (300 MHz, CDCl_3) δ 5.75 (s, 1H), 5.73-5.54 (m, 3H), 3.64 (s, 1.7H), 3.60 (s, 1.3H), 2.70 (dd, J = 10.3, 5.4 Hz, 0.42H), 2.59 (dd, J = 7.3, 6.2 Hz, 0.58H), 2.60-1.86 (m, 7H), 1.70-1.54 (m, 1H); mixture of diastereomers ^{13}C NMR (75 MHz, CDCl_3) δ 175.08(s), 174.96(s), 137.54(d), 135.49(d), 130.68(d), 129.96(d), 126.02(d), 125.65(d), 125.28(d), 124.47(d), 51.42(d), 51.06(d), 50.18(s), 49.50(s), 47.39(q), 46.38(q), 37.62(t), 37.09(t), 35.94(t), 31.05(t), 31.00(t), 29.56(t), 26.59(t), 26.08(t); MS (EI) 192, 160, 138, 106, 79; HRMS (EI) m/z (M^+) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$ 192.11503, found 192.11371.



Compound 136: (1*R, 2*S**, 6*S**, 7*R**)-2-Bromo-1,6-[6,7-(2*H*)-furan-12-one] spiro[5.5]-9-undecene**

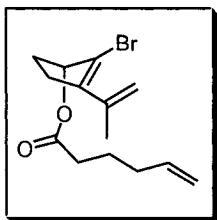
Ester 138 was dissolved in 8.0 mL of ethanol and 2.0 mL of a 10 M solution of NaOH added. The resulting mixture was refluxed 2 h and then cooled at room temperature. The solution was acidified with 10 % HCl until $\text{pH} \leq 2$ and extracted with dichloromethane. The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude was purified by flash chromatography with 10 % ether with 1 % AcOH in hexanes to obtain 34 mg (72 %) of pure carboxylic acid as a colorless oil. IR (film) 3560-2160 (br), 3027, 2926, 1698, 1422, 1218 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 11.40 (br s, COOH), 5.78-5.61 (m, 4H), 2.53 (t, J = 6.5 Hz, 1H), 2.38-2.21 (m, 3H), 1.96-1.91 (m, 3H), 1.65-1.48 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.43(s), 131.26(d), 127.86(d), 125.42(d), 123.31(d), 48.17(d), 37.40(t), 34.51(s), 34.24(t), 25.68(t), 25.13(t), 18.72(t); MS (EI) 192, 162, 138, 105; HRMS (EI) m/z (M^+) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$ 192.11503, found 192.11486. The resulting acid (82.0 mg, 0.427 mmol) was dissolved in a mixture of 5.0 mL of THF with 1.0 mL of water. Solid sodium bicarbonate (72.3 mg, 0.857 mmol) was added followed by NBS (85.1 mg, 0.478 mmol) at 0 $^\circ\text{C}$. The resulting mixture was stirred 1 hour and then poured into 50.0 mL of ether. The organic layer was washed with water twice, brine and dried (MgSO_4) to give 110 mg of crude material. The crude was purified on silica gel with 10% EtOAc in hexanes to give 99 mg (93%, 2 steps from the ester 138) of pure bromolactone 136. IR (film) 2961, 1772, 1651; ^1H NMR (300 MHz, CDCl_3) δ 5.65-5.57 (m, 2H), 4.20 (d, J = 8.8 Hz, 1H), 4.00-3.92 (m, CHBr, 2.71-2.68

(m, 1H), 2.59-2.53 (m, 1H), 2.34-2.20 (m, 3H), 2.07-2.02 (m, 1H), 1.95-1.88 (m, 1H), 1.84-1.67 (m, 2H), 1.54-1.35 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.2(s), 123.6(d), 123.4(d), 88.3(d), 50.2(d), 41.5(s), 37.9(t), 34.6(t), 34.4(t), 31.6(t), 21.5(t), 20.5(t); MS (EI) 270, 191, 169, 145, 91; HRMS (EI) m/z (M^+) calcd for $\text{C}_{12}\text{H}_{15}\text{BrO}_2$: 270.02554, found 270.02735.



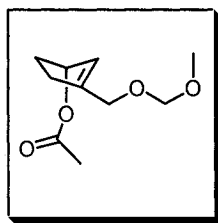
Compound 139: 2-Bromo-3-isopropenylcyclopent-2-enone

Anhydrous CeCl_3 (Aldrich, 99%+, 1.56 g, 6.33 mmol) was quickly ground to a fine powder then placed in a 100 mL flask equipped with a stirring bar. The flask was immersed in an oil bath and heated gradually to 140-145 °C under reduced pressure. The CeCl_3 was stirred under these conditions for 4 h. The flask was cooled to room temperature under a stream of nitrogen before 40.0 mL of THF was added slowly with vigorous stirring and ice-bath cooling. The ice-bath was removed and the white milky suspension was stirred at room temperature for 12 h. A solution of 2-bromo-3-ethoxycyclopent-2-enone (1.00 g, 4.90 mmol) in THF (15 mL) was added and the resulting suspension stirred at room temperature 4 h. A 0.5M solution of isopropenylmagnesium bromide (12.0 mL, 6.00 mmol) in THF was then introduced dropwise at 0 °C over 10 minutes and the resulting mixture allowed to warm up slowly to room temperature. After 10 minutes of stirring, the reaction mixture was quenched with 10 mL of a saturated aqueous solution of ammonium chloride and 10 mL of 10% HCl was added to dissolve all salts formed. The resulting solution was extracted with ether (2 x 50 mL). The combined organic phases were washed with water (2 x 20 mL), a saturated aqueous solution of sodium bicarbonate, brine, dried with MgSO_4 and filtered. The filtrate was concentrated under reduced pressure to obtain a red oil. Flash chromatography (15% EtOAc in hexanes) gave compound 139 (671 mg, 68%) as a yellowish oil. IR (film) 3010, 2977, 1723; ^1H NMR (300 MHz, CDCl_3) δ 5.67 (br s, 1H), 5.45 (br s, 1H), 2.81 (t, $J = 4.3\text{Hz}$, 2H), 2.56 (t, $J = 4.3\text{ Hz}$, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.0(s), 168.6(s), 139.4(s), 121.7(t), 121.5(s), 32.1(t), 29.9(t), 21.6(q); MS (EI) 200, 187, 159, 123, 91; HRMS (EI) m/z (M^+) calcd for $\text{C}_8\text{H}_9\text{BrO}$: 199.98368, found 199.98377.



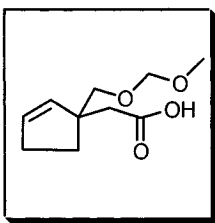
Compound 141: (2-Bromo-3-isoprenylcyclopent-2-enyl)-5-hexenoate
 Enone 139 (0.500 g, 2.50 mmol) was dissolved in MeOH (10 mL) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.00 g, 2.68 mmol) added. The solution was cooled with an ice bath and sodium borohydride (0.100 g, 2.64 mmol) added in small portions. The solution was stirred for 15 minutes then quenched with 20 mL of a saturated aqueous solution of ammonium chloride. Water was added until all salts had dissolved and the resulting mixture was extracted with EtOAc (3 x 75 mL). The combined organic phases were washed with water (3x 50 mL), brine, dried over MgSO_4 and filtered. Removal of solvent *in vacuo* afforded 140 as a yellowish oil (489 mg, 97%). ^1H NMR (300 MHz, CDCl_3) δ 5.19 (br s, 1H), 5.15 (br s, 1H), 4.72 (t, $J = 6.2$ Hz, 1H), 2.68-2.58 (m, 1H), 2.48-2.26 (m, 3H), 2.05 (s, 3H), 1.87-1.77 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.2(s), 139.3(s), 120.0(s), 117.5(t), 81.0(d), 32.8(t), 30.3(t), 21.9(q). The crude alcohol 140 (0.479 g, 2.37 mmol) was dissolved in dichloromethane (20 mL). DIPEA (0.83 mL, 4.76 mmol), a catalytic amount (15 mg) of DMAP, 5-hexenoic acid (0.375 g, 3.29 mmol) and EDCI (0.727 g, 3.79 mmol) were added in that order. After 36 h of stirring, the resulting mixture was diluted in EtOAc (125 mL) and washed with a saturated aqueous solution of NaHCO_3 (2 x 25 mL), water and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. Flash chromatography (2% ether in hexanes) afforded ester 141 (0.647 g, 92 %) as a colorless oil. IR (film) 3076, 2943, 1734, 1641; ^1H NMR (300 MHz, CDCl_3) δ 5.84-5.71 (m, 2H), 5.22 (br s, 1H), 5.17 (br s, 1H), 5.05-4.96 (m, 2H), 2.70-2.58 (m, 1H), 2.51-2.32 (m, 4H), 2.14-2.06 (m, 5H), 1.87-1.70 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.1(s), 145.1(s), 139.0(s), 137.6(d), 118.0(t), 115.4(t), 114.5(s), 82.7(d), 33.7(t), 33.1(t), 33.0(t), 28.7(t), 24.1(t), 21.9(q); MS (EI) 219, 186, 123, 105; HRMS (EI) m/z (M^+) calcd for $\text{C}_{14}\text{H}_{19}\text{BrO}_2$: 298.05684, found 298.05421.

5.1.4 Procedures and characterizations of compounds relative to chapter 4



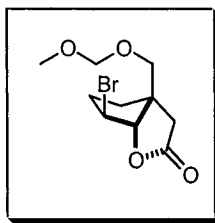
Compound 150: 3-Methoxymethoxymethylcyclopent-2-enyl acetate

To a solution of $\text{Bu}_3\text{SnCH}_2\text{OMOM}$ ⁸⁷ (1.82 g, 4.98 mmol) in THF at -78°C was added dropwise $n\text{-BuLi}$ (2.35 M in hexanes, 2.1 mL, 4.94 mmol) under a stream of nitrogen. After stirring 10 minutes, a solution of enone **112d** (0.617 g, 4.89 mmol) in 5.0 mL of THF was added and the resulting mixture was stirred 30 min. The reaction was deemed complete by TLC (EtOAc:hexanes 1:1) and quenched with 1.0 mL of glacial acetic acid. The cooling bath was removed and the mixture allowed to warm up slowly at room temperature. The solution was diluted in 75.0 mL of ether, washed with 10.0 mL of 5 % HCl, a saturated aqueous solution of NaHCO_3 and then brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was flashed on silica gel with 30 % to 50 % of EtOAc in hexanes to give 487 mg (63 %) of a colorless oil which was reduced following Luche protocol in quantitative yield. The crude so obtained after reduction was diluted in 10.0 mL of dry dichloromethane. Triethylamine (0.620 mL, 4.45 mmol) and a catalytic amount of DMAP (25 mg) were charged followed by acetic anhydride (0.310 mL, 3.29 mmol). The resulting solution was stirred 16 h and then quenched with 1.0 mL of MeOH and stirred 30 min more. 30.0 mL of dichloromethane was added and the organic phase was washed with 15.0 mL of a saturated aqueous solution of NaHCO_3 and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo* to obtain 418 mg (70 %) of **150** as a colorless oil. IR (film) 2941, 1717 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.74 (s, 1H), 5.66 (br s, 1H), 4.63 (s, 2H), 4.13 (s, 2H), 3.36 (s, 3H), 2.52-2.22 (m, 3H), 2.00 (s, 3H), 1.91-1.83 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.9(s), 148.3(s), 124.7(d), 95.9(t), 80.2(d), 65.6(t), 55.3(q), 31.2(t), 30.2(t), 21.2(q); MS (EI) 138, 119, 96, 79.



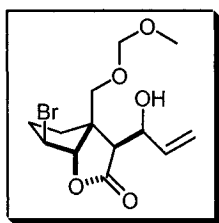
Compound 151: 1-(Methoxymethoxymethylcyclopent-2-ene) acetic acid

Ester 150 (0.212 g, 1.06 mmol) was dissolved in 7.0 mL of toluene and cooled at -78 °C under a stream of nitrogen. KHMDS (2.4 mL, 0.49 M in toluene, 1.18 mmol) was added in one portion. The resulting solution was stirred 10 min and was added TMSCl (0.175 mL, 1.38 mmol). The solution was allowed to warm up slowly at room temperature over an hour and then refluxed 90 min. The reaction mixture was cooled a room temperature and 2 mL of glacial acetic acid added. The mixture was stirred for 10 min and then concentrated under reduced pressure. The crude was purified on silica gel with 5 % to 15 % EtOAc in hexanes with 2 % of AcOH to afford 79 mg (37%) of Ireland-Claisen product 151 as a colorless oil with 85 mg of starting material 150. IR (film) 3683-2299 (br), 2937, 1706, 1044 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.83 (dt, J = 5.6, 2.5 Hz, 1H), 5.69 (dt, J = 5.6, 1.9 Hz, 1H), 4.63 (s, 2H), 3.49 (s, 2H), 3.36 (s, 3H), 2.56 (s, 2H), 2.41-2.36 (m, 2H), 1.89-1.84 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.0(s), 134.5(d), 132.3(d), 96.6(t), 73.2(t), 55.2(q), 51.7(s), 40.8(t), 32.4(t), 31.4(t); MS (ci/iso) 201, 183, 169, 151, 139, 125, 107.



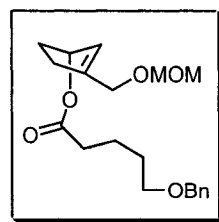
Compound 152: (1*R, 2*S**, 5*R**)-2-Bromo-5-(methoxymethoxymethyl)-8-oxabicyclo[3.3.0]octan-7-one**

Acid 151 (91 mg, 0.455 mmol) was dissolved in a mixture of 5.0 mL of THF with 1.0 mL of a saturated aqueous solution of sodium bicarbonate. NBS (135 mg, 0.758 mmol) was added and the resulting mixture was stirred 1 hour at room temperature. The reaction mixture was diluted in EtOAc and washed with water and brine, dried over MgSO_4 and filtered. The residue (185 mg) isolated after concentration *in vacuo* was purified on silica gel with 20% EtOAc in hexanes to give 115 mg (91%) of pure bromolactone 152. IR (film) 2932, 1778; ^1H NMR (300 MHz, CDCl_3) δ 4.95 (s, 1H), 4.67 (s, 2H), 4.39 (d, J = 5.0Hz, 1H), 3.67 and 3.66 (2s, 2H), 3.39 (s, 3H), 3.01 (d, J = 18.6 Hz, 1H), 2.41 (d, J = 18.6Hz, 1H), 2.33-2.24 (m, 1H), 2.19-2.08 (m, 2H), 1.84-1.76 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.5(s), 96.4(t), 91.6(d), 72.2(t), 55.5(q), 52.1(d), 49.8(s), 38.4(t), 35.1(t), 33.0(t), MS (ci/iso) 279.



Compound 153: (1*R, 2*S**, 5*R**, 6*R**)-2-Bromo-6-[(1*S**)-1-hydroxy-1-allyl]-5-(methoxymethoxymethyl)-8-oxabicyclo[3.3.0]octan-7-one**

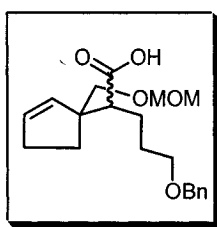
To a solution of DIPA (75 μ L, 0.53 mmol) in 4.0 mL of THF was added at 0 $^{\circ}$ C n-BuLi (2.35 M in hexanes, 190 μ L, 0.45 mmol) under a stream of nitrogen and stirred 5 min. The resulting mixture was then cooled at -78 $^{\circ}$ C and a solution of ester 152 (112 mg, 0.403 mmol) in 10 mL of THF was added via a canula dropwise. The solution was kept stirring for 10 min and freshly distilled acrolein (30 μ L, 0.45 mmol) added neat with a syringe. After stirring 15 min, the reaction mixture was quenched with 0.5 mL of AcOH, then allowed to warm up slowly at room temperature and diluted in 50 mL of ether. The organic phase was washed with 10 mL of 5 % HCl, a saturated aqueous solution of NaHCO₃, brine and dried over MgSO₄. The organic was concentrated *in vacuo* to give 116 mg of crude which was purified on silica gel with 25 % to 40 % ethyl acetate in hexanes to afford 70 mg (52%) of 153 as a single diastereomer. IR (film) 3447 (w), 2948, 2887, 1771, 1152, 1109, 1040 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃) δ 6.16 (ddd, *J* = 16.7, 10.5, 5.0 Hz, 1H), 5.41 (dt, *J* = 16.7, 1.2 Hz, 1H), 5.27 (dt, *J* = 10.5, 1.9 Hz, 1H), 4.85 (d, *J* = 2.5 Hz, 1H), 4.71-4.65 (m, 3H), 4.31-4.27 (m, 1H), 4.01 (d, *J* = 9.9 Hz, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 3.40 (s, 3H), 3.20 (d, *J* = 6.8 Hz, OH), 2.68 (d, *J* = 6.2 Hz, 1H), 2.42-2.29 (m, 1H), 2.19-2.09 (m, 2H), 1.93-1.84 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 175.1(s), 138.2(d), 116.0(t), 96.7(t), 91.4(d), 70.3 (d), 70.3 (t), 56.1(d), 54.4(q), 52.4(s), 51.0(d), 36.0(t), 34.0(t); MS (ci/iso) 335, 319, 305, 287, 274.



Compound 154: 3-[(methoxymethoxymethyl)cyclopent-2-enyl]-5-benzyloxypentanoate

To 3-methoxymethoxymethyl-cyclopent-2-enol (2.35 mmol, theoretical yield) was dissolved in 20 mL of dichloromethane (see synthesis of 150). DIPEA (0.85 mL, 4.8 mmol), a catalytic amount (1 crystal) of DMAP, 5-benzyloxy-pentanoic acid (0.624 g, 3.00 mmol) and EDCI (0.500 g, 2.61 mmol) were added in that order. After 24 h of stirring at room temperature, the resulting mixture was diluted in 100 mL of EtOAc and washed with a saturated aqueous solution of NaHCO₃ (2 x 25 mL), water and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in*

vacuo. Flash chromatography (10% to 20% of EtOAc in hexanes) afforded ester **154** (510 mg, 62 %) as a colorless oil. IR (film) 3071, 3005, 2928, 1732; ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.28 (m, 5H), 5.74 (br s, 1H), 5.69 (br s, 1H), 4.64 (s, 2H), 4.48 (s, 2H), 4.11 (s, 2H), 3.45 (t, J = 6.2 Hz, rotamer, 2H), 3.35 (s, 3H), 2.52-2.26 (m, 5H), 1.90-1.82 (m, 1H), 1.76-1.62 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.4(s), 148.2(s), 138.5(s), 128.3(d), 127.5(d), 127.4(d), 124.8(d), 95.9(t), 80.1(d), 72.8(t), 69.8(t), 65.6(t), 55.3(q), 34.2(t), 31.2(t), 30.3(t), 29.1(t), 21.7(t); MS (ci/iso) 287 (-OMOM).

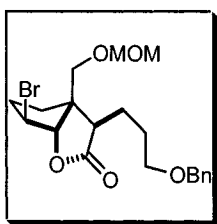


Compound 155: 2-[1-(methoxymethoxymethyl)cyclopent-2-enyl]-5-benzyloxypentanoic acid

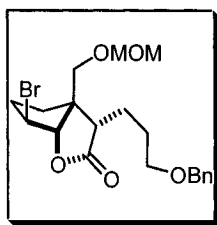
Ester **154** (0.463 g, 1.33 mmol) was dissolved in toluene (7.0 mL) and the resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$ under a stream of nitrogen. KHMDS (3.2 mL, 0.5M in toluene, 1.6 mmol) was then added rapidly. The resulting solution was stirred for 15 minutes before a mixture of TMSCl (0.27 mL, 2.1 mmol) and Et_3N (0.37 mL, 2.7 mmol) diluted in 3.0 mL of toluene was added via a canula. The solution was allowed to warm slowly to room temperature and then refluxed 15 h. The reaction mixture was cooled at $0\text{ }^{\circ}\text{C}$ and 20 mL of 10% HCl was added. The mixture was stirred for 5 minutes then extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure to give 600 mg of crude product. Flash chromatography with 10 % to 20 % EtOAc in hexanes with 1 % of acetic acid afforded Ireland-Claisen product **155** (392 mg, 85%) as a mixture of 3:2 of diastereomers. IR (film) 3350-2350, 1702; ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.27 (m, 5H), 5.84-5.79 (m, 1H), 5.71-5.69 (m, 0.5H), 5.54-5.52 (m, 0.5H), 4.60 (d, J = 3.1 Hz, 2H), 4.49 (s, 2H), 3.51-3.38 (m, 4H), 3.34 and 3.33 (2s, 3H), 2.70-2.68 (m, 1H), 2.40-2.32 (m, 2H), 2.11-1.90 (m, 1H), 1.79-1.58 (m, 5H); MS (ci/iso) 349, 317, 299, 287, 269, 255, 241, 209, 197, 179, 165, 149, 131, 119, 107.

Compound 156: (1*R, 2*S**, 5*R**, 6*R* and 6*S*)-6-(3-benzyloxypropyl)-2-bromo-5-(methoxymethoxymethyl)-8-oxabicyclo[3.3.0]octan-7-one**

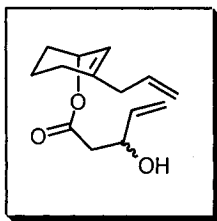
Acid 155 (335 mg, 0.964 mmol) was dissolved in a mixture of 10.0 mL of THF with 1.0 mL of a saturated aqueous solution of sodium bicarbonate. NBS (186 mg, 1.04 mmol) was added and the resulting mixture was stirred 1 hour at room temperature. The reaction mixture was diluted in 75 mL of EtOAc and washed with a saturated aqueous solution of sodium bicarbonate (2x), water, brine and dried over MgSO₄ and filtered. The residue obtained after concentration *in vacuo* was purified on silica gel with 20% EtOAc in hexanes to give 371 mg (90%) of pure bromolactone 156 as a mixture of diastereomers.



IR (film) 3005, 2975, 2935, 1772. ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.24 (m, 5H), 4.78 (d, J = 3.1 Hz, 1H), 4.57 (s, 2H), 4.46 (s, 2H), 4.22-4.18 (m, 1H), 3.71 (d, J = 9.3 Hz, rotamer, 1H), 3.56-3.43 (m, 3H), 3.32 (s, 3H), 2.39 (t, J = 6.8 Hz, 1H), 2.33-2.22 (m, 1H), 2.12-1.65 (m, 7H); ¹³C NMR (75 MHz, CDCl₃) δ 177.5(s), 138.3(s), 128.3(d), 127.6(d), 127.5(d), 96.7(t), 91.8(d), 73.0(t), 70.4(t), 69.9(t), 55.8(q), 51.9(s), 51.2(CHBr), 46.7(d), 34.4(t), 33.8(t), 27.8(t), 22.7(t); MS (ci/iso) 427, 397, 367, 319, 305, 275, 259, 241.

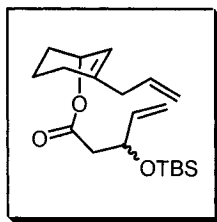


IR (film) 3002, 2965, 2935, 1776. ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.28 (m, 5H), 4.91 (s, 1H), 4.66 (d, J = 6.8 Hz, rotamer, 1H), 4.62 (d, J = 6.8 Hz, rotamer, 1H), 4.50 (s, 2H), 4.38-4.37 (m, 1H), 3.75 (d, J = 9.9 Hz, rotamer, 1H), 3.56 (d, J = 9.9 Hz, rotamer, 1H), 3.53-3.46 (m, 2H), 3.37 (s, 3H), 3.00 (t, J = 6.8 Hz, 1H), 2.34-2.09 (m, 2H), 1.99-1.89 (m, 2H), 1.86-1.51 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 177.6(s), 138.3(s), 128.3(d), 127.6(2xCH), 96.4(t), 88.8(d), 72.9(t), 71.3(t), 69.8(t), 55.5(q), 53.8(s), 51.6(CHBr), 42.3(d), 33.5(t), 27.8(t), 27.7(t), 23.7(t); MS (ci/iso) 427, 397, 367, 319, 305, 275, 263, 241.



Compound 159: 3-Hydroxy-4-pentenoic acid 3-allylcyclohex-2-enyl ester

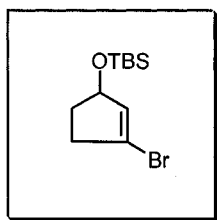
Silyl ether **160** was dissolved in 10.0 mL of THF and TBAF (2.0 mL, 1 M in THF, 2.0 mmol) added at 0°C. The reaction mixture was kept stirring 1 h at 0°C and then diluted in 50.0 mL of ether, washed with water (2x) and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to afford 209 mg of crude alcohol. Flash chromatography with 10 % to 30 % EtOAc in hexanes with 1 % TEA gave 192 mg (92 %) of pure **159** as a colorless oil. Mixture of diastereomers : IR (film) 3450 (br), 3079, 2938, 1727, 1668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.94-5.70 (m, 2H), 5.48 (br s, 1H), 5.35-5.28 (m, 2H), 5.16 (dt, J = 10.5, 1.9 Hz, 1H), 5.09-5.03 (m, 2H), 4.58-4.49 (m, 1H), 3.05 (dd, J = 8.1, 4.3 Hz, 1H), 2.73 (d, J = 6.8 Hz, 2H), 2.63-2.46 (m, 2H), 2.06-1.90 (m, 2H), 1.81-1.59 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 171.99(s), 143.53(s), 143.44(s), 138.72(d), 135.41(d), 120.07(d), 120.02(d), 116.62(t), 115.30(t), 69.29(d), 68.92(d), 68.88(d), 41.95(t), 41.33(t), 41.30(t), 28.23(t), 28.07(t), 18.98(t), 18.95(t); MS (ci/iso) 238, 195, 168, 154, 145, 121, 112.



Compound 160: 3-(*tert*-Butyldimethylsilyloxy)-4-pentenoic acid 3-allylcyclohex-2-enyl ester

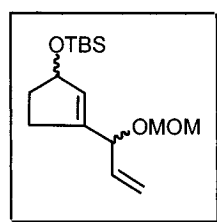
Allylic alcohol **104a** (0.197 g, 1.43 mmol) was dissolved in 12.0 mL of dichloromethane. Diisopropylamine (0.42 mL, 2.41 mmol), a catalytic amount (10 mg) of 4-dimethylaminopyridine (DMAP), 3-(*tert*-Butyldimethylsilyloxy)-4-pentenoic acid ⁹⁴ (0.276 g, 1.20 mmol) and EDCI (0.368 g, 1.92 mmol) were added in that order. After 26 h of stirring under nitrogen, the resulting mixture was diluted in 100.0 mL of ether and washed with a saturated aqueous solution of sodium bicarbonate (2x 20.0 mL), water/brine 1:1, and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Flash chromatography on silica gel with 5 % of ether in hexanes afforded 311 mg (74 %) of **160** as a colorless oil. IR (film) 3079, 2951, 2857, 1731, 1638 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.89-5.71 (m, 2H), 5.48 (br s, 1H), 5.27-5.19 (m, 2H), 5.07-5.02 (m, 3H), 4.61-4.55 (m, 1H), 2.72 (d, J = 6.8 Hz, 2H), 2.57-2.38 (m, 2H), 2.05-1.86 (m, 2H), 1.81-1.58 (m, 4H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.80(s), 142.88(s), 142.82(s), 140.35(d), 140.33(d), 135.57(d),

120.63(d), 120.57(d), 116.51(t), 114.55(t), 70.92(d), 70.88(d), 68.86(d), 68.83(d), 43.94(t), 43.92(t), 42.0(t), 28.28(t), 28.26(t), 28.18(t), 28.15(t), 25.75 (3xCH₃), 19.11(t), 18.09(s), 18.07(s), -4.4(q), -5.1(q); MS (ci/iso) 231, 213, 196, 173, 137, 121.



Compound 162: 3-Bromo-1-(*tert*-butyldimethylsilyloxy)-2-cyclopentene

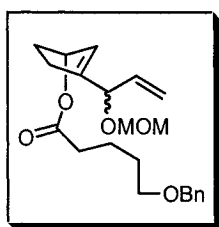
3-Bromo-cyclopent-2-enol ^{95, 96} (0.327 g, 2.02 mmol) was dissolved in 7 ml of DMF with imidazole (0.275 g, 4.04 mmol) and DMAP (1 crystal). TBSCl (0.375 g, 2.49 mmol) was then added and the resulting mixture stirred overnight. The solution was first poured into 75 mL of water and extracted with hexanes (3x 75 mL). The combined organic layers was washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 2% of ether in hexanes to obtain 342 mg (62%) of a colorless oil. IR (film) 3071, 2932, 1621; ¹H NMR (300 MHz, CDCl₃) δ 5.85 (dd, J = 4.3, 1.9 Hz, 1H), 4.83-4.80 (m, 1H), 2.81-2.69 (m, 1H), 2.55-2.45 (m, 1H), 2.38-2.27 (m, 1H), 1.86-1.75 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 134.1(d), 125.8(s), 76.8(d), 38.3(t), 34.5(t), 25.9(5xCH₃), 18.2(s). HRMS (EI) *m/z* (M⁺) calcd for C₁₁H₂₁BrOSi: 276.05450, found 276.05641.



Compound 163: 1-(*tert*-Butyldimethylsilyloxy)[3-(1-methoxymethoxyallyl)-2-cyclopentene

Compound 162 (185 mg, 0.673 mmol) was dissolved in THF and cooled at -78 °C. A 1.4 M solution of *t*-BuLi in pentane (1.0 mL, 1.4 mmol) was added dropwise and the resulting solution stirred 30 min under nitrogen atmosphere. Acrolein (50 μL, 0.749 mmol) was added and the reaction stirred 10 min before to be quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the combined organic phases were washed with water, brine and dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give 135 mg of crude material. The residue was dissolved in 5 mL of DCM and DIPEA (0.230 mL, 1.32 mmol) was added followed by chloromethyl methyl ether⁹⁷ (75 μL,

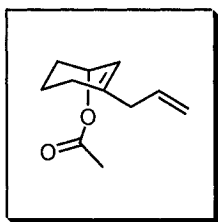
0.987 mmol). After stirring 20 h at room temperature, the reaction mixture was diluted in 30 mL of dichloromethane then washed with a saturated aqueous solution of sodium bicarbonate, water and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo* to obtain a residue which was purified by flash chromatography (2.5% to 5 % ether in hexanes) to give 117 mg (58%, 2 steps) of product **163**. IR (film) 3072, 2928, 1641; ^1H NMR (300 MHz, CDCl_3) δ 5.83-5.70 (m, 1H), 5.67-5.61 (m, 1H), 5.30-5.19 (m, 2H), 4.91 (m, 1H), 4.68-4.65 (m, 1H), 4.62-4.59 (m, 2H), 3.36 (s, 3H), 2.46-2.38 (m, 1H), 2.31-2.09 (m, 2H), 1.75-1.64 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.60(s), 145.45(s), 136.23(d), 136.16(d), 130.21(d), 129.99(d), 117.45(t), 117.31 (t), 93.51(t), 93.42(t), 77.92(d), 77.84(d), 75.50(d), 55.40 (q), 34.03(t), 33.96(t), 30.16(t), 29.96(t), 25.96(3x CH_3), -4.59(2x CH_3); MS (ci/iso) 297, 253, 237, 211, 179, 167, 149, 135, 119, 105.



Compound 164: 3-[1-(methoxymethoxyallyl)cyclopent-2-enyl]-5-benzyloxypentanoate

To a solution of compound **163** (120 mg, 0.402 mmol) in 5 ml of THF was added TBAF (1 M in THF, 0.5 mL, 0.500 mmol). The solution was stirred 2 h under nitrogen atmosphere and then poured into 25 mL of water. The product was extracted three times with ethyl acetate and the combined organics were washed with water, brine, dried over MgSO_4 and filtered to give 97 mg of a yellowish oil after concentration *in vacuo*. The crude alcohol so obtain (0.402 mmol, theoretical yield) was dissolved in 7 mL of dichloromethane. DIPEA (0.14 mL, 0.80 mmol), a catalytic amount (1 crystal) of DMAP, 5-benzyloxy-pentanoic acid (0.167 g, 0.802 mmol) and EDCI (0.125 g, 0.652 mmol) were added in that order. After 18 h of stirring at room temperature, the resulting mixture was diluted in EtOAc (75 mL) and washed with a saturated aqueous solution of NaHCO_3 (25 mL), water and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. Flash chromatography (5% ether in hexanes buffered with 5% of triethylamine) afforded ester **164** (150 mg, 100 %) as a colorless oil. IR (film) 3069, 2975, 1728; ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.26 (m, 5H), 5.82-5.73 (m, 2H), 5.71-5.67 (m, 1H), 5.32-5.23 (m, 2H), 4.70-4.67 (m, 2H), 4.60 (dd, J = 6.8, 2.5 Hz, 1H), 4.49 (s, 2H), 3.47 (t, J = 6.2 Hz, 2H), 3.37 (s, 3H), 2.55 (m, 5H), 1.87-1.80 (m, 1H), 1.76-1.60 (m, 4H);

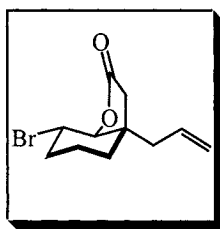
^{13}C NMR (75 MHz, CDCl_3) δ 173.45(s), 150.09(s), 150.07(s), 138.47(s), 135.84(d), 135.76(d), 128.32(d), 127.56(d), 127.48(d), 125.20(d), 125.17(d), 117.96(t), 117.81(t), 93.50(t), 80.01(d), 79.99(d), 75.25(d), 75.20(d), 72.83(t), 69.78(t), 55.44(q), 34.18(t), 30.27(t), 30.16(t), 30.09(t), 29.10(t), 21.72(t) ; MS (ci/iso) 313 (-OMOM).



Compound 165: (3-allylcyclohex-2-enyl) acetate

3-Isopropoxy-cyclohex-2-enone (3.717 g, 24.1 mmol) was dissolved in 50.0 mL of THF and cooled at $-78\text{ }^{\circ}\text{C}$ with an acetone dry-ice bath. A solution of 2M allylmagnesium chloride (15.0 mL, 30.0 mmol) was added dropwise over 30 min and the reaction mixture allowed to warm up slowly at room temperature. After 30 min of stirring at room temperature, 100.0 mL of ether was added and the solution quenched with 25 mL of 10% HCl. The resulting mixture was extracted with ether (3x 50.0 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate, water, brine and dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude so obtained as a yellowish oil was dissolved in 60.0 mL of MeOH and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (8.94 g, 24.1 mmol) added. The solution was cooled with an ice bath and sodium borohydride (0.636 g, 16.8 mmol) added by small portions over 5 min to control gas evolution. The solution was kept stirring for 15 min, concentrated under reduced pressure to one third volume then quenched with 20.0 mL of a saturated aqueous solution of ammonium chloride. Water was added until all salts formed had dissolved and the product was extracted with ether (3x 100 mL). The combined organic extracts were washed with water (3x 25 mL), brine, dried over MgSO_4 and filtered to give 3.75 g of a yellowish oil after concentration *in vacuo*. 1.835 g (approx. 12.0 mmol) of crude was dissolved in 20.0 mL of dry dichloromethane. Triethylamine (2.5 mL, 18.0 mmol) and DMAP (0.150 g, 1.22 mmol) were added and the resulting mixture stirred to dissolve all materials. Acetic anhydride (1.40 mL, 14.8 mmol) was added and the solution was stirred 7 h under a stream of nitrogen. The reaction was quenched with 1 mL of methanol and stirred 10 min. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified on silica gel with 5 % to 10 % EtOAc in hexanes to afford 1.704 g (80% for 3 steps) of 165 as a colorless

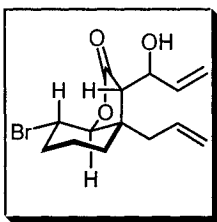
oil. IR (film) cm^{-1} 3077, 2938, 1725; ^1H NMR (300 MHz, CDCl_3) δ 5.84-5.71 (m, 1H), 5.49-5.48 (m, 1H), 5.27-5.26 (m, 1H), 5.08-5.06 (m, 1H), 5.03-5.02 (m, 1H), 2.73 (d, $J = 6.8$ Hz, 2H), 2.04 (s, 3H), 1.98-1.59 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.8(s), 142.9(s), 135.5(d), 120.5(d), 116.5(t), 68.7(d), 42.0(t), 28.2(t), 28.1(t), 21.4(q), 19.1(t); MS (EI) 180, 162, 139, 120, 105, 97, 91, 79; HRMS (EI) m/z (M^+) calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$: 180.11503, found 180.11499.



Compound 167: (1*R, 2*S**, 6*S**)-6-Allyl-2-bromo-9-oxabicyclo[4.3.0]nonan-8-one**

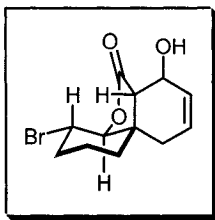
Ester 165 (0.490 g, 2.72 mmol) was dissolved in toluene (7.0 mL) and the resulting solution was cooled to -78 $^{\circ}\text{C}$ under a stream of nitrogen. KHMDS (6.4 mL, 0.5M in toluene, 3.1 mmol) was then added rapidly.

The resulting solution was stirred for 15 minutes before TMSCl (0.45 mL, 3.5 mmol) was added via a canula. The solution was allowed to warm up slowly to room temperature and then refluxed 18 h. The reaction mixture was cooled at 0 $^{\circ}\text{C}$ and 20 mL of 10% HCl was added. The mixture was stirred for 5 minutes then extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography with 5 % EtOAc in hexanes with 3 % of acetic acid afforded Ireland-Claisen product 166 (175 mg, 36%). Acid 166 (108 mg, 0.605 mmol) was dissolved in a mixture of 5.0 mL of THF with 1.0 mL of a saturated aqueous solution of sodium bicarbonate. NBS (115 mg, 0.646 mmol) was added and the resulting mixture was stirred 1 hour at room temperature. The reaction mixture was diluted in EtOAc and washed with 10 mL of water and brine, dried over MgSO_4 and filtered. The residue obtained after concentration *in vacuo* was purified on silica gel with 25% EtOAc in hexanes to give 173 mg (75%) of pure bromolactone 167. IR (film) 2957, 1777, 1642; ^1H NMR (300 MHz, CDCl_3) δ 5.83-5.69 (m, 1H), 5.22-5.13 (m, 2H), 4.40 (d, $J = 5.6$ Hz, 1H), 4.22-4.17 (m, 1H), 2.48-2.29 (m, 4H), 2.22-2.12 (m, 1H), 1.96-1.76 (m, 2H), 1.69-1.42 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.8(s), 132.2(d), 120.2(t), 85.7(d), 48.9(d), 43.0(s), 42.2(t), 39.4(t), 31.6(t), 30.4(t), 18.7(t); MS (ci/iso) 259, 219, 179, 119, 109.



Compound 168: (1*R, 2*S**, 6*S**, 7*R**)-6-allyl-2-bromo-7-[(1*S**)-1-hydroxy-1-allyl]-9-oxabicyclo[4.3.0]nonan-8-one**

To a solution of DIPA (0.12 mL, 0.86 mmol) in 5 mL of THF was added at 0 °C a 2.25 M solution of *n*-BuLi in hexanes (0.32 mL, 0.72 mmol) dropwise. After stirring 5 minutes under nitrogen atmosphere, the resulting mixture was cooled at -78 °C and the bromolactone **167** (173 mg, 0.67 mmol) diluted in 4 mL of THF was added via a canula. The solution was kept stirring 15 minutes before the addition of freshly distilled acrolein neat (50 µL, 0.75 mmol). The reaction mixture was stirred 30 minutes and then quenched with 0.5 mL of acetic acid and diluted in 50 mL of ether. The organic phase was washed with 10 mL of 10% HCl, a saturated aqueous solution of sodium bicarbonate and then brine. The ethereal layer was dried over MgSO₄ and concentrated *in vacuo* to obtain 206 mg of crude material. The residue was purified by flash column chromatography with 25% EtOAc in hexanes to obtain 2 products. The more polar compound isolated (97 mg, 46%) corresponded to the desire product **168**. IR (film) 3442, 2947, 1777, 1643; ¹H NMR (300 MHz, CDCl₃) δ 6.29-6.18 (m, 1H), 5.88-5.74 (m, 1H), 5.40 (d, *J* = 17.4 Hz, 1H), 5.28-5.13 (m, 3H), 4.58-4.56 (m, 1H), 4.35 (d, *J* = 8.6 Hz, 1H), 3.95-3.87 (m, 1H), 2.77 (d, *J* = 7.4 Hz, 1H), 2.41 (d, *J* = 7.4 Hz, 2H), 2.25-2.14 (m, 3H), 1.79-1.42 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 175.1(s), 138.6(d), 132.4(d), 120.6(t), 116.2(t), 84.7(d), 69.6(d), 51.2(d), 50.1(d), 48.1(s), 38.4(t), 34.2(t), 29.6(t), 21.0(t); MS (ci/iso) 315, 299, 269, 253, 235, 217, 199, 173, 137, 119.



Compound 169: (1*R, 2*S**, 6*S**, 7*R**, 8*S**)-2-Bromo-1,6-[6,7-(2*H*)-furan-12-one] spiro[5.5]-9-undecen-8-ol**

The bromolactone 168 (71 mg, 0.226 mmol) was dissolved in 20.0 mL of degassed DCM and the second generation Grubbs' catalyst added (13 mg, 0.015 mmol). After stirring overnight at room temperature, the solution was concentrated under reduced pressure. The residue so obtained was purified by flash chromatography with 5% to 40% EtOAc in hexanes to give 59 mg (91%) of ring-closing metathesis product 169 as a colorless oil. IR (film) 3445, 2939, 1775, 1641; ¹H NMR (300 MHz, C₆D₆) δ 5.79-5.73 (m, =CH), 5.22-5.15 (m, =CH), 4.36 (d, J = 10.5 Hz, OH), 4.10-4.04 (m, H-COH), 3.76 (d, J = 8.7 Hz, -CH-), 3.19-3.10 (m, H-CBr), 2.40 (d, J = 6.2 Hz, -CH-), 1.81 (dq, J = 19, 3.1 Hz, 1H), 1.66-1.59 (m, 1H), 1.22-1.11 (m, 3H), 0.88-0.76 (m, 1H), 0.60-0.41 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 176.9(s), 129.1(d), 126.0(d), 88.5(d), 63.5(d), 49.3(d), 44.3(d), 44.1(s), 35.3(t), 33.9(t), 32.8(t), 20.8(t); MS (ci/iso) 287, 271, 225, 217.

CLAIMS TO ORIGINAL RESEARCH

1. Developed a new approach to the synthesis of spirocyclic compounds via an Ireland-Claisen/ring-closing metathesis strategy.
2. Studied the production of medium-sized ring macrolactones as templates for the synthesis of spirocyclic compounds via an Ireland-Claisen ring contraction.
3. Surveyed the ring-closing metathesis of *E* silyl ketene acetals for the construction of medium-sized rings.
4. Studied towards the synthesis of spiroiridal-type triterpenoids like Iridotectoral B and 28-deacetylbelamcandal via an Ireland-Claisen rearrangement.

PUBLICATION

“A sequential Claisen/ring-closing metathesis approach to the synthesis of spirocyclic cyclopentanes and cyclohexanes” Beaulieu, P.; Ogilvie, W. W. *Tetrahedron Lett.* **2003**, 44, 8883.

ORAL PRESENTATIONS

“Approach to the synthesis of spiroiridal-type triterpenoids via an Ireland-Claisen rearrangement” P. Beaulieu and W. W. Ogilvie (i) March 24, 2004, Merck-Frosst Canada, Montréal Québec, Canada (ii) March 30, 2004, Boehringer Ingelheim, Montréal Québec, Canada.

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APPENDIX

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

GEMINI-200 "gemin1200"

PULSE SEQUENCE

Pulse 45.0 degrees

Acq. time 3.002 sec

Width 3800.0 Hz

16 repetitions

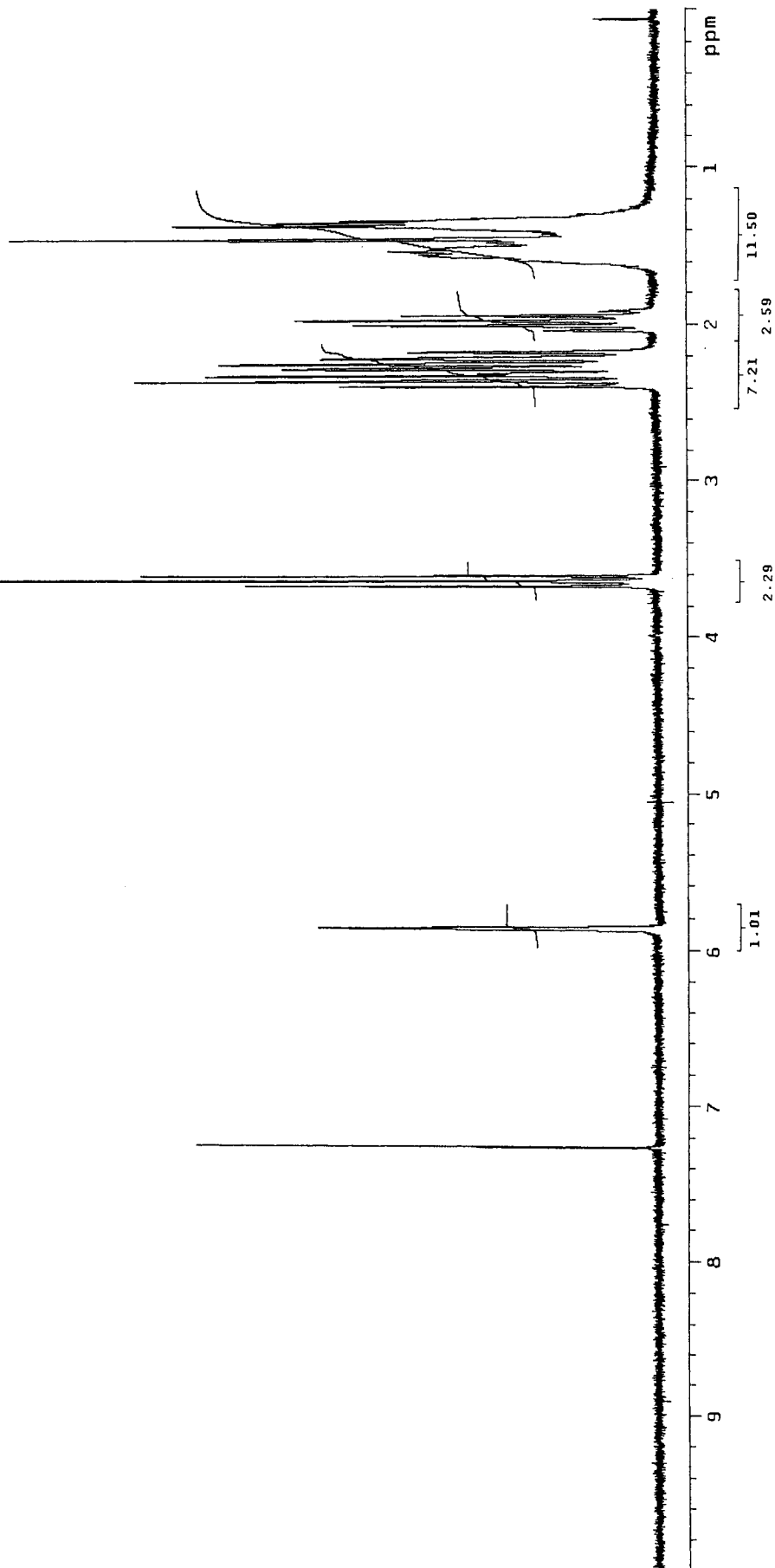
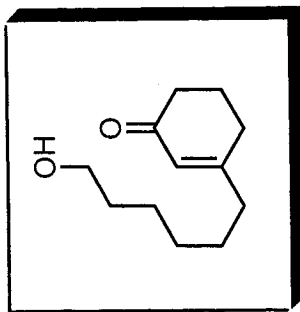
OBSERVE H1, 199.9659296 MHz

DATA PROCESSING

Resol. enhancement -0.0 Hz

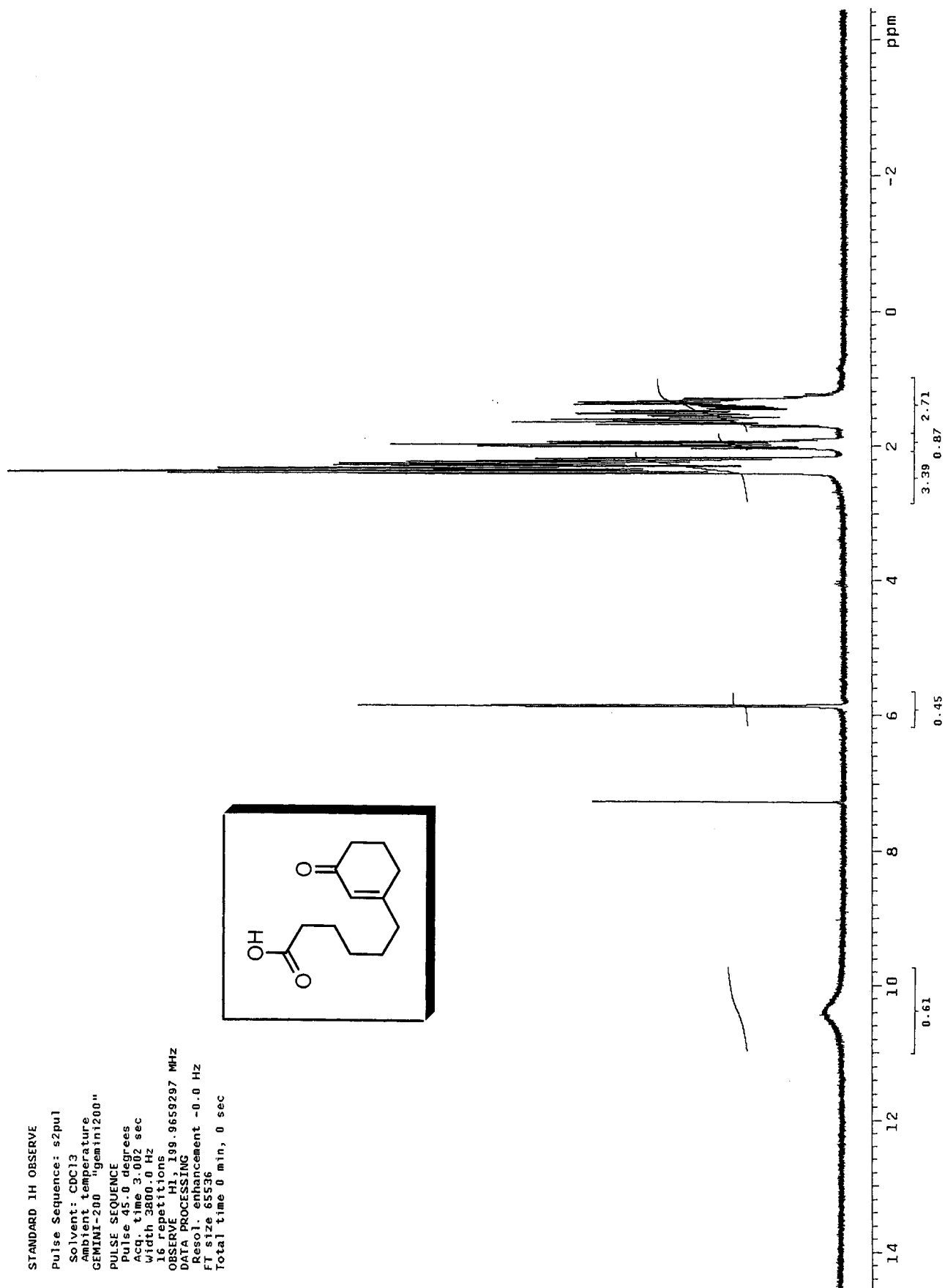
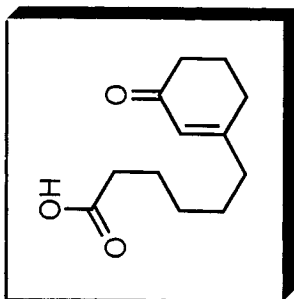
FT size 65536

Total time 0 min, 50 sec



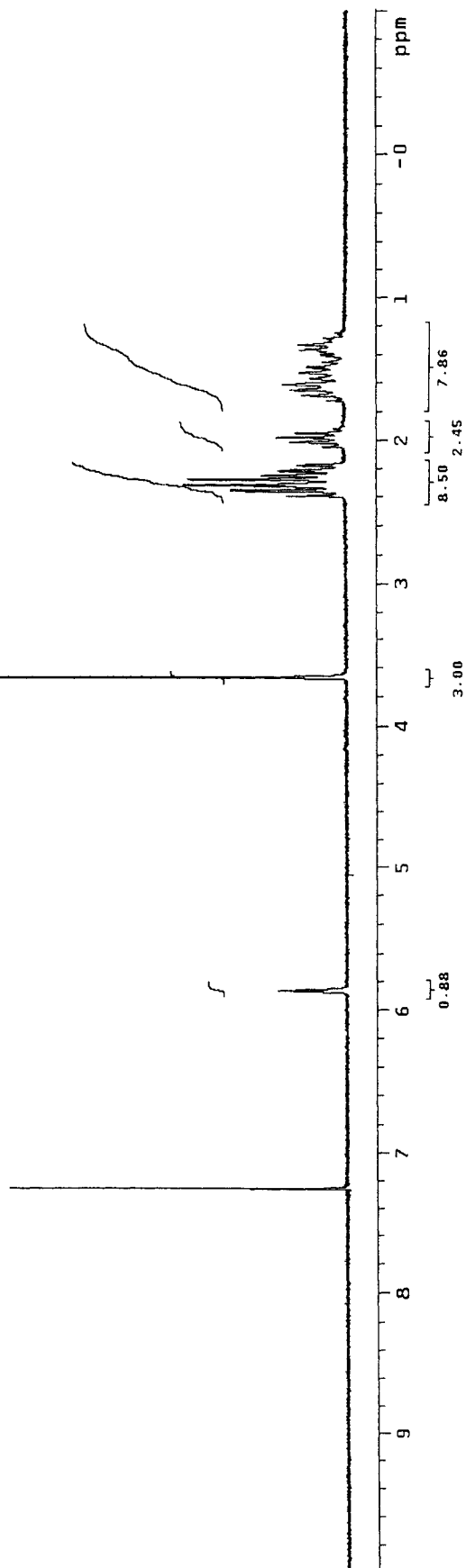
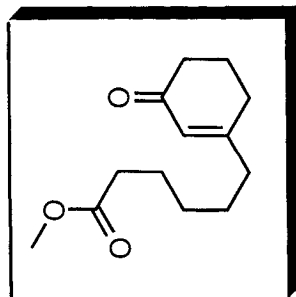
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 GEMINI-200 "gemin200"
 PULSE SEQUENCE
 Pulse 45.0 degrees
 Acq. time 3.002 sec
 Width 3800.0 Hz
 16 repetitions
 OBSERVE H1, 199.9659297 MHz
 DATA PROCESSING
 Resol. enhancement -0.0 Hz
 FT size 65536
 Total time 0 min, 0 sec



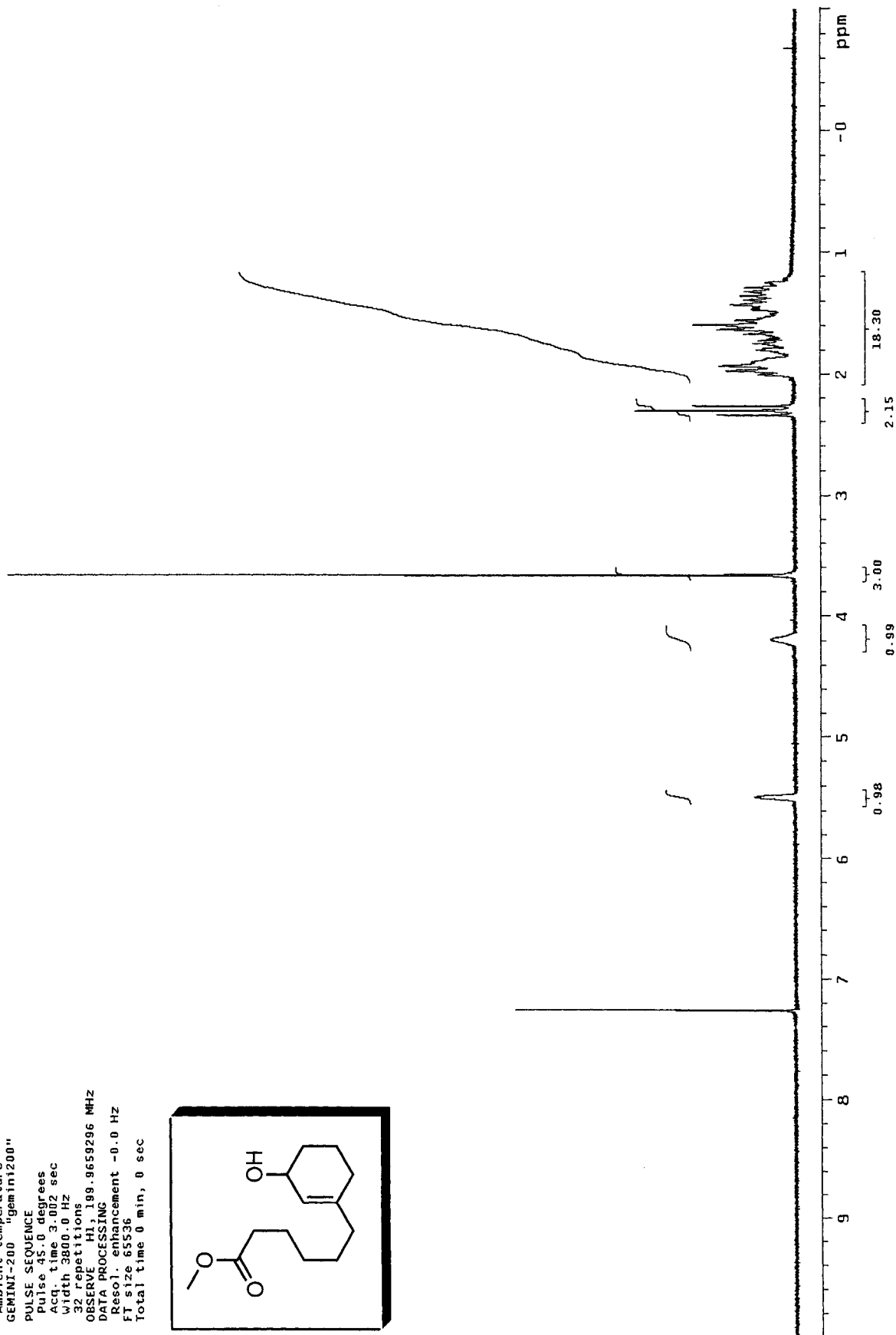
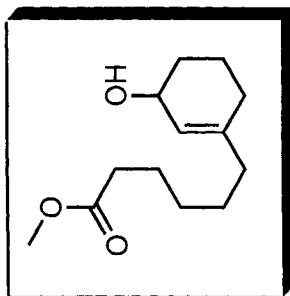
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 GEMINI-200 "gemin1200"
 PULSE SEQUENCE
 Pulse 45.0 degrees
 Acq time 3.002 sec
 Width 3800.0 Hz
 50 repetitions
 OBSERVE H1, 199.9659297 MHz
 DATA PROCESSING
 Resol enhancement -0.0 Hz
 FT size 65536
 Total time 0 min, 0 sec



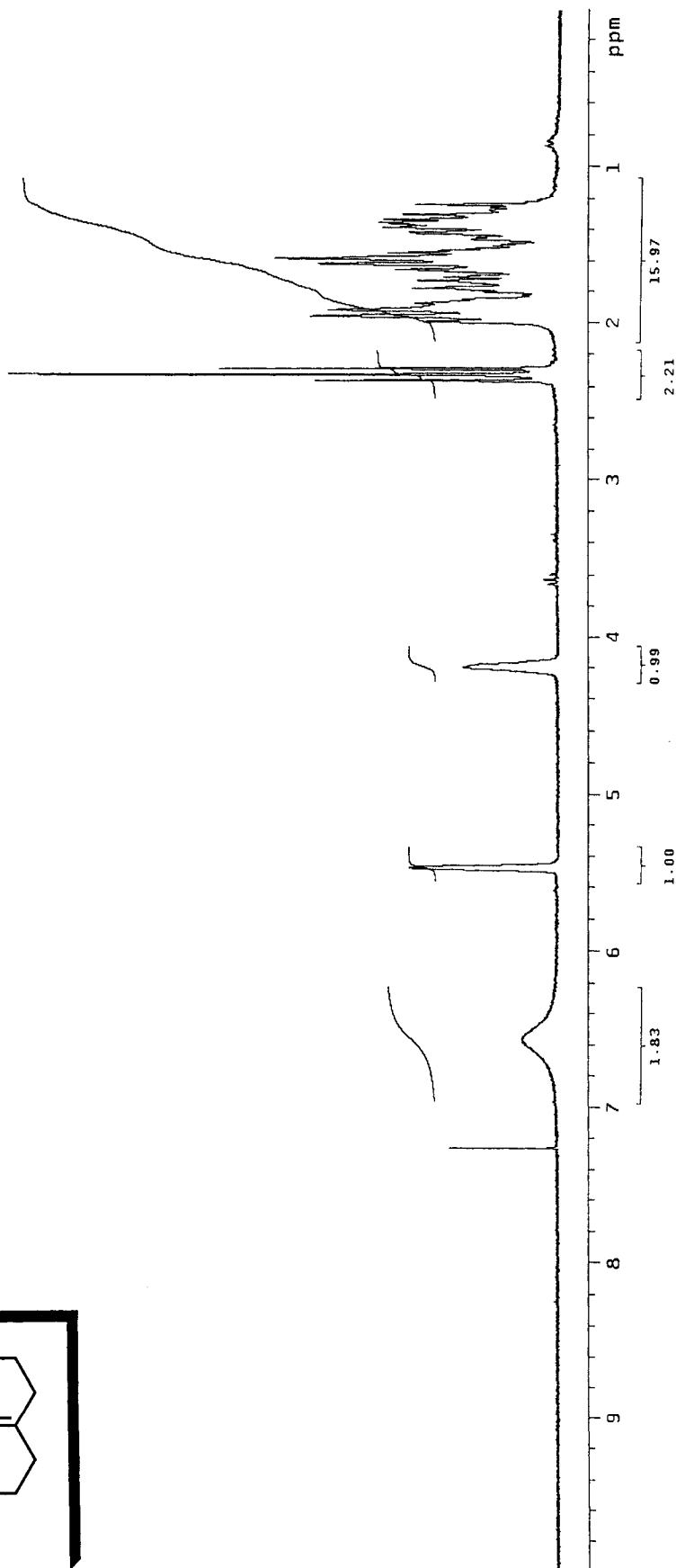
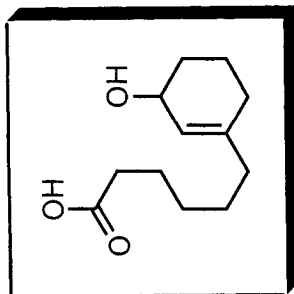
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 GEMINI-200 "gemin1200"
 PULSE SEQUENCE
 Pulse 45.0 degrees
 Acq. time 3.002 sec
 Width 3800.0 Hz
 32 repetitions
 OBSERVE H1, 199.9659296 MHz
 DATA PROCESSING
 Resol. enhancement -0.0 Hz
 FI size 65536
 Total time 0 min, 0 sec



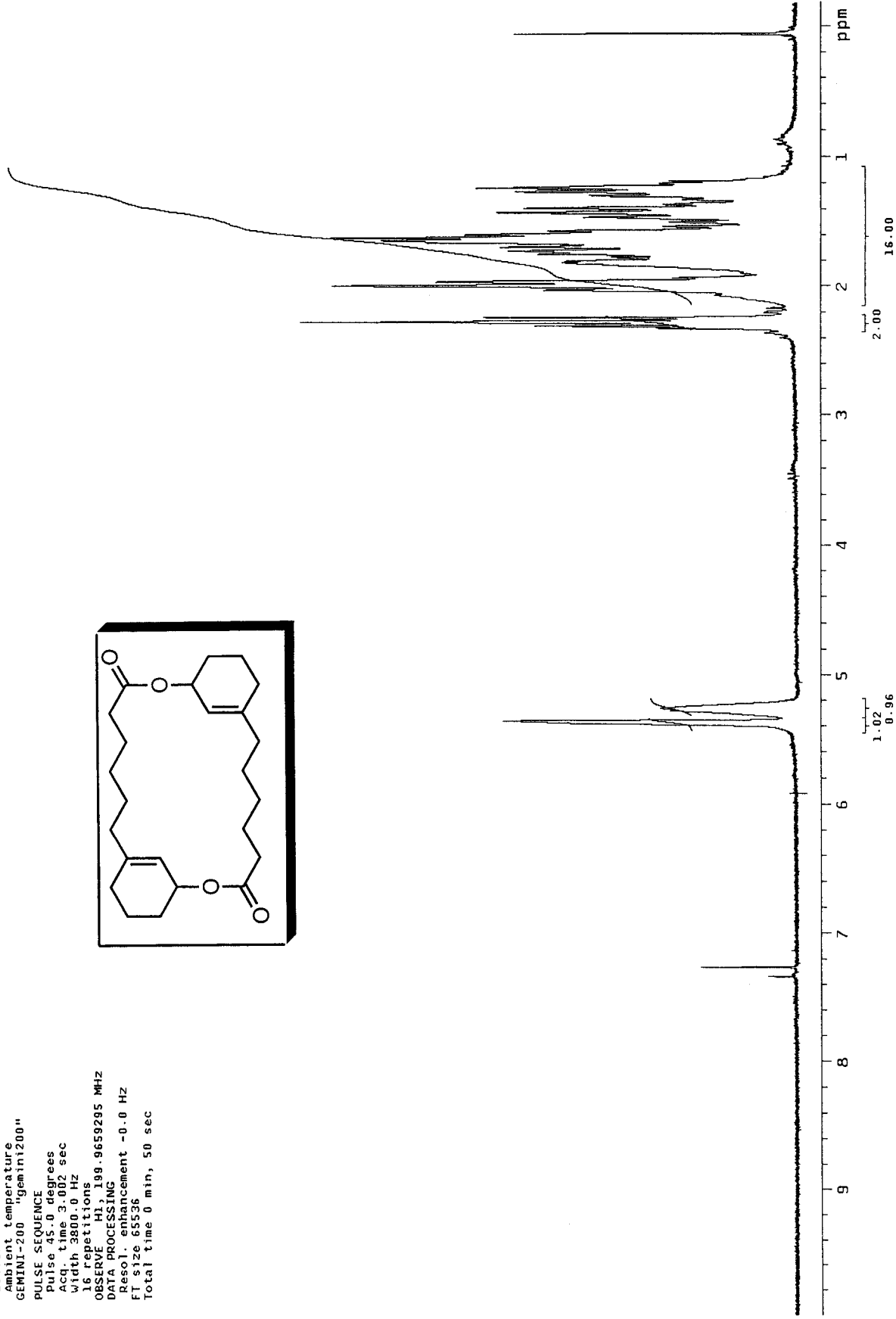
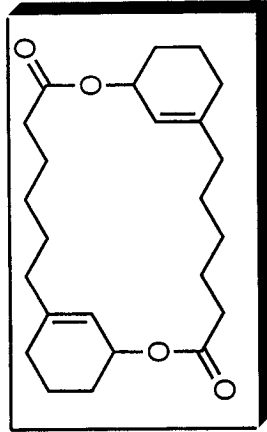
STANDARD 1H OBSERVE

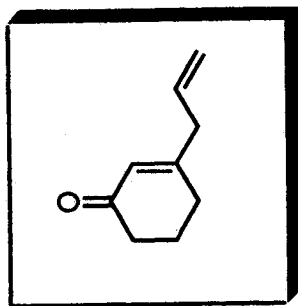
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 GEMINI-200 "geminiz200"
 PULSE SEQUENCE
 Pulse 45.0 degrees
 Acq. time 3.002 sec
 Width 3800.0 Hz
 16 repetitions
 OBSERVE H1; 199.9659297 MHz
 DATA PROCESSING
 Resol. enhancement -0.0 Hz
 FT size 65536
 Total time 0 min, 0 sec



STANDARD 1H OBSERVE

Pulse Sequence: s2pu]
Solvent: CDCl3
Ambient temperature
GEMINI-200 "gemin200"
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 3.002 sec
width 3800.0 Hz
16 repetitions
OBSERVE H1, 199.9659295 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FI size 65536
Total time 0 min, 50 sec





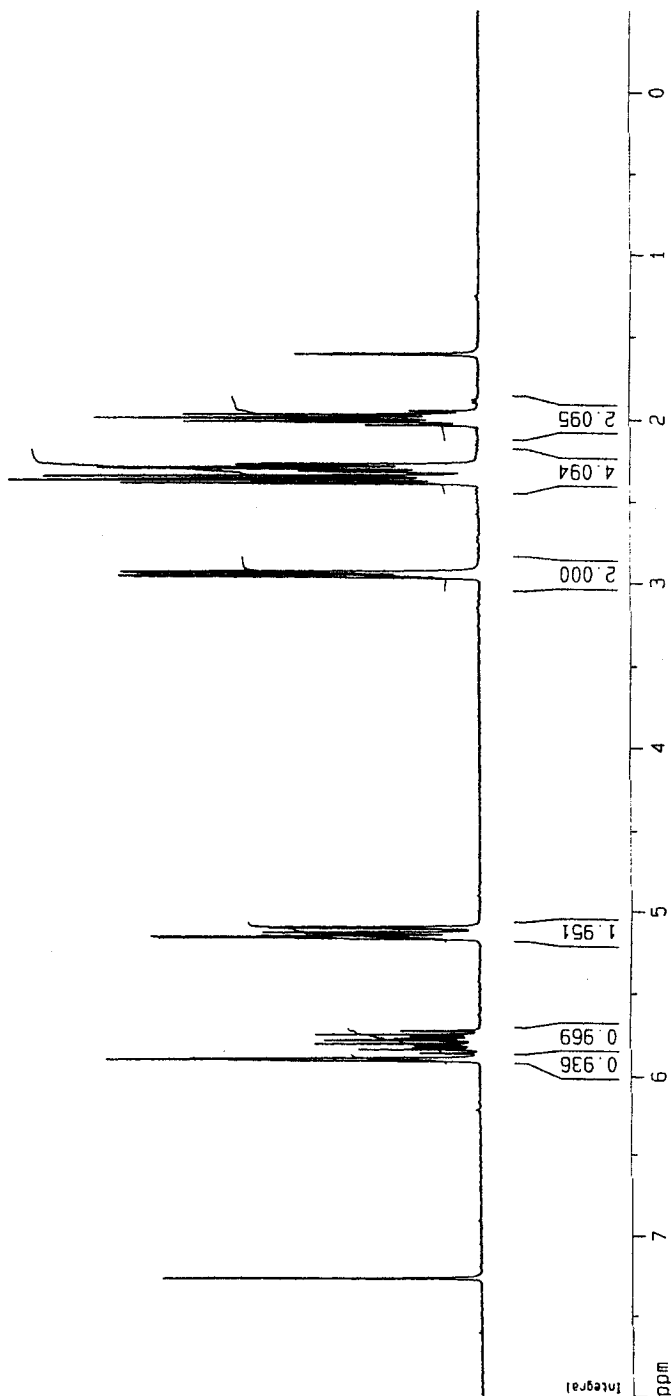
Current Data Parameters
NAME pb-01-160h
EXPNO 1
PROCNO 1

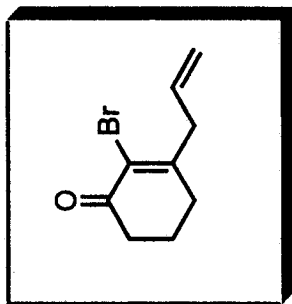
F2 - Acquisition Parameters
Date_ 20020905
Time 20.04
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 812.7
DM 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.75 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1299942 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.42500 ppm/cm
HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-95
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021119
 Time 18.48
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

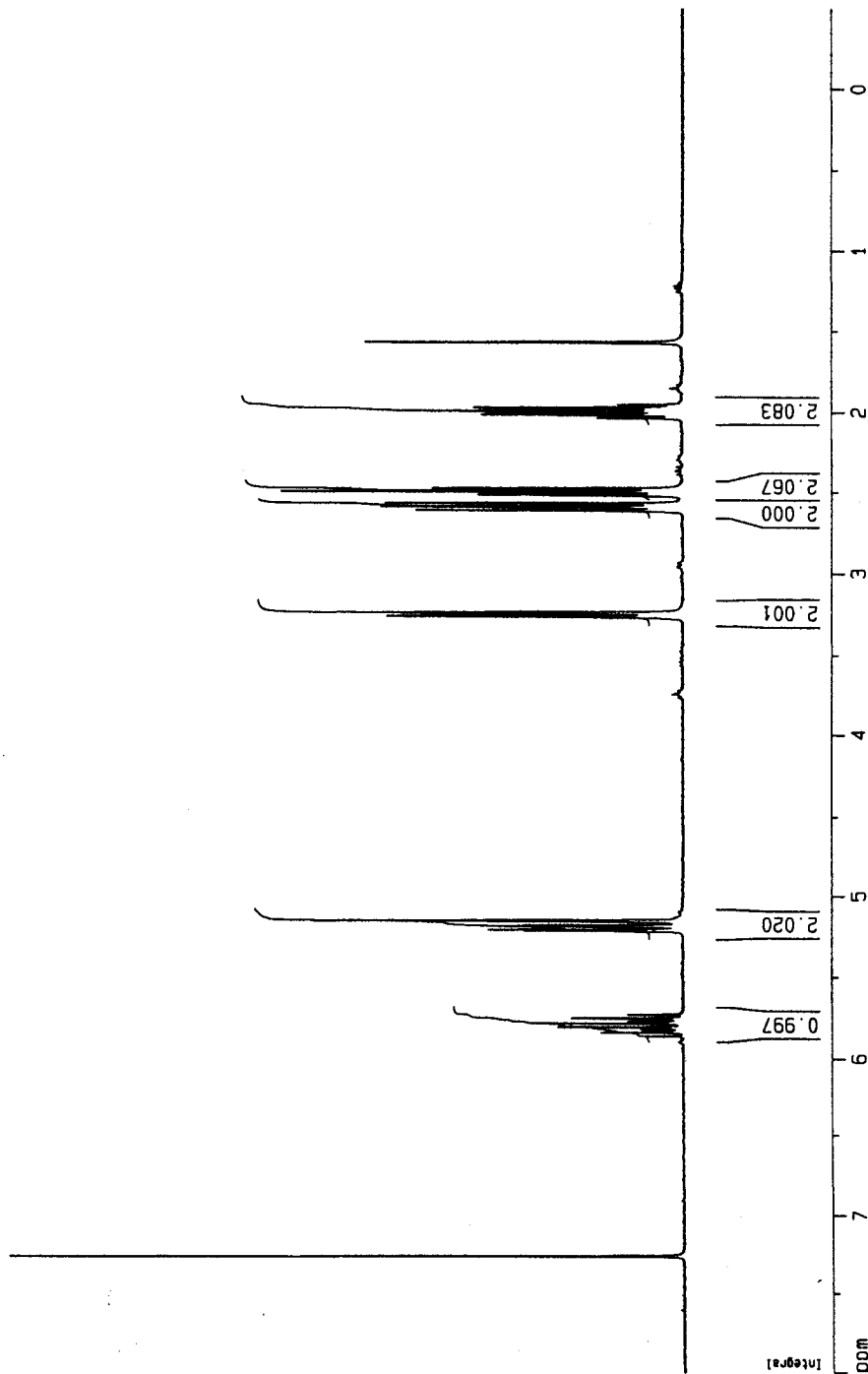
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

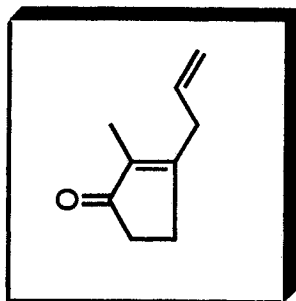
F2 - Processing parameters

SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-89
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021115
 Time 19.21
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 456.1
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

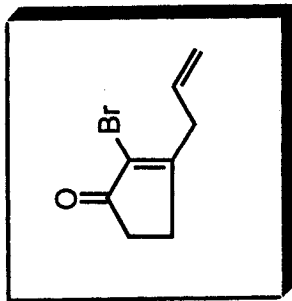
F2 - Processing parameters

SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

ID NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-21
 EXPNO 1
 PROCNO 1

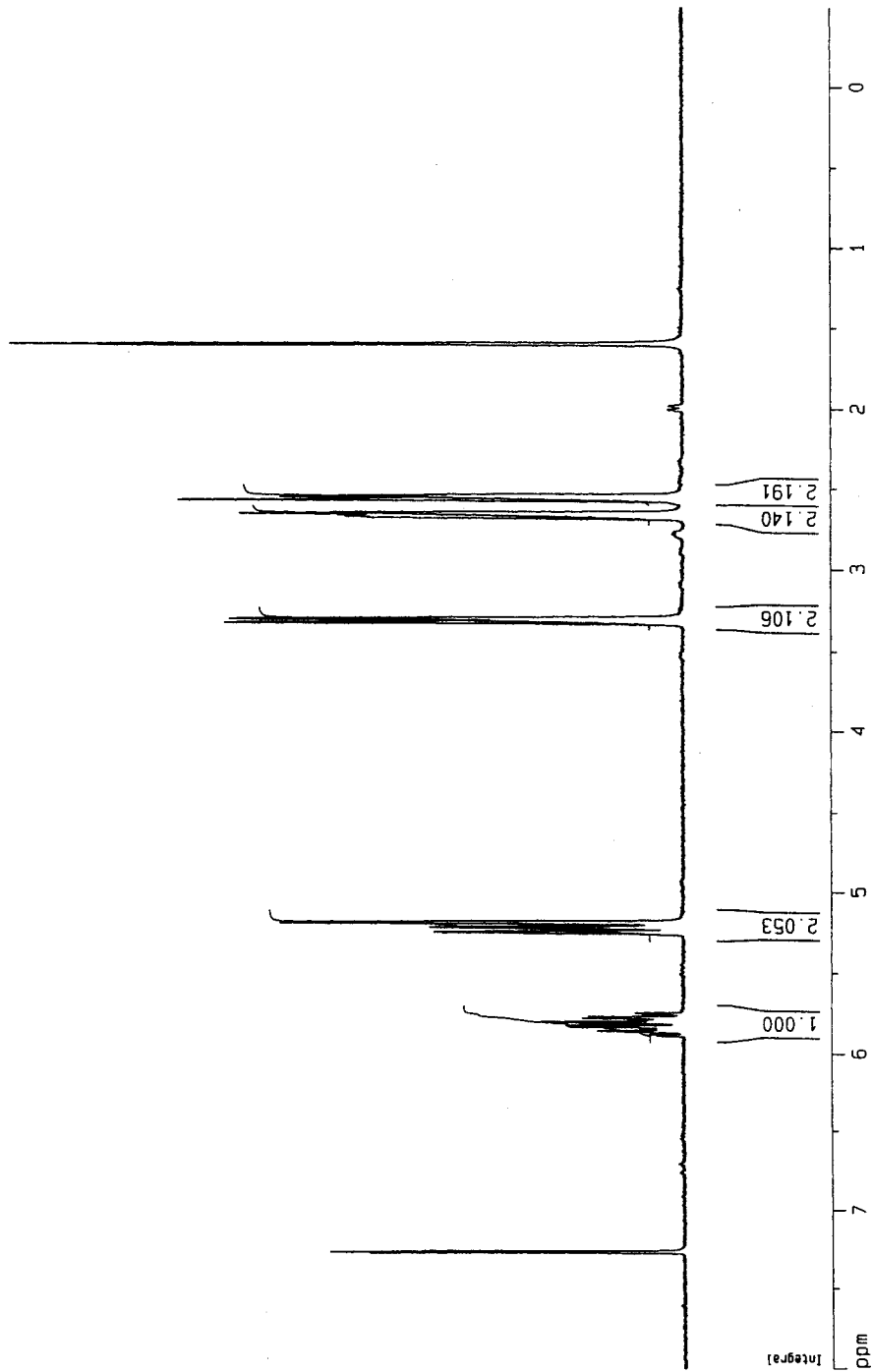
F2 - Acquisition Parameters

Date_ 20020826
 Time 14.11
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

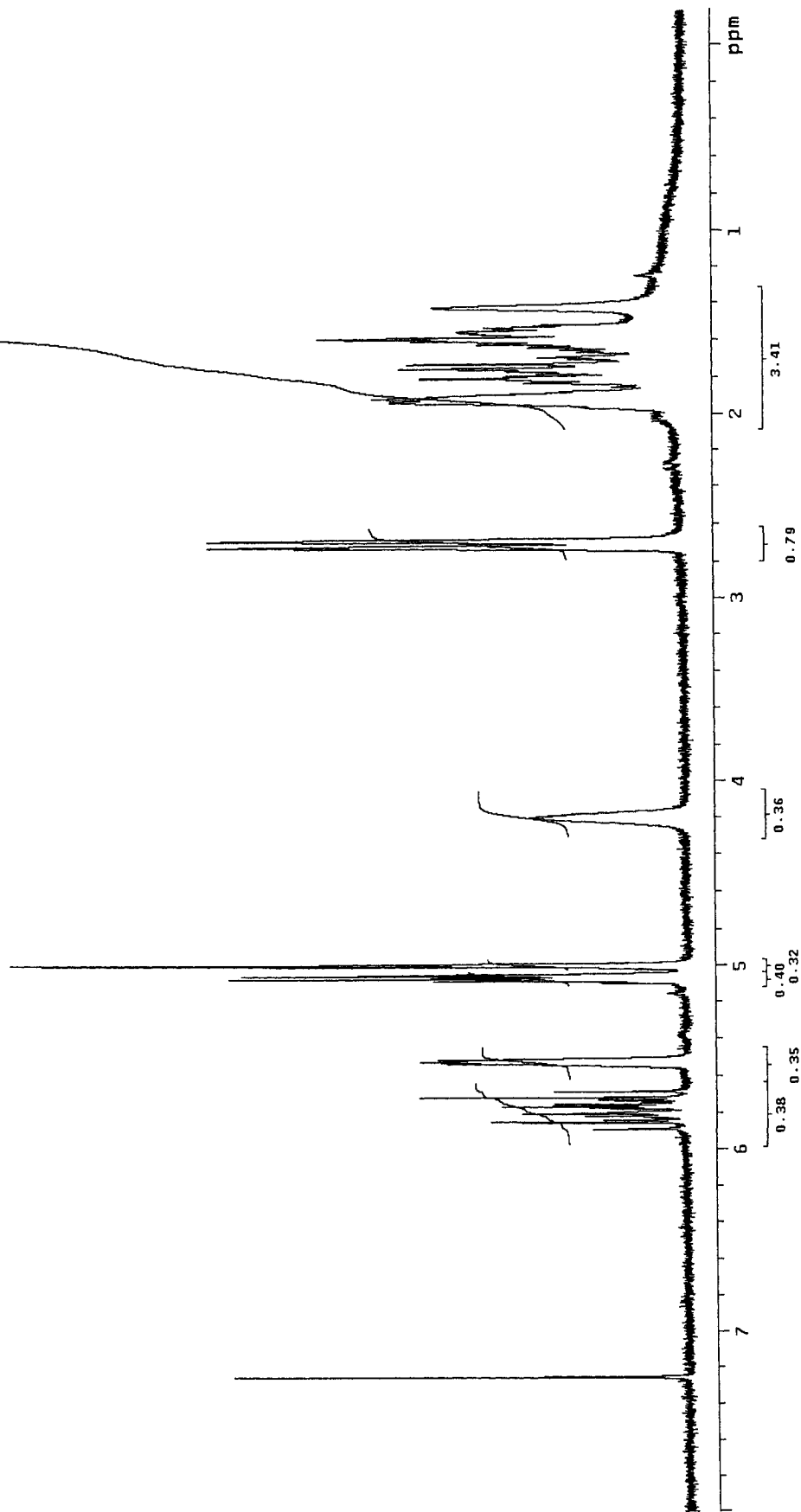
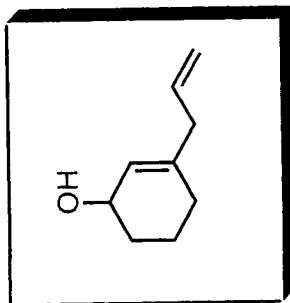
F2 - Processing parameters
 SI 65536
 SF 300.1299927 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

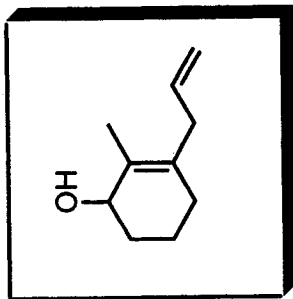
1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 GEMINI-200 "gemin200"
 PULSE SEQUENCE
 pulse 45.0 degrees
 Acq. time 3.002 sec
 Width 3800.0 Hz
 16 repetitions
 OBSERVE H1, 199.9659300 MHz
 DATA PROCESSING
 Resol. enhancement -0.0 Hz
 FT size 65536
 Total time 0 min, 50 sec





Current Data Parameters
 NAME pb-01-135H
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20020617
 Time 10.53
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 80.6
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

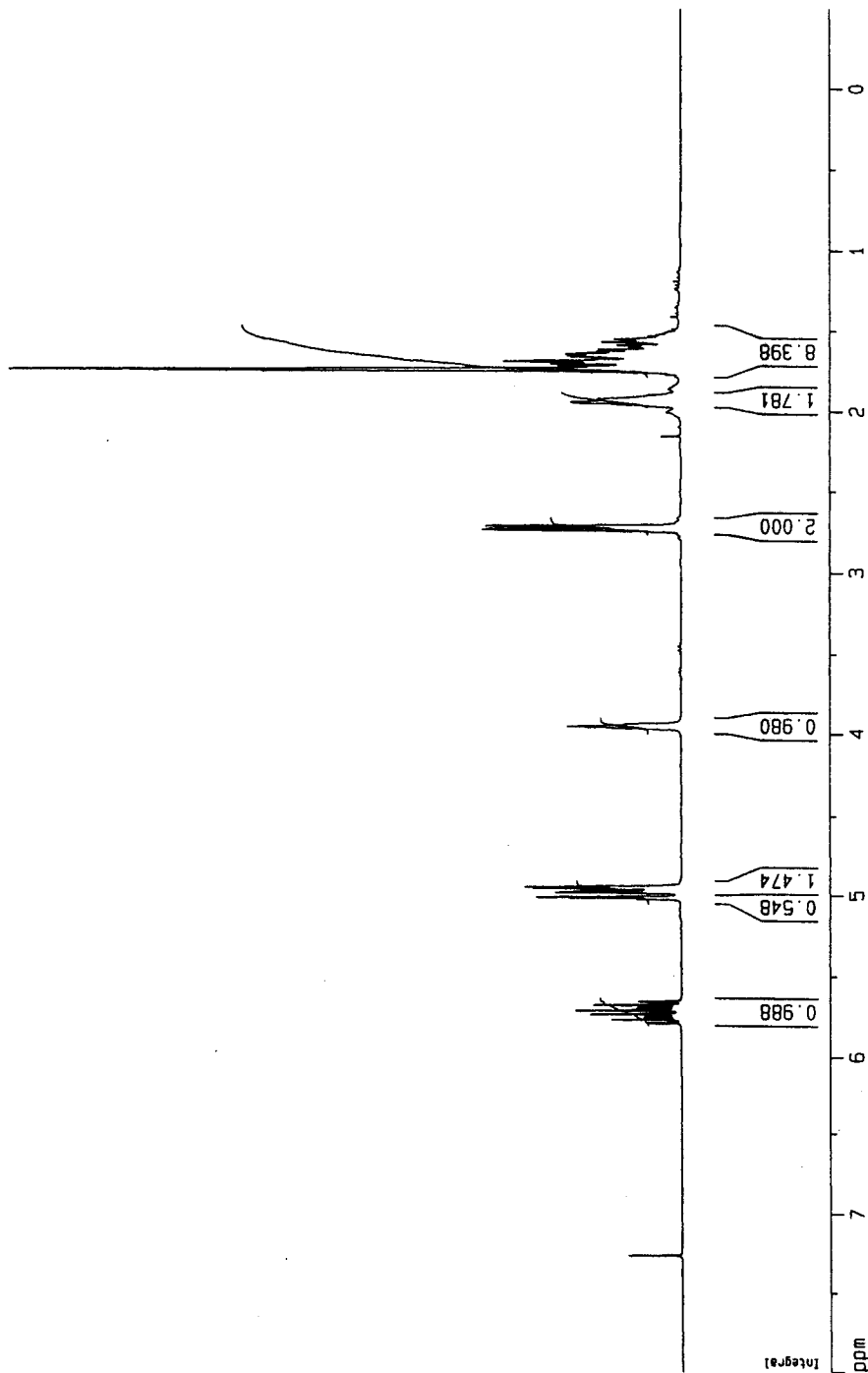
NUC1 1H
 P1 20.00 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299940 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -150.06 Hz
 F2 -0.500 ppm
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-02-96
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021119
 Time 20.54
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 362
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

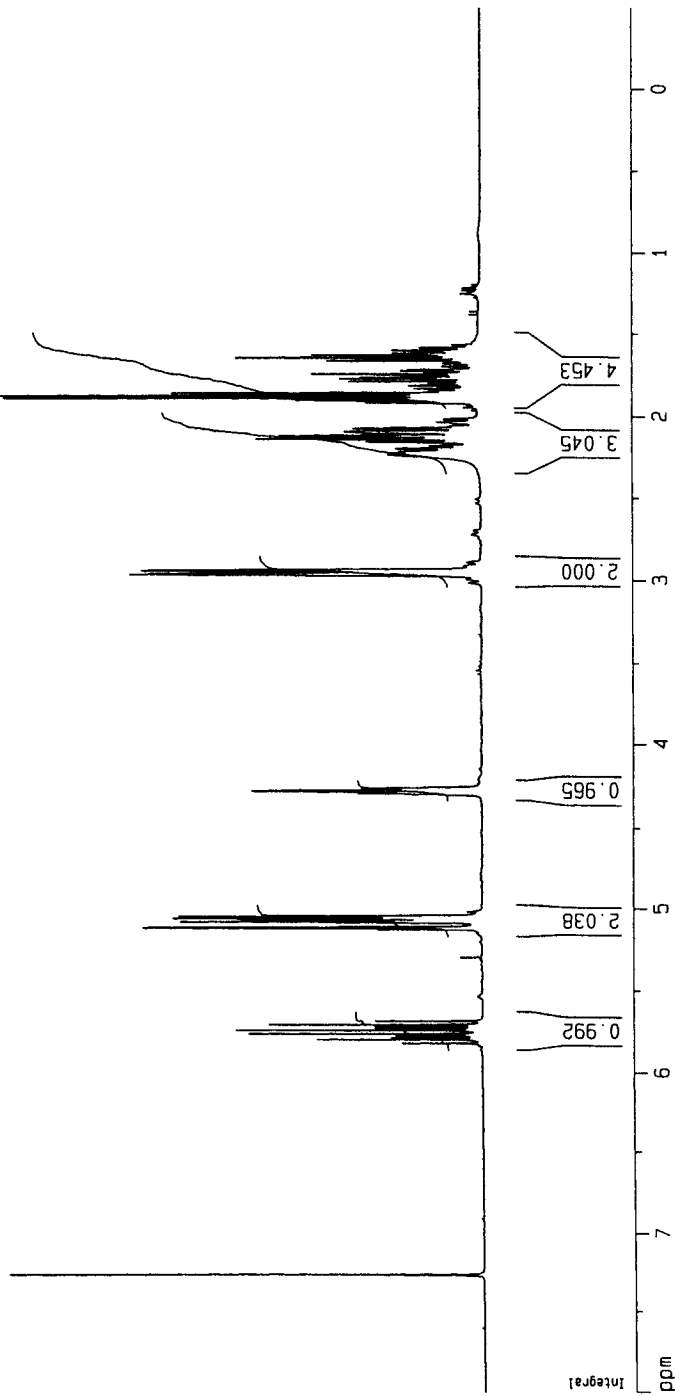
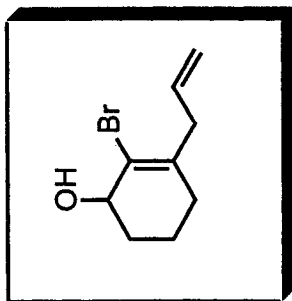
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



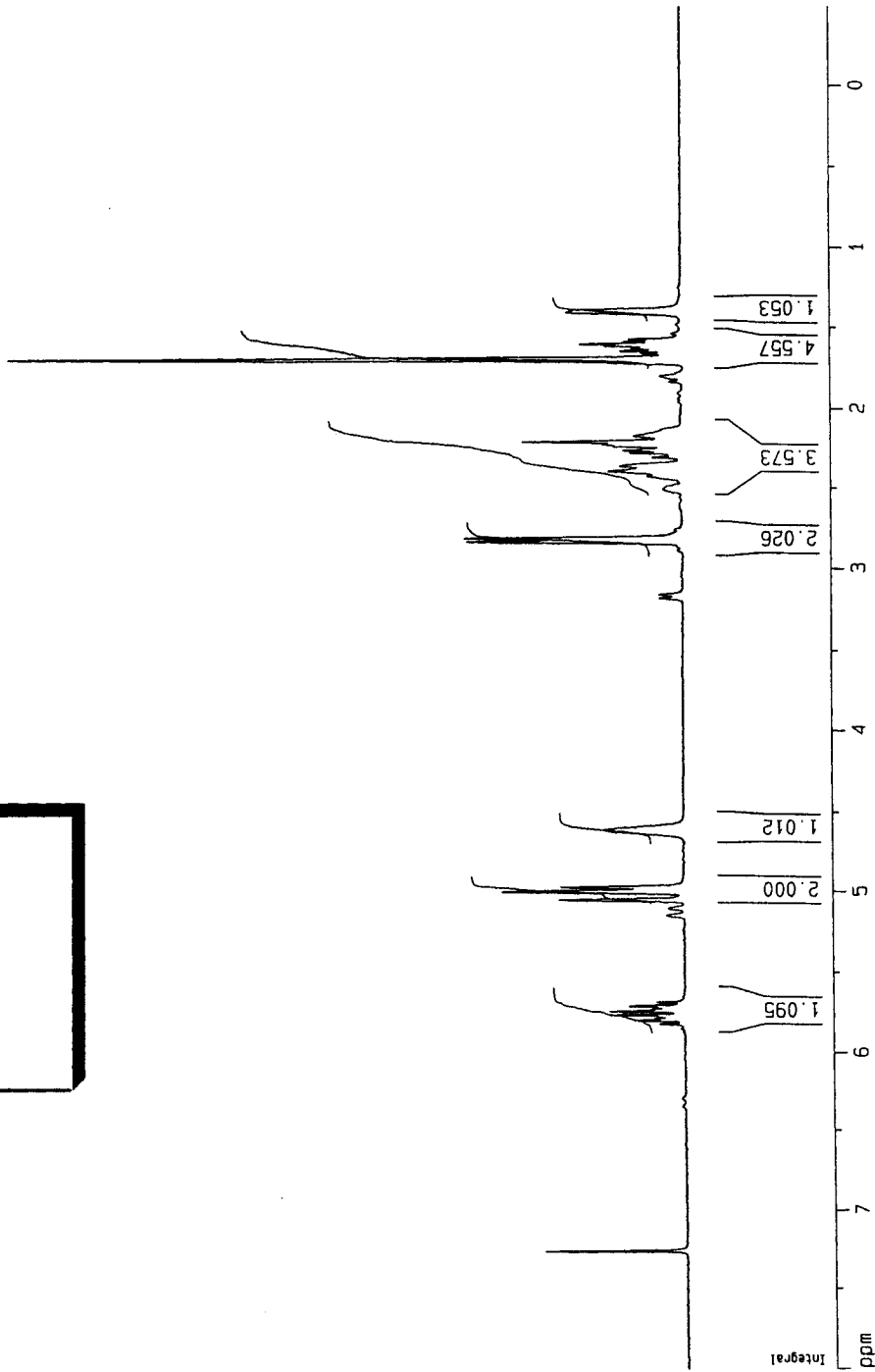
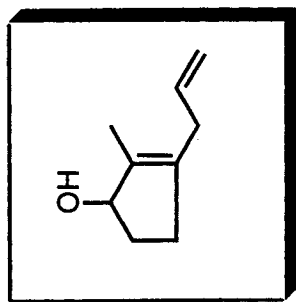
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 NAME pb-02-92
 EXPNO 1
 PROCNO 1

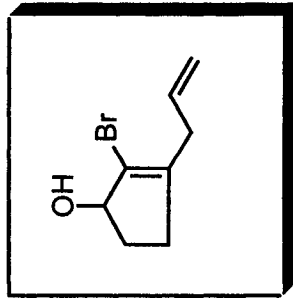
F2 - Acquisition Parameters
 Date_ 20021115
 Time 20.05
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TO 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 406.4
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.59524 Hz/cm





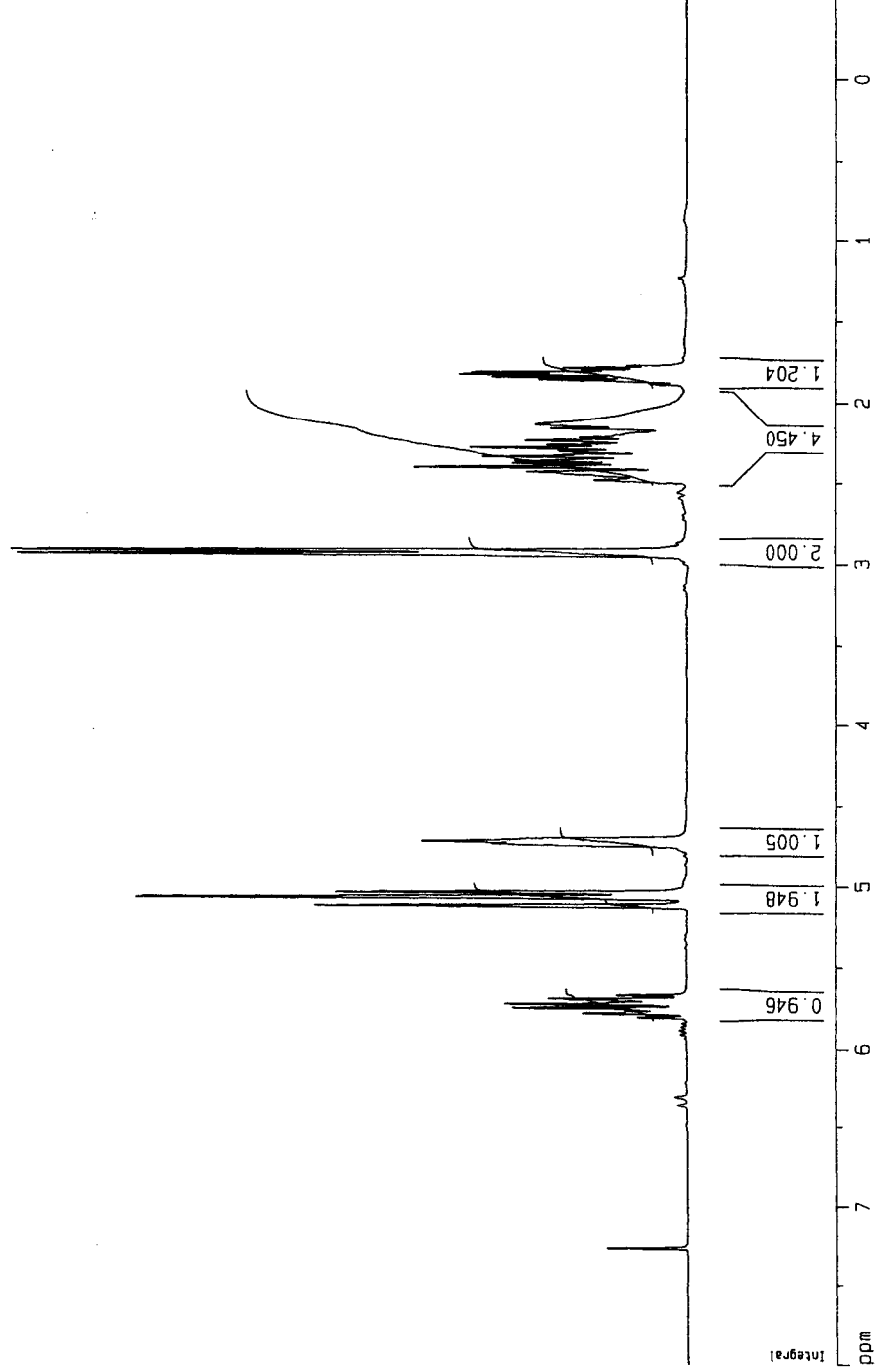
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 NAME pb-Q2-g
 EXPNO 1
 PROCNO 1

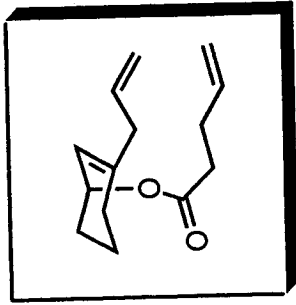
F2 - Acquisition Parameters
 Date_ 20020812
 Time 18.48
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 143.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.00 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299935 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-01-112
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20020529
 Time 8.26
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 128
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

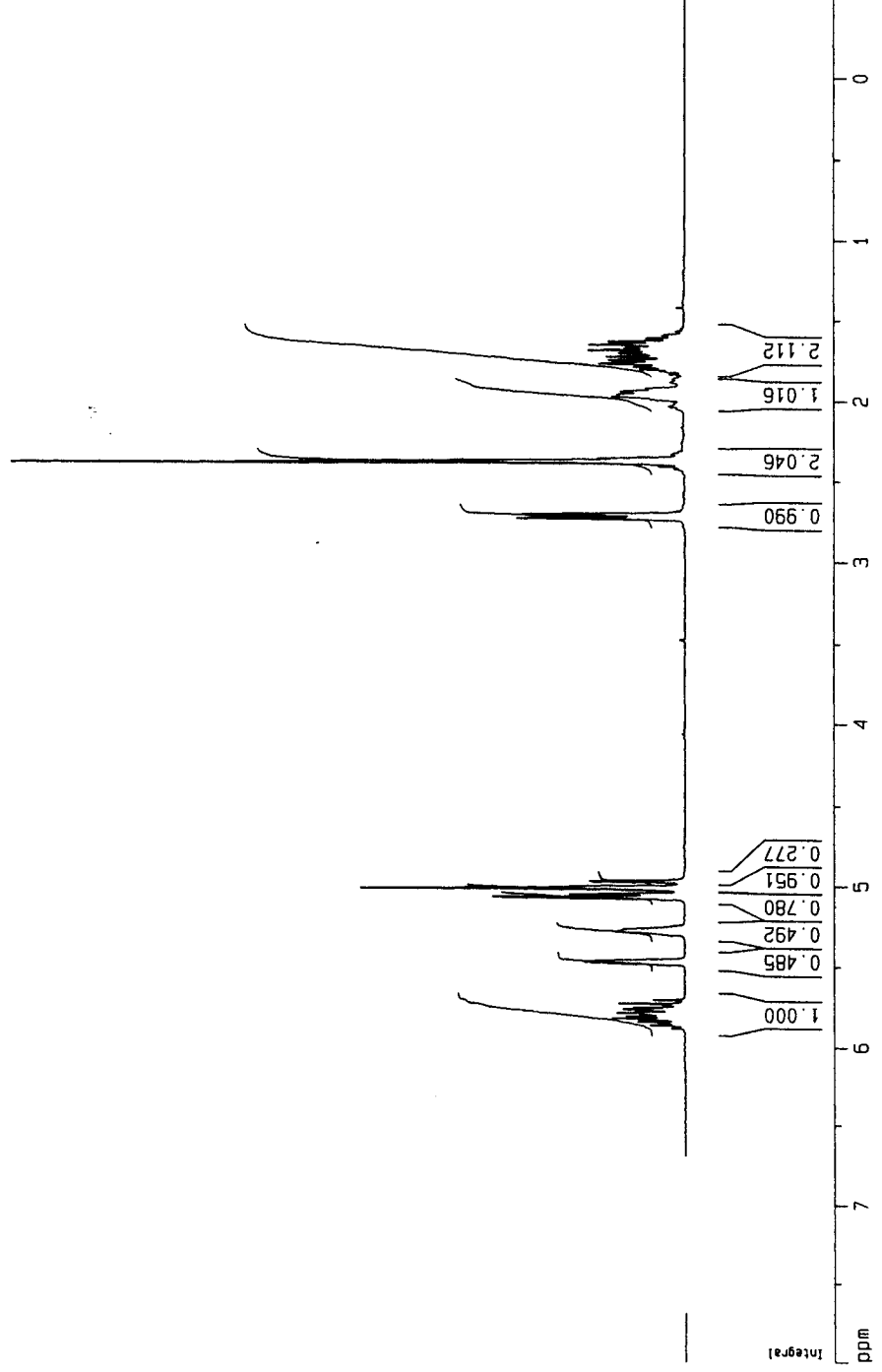
NUC1 1H
 P1 15.00 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299940 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-01-136
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20020801
 Time 18.04
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 28.5
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

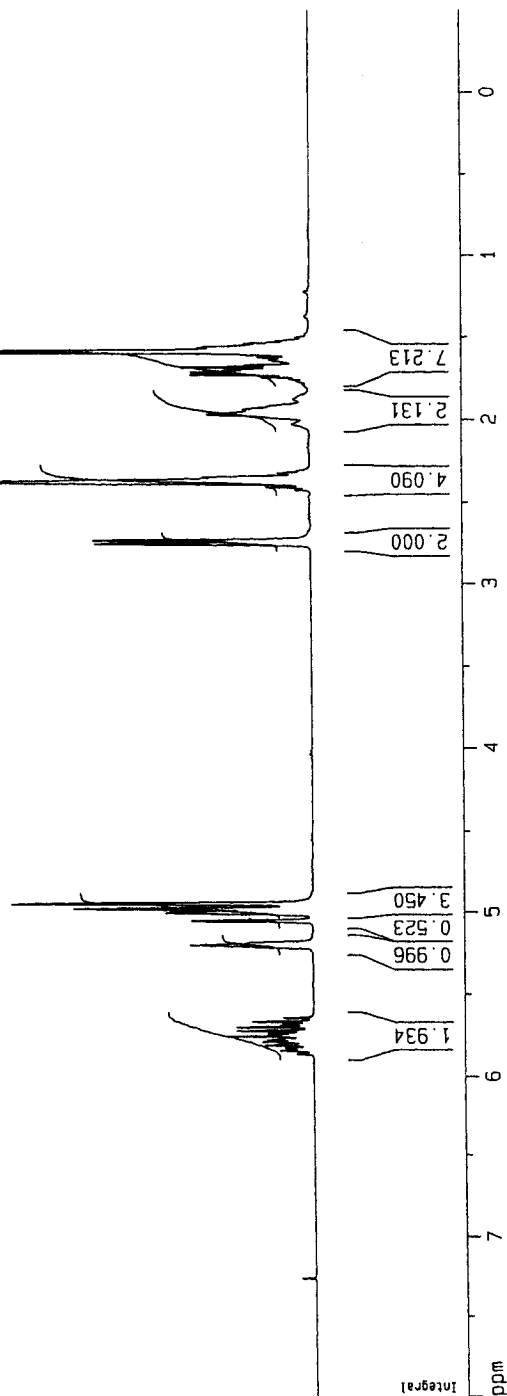
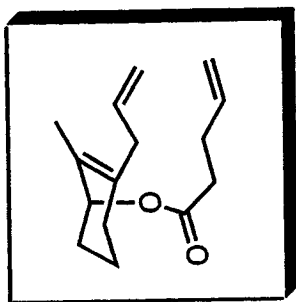
NUC1 1H
 P1 8.00 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

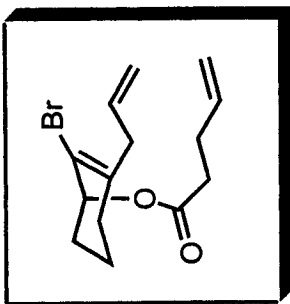
F2 - Processing parameters

SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





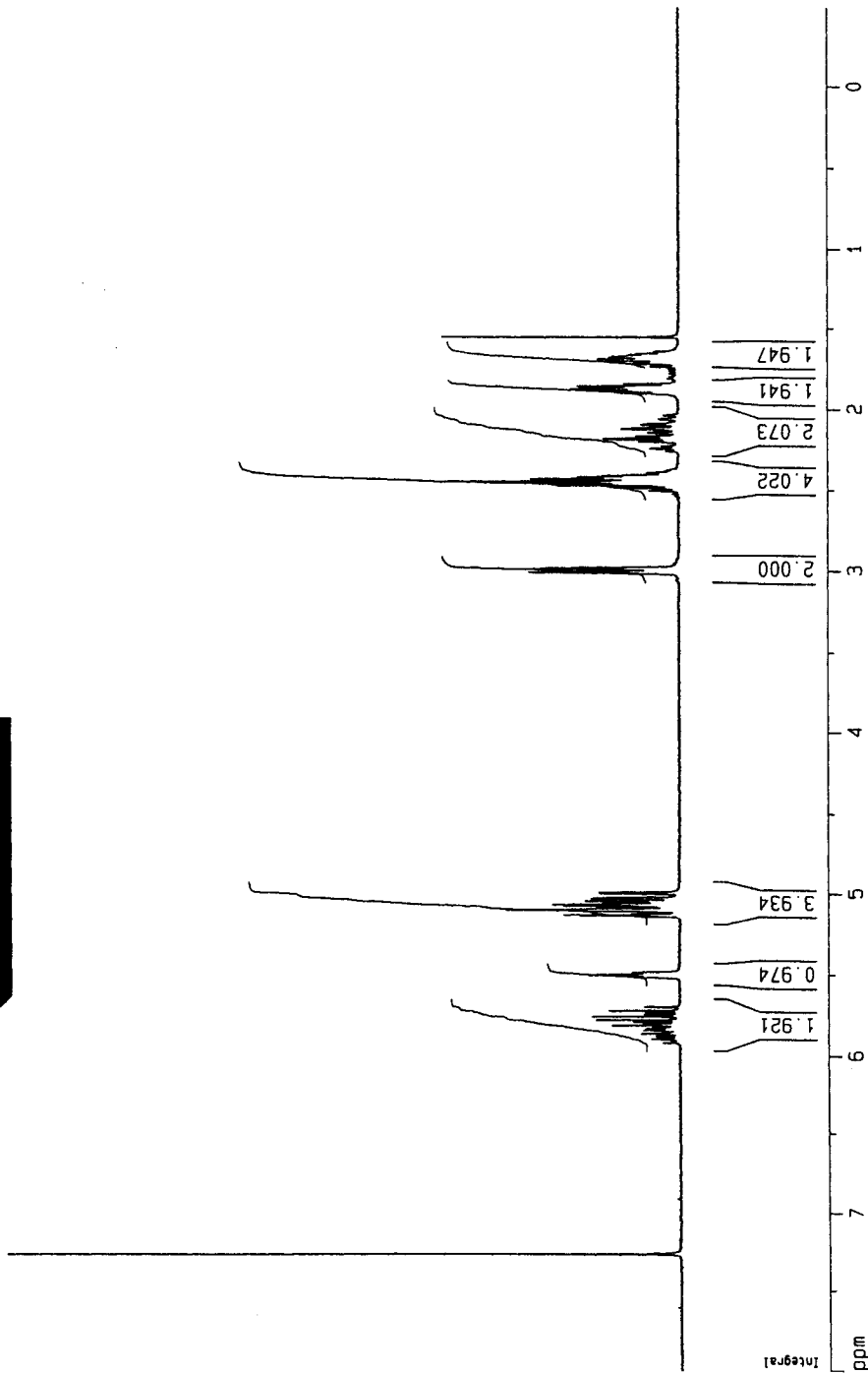
Current Data Parameters
 NAME pb-02-97
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20021120
 Time 15.49
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-02-170
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030219
 Time 18.15
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 512
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

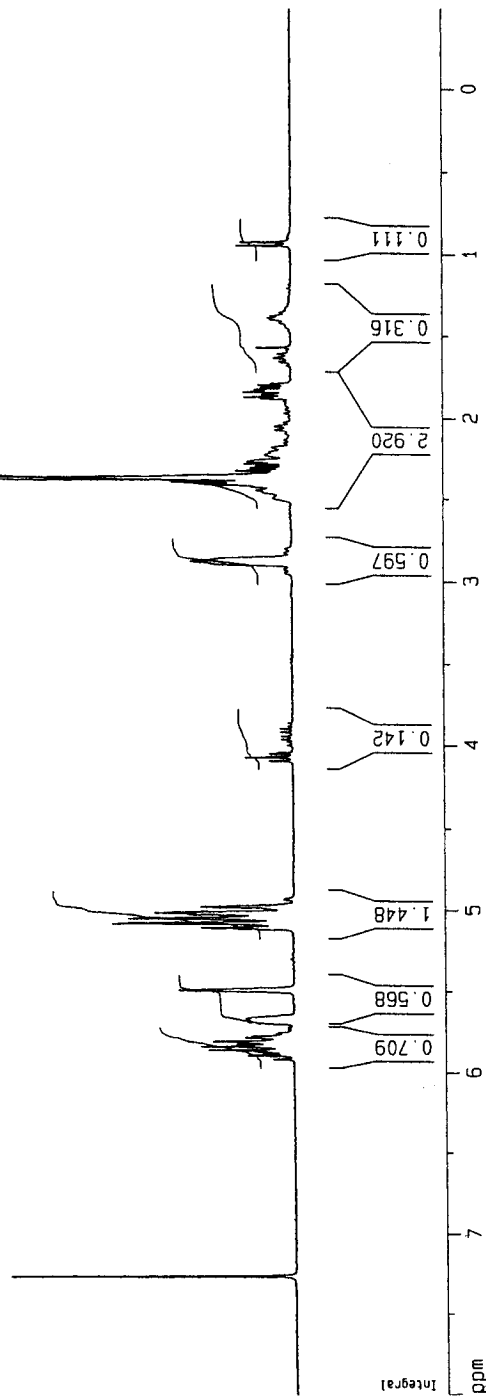
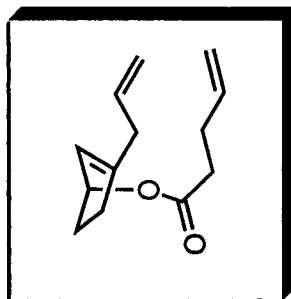
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

10 NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-02-176
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

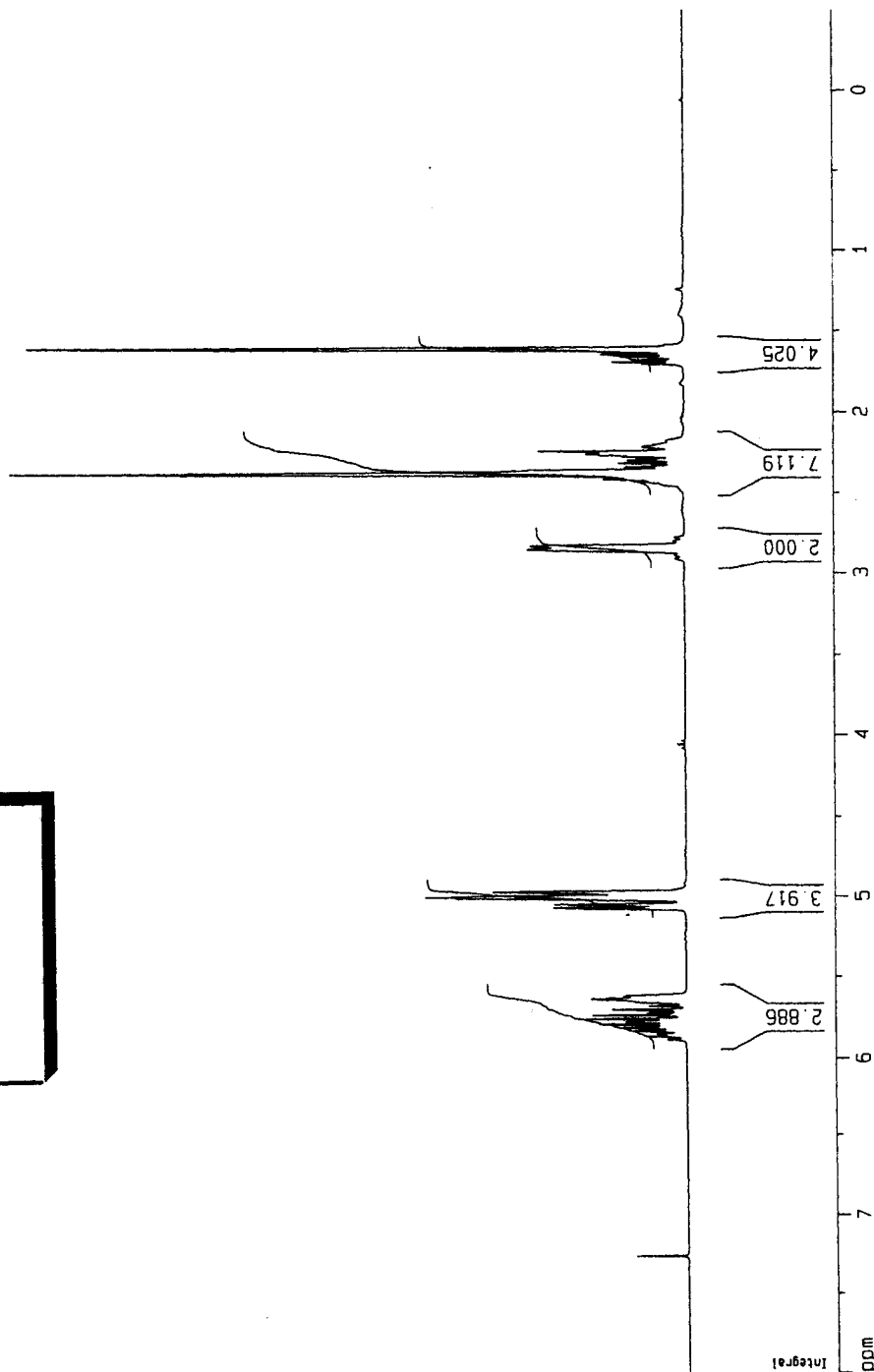
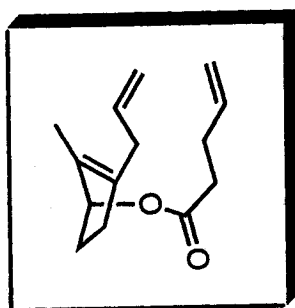
Date_ 20030225
 Time 14.29
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT COCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.163407 Hz
 AQ 3.0228980 sec
 RG 90.5
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

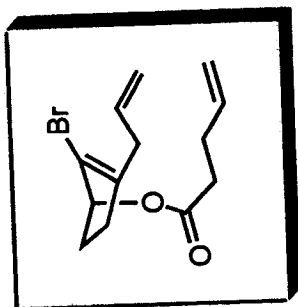
===== CHANNEL f1 =====

NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299936 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00
 ID NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-25
 EXPNO 1
 PROCNO 1

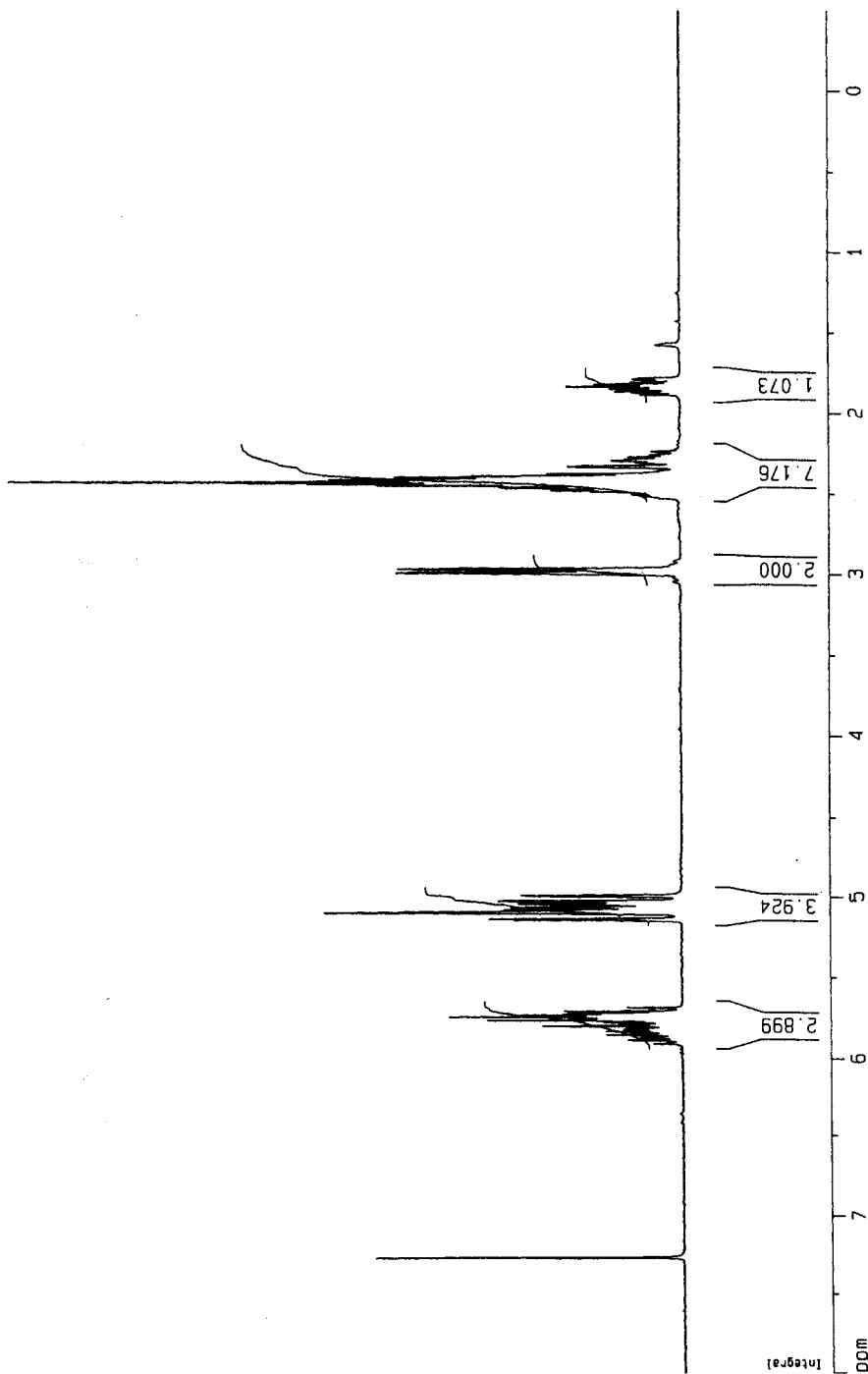
F2 - Acquisition Parameters

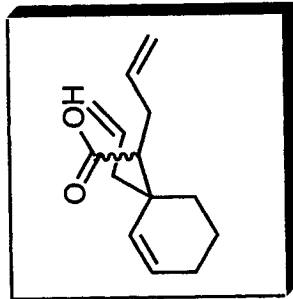
Date_ 20020827
 Time 15:50
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 456.1
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
NAME pb-01-114pure
EXPNO 3
PROCNO 1

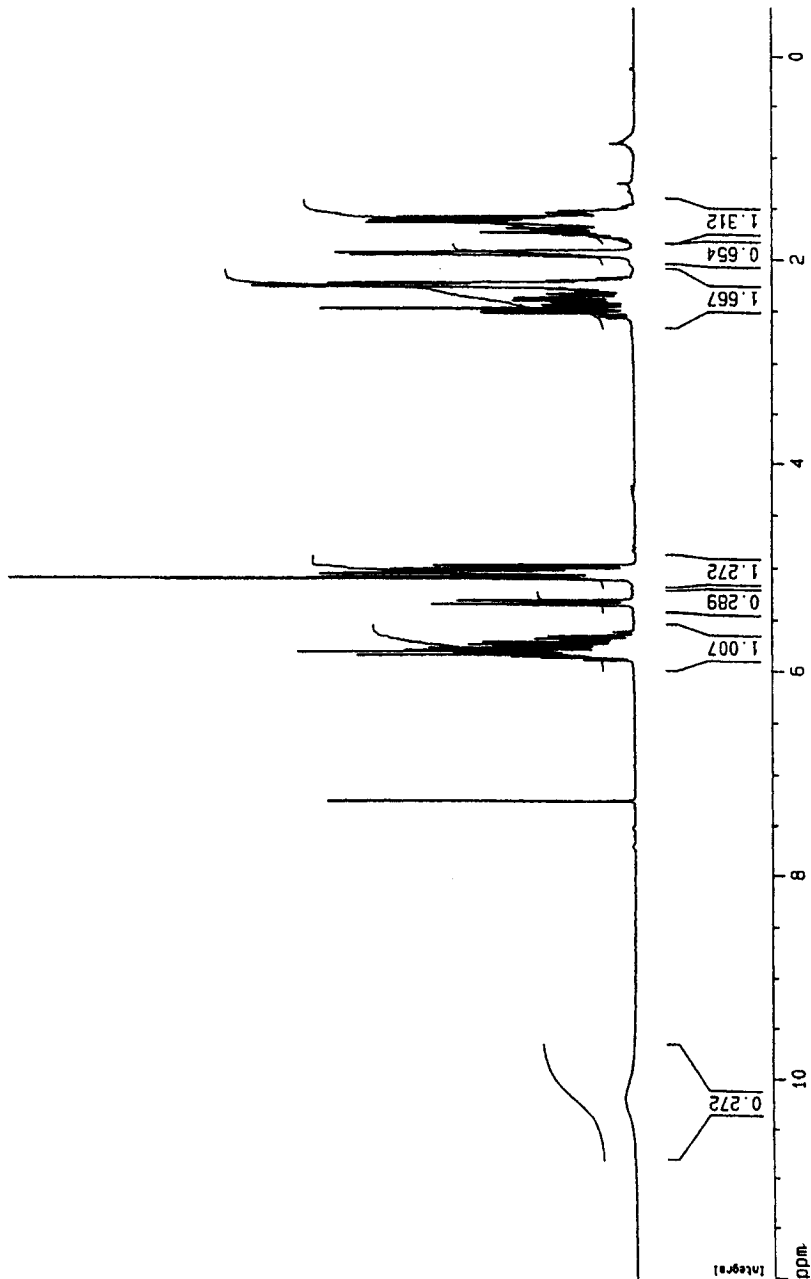
F2 - Acquisition Parameters

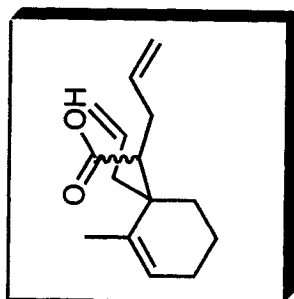
Date_ 20020531
Time 11.02
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228960 sec
RG 228.1
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.0000000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 15.00 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
SF 300.1299942 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 12.000 ppm
F1 3601.56 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.62500 ppm/cm
HZCM 187.58125 Hz/cm





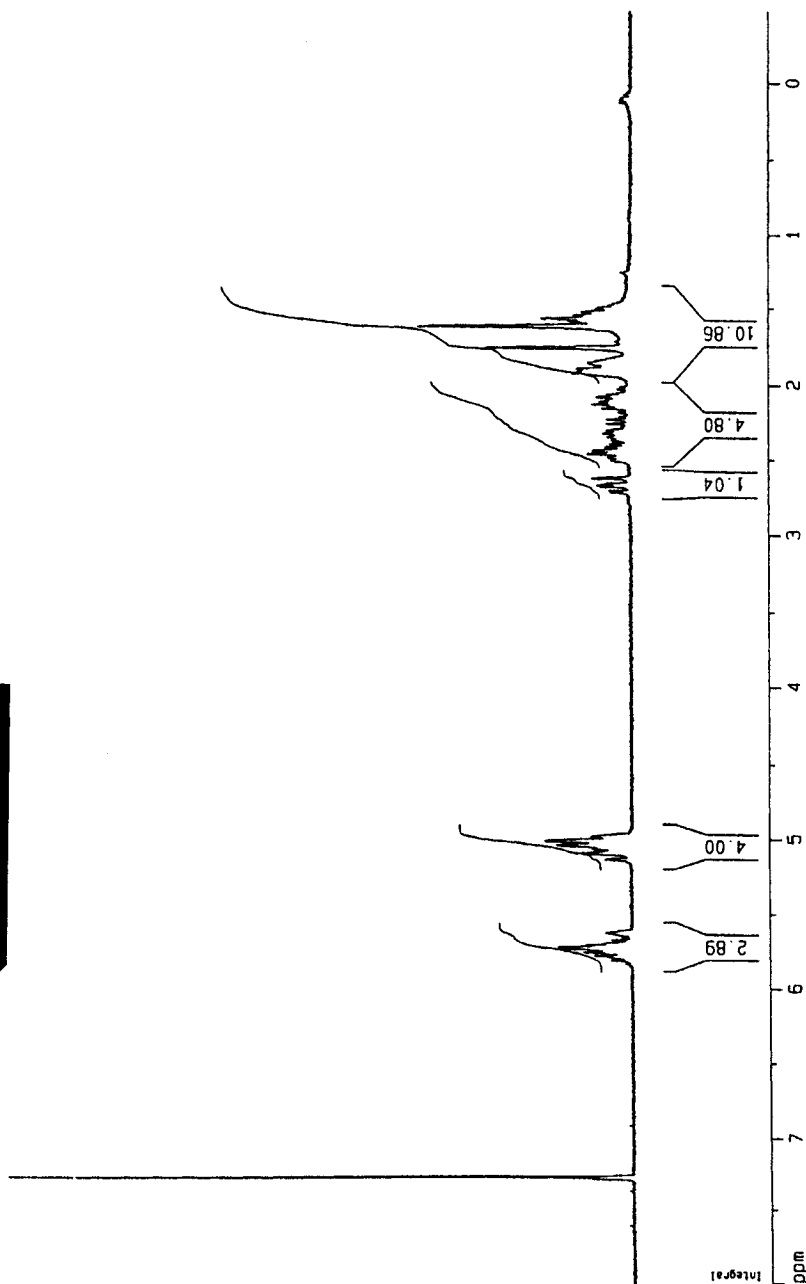
Current Data Parameters
NAME po-02-64
EXPNO 1
PROCNO 1

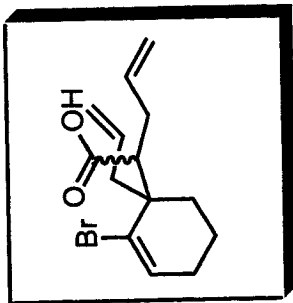
F2 - Acquisition Parameters
Date_ 20021007
Time 12.00
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT COC13
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 1024
DM 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

***** CHANNEL f1 *****
NUC1 1H
P1 9.75 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1299936 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2 -150.06 Hz
PPMCH 0.42500 ppm/cm
HZCM 127.55524 Hz/cm





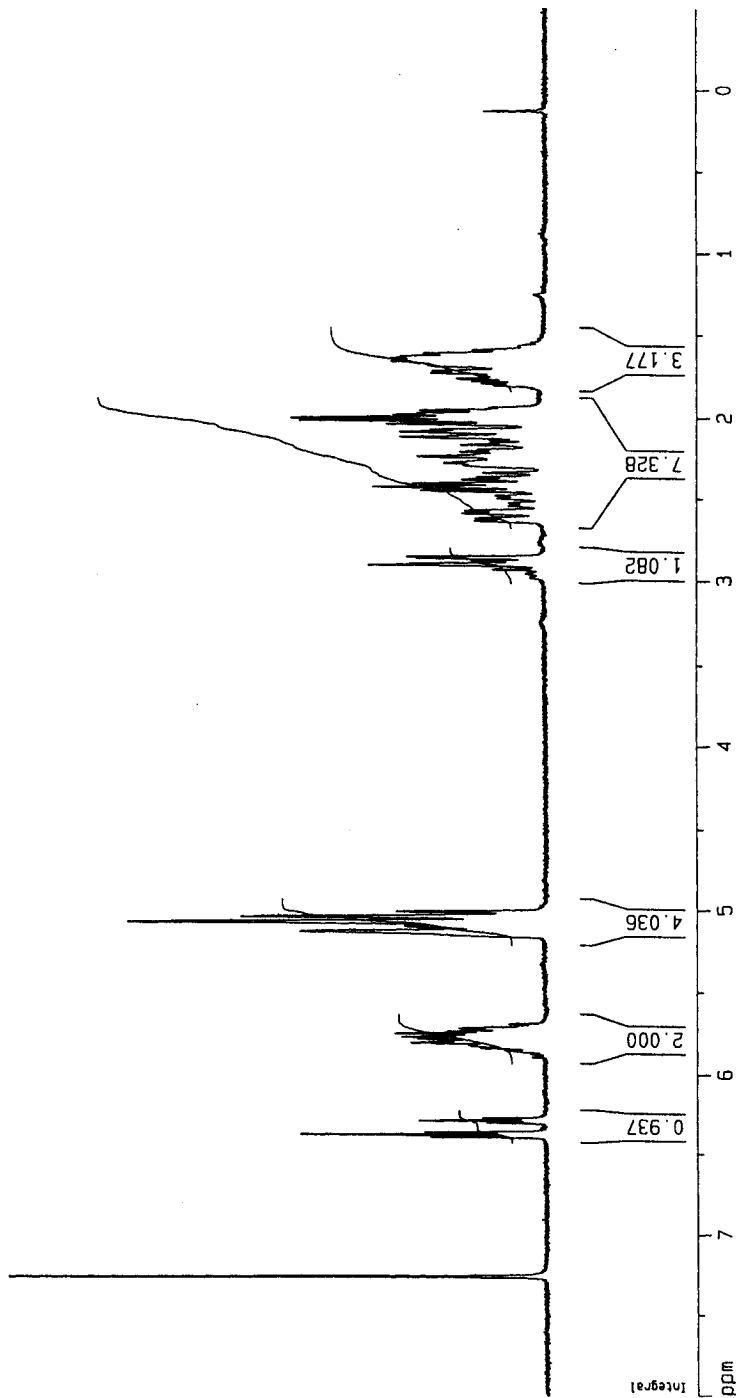
Current Data Parameters
NAME pb-02-99f
EXPNO 1
PROCNO 1

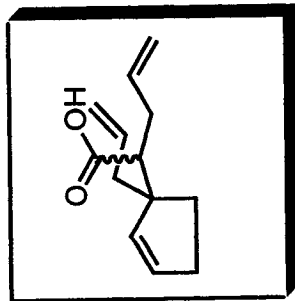
F2 - Acquisition Parameters
Date_ 20021121
Time 20.48
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0229980 sec
RG 645.1
DM 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.0000000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.75 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1299942 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.42500 ppm/cm
HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-171
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030220
 Time 16.38
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 114
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

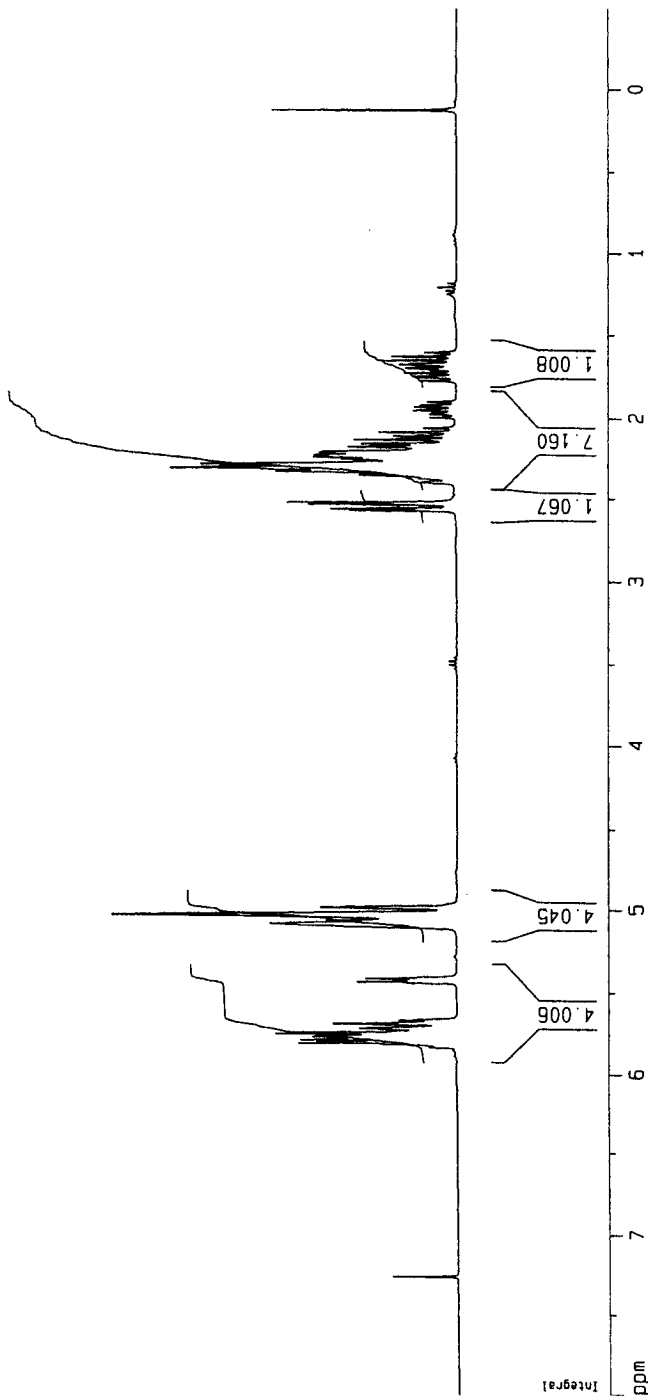
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

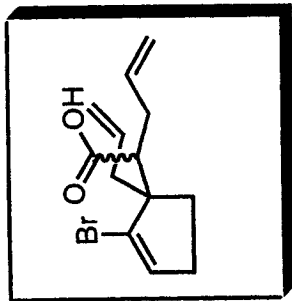
F2 - Processing parameters

SI 65536
 SF 300.1299940 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 5.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPNM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





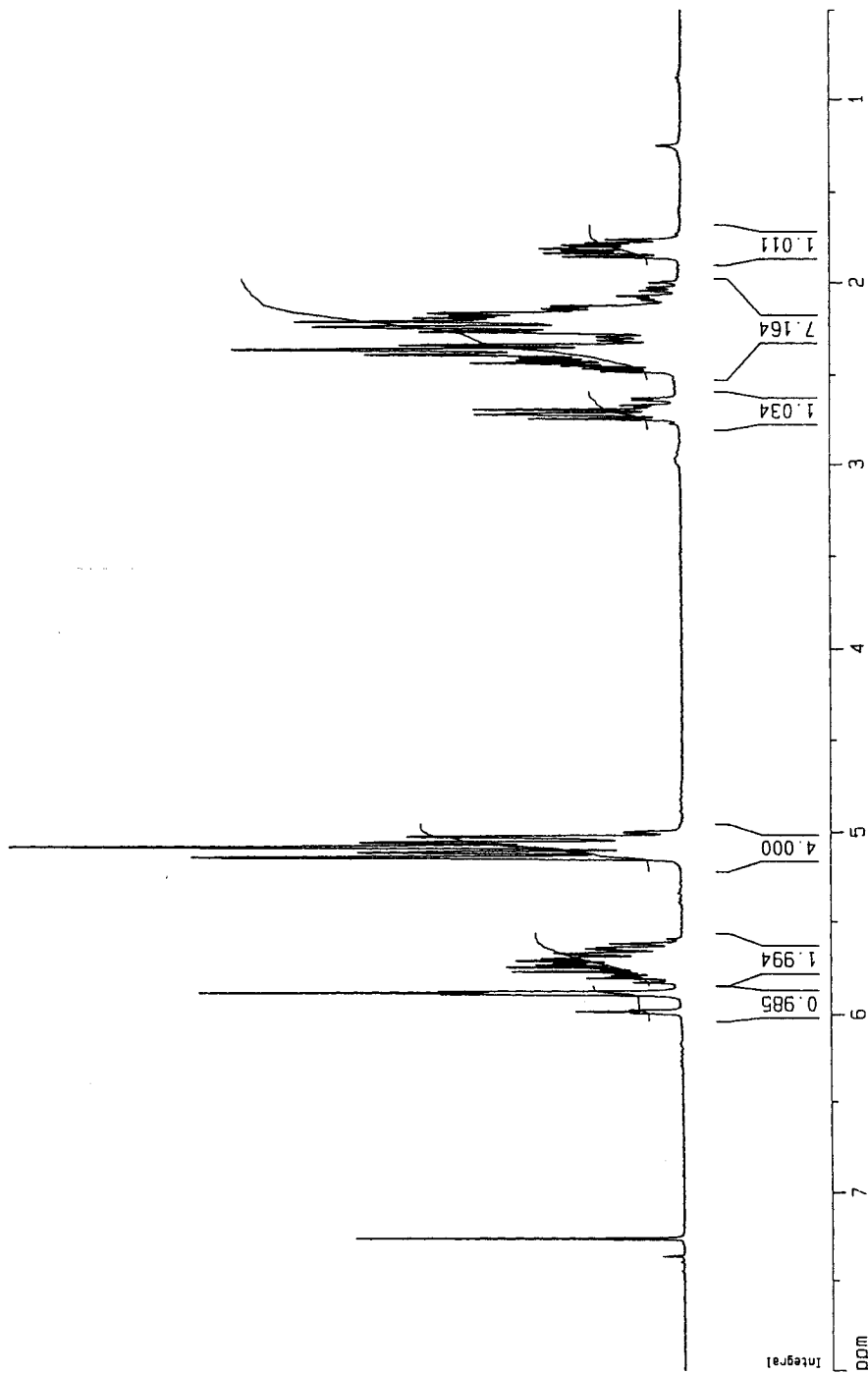
Current Data Parameters
 NAME pb-02-72
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20021017
 Time 13.41
 INSTRUM av300
 PROBD 5 mm QNP 1H/1
 PULPROG zg30
 TO 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 287.4
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P 0.500 ppm
 F2 150.06 Hz
 PPMCM 0.37500 ppm/cm
 HZCM 112.54876 Hz/cm



Current Data Parameters
 NAME pbester
 EXPNO 1
 PROCNO 1

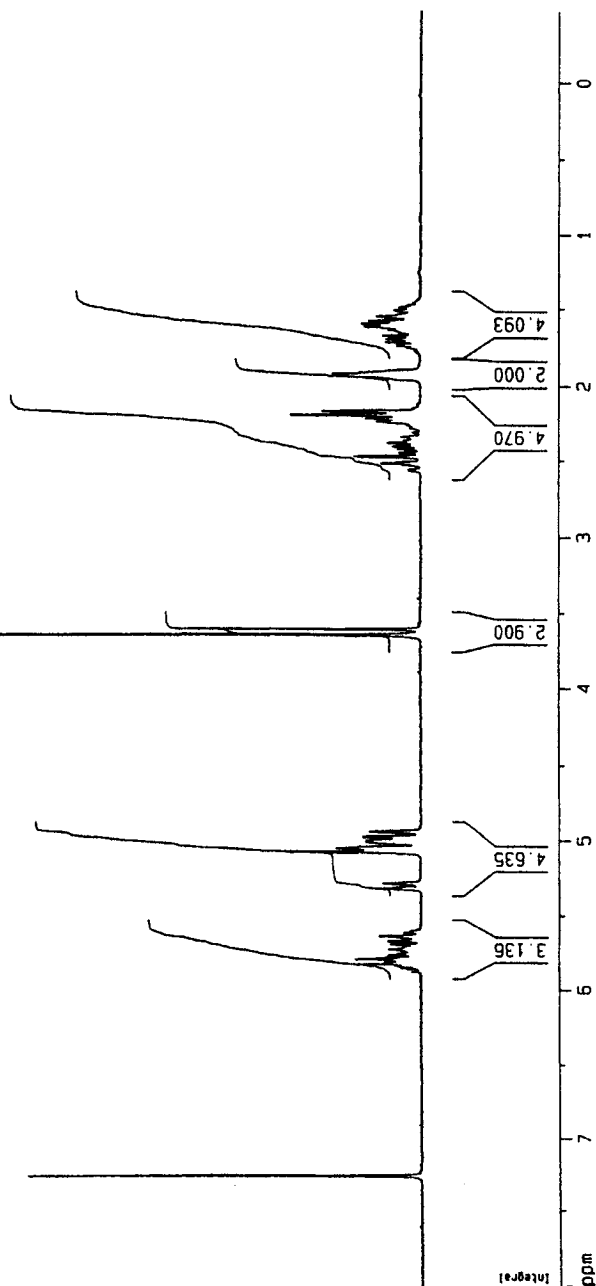
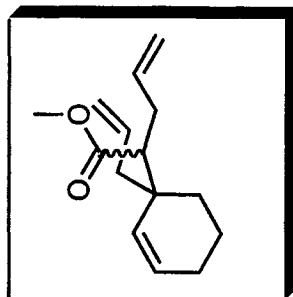
F2 - Acquisition Parameters

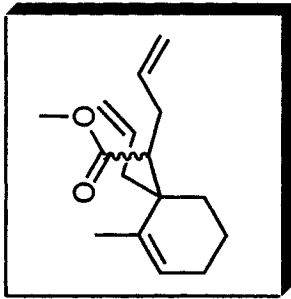
Date_ 20030124
 Time 15.33
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDC13
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 724.1
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.129939 MHz
 HSW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2p -0.500 ppm
 F2 -150.06 Hz
 PRMCH 0.42500 ppm/cm
 HZCH 127.55524 Hz/cm





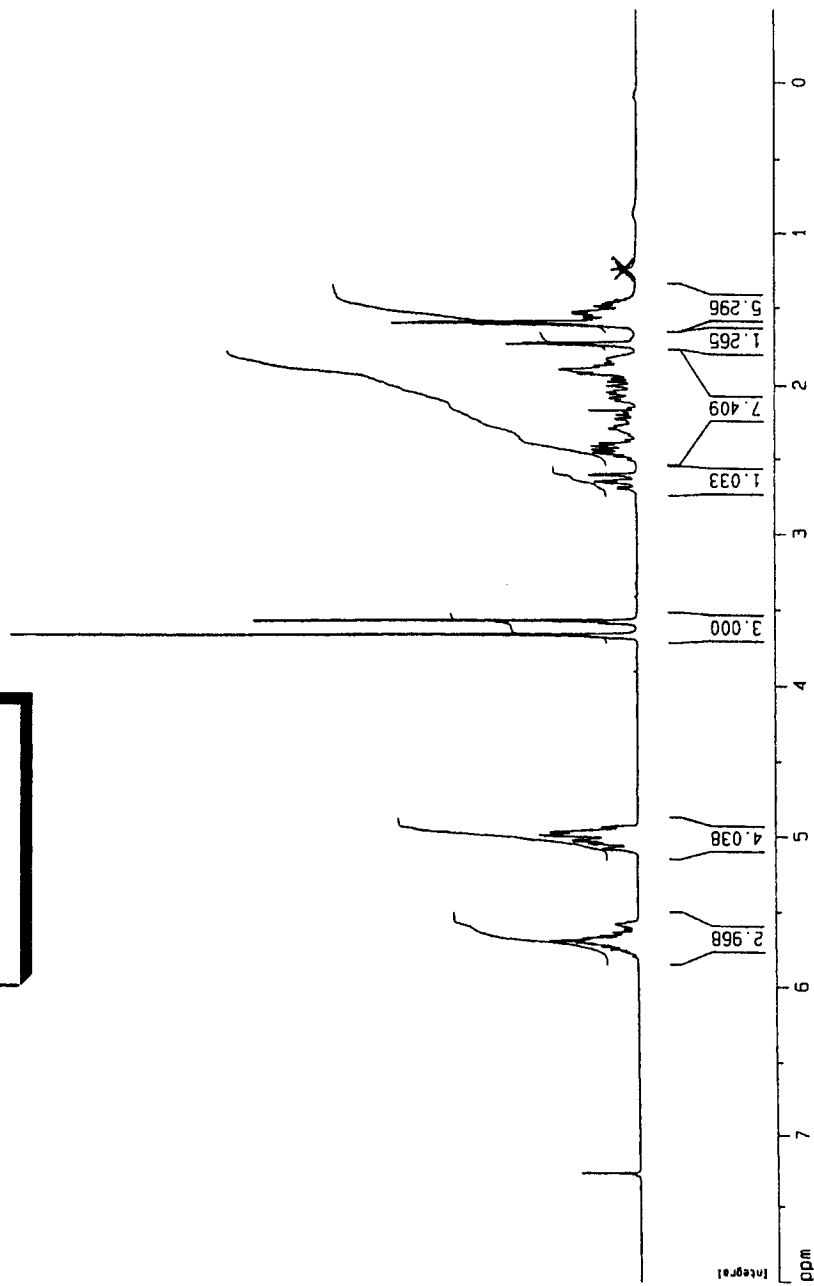
Current Data Parameters
 NAME DD-02-70
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20021007
 Time 16.07
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TO 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 143.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299335 MHz
 HDM EM
 SS0 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-02-100
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021122
 Time 15.23
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 203.2
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

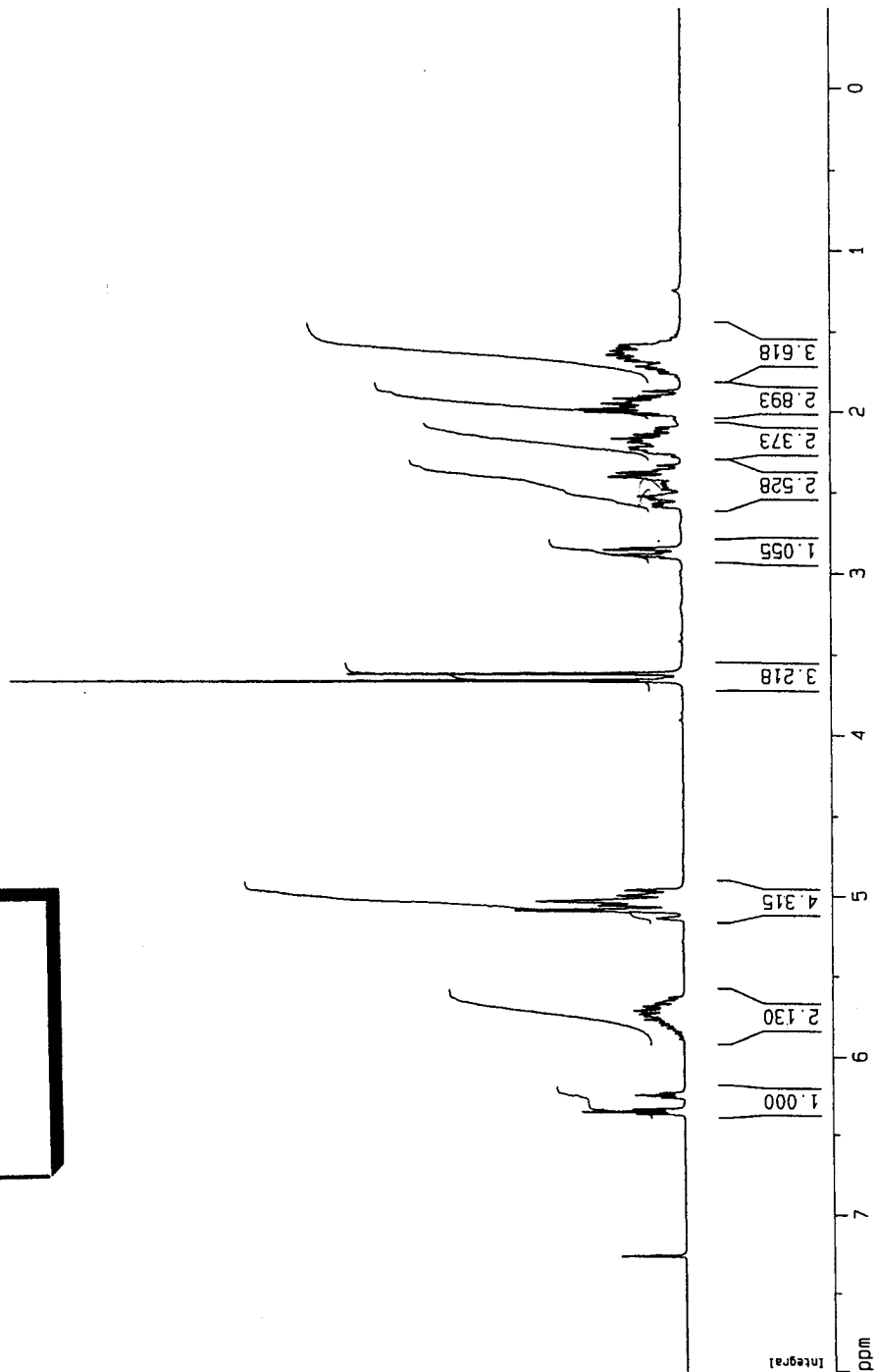
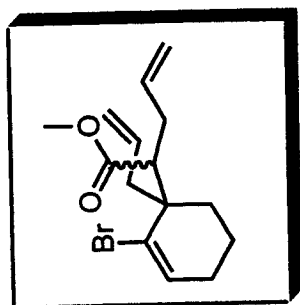
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299944 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



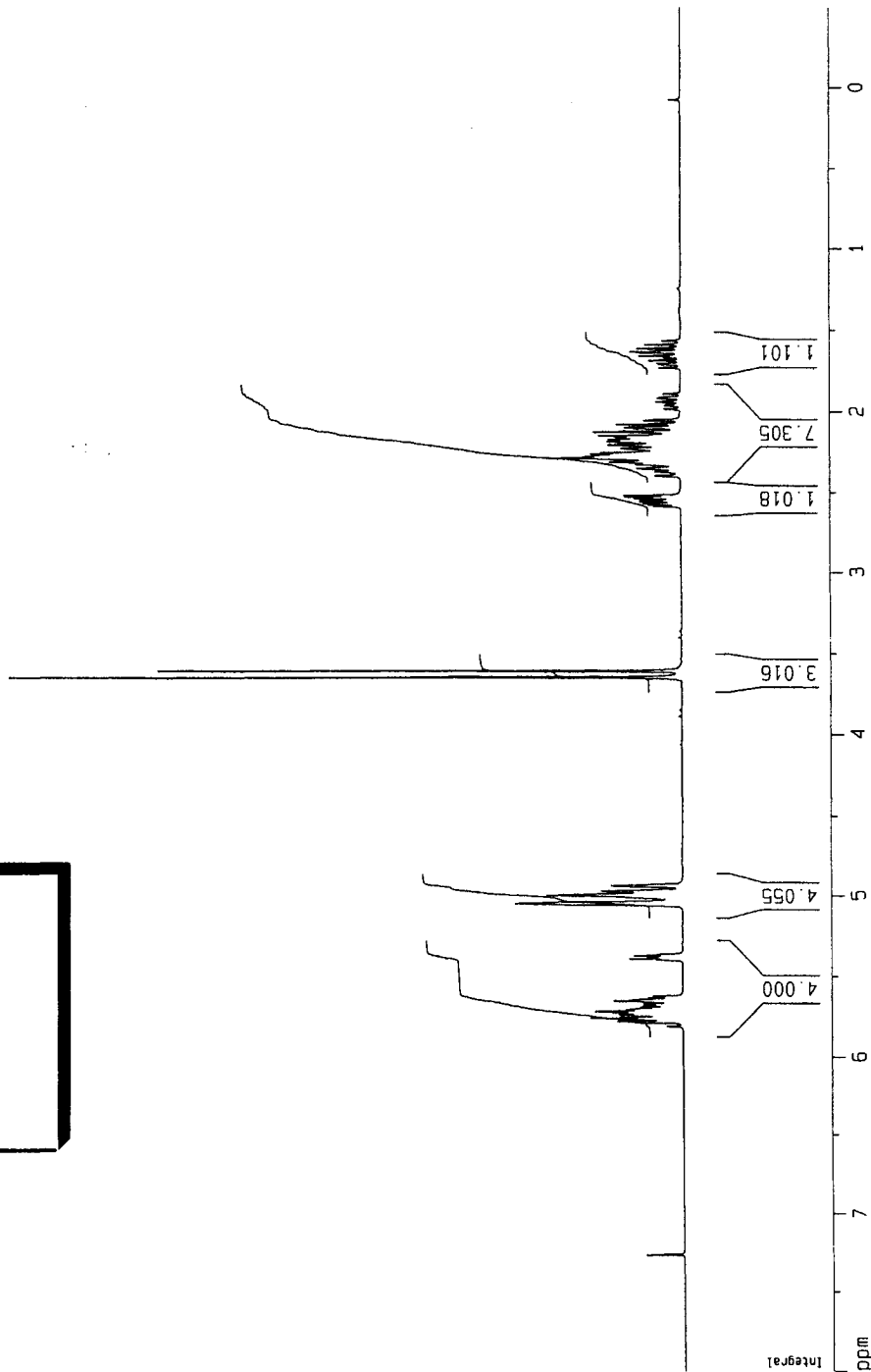
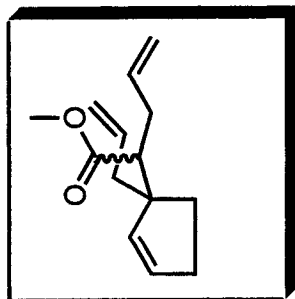
Current Data Parameters
 NAME pb-02-172
 EXPNO 1
 PROCNO 1

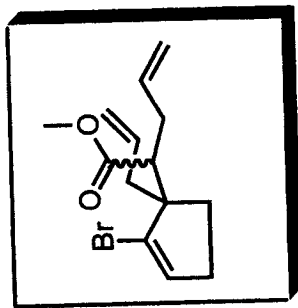
F2 - Acquisition Parameters
 Date_ 20030221
 Time 16.18
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 114
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-74
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021017
 Time 20.47
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 267.4
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

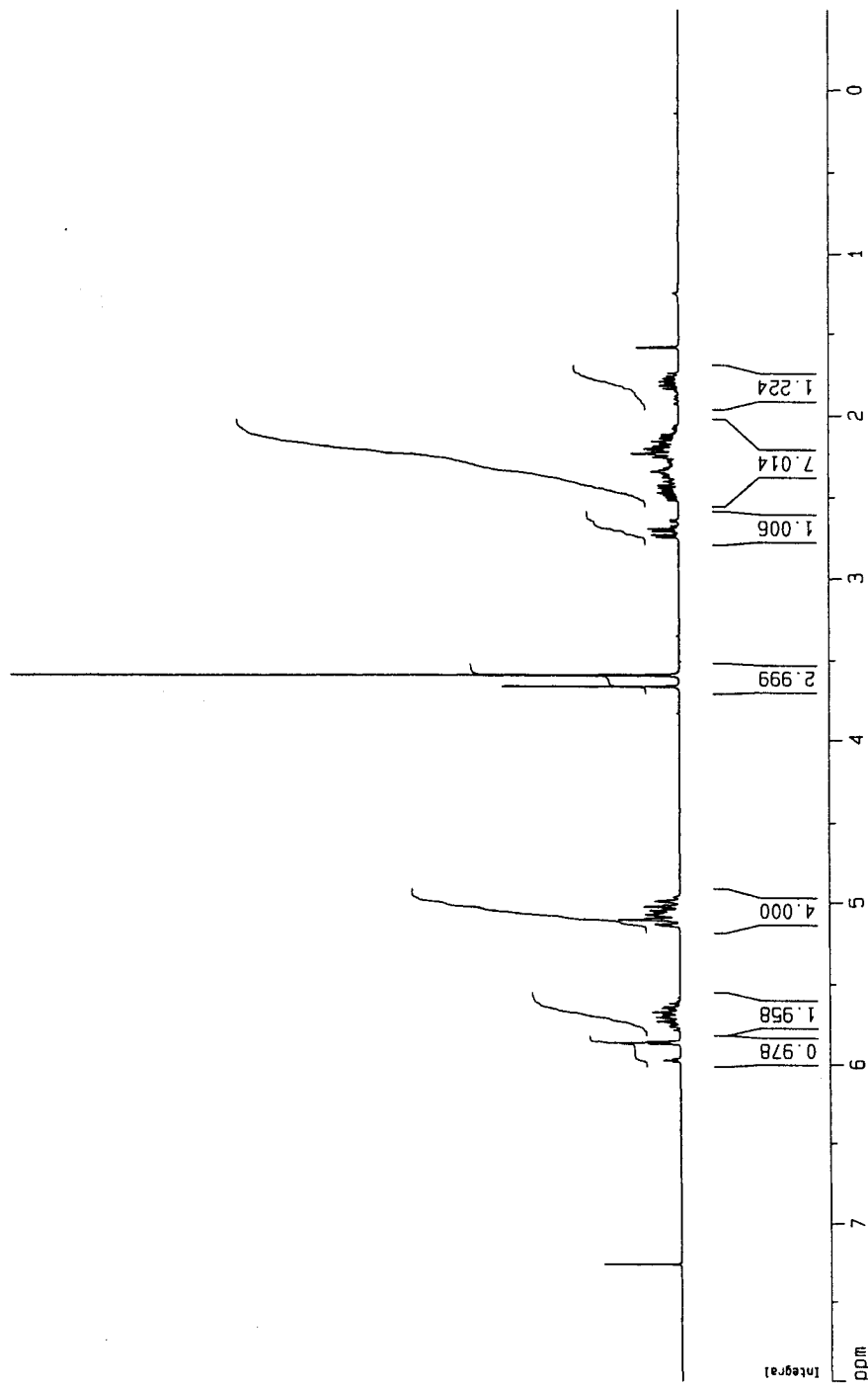
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

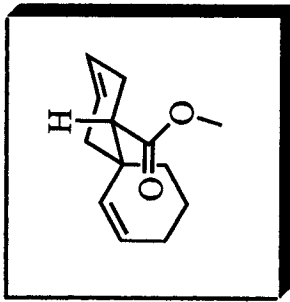
F2 - Processing parameters

SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





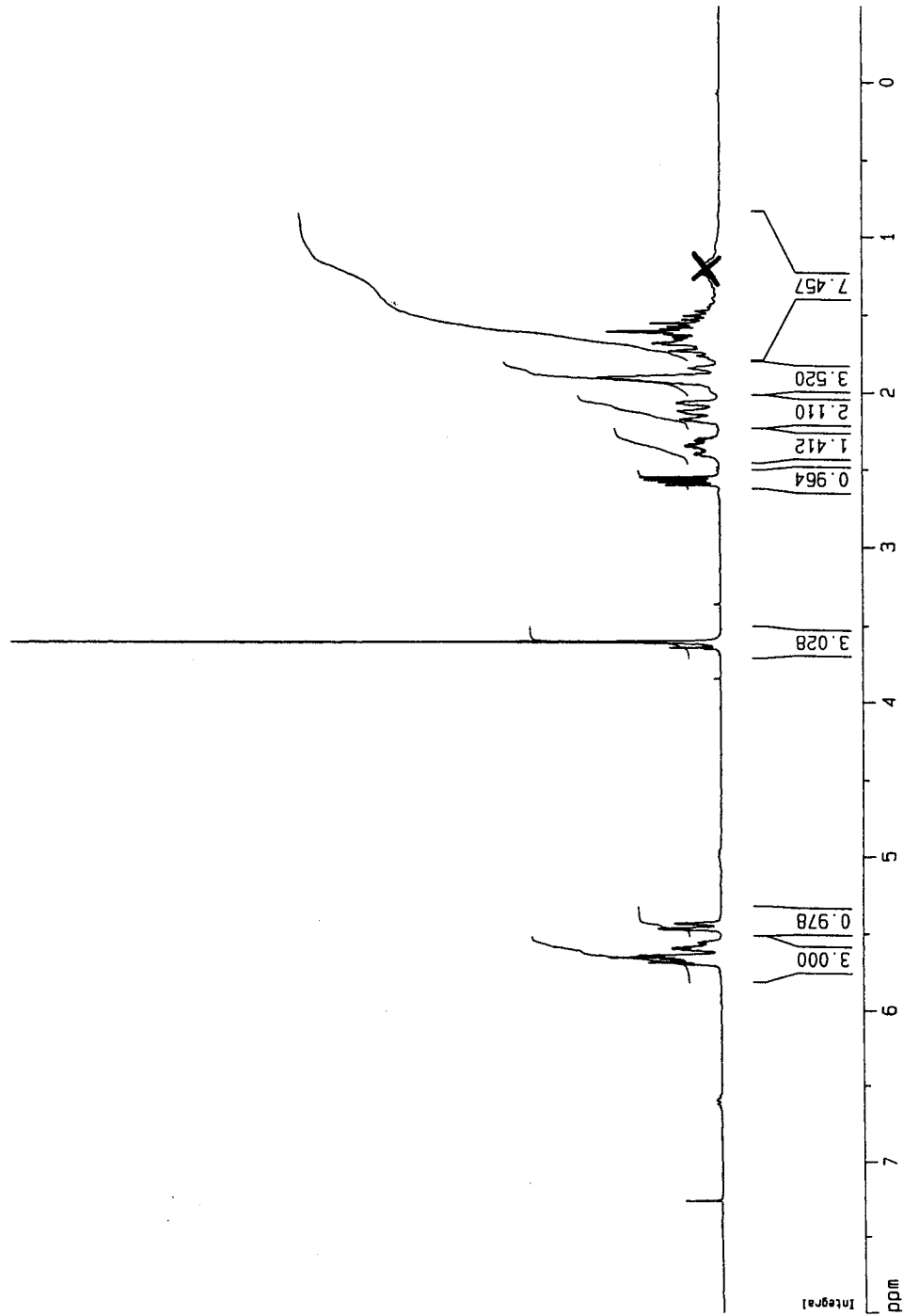
Current Data Parameters
 NAME pb-02-69lesspol
 EXPNO 1
 PROCNO 1

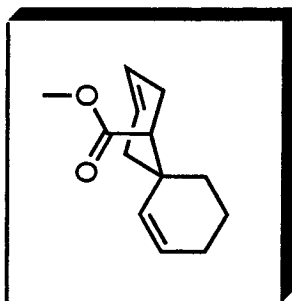
F2 - Acquisition Parameters
 Date_ 20030619
 Time 18.21
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 45.3
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 20.00 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2 -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-69morepol
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030620
 Time 11.39
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDC13
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 64
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

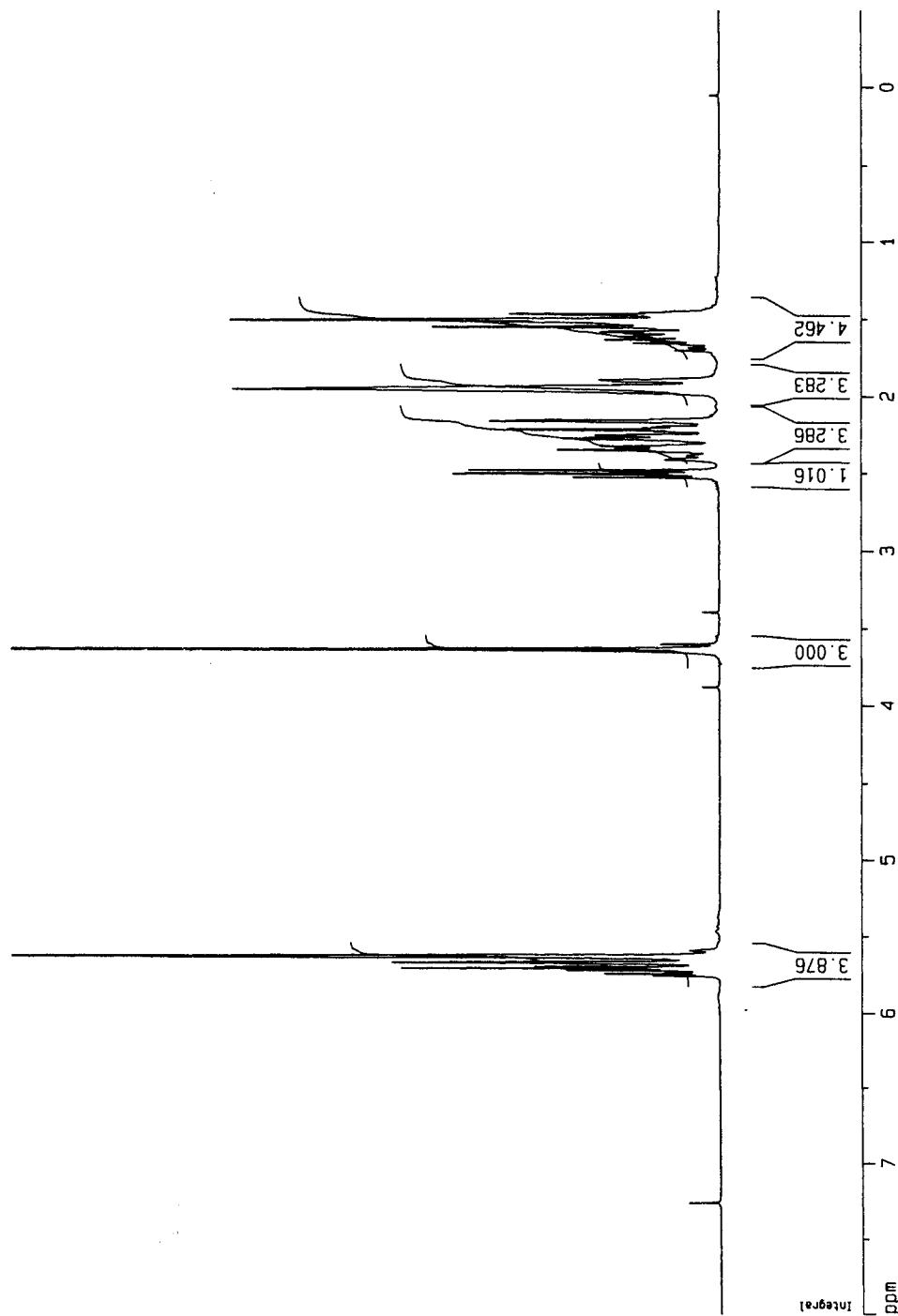
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

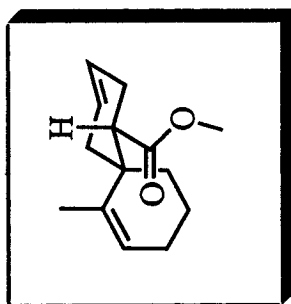
F2 - Processing parameters

SI 65536
 SF 300.1299938 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 50.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-02-71
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021008
 Time 14.05
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 512
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

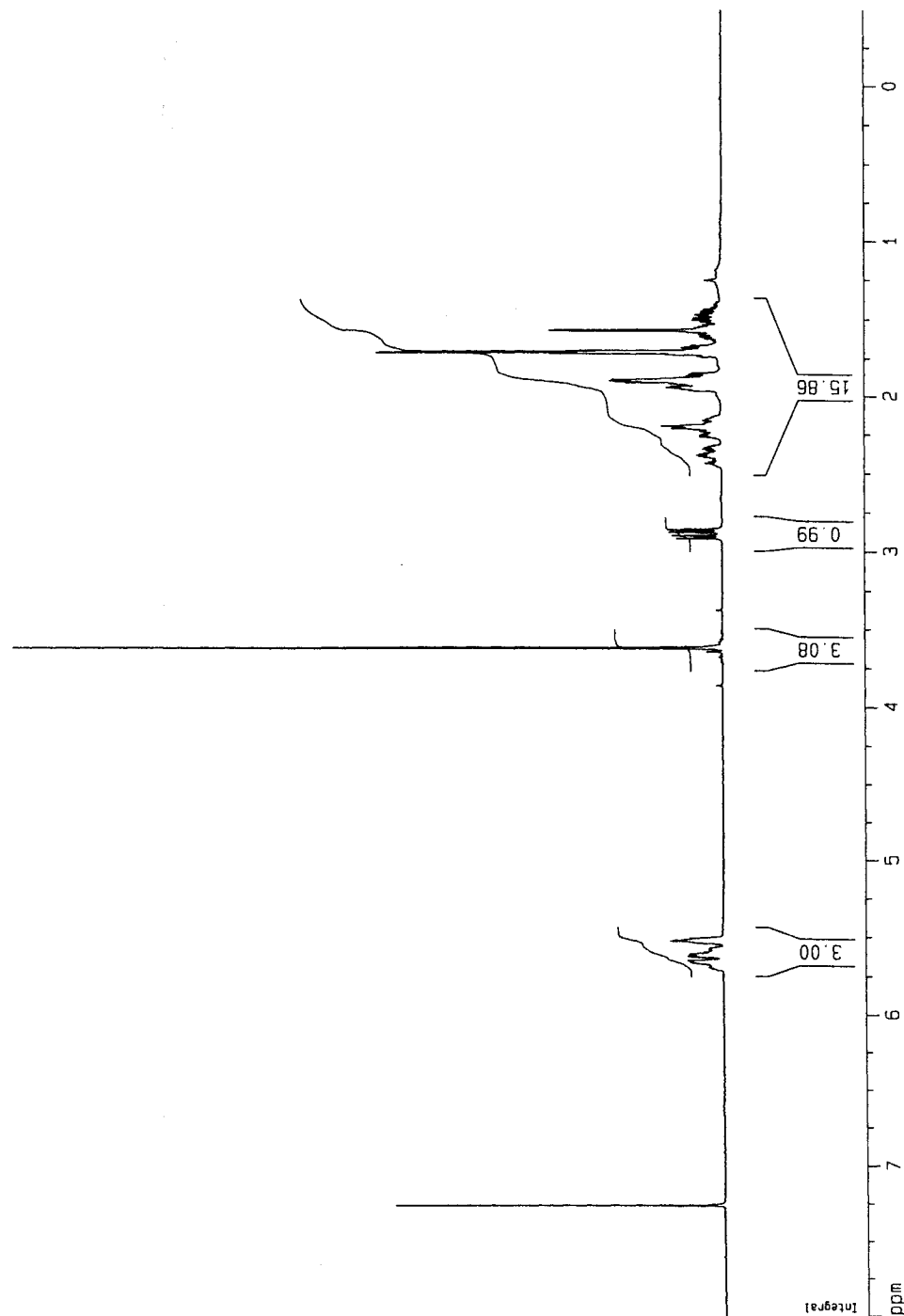
===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 20.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



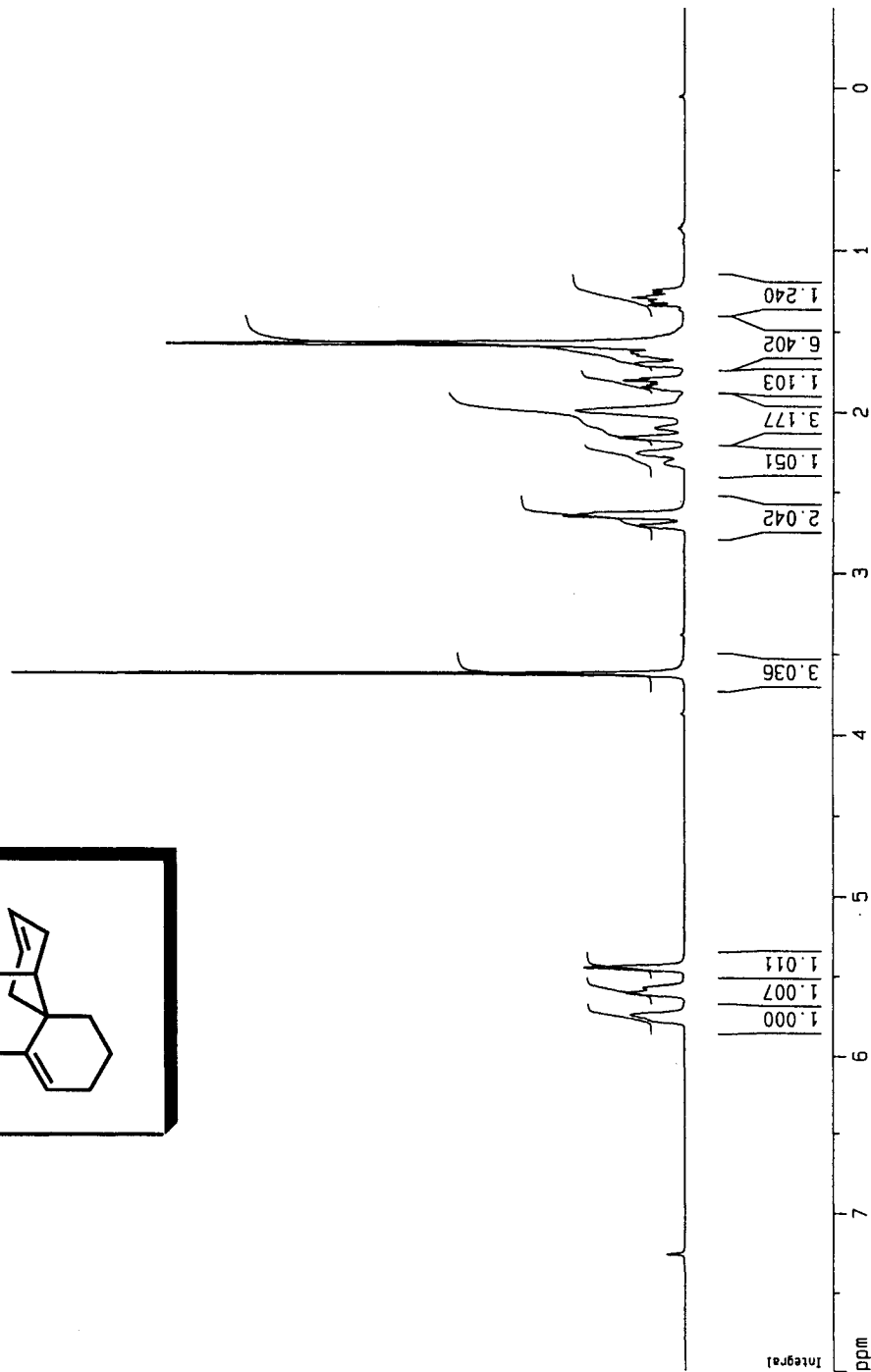
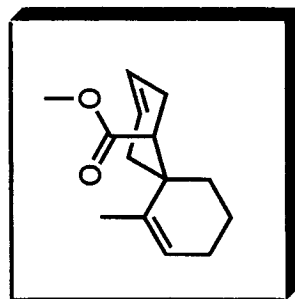
Current Data Parameters
 NAME pb-02-71
 EXPNO 1
 PROCNO 1

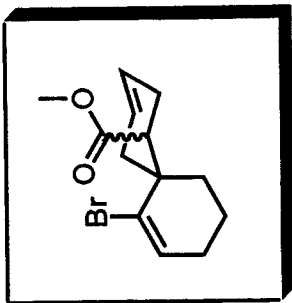
F2 - Acquisition Parameters
 Date_ 20030618
 Time 17.57
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 71.8
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





26-02-158

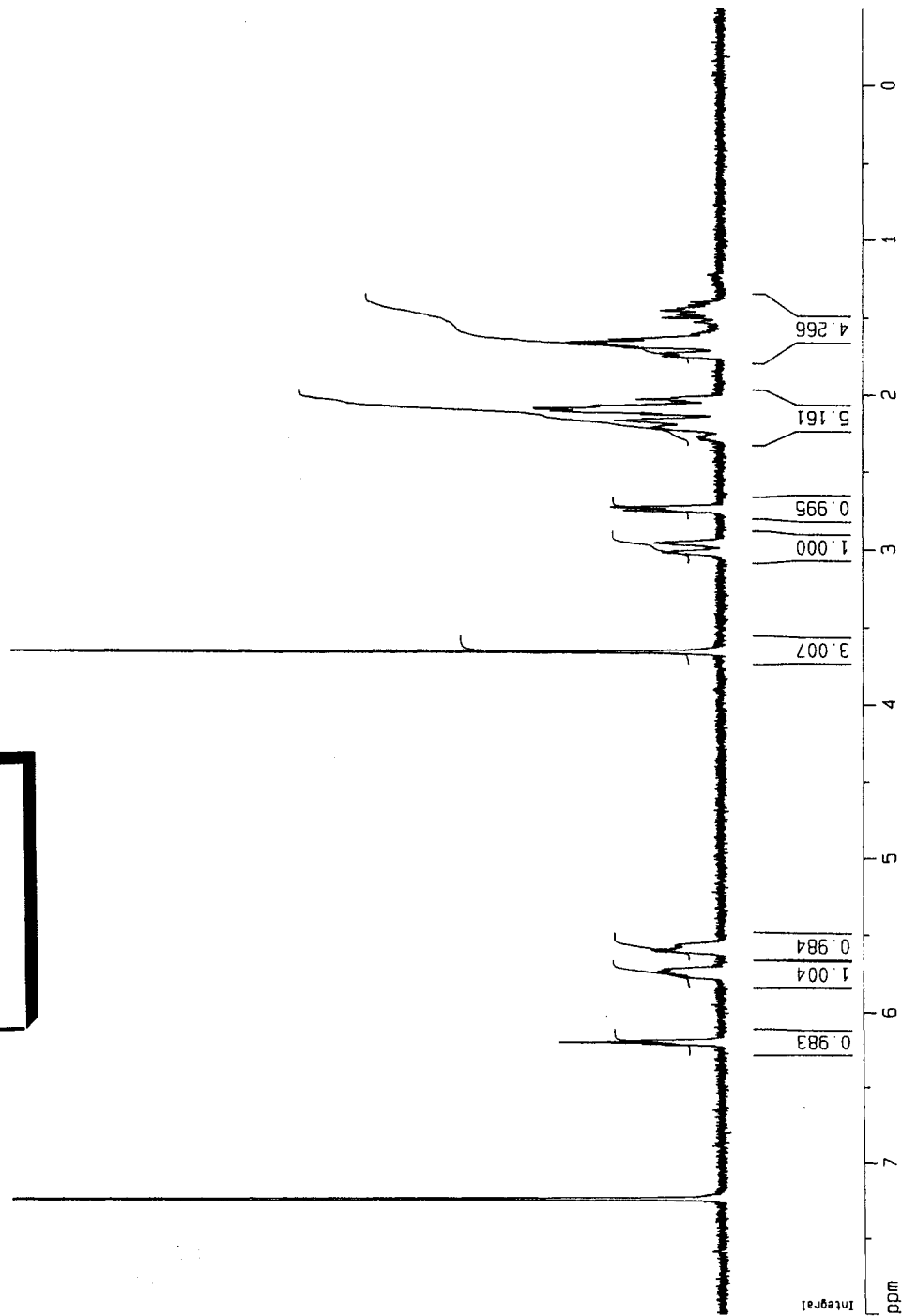
Current Data Parameters
NAME pb-02-15x
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030211
Time 10.07
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 16
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 1290.2
DM 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.75 usec
PL1 -3.00 dB
SFO1 300.1319477 MHz

F2 - Processing parameters
SI 65536
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
FIP 8.000 ppm
F1 2401.04 Hz
F2 -0.500 ppm
F2 -150.06 Hz
PPMCM 0.42500 ppm/cm
HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-02-75
 EXPNO 1
 PROCNO 1

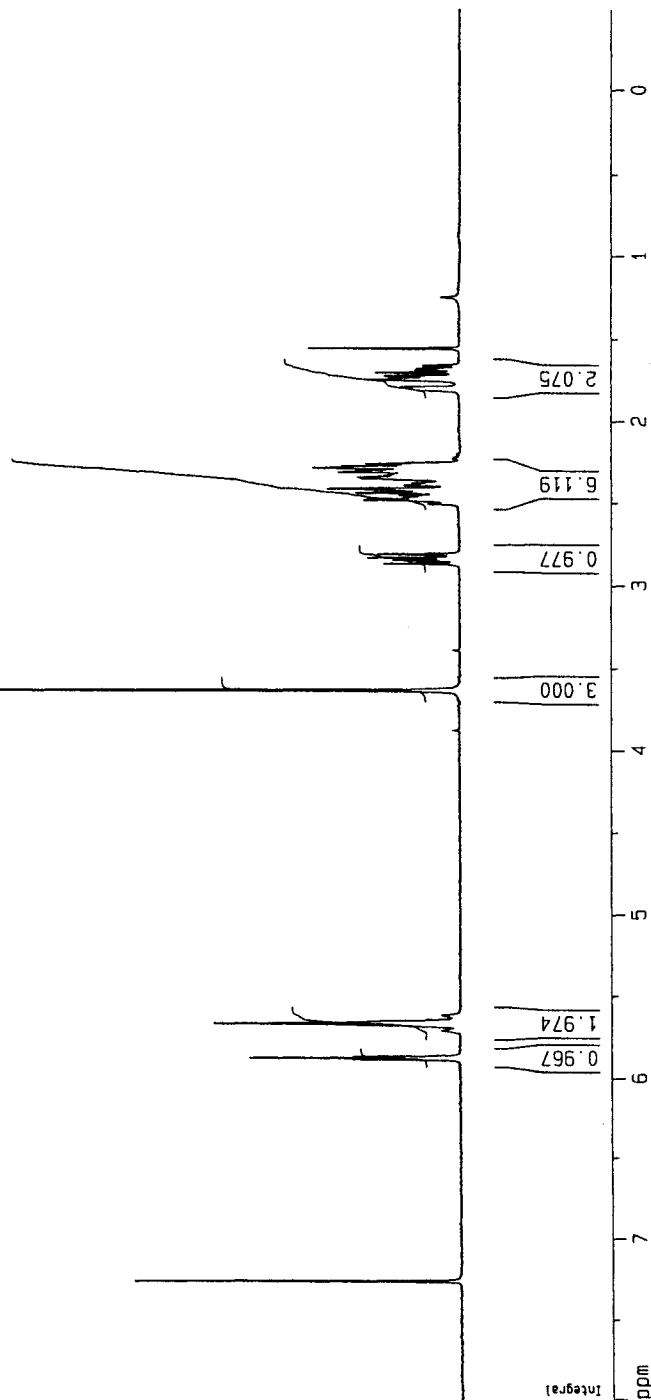
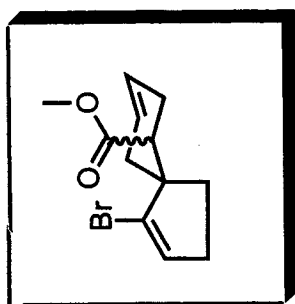
F2 - Acquisition Parameters

Date_ 20021021
 Time 18.15
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 724.1
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299940 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 20.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-04-32
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030921
 Time 16.58
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TO 30720
 SOLVENT CDC13
 NS 13
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 45.3
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

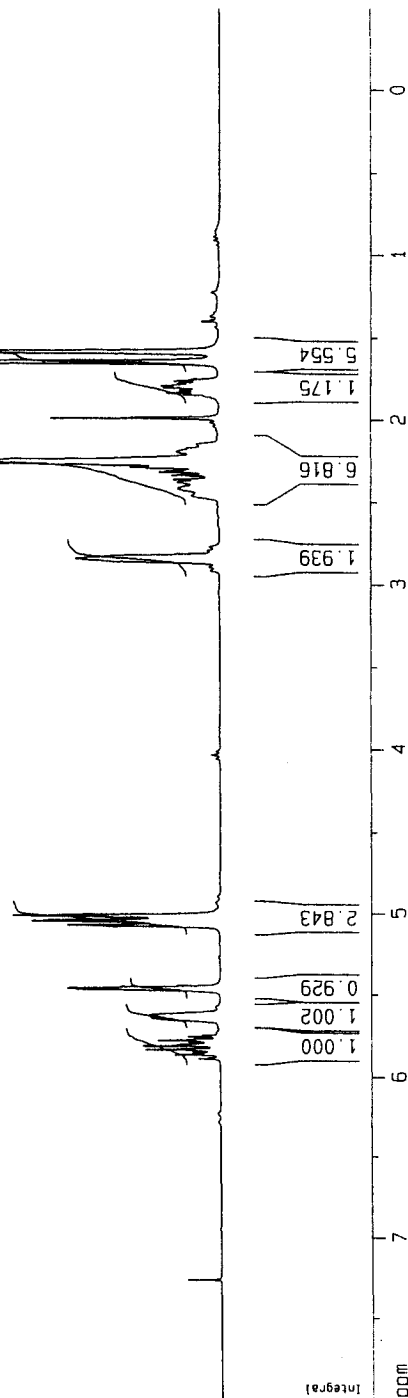
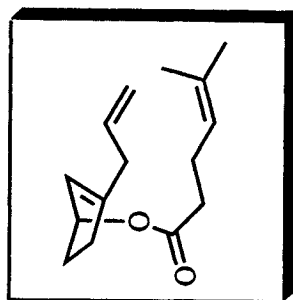
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

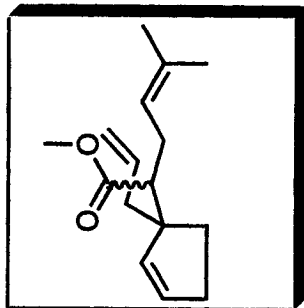
F2 - Processing parameters

SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

10 NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-04-38test
 EXPNO 1
 PROCNO 1

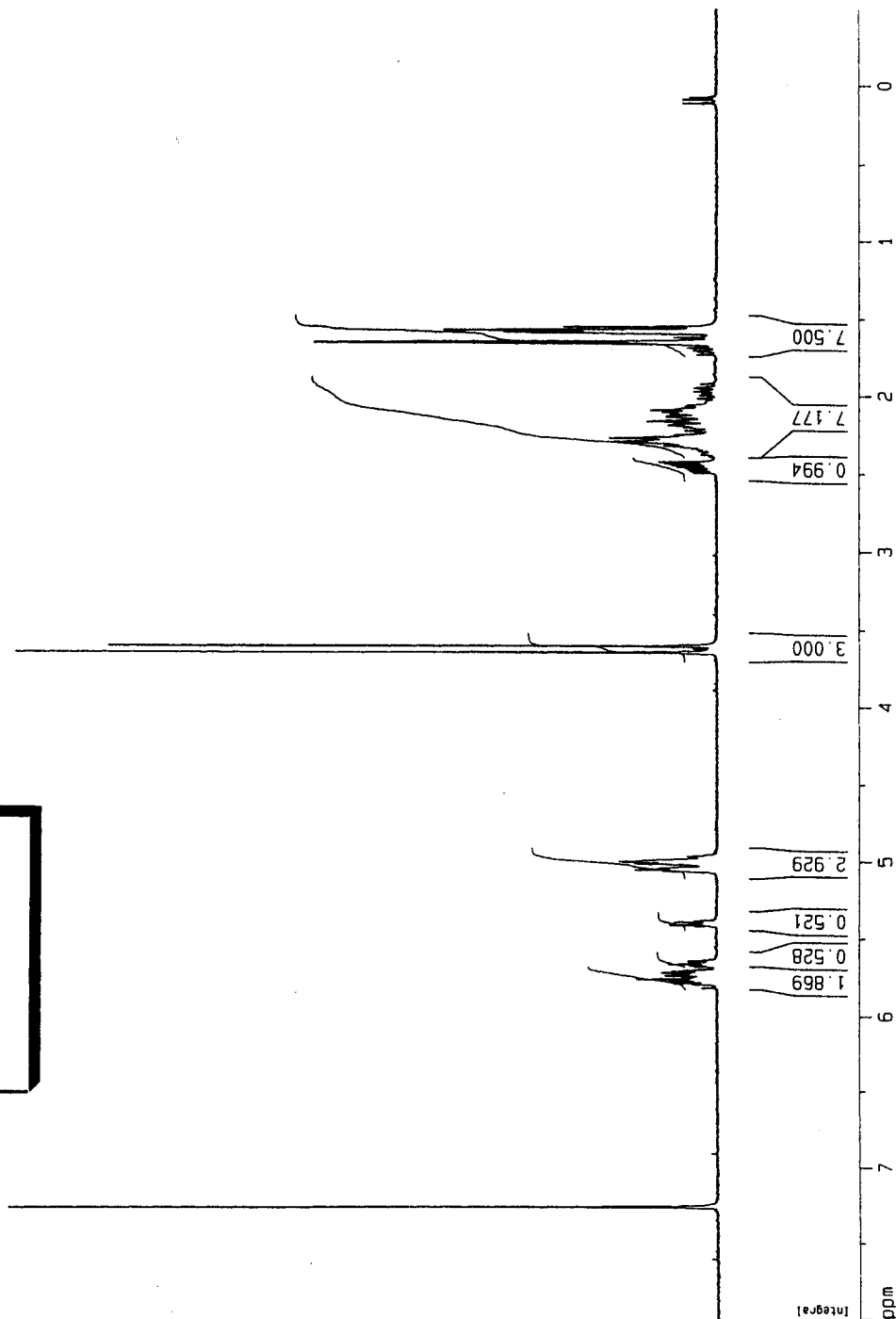
F2 - Acquisition Parameters

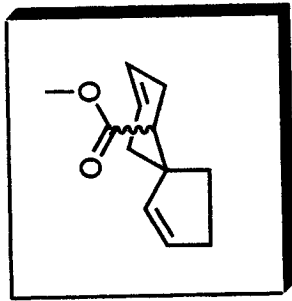
Date_ 20030924
 Time 12.45
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 912.3
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 15.00 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2 -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-04-38
 EXPNO 1
 PROCNO 1

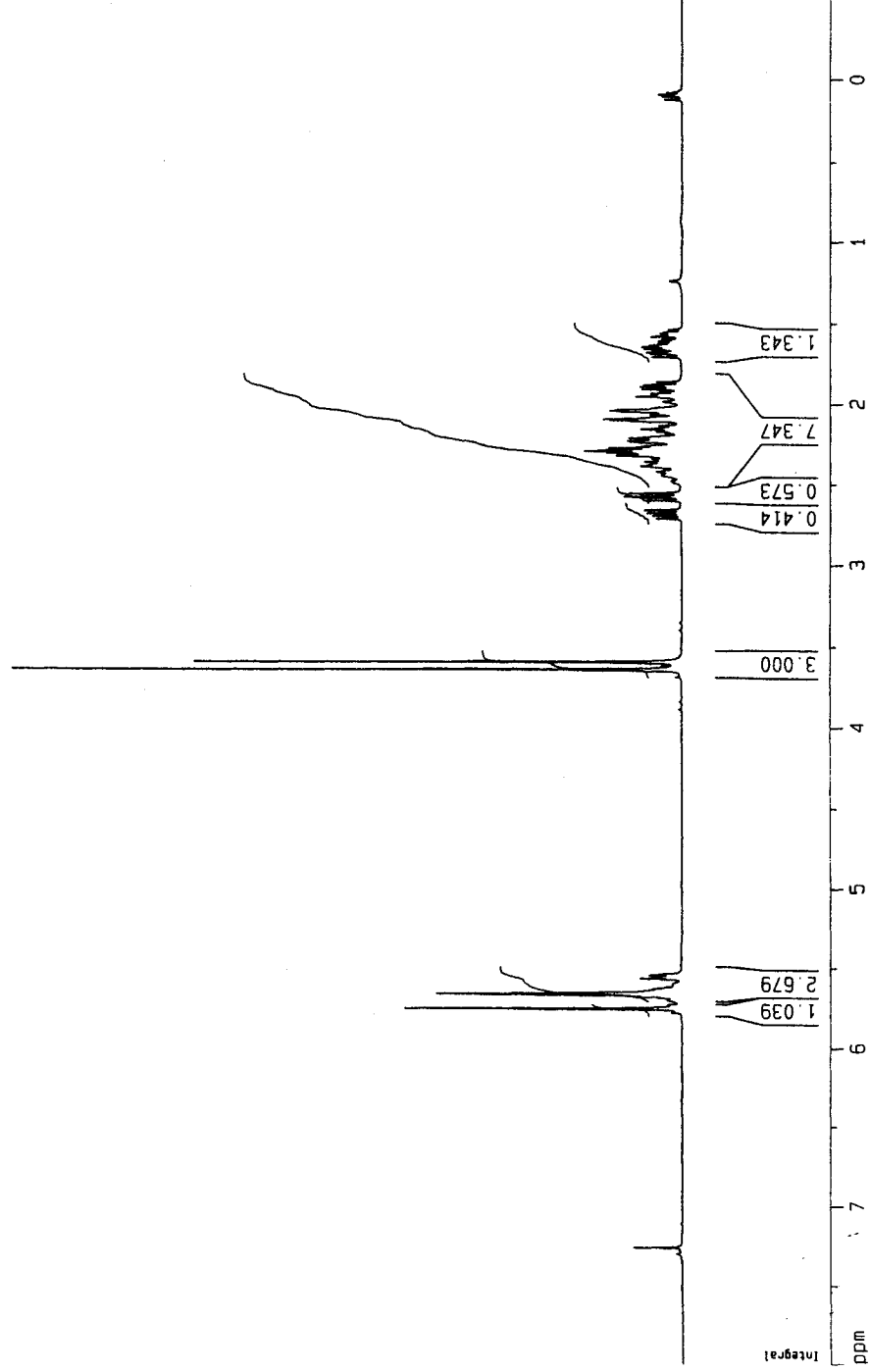
F2 - Acquisition Parameters

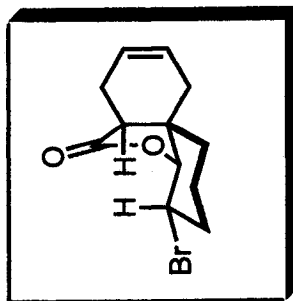
Date_ 20030923
 Time 20.44
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 143.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SFO1 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
NAME pb-04-04pure
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters

Date_ 20030829
Time 12.43
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TO 30720
SOLVENT CDCl3
NS 5
DS 0
SWH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec
RG 114
DM 98.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

===== CHANNEL f1 =====

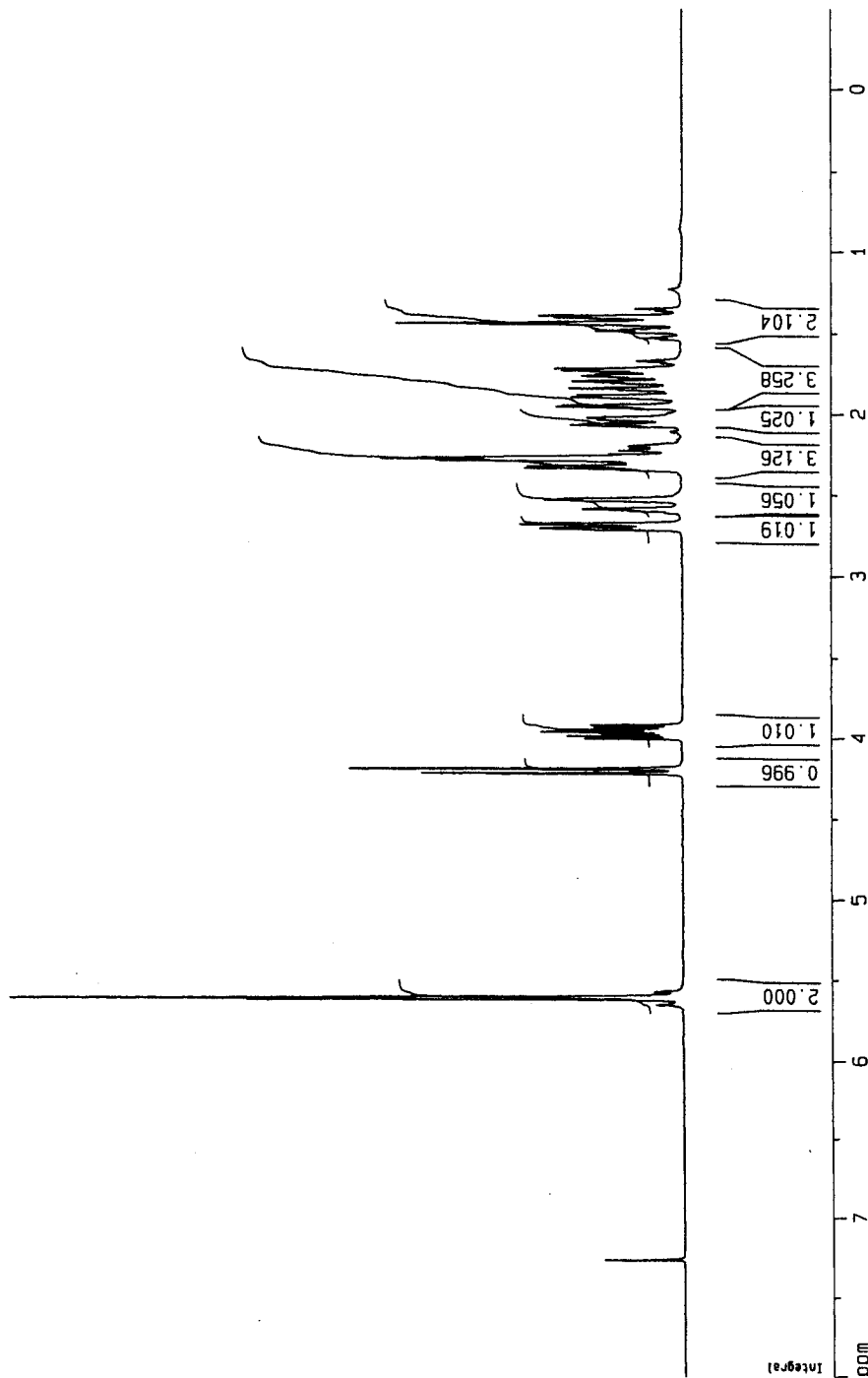
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
SF 300.1299938 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters

CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.42500 ppm/cm
HZCM 127.55524 Hz/cm



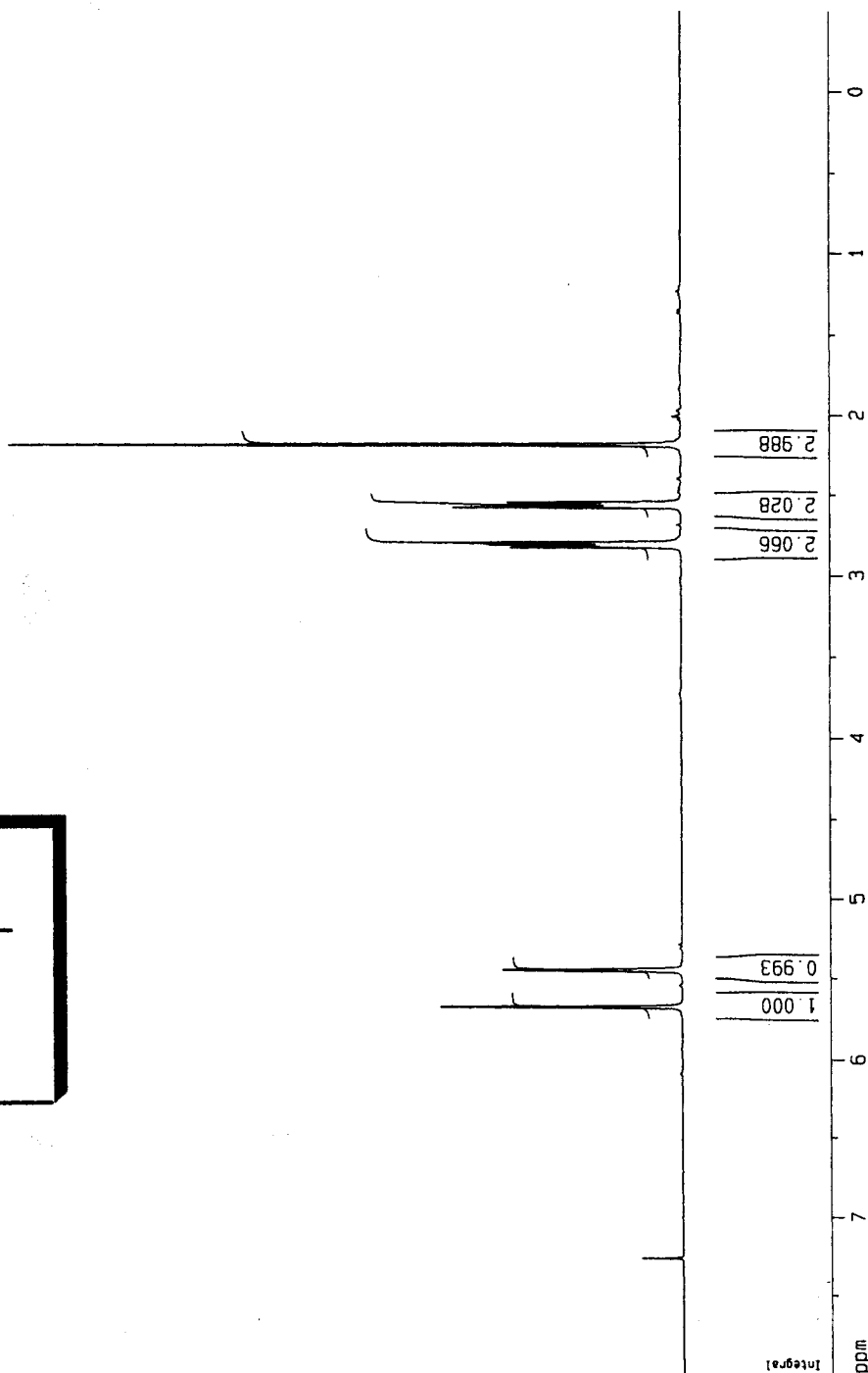
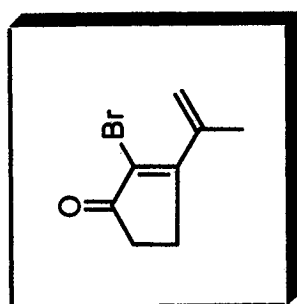
Current Data Parameters
 NAME pb-03-06
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20030314
 Time 17.20
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 228.1
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCH 127.55524 Hz/cm



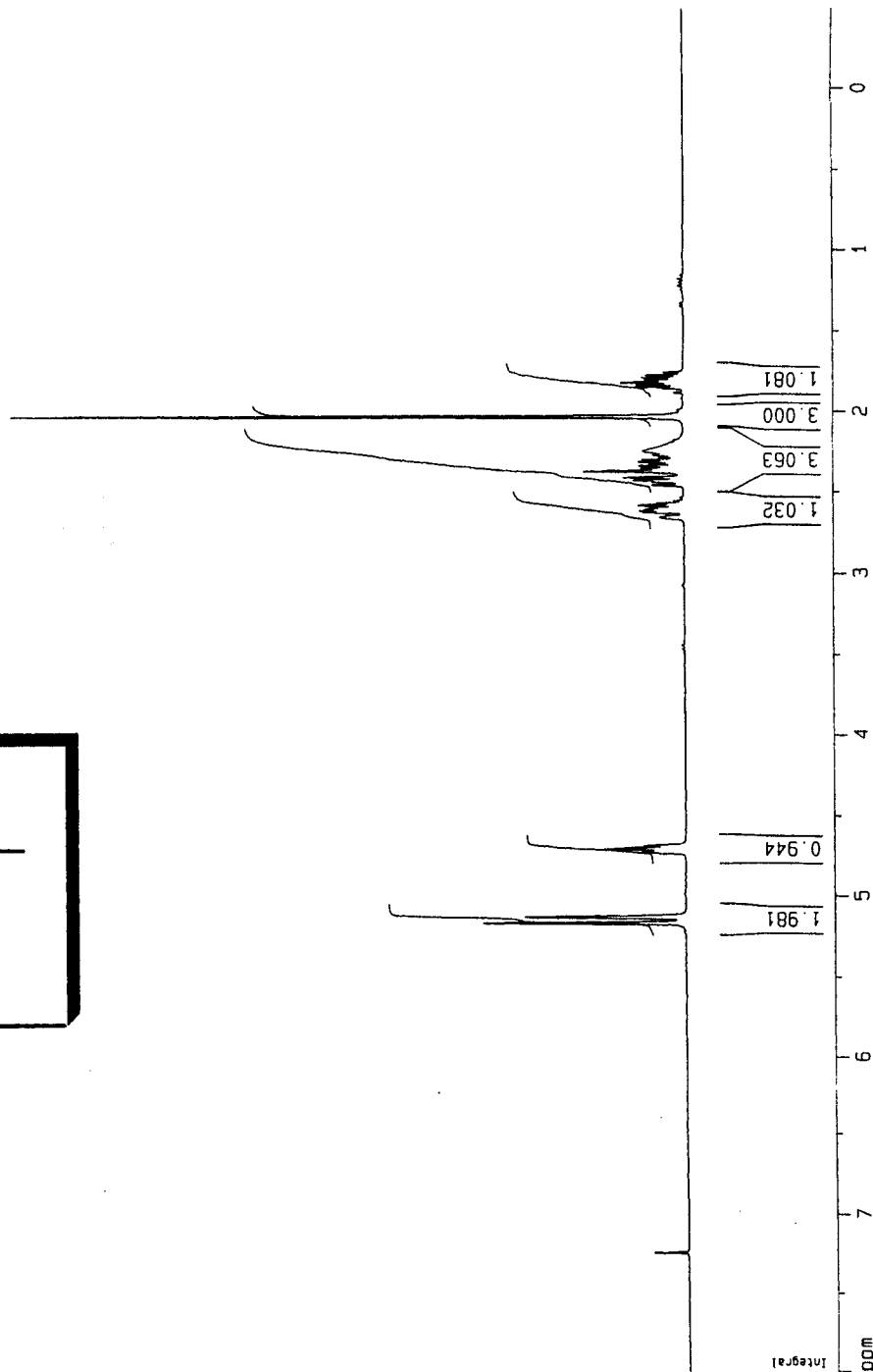
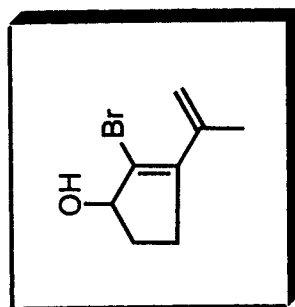
Current Data Parameters
 NAME pb-03-08
 EXPNO 1
 PROCNO 1

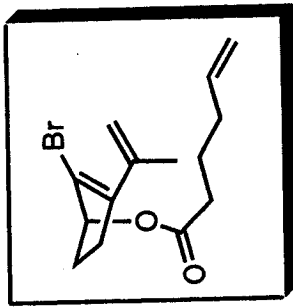
F2 - Acquisition Parameters
 Date_ 20030314
 Time 19.11
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 161.3
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1300000 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





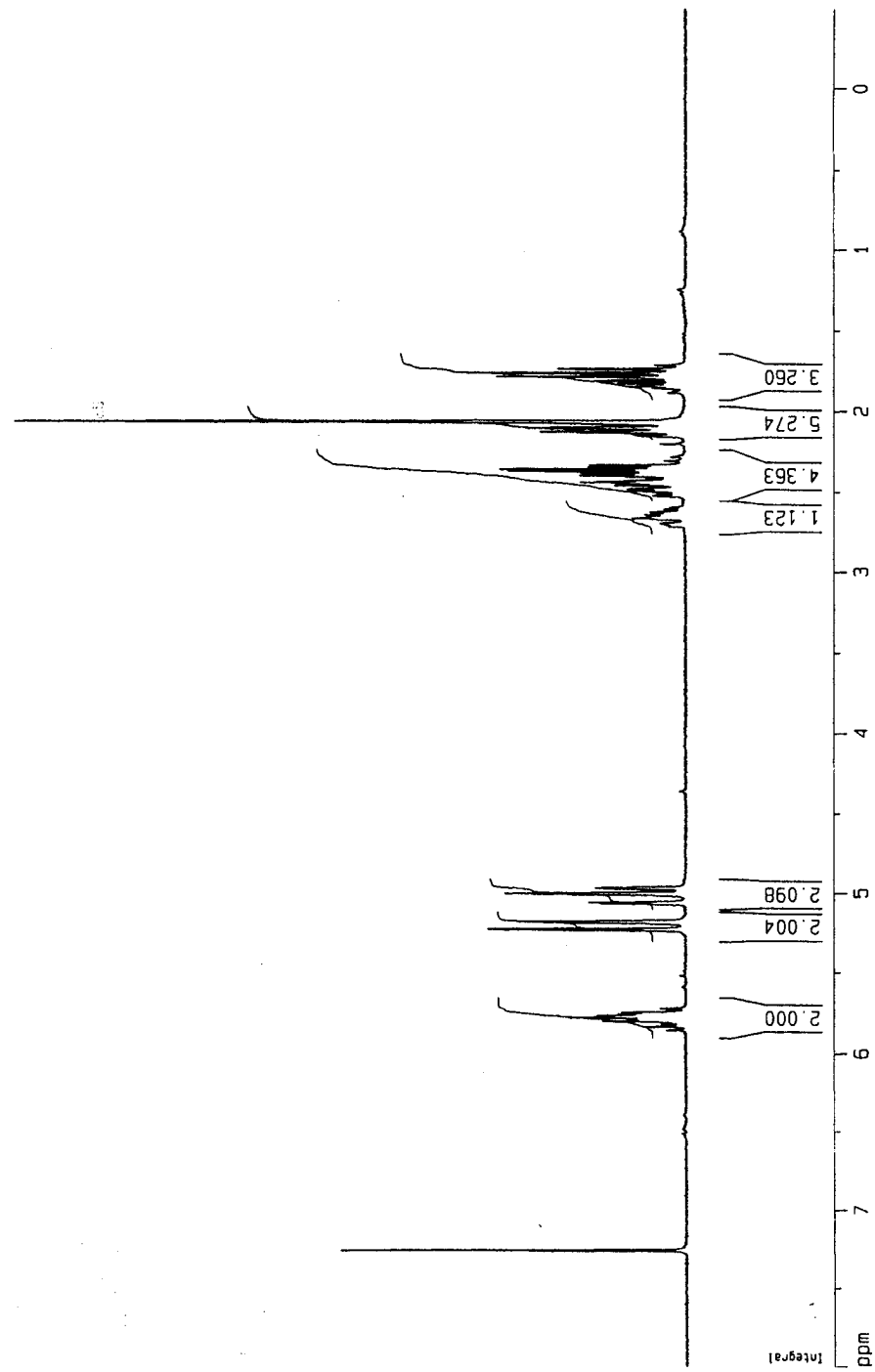
Current Data Parameters
 NAME pb-03-09
 EXPNO 4
 PROCNO 1

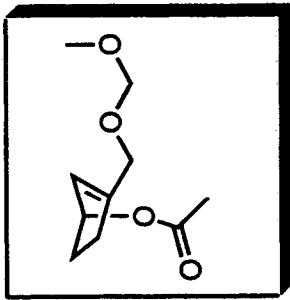
F2 - Acquisition Parameters
 Date_ 20030316
 Time 17.51
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT COCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSF 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-29
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030404
 Time 18.09
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 114
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

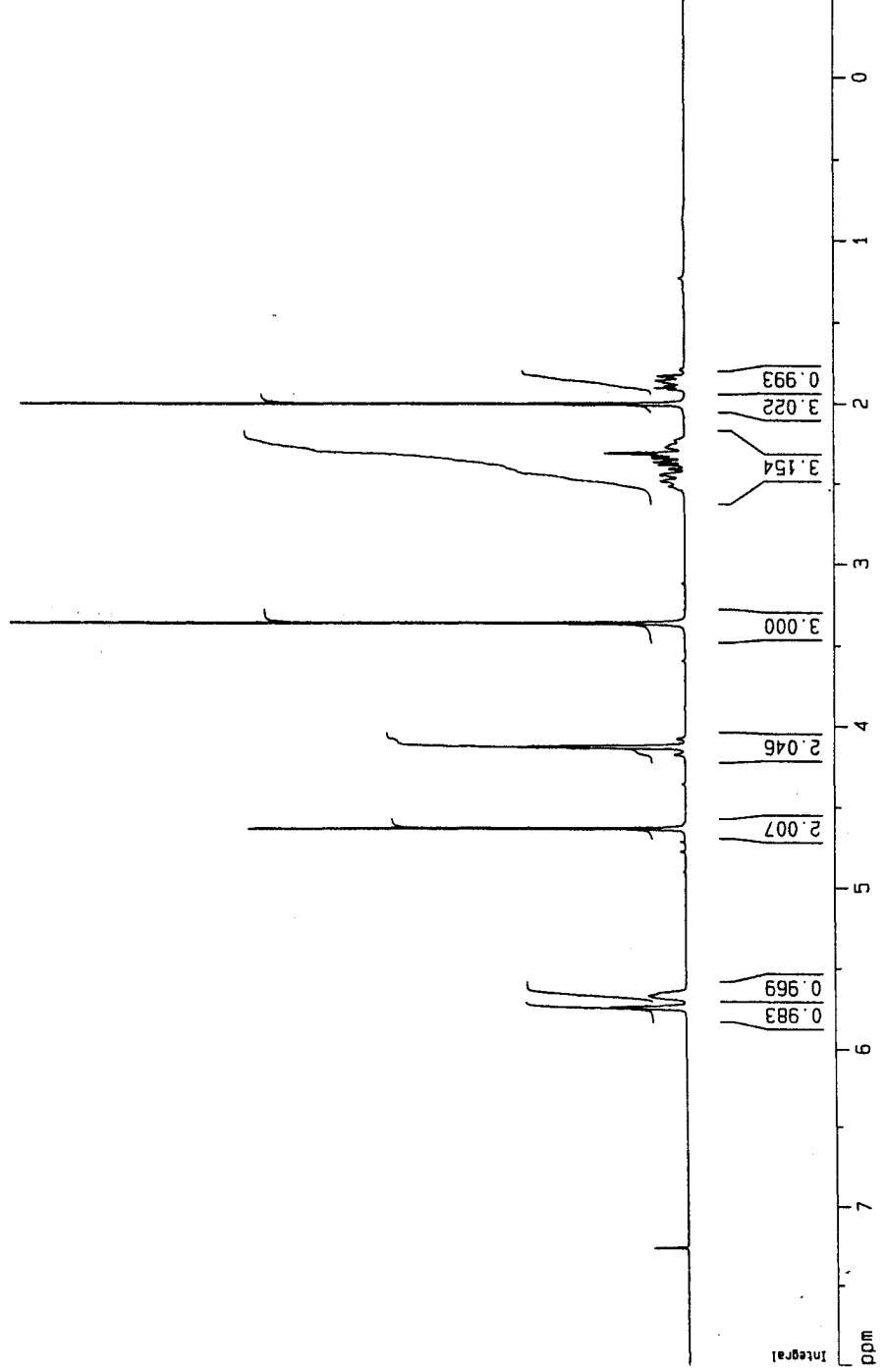
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

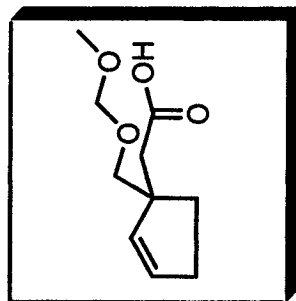
F2 - Processing parameters

SI 65536
 SF 300.1299938 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-31
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030407
 Time 10.36
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TO 30720
 SOLVENT CDCl3
 NS 32
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

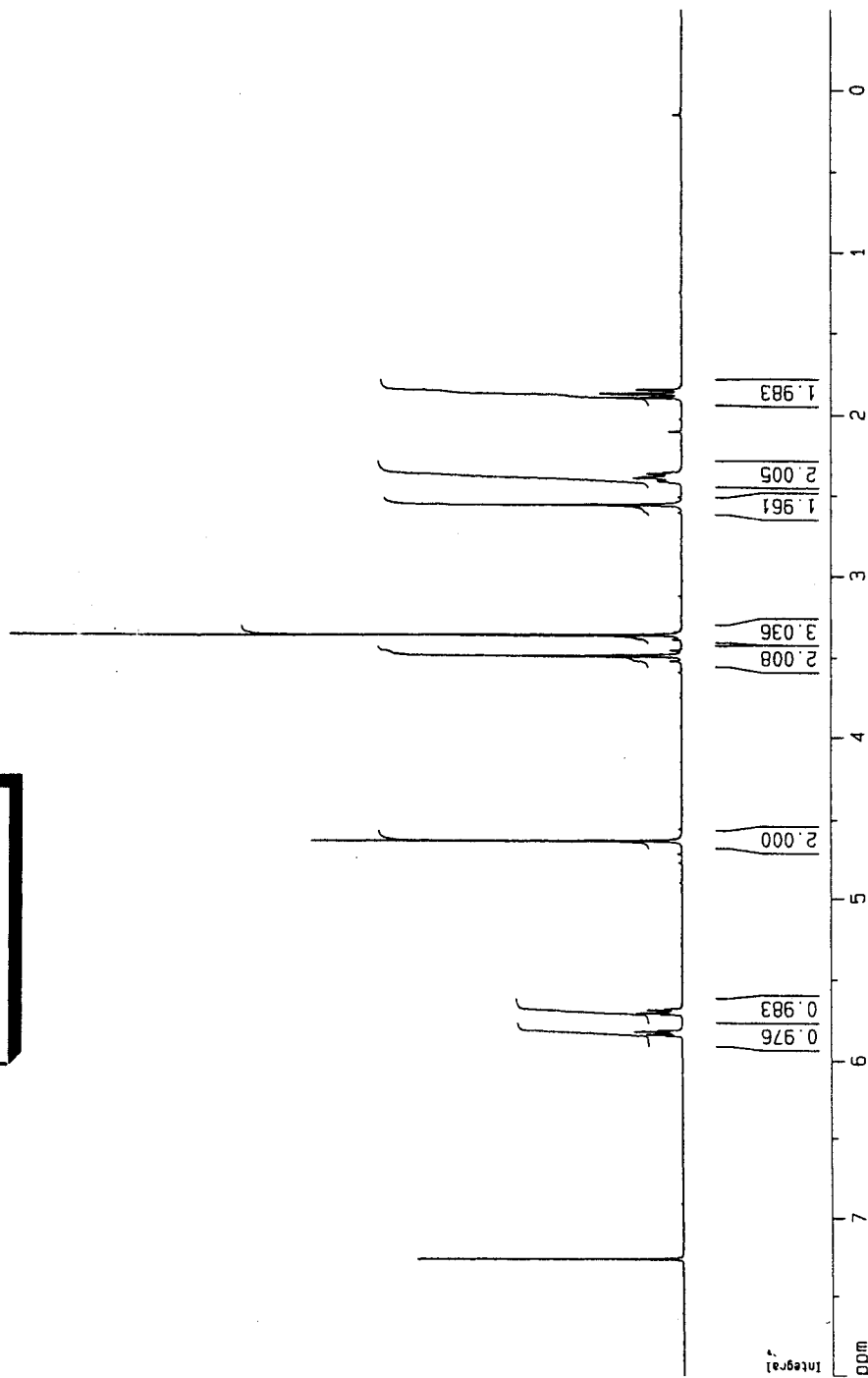
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299941 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCH 127.55524 Hz/cm



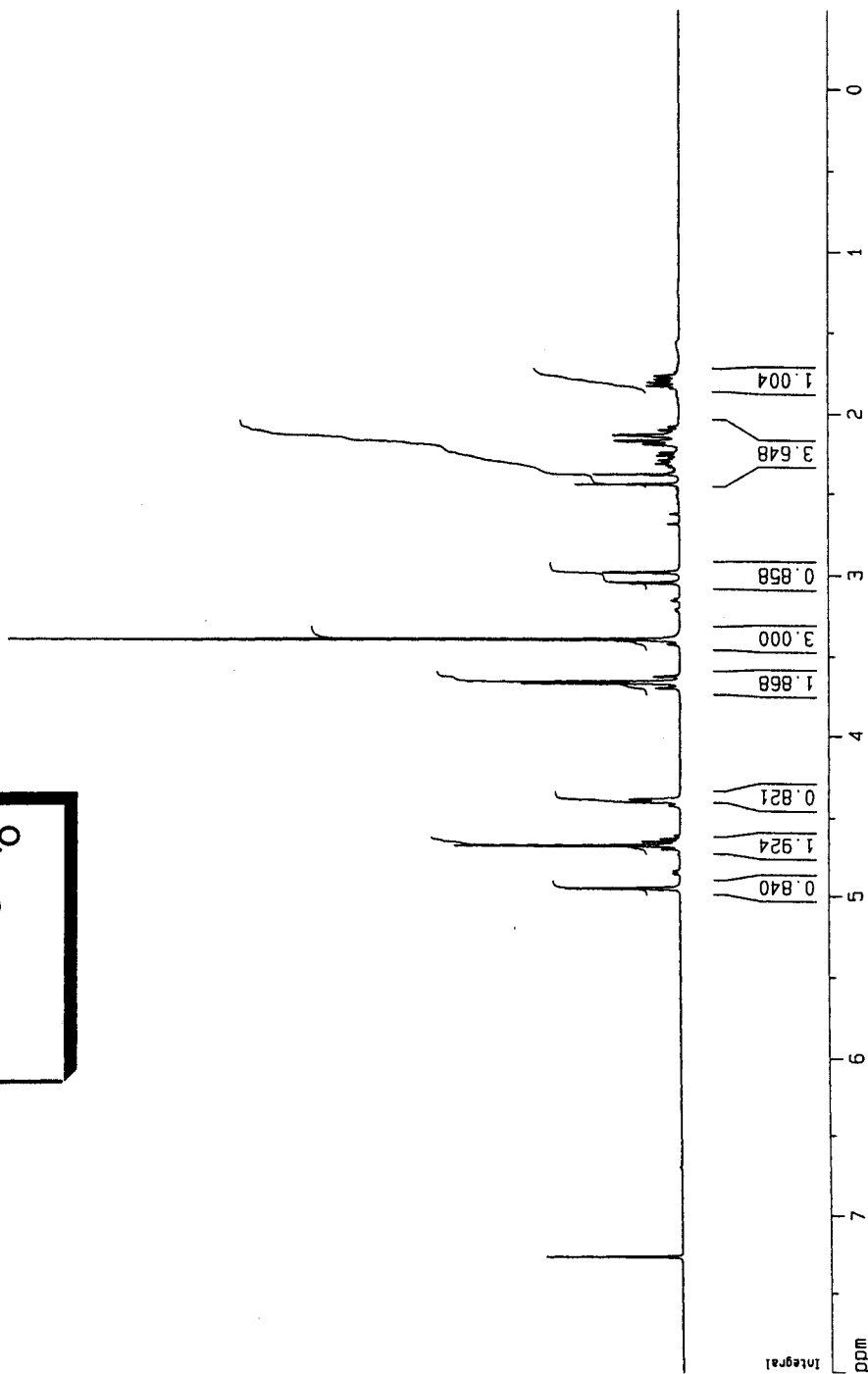
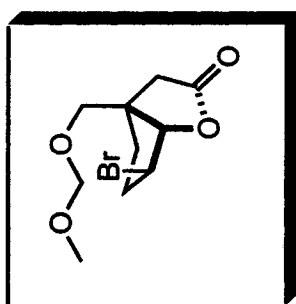
Current Data Parameters
 NAME pb-03-33
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20030408
 Time 15.08
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 406.4
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.59524 Hz/cm



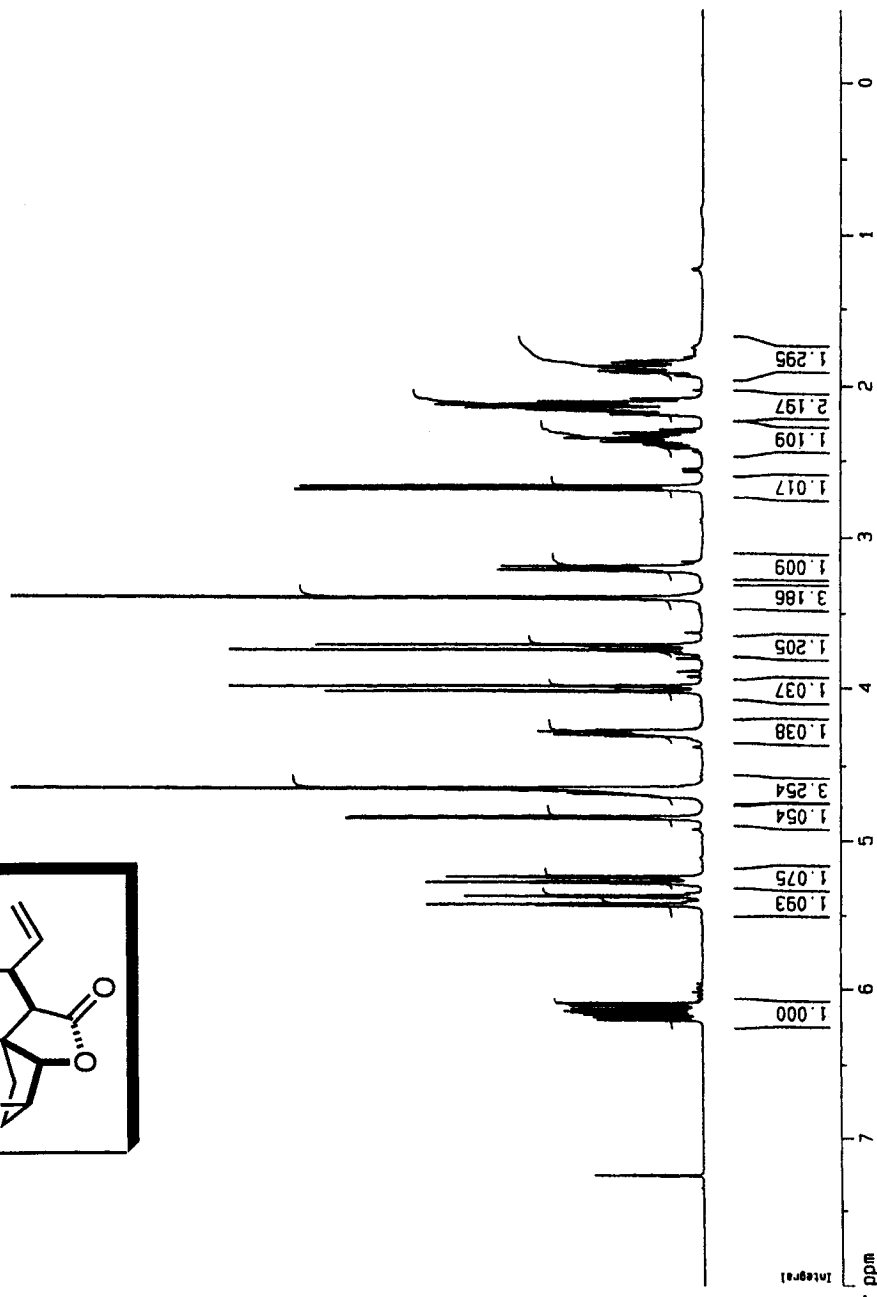
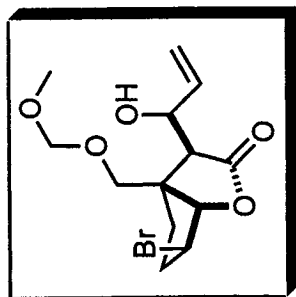
Current Data Parameters
 NAME pb-03-35
 EXPNO 2
 PROCNO 1

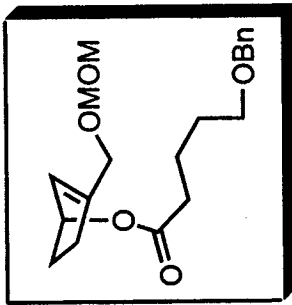
F2 - Acquisition Parameters
 Date_ 20030409
 Time 15.17
 INSTRUM av300
 PROBO 5 mm QNP
 PULPROG zg30
 TO 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 128
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

***** CHANNEL f1 *****
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.129939 MHz
 MDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 50.00 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-79
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030603
 Time 19.01
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 80.6
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

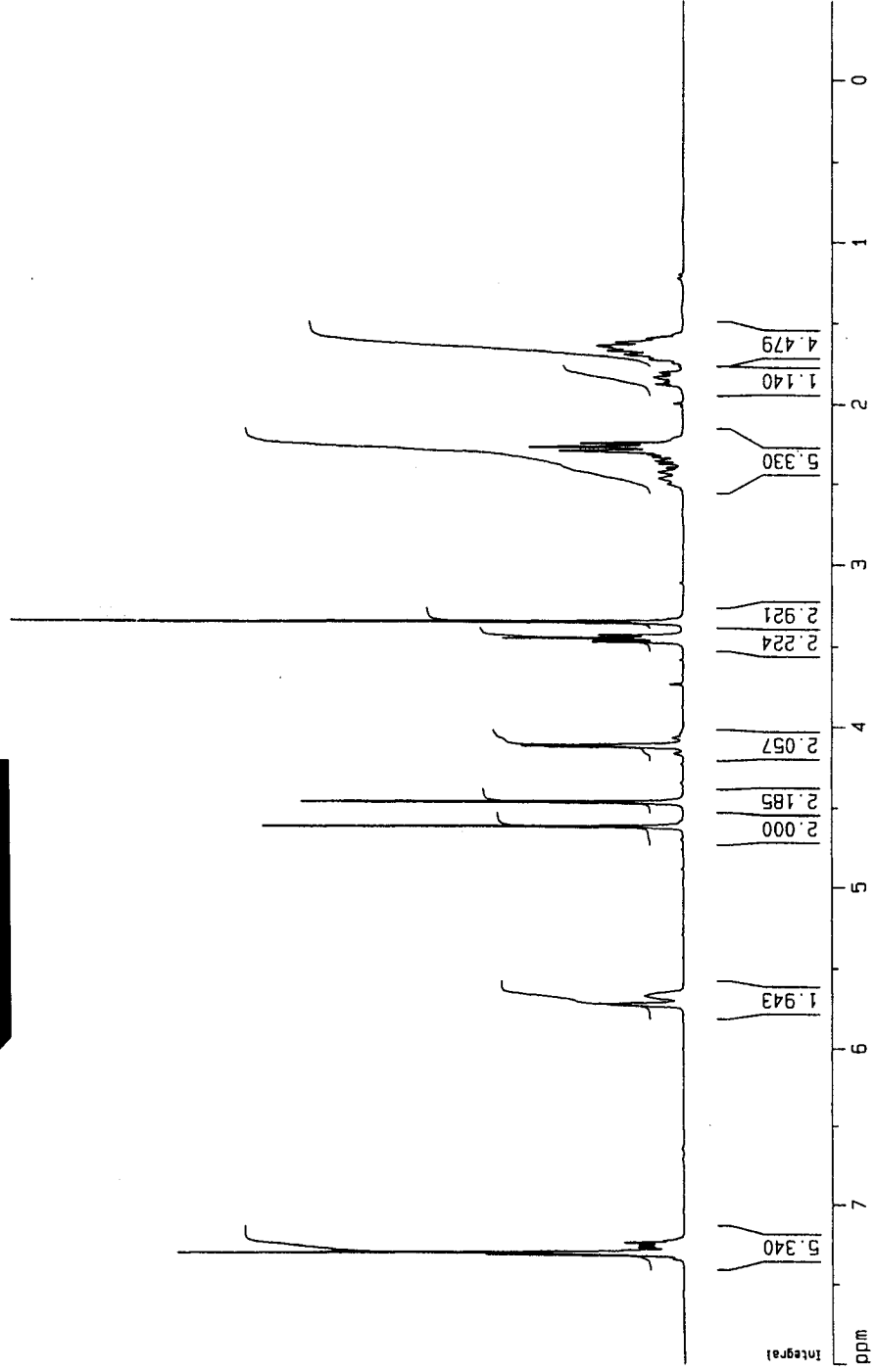
===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

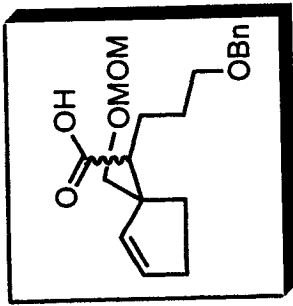
F2 - Processing parameters

SI 65536
 SF 300.1300000 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-B1
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030604
 Time 18.33
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 256
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====

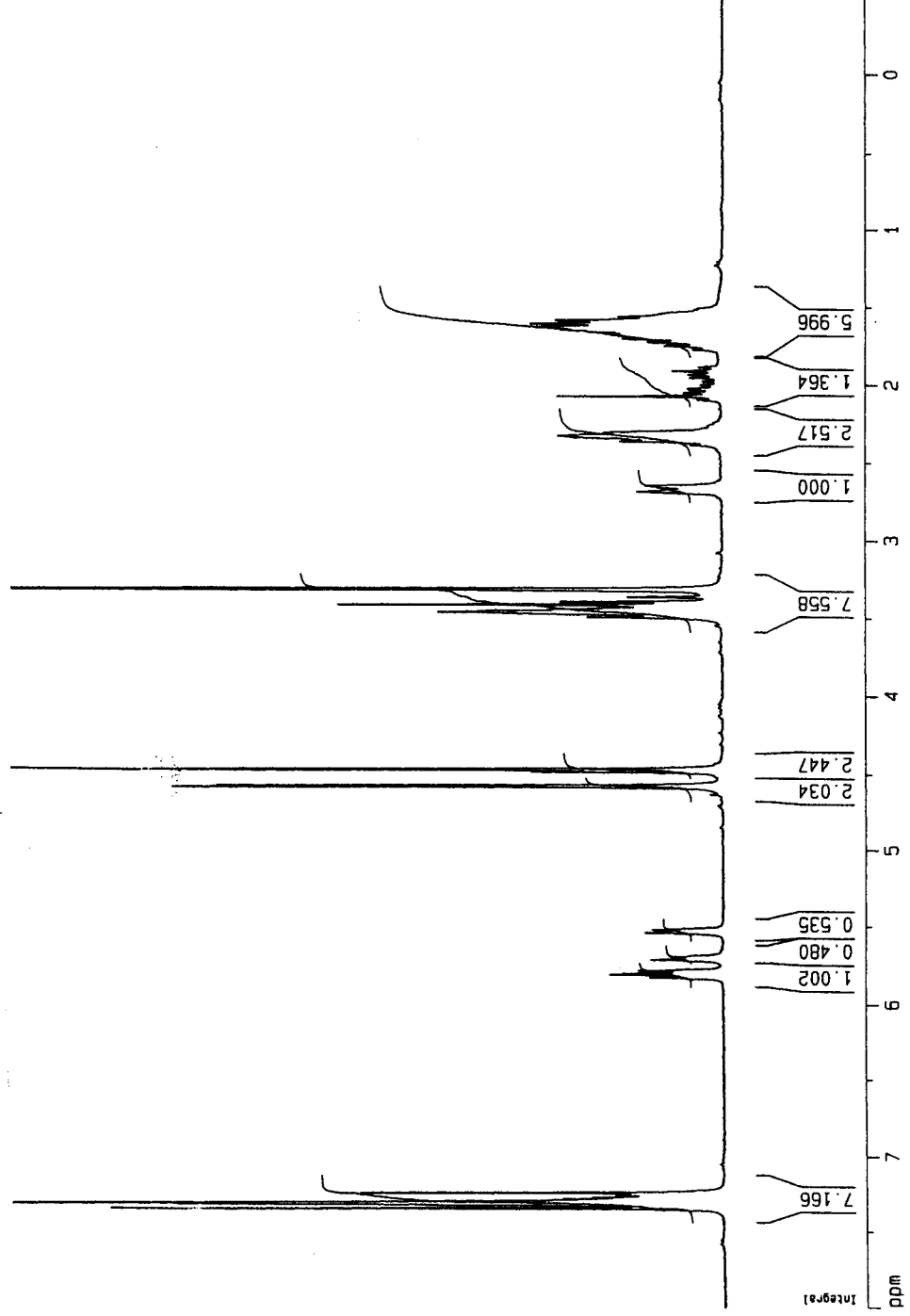
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

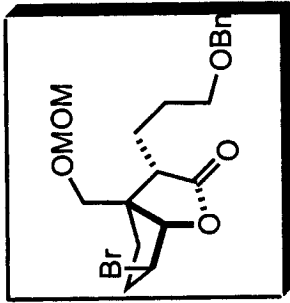
F2 - Processing parameters

SI 65536
 SF 300.1300000 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 20.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-83minor
 EXPNO 3
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030606
 Time 20.38
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 101.6
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

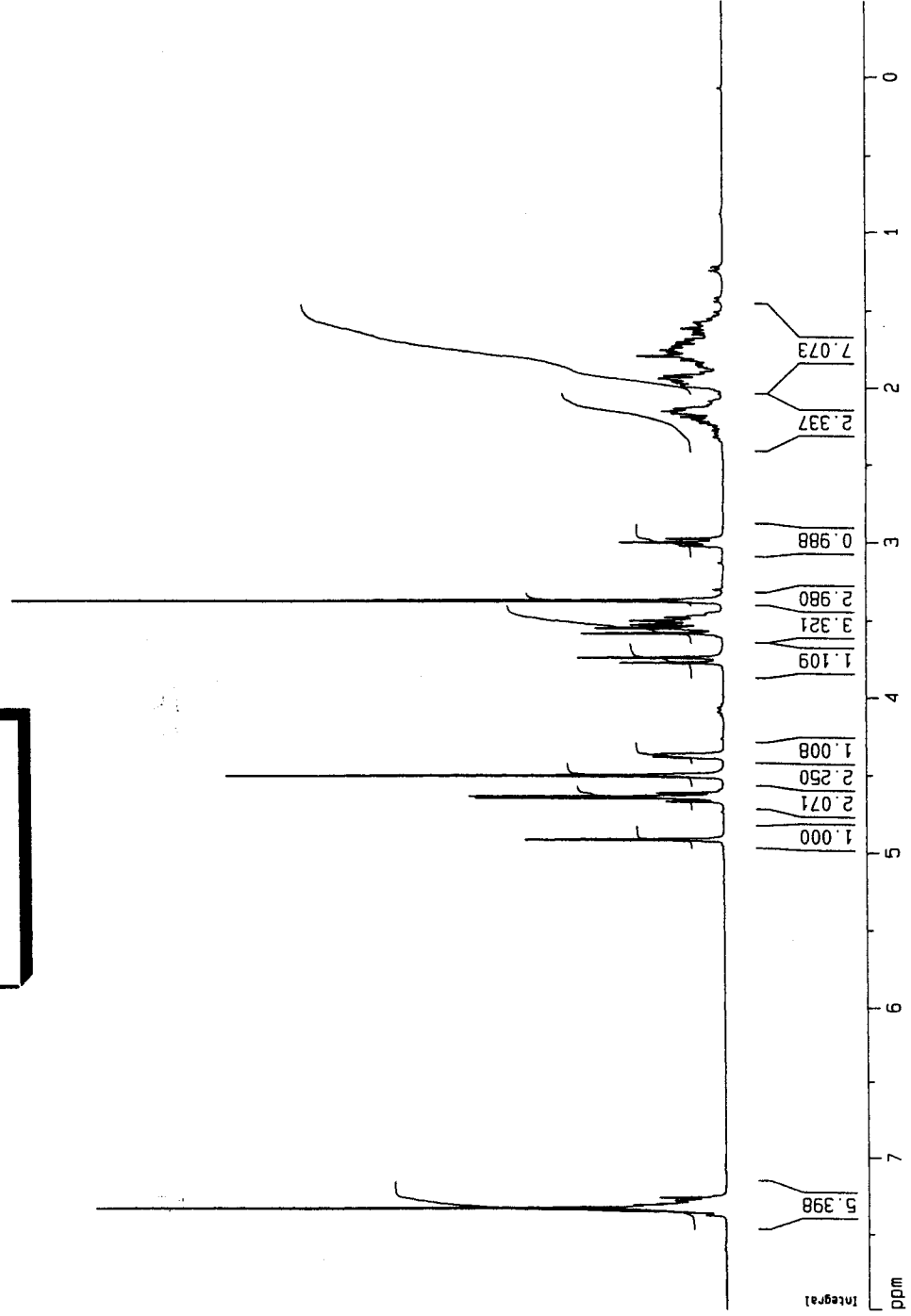
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

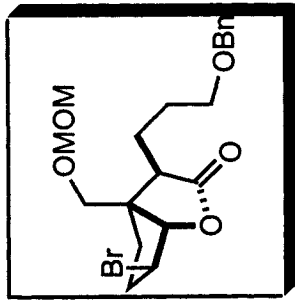
F2 - Processing parameters

SI 65536
 SF 300.1299940 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 15.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-83major
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030607
 Time 18.35
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.163407 Hz
 AQ 3.0226980 sec
 RG 71.8
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

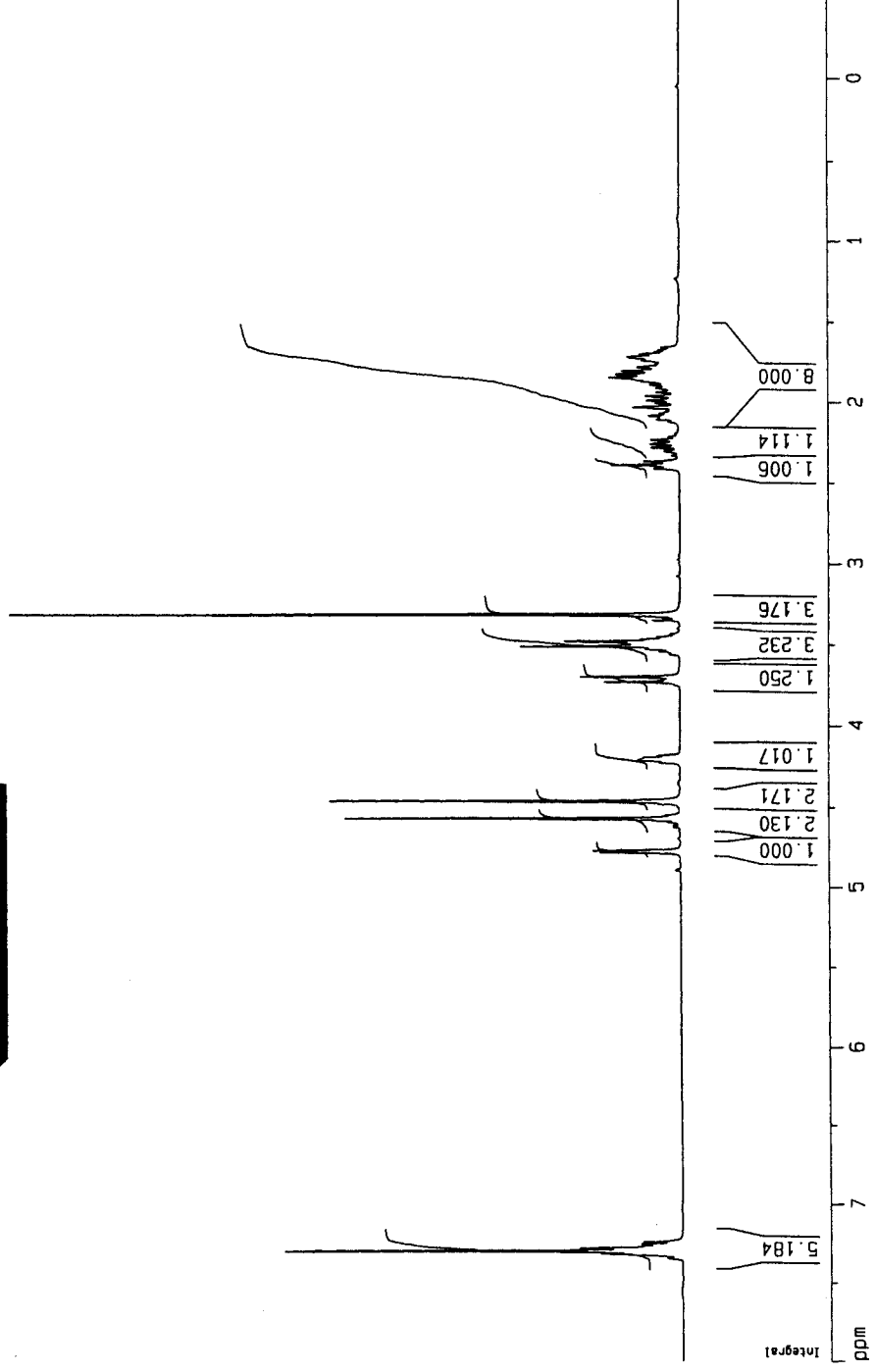
===== CHANNEL f1 =====

NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1300000 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2 -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



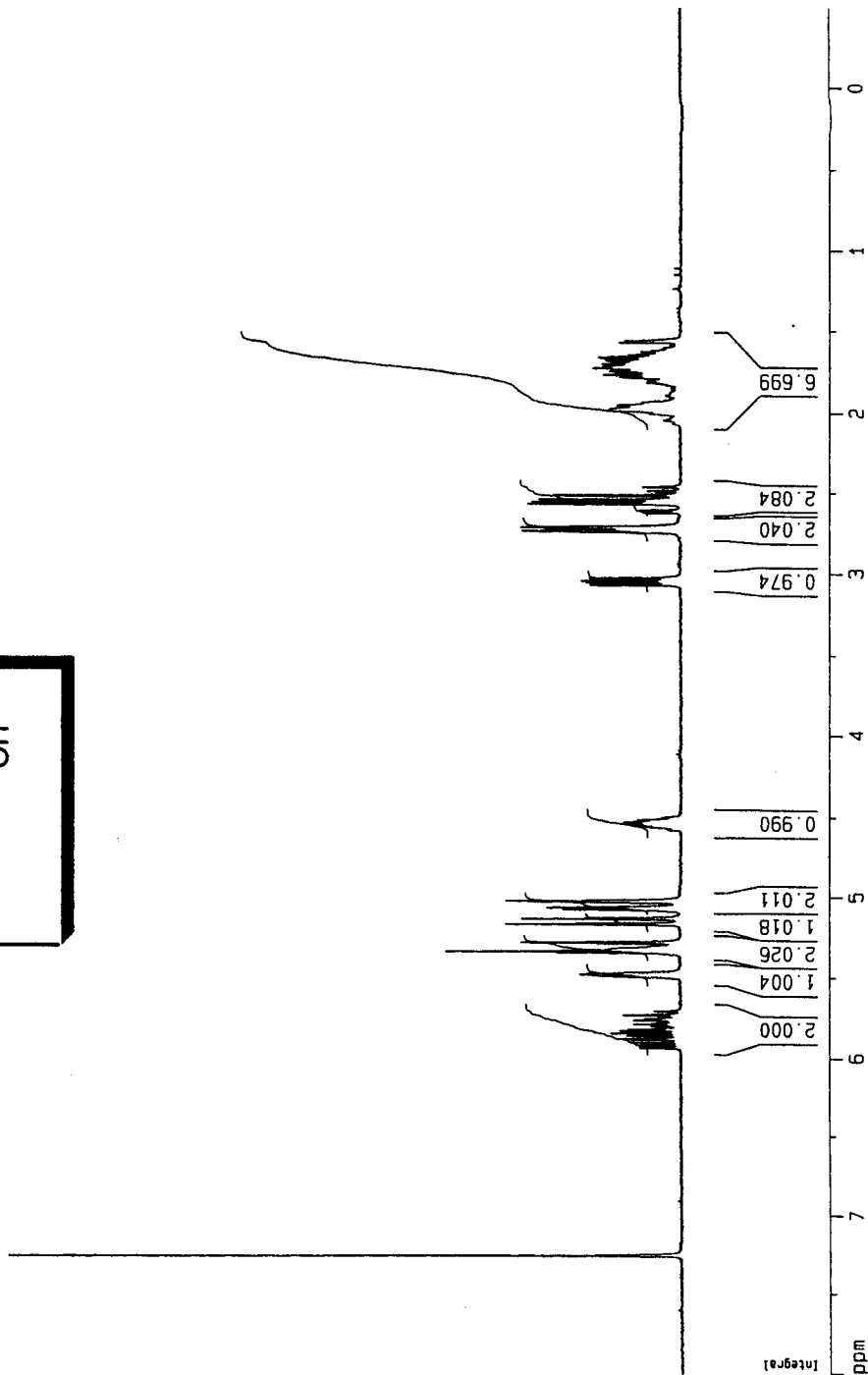
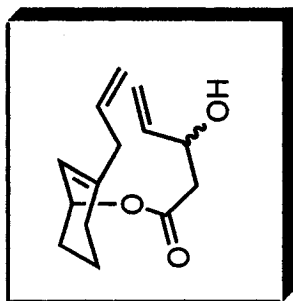
Current Data Parameters
 NAME pb-02-104
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20021125
 Time 20.39
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 724.1
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299944 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCH 127.59524 Hz/cm



Current Data Parameters
 NAME db-02-102
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20021125
 Time 12.52
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SMH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

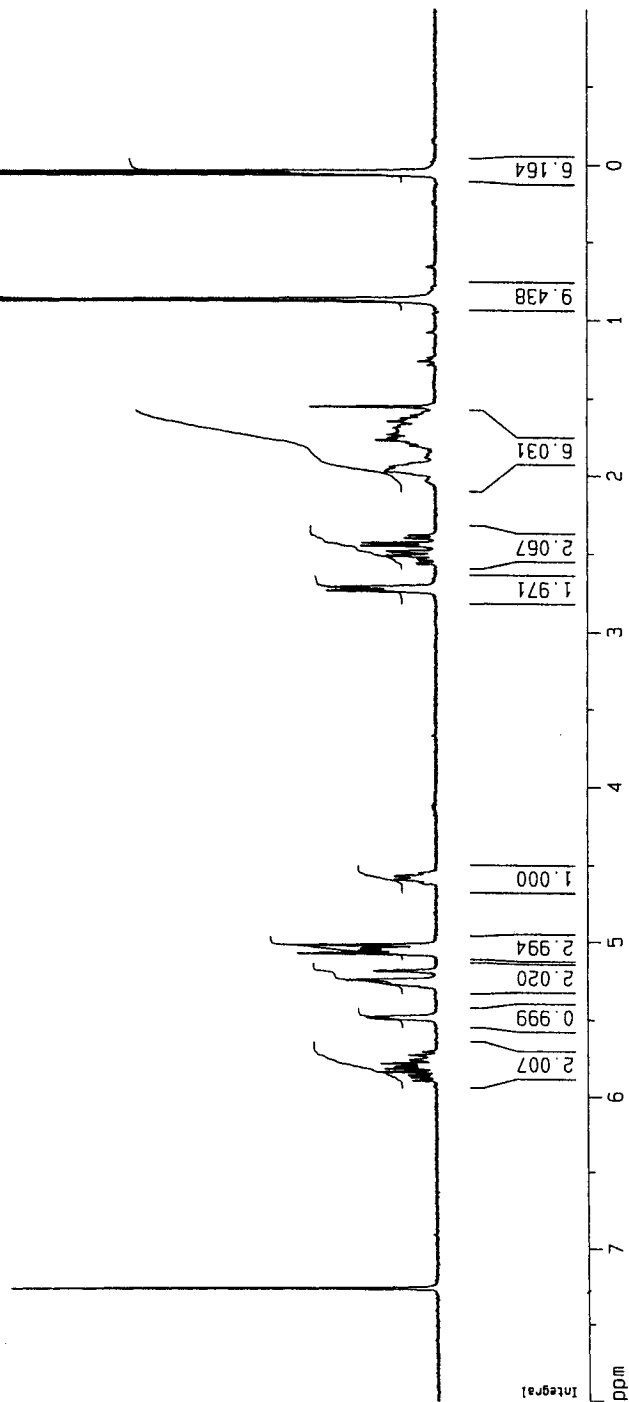
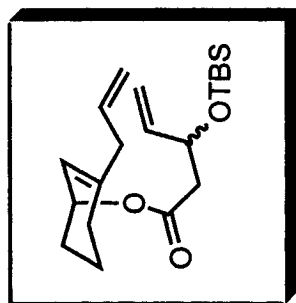
NUC1 1H
 P1 9.75 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

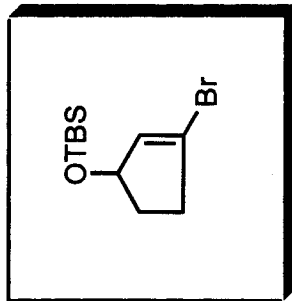
F2 - Processing parameters

SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 25.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -1.000 ppm
 F2 -300.13 Hz
 PPMCM 0.45000 ppm/cm
 HZCM 135.05850 Hz/cm





Current Data Parameters
 NAME pb-04-20
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

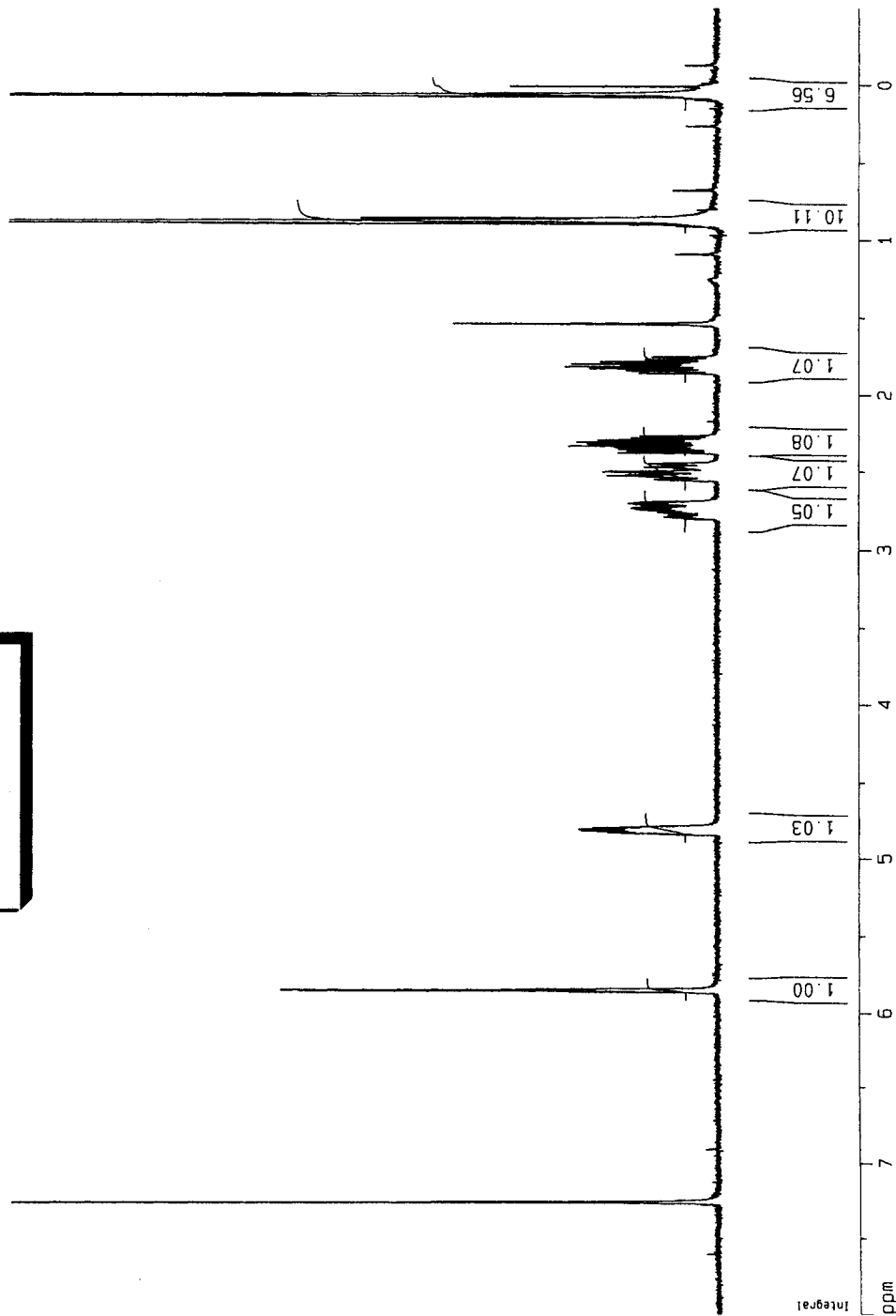
Date_ 20030910
 Time 22.14
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 912.3
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 200.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-04-22
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030914
 Time 18.51
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 1149.4
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

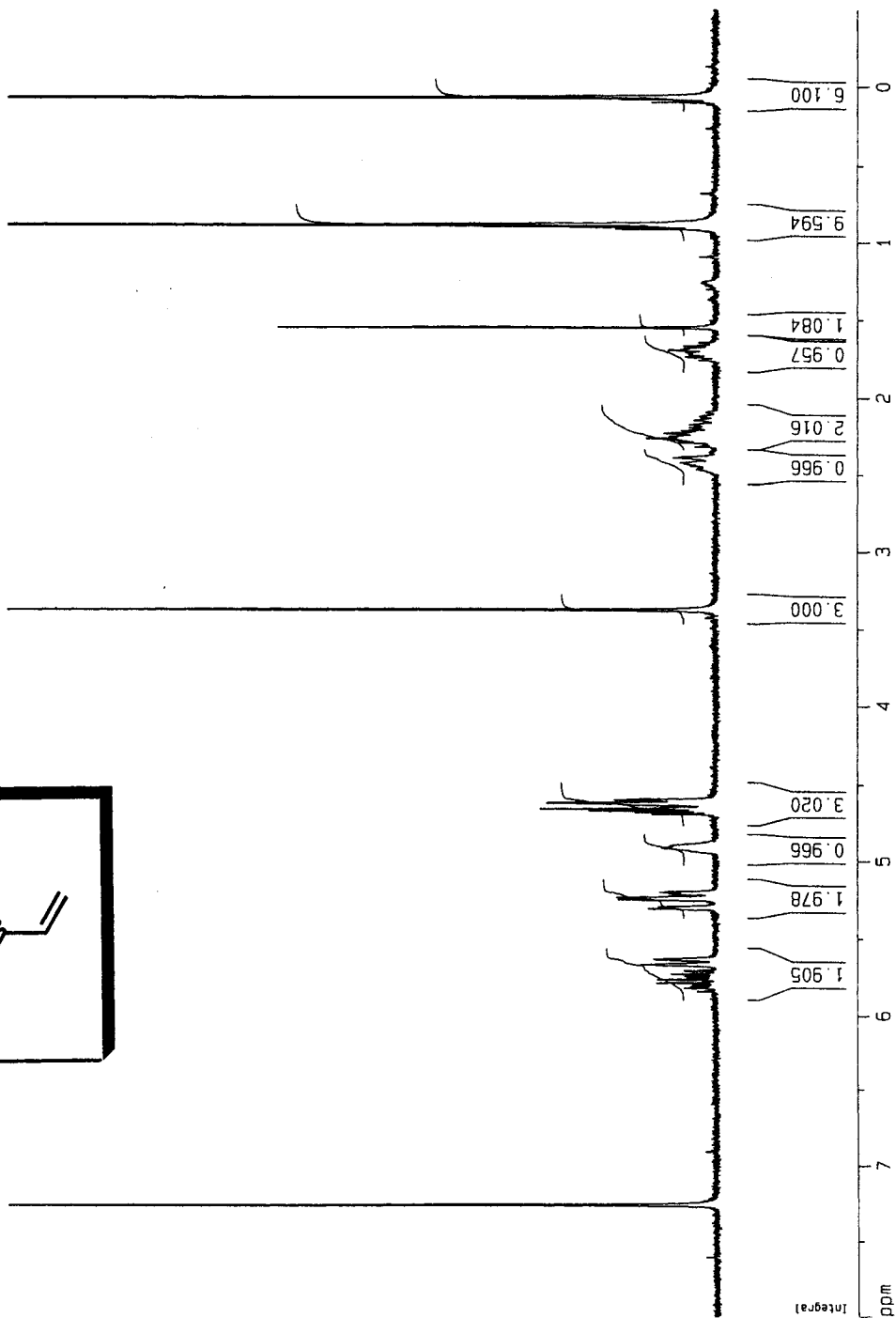
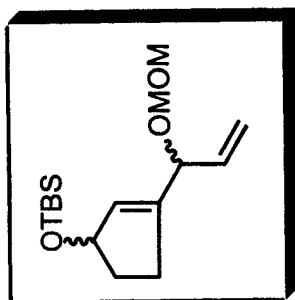
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

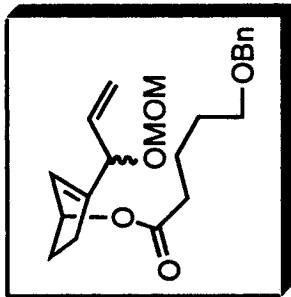
F2 - Processing parameters

SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 50.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





Current Data Parameters
 NAME pb-03-124
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030719
 Time 12.56
 INSTRUM av300
 PROBHD 5 mm GNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 128
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

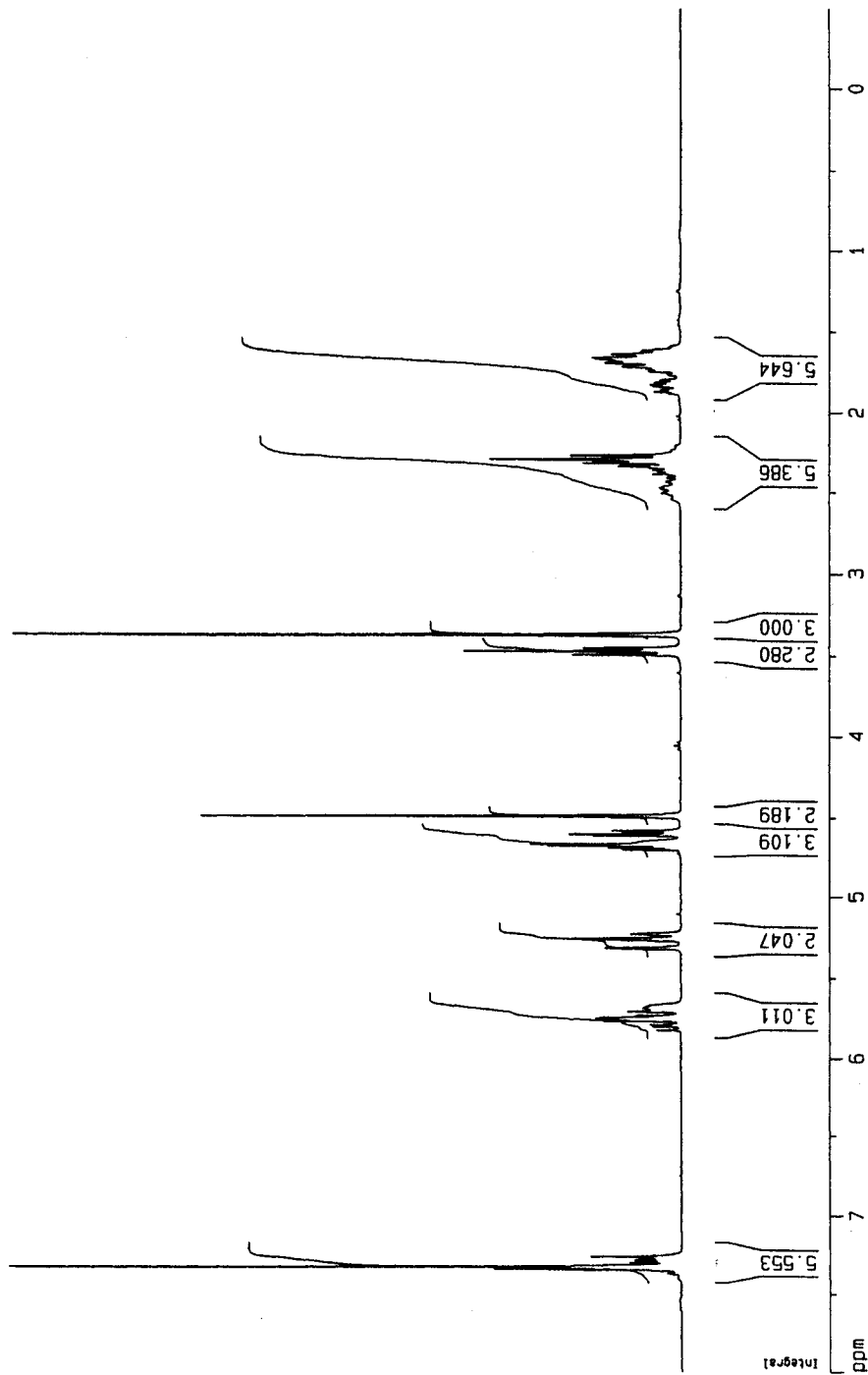
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



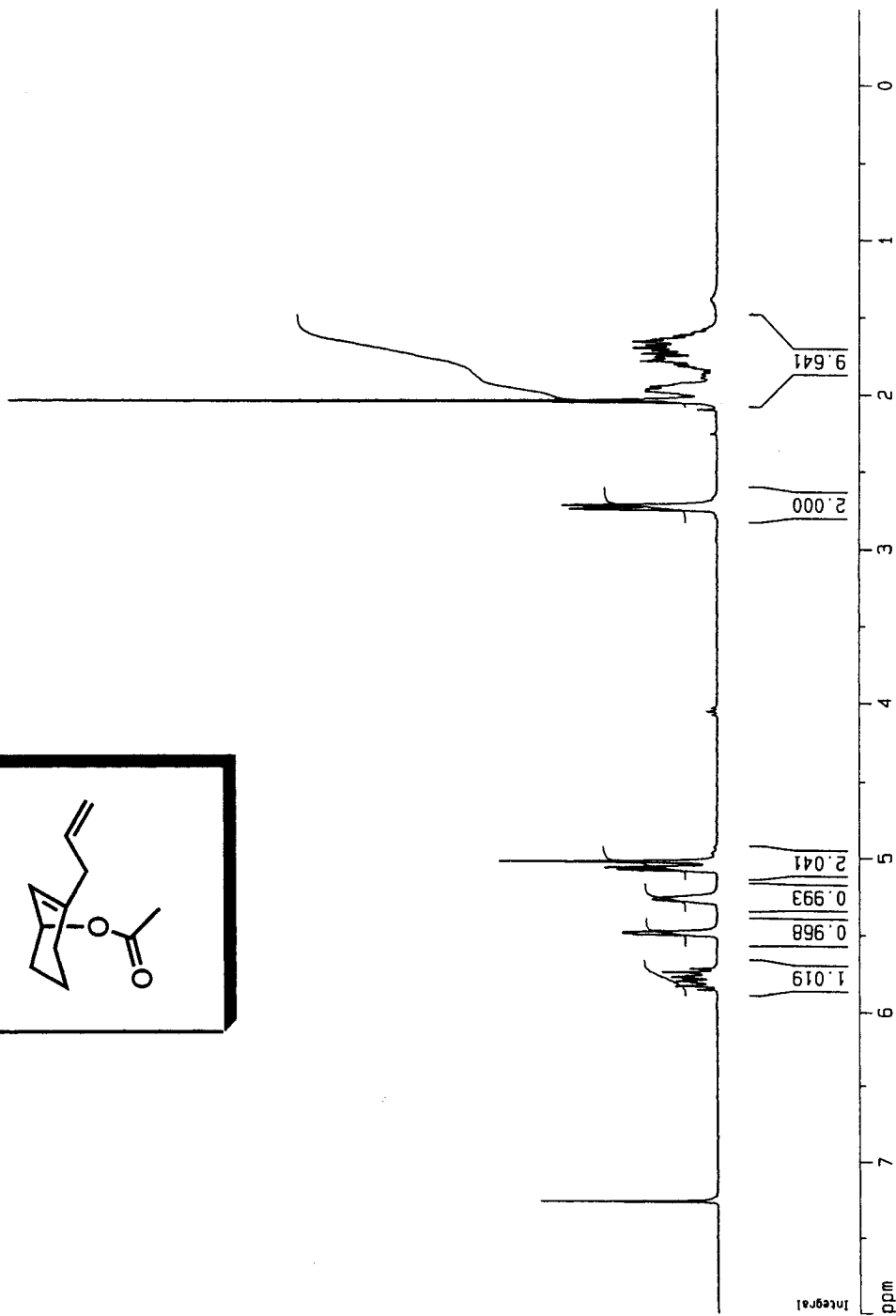
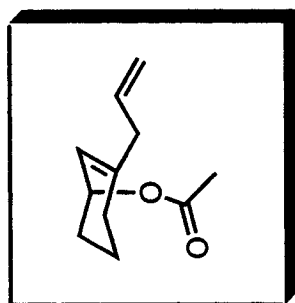
Current Data Parameters
 NAME pb-03-53
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20030507
 Time 19.09
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0228980 sec
 RG 512
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1299939 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 20.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm



Current Data Parameters
 NAME pb-03-75
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters

Date_ 20030602
 Time 8.24
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zg30
 TD 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.105407 Hz
 AQ 3.0228980 sec
 RG 812.7
 DW 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.0000000 sec

===== CHANNEL f1 =====

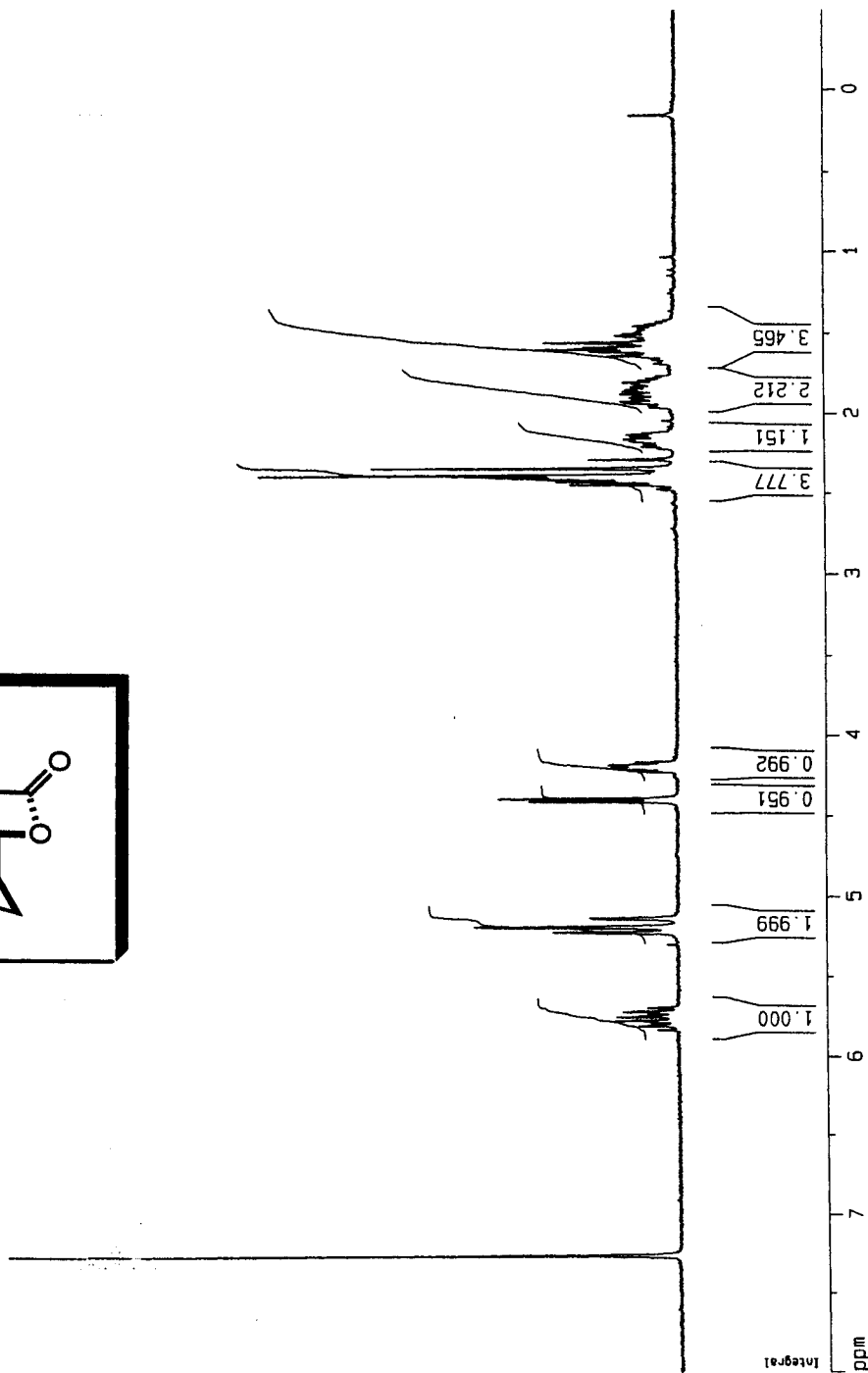
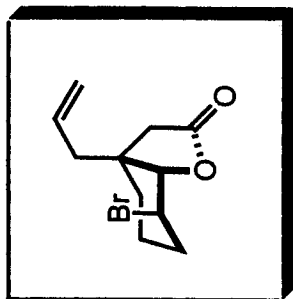
NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

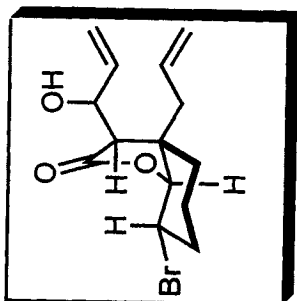
F2 - Processing parameters

SI 65536
 SF 300.1299942 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 CY 10.00 cm
 F1P 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPHCM 0.42500 ppm/cm
 HZCM 127.55524 Hz/cm





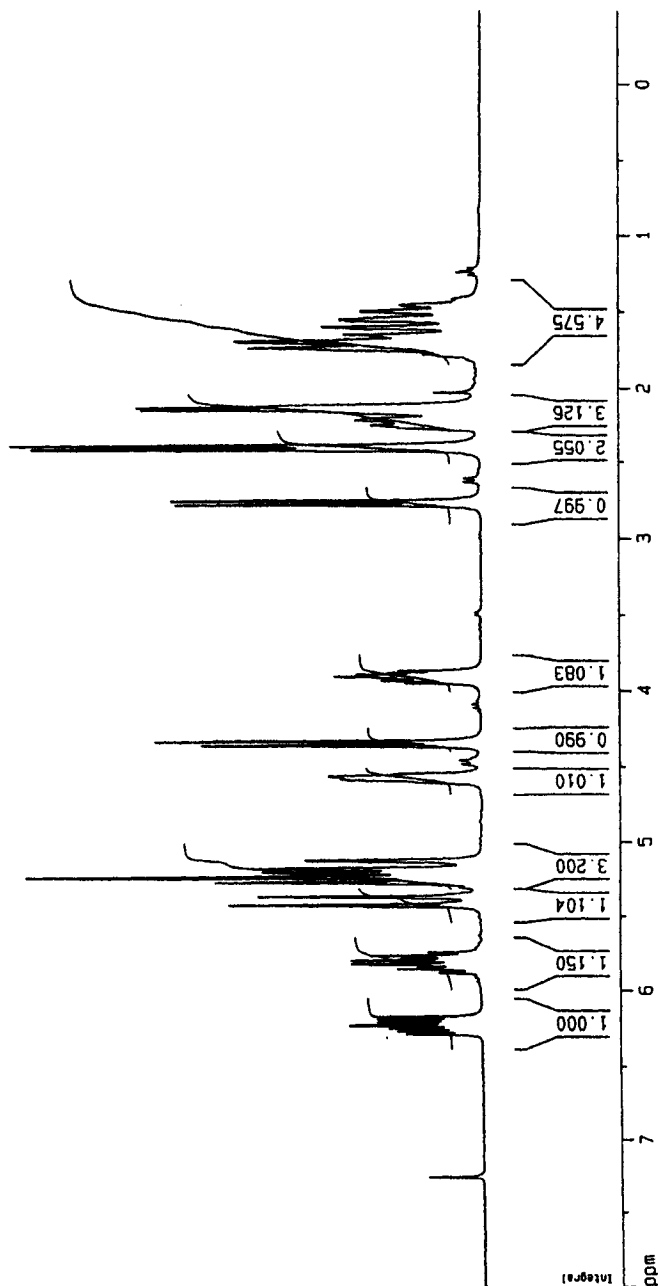
Current Data Parameters
 NAME pb-03-64(morepol1)
 EXPNO 1
 PROCNO 1

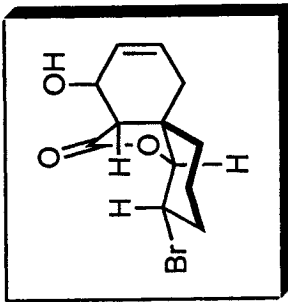
F2 - Acquisition Parameters
 Date_ 20030519
 Time 15.53
 INSTRUM av300
 PROBHD 5 mm QNP 1H/1
 PULPROG zgpg30
 TO 30720
 SOLVENT CDCl3
 NS 16
 DS 0
 SWH 5081.301 Hz
 FIDRES 0.165407 Hz
 AQ 3.0226980 sec
 RG 228.1
 DM 98.400 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 10.50 usec
 PL1 -3.00 dB
 SF01 300.1319477 MHz

F2 - Processing parameters
 SI 65536
 SF 300.1259539 MHz
 MDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 CY 7.50 cm
 FIP 8.000 ppm
 F1 2401.04 Hz
 F2P -0.500 ppm
 F2 -150.06 Hz
 PPMCH 0.42500 ppm/cm
 HZCN 127.55524 Hz/cm





Current Data Parameters
NAME pb-03-74
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030528
Time 18.54

INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 30720

SOLVENT benzene
NS 32
DS 0

SMH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.0228980 sec

RG 256
DM 98.400 usec
DE 6.00 usec

TE 300.0 K
D1 1.0000000 sec

***** CHANNEL f1 *****

NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters

SI 65536
SF 300.1299989 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 8.000 ppm
F1 2401.04 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.42500 ppm/cm
HZCM 127.55524 Hz/cm

