A Synthetic and Computational Investigation of Pentacycloundecane Amino Acid Derivatives

by

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As the candidates supervisor I have approved this dissertation for submission.

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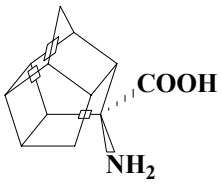
ABSTRACT

Computational studies have shown that cage skeletons (**7**) have the tendency to impose a 3_{10}-helix as well as an α_L-helix on the polypepeptide chain. Residues such as **7** are the useful tools for study of the conformational preferences of peptide models, the design of peptide analogues with improved pharmacokinetics profiles and the development of pharmacophore models. Synthesis of pentacycloundecane amino acid analogue suitable for peptide synthesis would enable us to verify the computational predictions and to contribute to this very active field of research.

The sterically hindered 8-amino-pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-carboxylic acid (**7**) was synthesised by hydrolysis of the novel bis-Boc protected pentacycloundecane-hydantoin (**30**).



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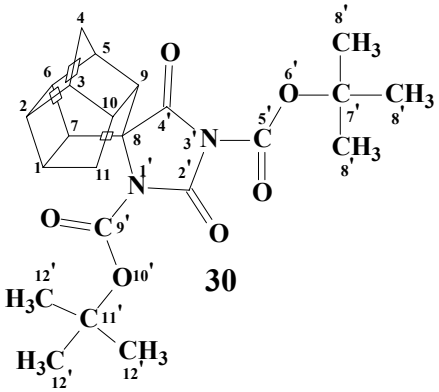

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Progress to incorporate **7** into a non-natural peptides is reported. A computational investigation on the regioselective acetylation of hydantoin derivatives which includes PCU hydantoin, 5.5-dimethylhydantoin and 5-methylhydantoin is also reported. The results of the computational investigation initiated the regioselective synthesis of the mono-Boc and bis-Boc derivatives of 5,5-dimethylhydantoin and 5-methylhydantoin. These compounds have not been reported before.

PREFACE

The experimental work described in this dissertation was carried out in the School of Pure and Applied Chemistry, University of KwaZulu-Natal, Durban, from February 2003 to December 2004, under the supervision of Dr. Hendrik G. Kruger.

These studies represent original work by the author and have not otherwise been submitted in any form for any degree or diploma to any tertiary institution. Where use has been made of the work of others it is duly acknowledged in the text.

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Phumlane Selby Mdluli

_____day of _____ 2005

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LIST OF ABBREVIATIONS

Aib	aminoisobutyric acid
ala	alanine
a.u.	atomic units
β	beta
BBB	Blood Brain Barrier
Boc_2O	di-tert-butyl dicarbonate
$CDCl_3$	deuterated chloroform
^{13}C NMR	carbon-13 nuclear magnetic resonance
CNS	central nervous system
COSY	correlation spectroscopy
DFT	density functional theory
DIPCDI	N,N-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
eq.	equivalent
Et_3N	triethylamine
FAB	fast atom bombardment
FmocAM	(p-[(R,S)-α-[1-(9H-fluoren-9-yl)methoxy-formamido]-2,4-dimethylbenzyl]-phenoxyacetic acid
Fmoc(-Cl)	9-fluorenylmethyl (chloro)formate
g	gram
G03	Gaussian 03
GTO	Gaussian-type atomic orbitals
HCl	hydrochloric acid
HMBC	heteronuclear multiple bond coherence
^{1}H NMR	hydrogen-1 nuclear magnetic spectroscopy
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HSQC	heteronuclear single quantum coherence

hν	electromagnetic radiation
Hz	Hertz
IRC	intrinsic reaction co-ordinate
IR	infrared
KBr	potassium bromide
KOH	potassium hydroxide
LCAO	linear combination of atomic orbitals
LiOH	lithium hydroxide
M	nuclear mass
MBHA	4-methylbenzhydrylamine
$MgSO_4$	magnesium sulphate
MHz	Mega Hertz
mmol	millimole
mol	mole
m.p.	melting point
MP2	second order Møller-Plesset model
MP4	fourth order Møller-Plesset model
MS	mass spectroscopy
MS-TOF	mass spectroscopy-time of flight
m/z	mass per charge
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
p	para
PCU	pentacyclo[$5.4.0.0^{2,6}.0^{3,10}.0^{5,9}$]undecane
R	rectus
RHF	restricted Hartree-Fock
S	sinister
SCF	self-consistent field
STO	Slater-type atomic orbitals
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TS	transition state
UHF	unrestricted Hartree-Fock
UKZN	University of KwaZulu-Natal
UV	ultra violet
Z	nuclear charge
ψ	wavefunction describing motion of electrons
Å	Ångstrom
α	alpha
ν_{max}	frequency of maximum absorption
°C	degrees Celsius
%	percent
ϕ	atomic orbitals
σ	sigma
π	pi

ACKNOWLEDGEMENTS

I would like to extend my thanks and gratitude to the following:-
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Sasol for financial support to upgrade our computational facilities at the University of KwaZulu-Natal on which some of the work was done.

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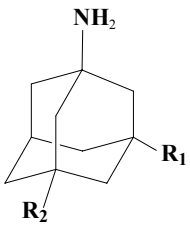
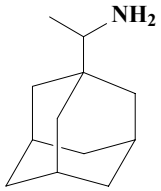
Finally, I would like to dedicate this work to my friends and family for always being there for me.

1. INTRODUCTION

Polycarbocyclic "cage" compounds have captured the attention, interest and imagination of many synthetic organic chemists over the past few years.[1,2,3,4,5,6] The attention was encouraged by the discovery of the anti-viral activities of amantadine (**1**) and memantine (**2**) against the influenza viruses.[6] The research interest was also stimulated by the discovery of the anti-Parkinson activity[7] of **1** and rimantadine (**3**). The two amino derivatives (**1** and **3)** show antagonist behaviour towards the clinically well tolerated N-methyl-D-aspartate receptor.[6]

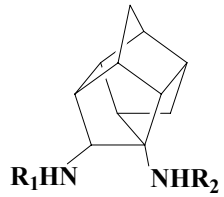


1 R_1=H, R_2=H
2 R_1=CH_3, R_2=CH_3

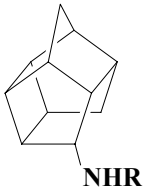


3

A number of amino-adamantane derivatives exist which have shown pharmacological effects including antiviral, antibacterial, antifungal and anti-protozoal activity.[6] Discovery of the anti-viral activity of adamantane derivatives initiated further studies into related polycyclic cage compounds.[6,8] Some 4-amino-(D_3)-trishomocubane derivatives have shown promising *in-vivo* activity against the Herp simplex II and influenza A2 viruses.[8] Pentacycloundecylamines such as **6** exhibit promising anticataleptic activity in comparison to that of adamantine (**1**). Further studies indicated that the series of D_3-trishomocubanes (**4** and **5**) show potential as anti-Parkinsonian agents.[8]



4 R_1=H, R_2=C_6H_5
5 R_1=C_2H_5, R_2=CH_3

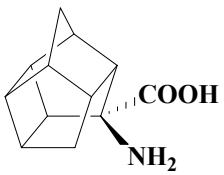


6

A number of pentacycloundecane derivatives were found to possess analgesic and anti-inflammatory properties,[9] calcium channel antagonism and neuroprotective activity.[6] Literature has revealed that the incorporation of cage structures into drugs induces a range of positive effects on the pharmaceutical action of the drugs.[10]

Successful therapeutic drugs must induce an optimal concentration of the drug at the site of action and should also maintain that for an adequate period of time.[11] The field of designing suitable delivery systems for drugs is crucial to the pharmaceutical industry. In the case of neurological drugs, whose site of action is the central nervous system (CNS), the blood brain barrier (BBB) may restrict entry into the CNS. Designing delivery systems for the brain directed drug is therefore very important. Various attempts have been made to develop a delivery system for drugs that are active in the CNS.[11] It was demonstrated that pentacycloundecane derived drugs, being hydrophobic, are able to cross the BBB.[6]

Novel cage amino acids could therefore potentially be utilised as delivery systems, which target the CNS when introduced into existing drugs. Cage systems incorporated into drugs are increasing the lipophilicity of the drugs and would promote transport of the drug across normal cell membranes as well.[10] The bulkiness of the cage system also retards the metabolic degradation of the drug.[10]



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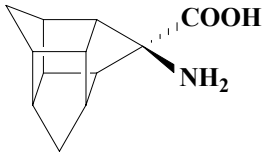

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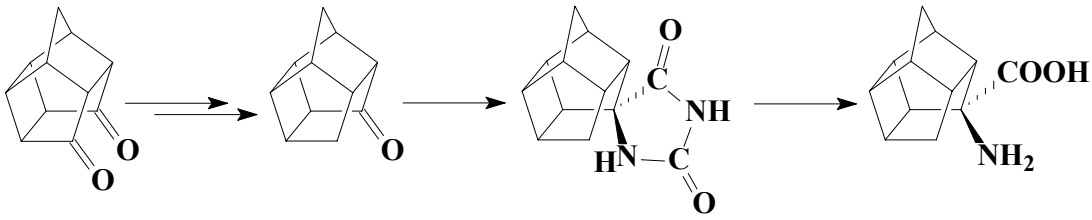
Amongst the forces that control protein folding and structural motifs of proteins, β-turns comprise about 25 % of all residues in proteins and is the most important motif for folding of proteins to produce their compact structure.[12,13]

A recent computational investigation has shown that the presence of cage skeletons such as **7** and **8** have a tendency to impose a 3_{10}-helix as well as an α-helix to the polypeptide chain.[14,15,16] A promising conformational feature of cage skeletons is the fact that they

induce quite active β-turn characteristics.[16] It is clear from the introduction above that the availability of readily accessible amino acids with cage skeletons can open exciting possibilities in a number of research fields, such as the modulation of the pharmacokinetics and pharmacodynamics of pharmaceutical drugs. The main purpose of this investigation is to establish an improved route to synthesise the racemic PCU amino acid (**7**). An attempt to incorporate the amino acid into a non-natural peptide will also be described. Lastly, this investigation will attempt to apply an existing computational model[17,18] for the regioselective protection of amines and alcohols to hydantoin systems.

2. SYNTHESIS OF 8-AMINO-PENTACYCLO-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]UNDECANE–8-CARBOXYLIC ACID

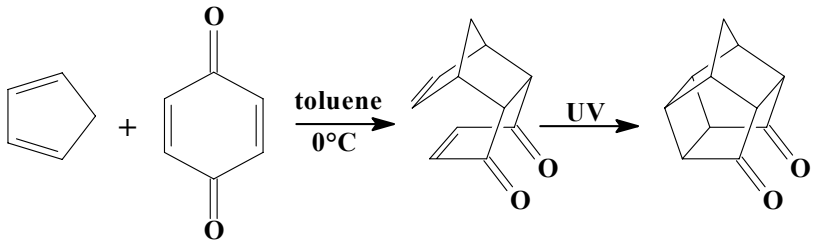
An approach for the synthesis of the PCU amino (**7**) has been reported[19,20]. It utilises the easily accessible pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**9**) as the starting material. This approach involves the conversion of **9** to PCU monoketone (**10**) which is subsequently converted to a hydantoin (**11**) followed by base hydrolysis to yield the corresponding PCU amino acid (**7**).



9 **10** **11** **7**

Scheme 1: Approach for synthesis of PCU amino acid

The Diels-Alder adduct 5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**14**) is easily obtained from the reaction between cyclopentadiene (**7**) and *p*-benzoquinone (**13**).[21,22]

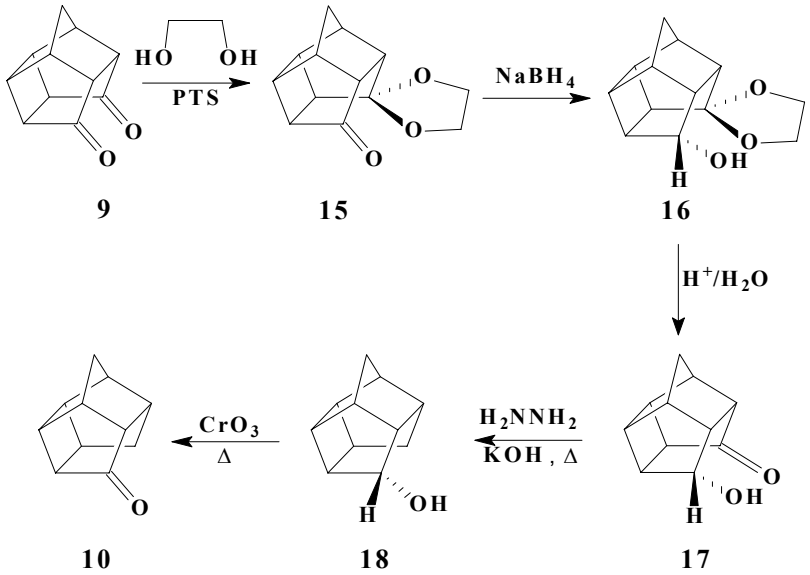


12 **13** **14** **9**

Scheme 2: Synthesis of PCU dione (9)

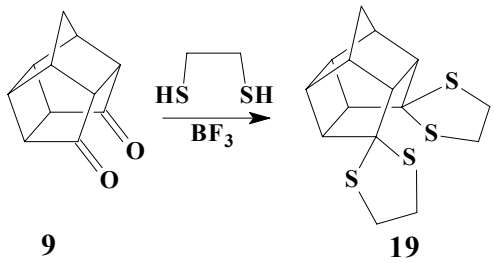
The experimental procedure of Cookson[21] and Marchand[22] was changed (see **Chapter 6**) in this study to obtain improved yields of **9**. The adduct (**14**) was dissolved in 10% acetone/hexane and irradiated by direct sunlight (3-5 days). It appears from literature[19,20,23,24,25] that the best route to obtain the PCU monoketone (**10**) from the

dione (**9**) is through the mono-protection of one ketone via ketal (**15**) formation followed by reduction of the remaining ketone. Ketal (**15**) is obtained upon refluxing (Dean-Stark apparatus) the dione (**9**) with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid in an azeotropic solvent such as toluene or benzene. It is interesting to note that according to Beilstein[26] the diketal has not yet been reported. This might be an indication of the huge expected steric hindrance of the diketal.



Scheme 3: Synthesis of PCUmonoketone (10)

Excess ethylene glycol (ratio of 1:1.5) also resulted in the formation of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-11-dione-monoethyleneketal (mono-ketal, **15**). Nucleophilic attack occurs almost exclusively at the *exo*-face of the keto-group due to the steric constraints induced by the other keto-group to any possible attack from the *endo*-face.[27]

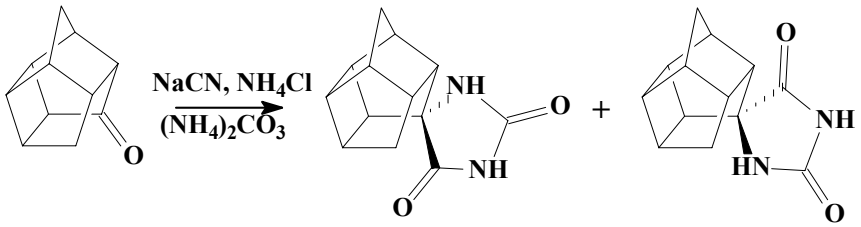


Scheme 4: Synthesis of PCU dithioketal (19)

Interestingly enough, the dithioketal (**19**) has been reported[28,29] before, indicating that the steric argument mentioned above is not so simple, as sulphur atoms are much larger than oxygen atoms.

The next step involves reduction of the keto-ketal (**15**) with sodium borohydride.[23,24,30] This resulted in the formation of 11-hydroxy-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8-one-ethylene ketal (hydroxyketal, **16**). The hydroxyketone (**17**) was obtained by hydrolysing the ketal (**16**) group with 10% hydrochloric acid.[23,24]

The next synthetic step involves the reduction of the keto-functional group of the hydroxyketone (**17**) to a methylene group via the modified Huang-Minlon reaction.[31] Purification can be achieved by steam distillation. After purification a quantitative yield of mainly *endo*-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-ol (*endo*-PCU alcohol, **18**) is obtained. The alcohol (**18**) is then oxidised using the Jones oxidation[32] which employs chromium trioxide as the oxidizing agent. A change of colour from dark red to blue indicates the completion of the oxidation process which results in the formation of pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanone (PCU monoketone, **10**). The monoketone (**10**) is obtained as a racemate. Conversion of the ketone via the Bucherer-Bergs method[33,34] yields the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane hydantoin (PCU hydantoin, **11**).

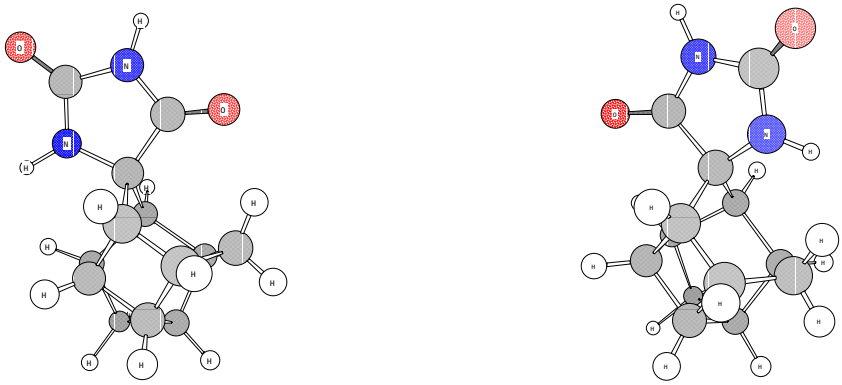


(±)**10** (S)-**11** (R)-**11**

Scheme 5: Synthesis of hydantoin (11)

The hydantoin can potentially exist as two diastereomeric forms [(R)-**11** and (S)-**11**]. Force field calculations[19] showed that (R)-**11** is of lower steric energy than (S)-**11**. A Density Functional Theory (DFT) calculation performed in the current study also

proved that (R)-**11** is the more stable isomer. The calculation was done using B3LYP with the 6-31+g(d) as basis set. Note that very little conformational flexibility is possible in the rigid cage hydantoin system. The results are presented in **Table 1**. It is clear that (S)-PCU hydantoin [(S)-**11**] is 1.41 kcal mol^{-1} higher in energy than the (R)-PCU hydantoin [(R)-**11**].



[(S)-**11**] [(R)-**11**]

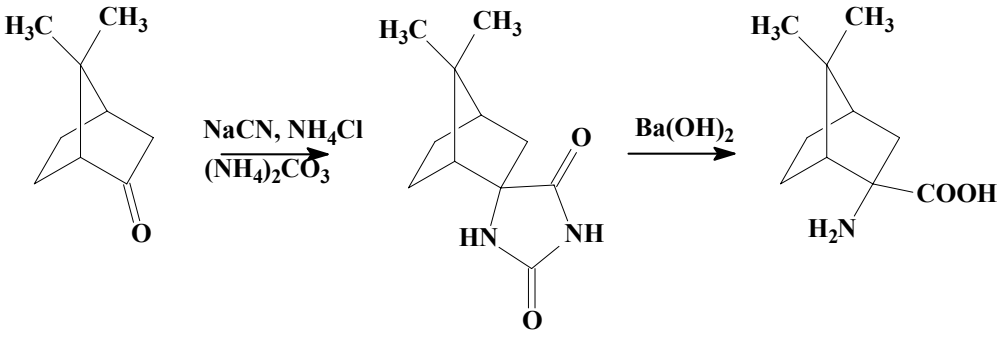
Figure 1: (R)- and (S)- structure of PCU hydantoin (11)[a]

Table 1: HF energies of (S)- and (R)-PCU hydantoin

	Energy /Hartree	**Relative Energy /kcal mol^{-1}**
(R)-PCU hydantoin [(R)-**11**]	-763.7949808	0.0
(S)-PCU hydantoin [(S)-**11**]	-763.7927321	1.41

Kruger[19] used both Strecker and Bucherer-Bergs conditions and obtained only the thermodynamically preferred product [(R)-**11**]. Norbornane (**20**) when treated with Bucherer-Bergs or Strecker type reactions produces two different hydantoins, which on hydrolysis yield the corresponding amino acids.[35] The Strecker route yields the product with the carbonyl group in the sterically more hindered position (kinetically preferred product, **22**).[36]

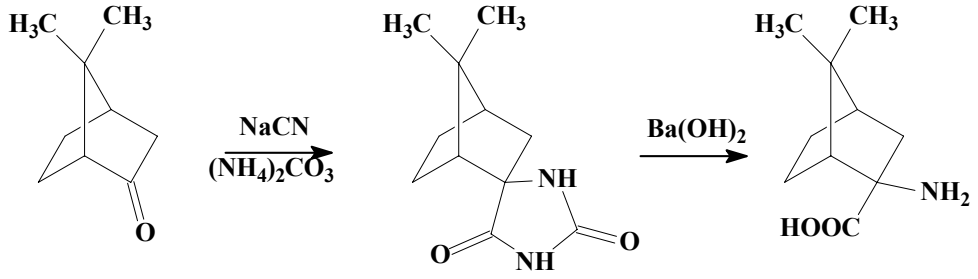
[a] The Cartesian coordinates of all optimized structures are available as supplementary material on the CD attached to this thesis.



20 **21** **22**

Scheme 6: Strecker route for synthesis of 22

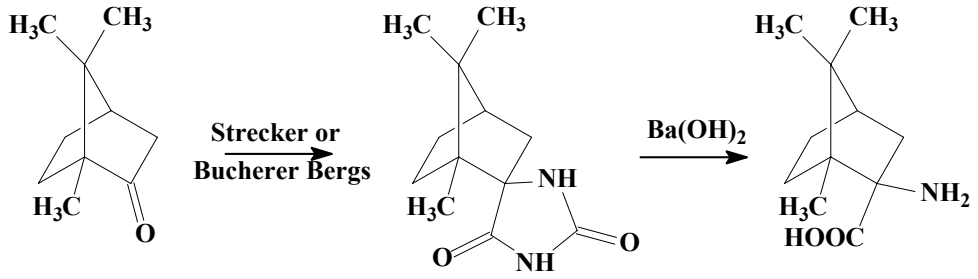
Under Bucherer-Bergs conditions the 4'-carbonyl group of the hydantoin ring is in the less sterically hindered position (thermodynamically preferred product, **24**).[35]



20 **23** **24**

Scheme 7: Bucherer-Bergs route for synthesis of 24

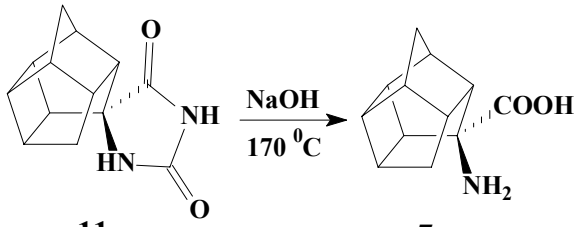
However, When (+)-Camphor (**25**) is used under the same reaction conditions, only one product is obtained, namely, the hydantoin (**26**) with its 4'-carbonyl in the less sterically hindered position.[36]



25 **26** **27**

Scheme 8: Bucherer and Strecker route for synthesis of 27

Steric hindrance of the nearby methyl group at the bridge carbon induces preferential nucleophilic attack from the less sterically hindered bottom side of the carbonyl carbon. It appears as if the PCU hydantoin exhibits similar characteristics as the Camphor hydantoin (**26**). The normal base hydrolysis of the cage hydantoin[20,34,37] requires elevated temperature.

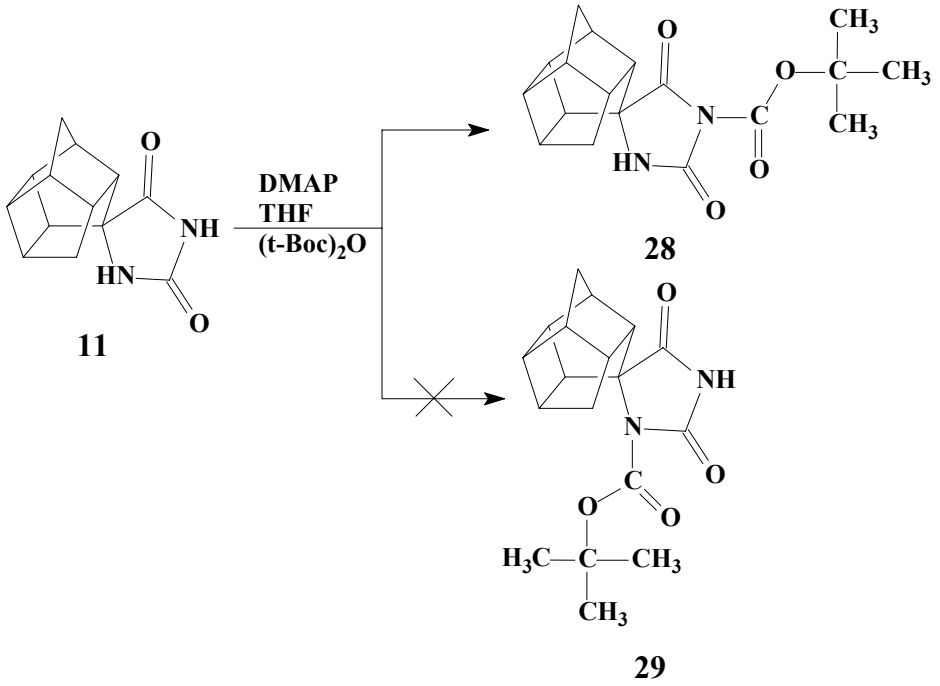


11 **7**

Scheme 9: Synthesis of PCU amino acid (7)

Kubik *et. al.*[38] have utilized a facile method for the hydrolysis of α,α-disubstituted hydantoins to obtain excellent yields of the corresponding amino acid. The method[38] introduces a Boc functional group on both the amide (N-3') and imide nitrogen (N-1') of the α,α-disubstituted hydantoin rings to form a bis-Boc protected hydantoin. Since the introduced Boc group is a strong electron withdrawing group, two Boc groups destabilise the hydantoin ring which permits a milder hydrolysis at room temperature with lithium hydroxide, ensuring better amino acid yields.[39]

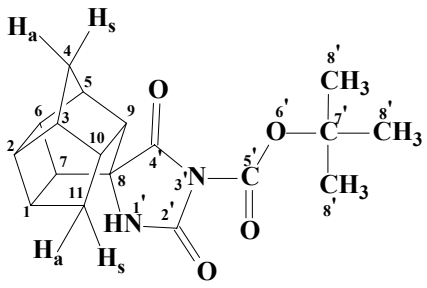
However, the method of Kubik *et. al.*[38] yielded a mono-Boc protected hydantoin (**28**) when applied to the PCU hydantoin system (**11**), as was the case with the trishomocubane hydantoin studied by Raasch *et. al.*[39,40] The NMR data revealed that protection only occurred on the less nucleophilic imide (N-3') nitrogen (**28**) as was reported[40] for the corresponding trishomocubane system (see **Spectrum 10**).



Scheme 10: Synthesis of mono-Boc protected hydantoin (28)

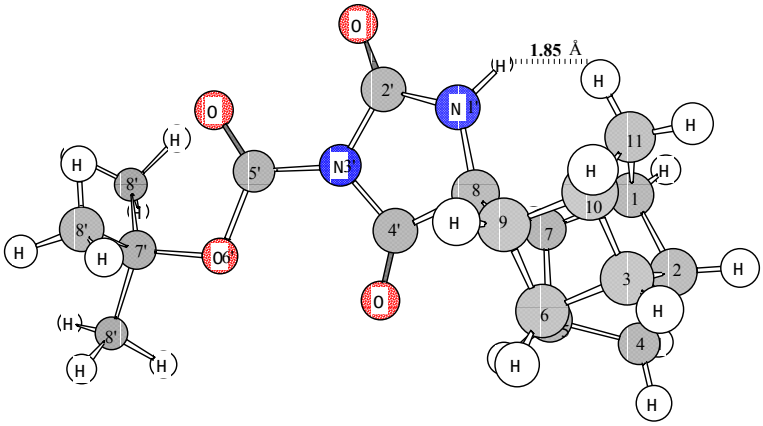
Raasch *et al*[39,41] argued that attachment of the Boc group to N-3' may have been forced due to excessive steric hindrance from the bulky cage skeleton at N-1'. The arguments will be explored in **Chapter 4** where a computational model was employed to predict the mechanistic pathway for the regioselective acetylation of the PCU hydantoin (**11**). The preferred mechanism[17] of protection of amines with anhydrides involves a six membered ring transition state (See **Chapter 4**, structure **65**) rather than a stepwise acyclic route. In this cyclic transition state the leaving acetate group serves as a base to remove the proton from the incoming nucleophile (-NH). A cyclic transition state at N-3' which is perpendicular to the hydantoin ring should be exposed to less steric hindrance as compared to a similar transition state[17] at N-1'. The structural elucidation of the novel compound (**28**) was made from an extensive ^{1}H and ^{13}C NMR investigation. It was evident that the mono-Boc derivative of the PCU hydantoin had been synthesised with the appearance of three carbonyl peaks in the ^{13}C NMR spectrum at 146.28, 173.08 and 152.62 ppm and the appearance of the expected molecular ion peak of m/z 329 $[M+H]^{+}$ in the mass spectrum. Further evidence for the formation of a mono-Boc-protected hydantoin was obtained form the presence of three carbonyl peaks

in the IR spectrum (1718, 1765, 1803 cm^{-1}). The previous reported[20] NMR elucidation of the PCU hydantoin was useful and the same numbering system was also adopted.



28

It was previously shown that H-4a is resonating upfield in comparison with H-4s. The chemical shift around 1.63-1.66 ppm can thus be allocated to H-4s and those around 1.24-1.27 ppm to H-4a. This was also confirmed by the reported[19] coupling constant of H-4a and H-4s which is around 10.7 Hz but in this case the coupling constant was found to be 10.9 Hz. The calculated distance between H-11s and H-1' is 1.85 Å. (**Figure 2**)



28

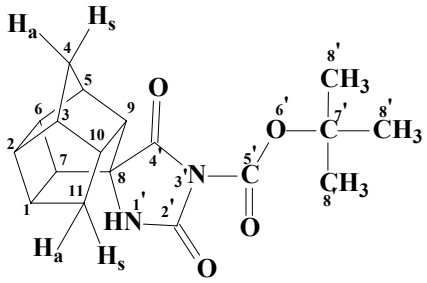
Figure 2: B3LYP/6-31+g(d) Optimised mono-Boc protected PCU hydantoin (28)

H-11s and H-1' are close enough to experience a Nuclear Overhauser Effect (NOE).[19] It is therefore not surprising that the Nuclear Overhauser Effect Spectroscopy (NOESY) indicates a strong correlation between H-11s and H-1'. The assignment of H-4s and H-4a helped on assigning C-4 at 34.26 ppm since it shows a HSQC correlation with both H-4s and H-4a. It was also previously shown[19] that the coupling constants of H-11a

and H-11s for related but the different systems are 3.4 and 13.7 Hz respectively. The coupling constants were experimentally found to be 3.3 and 12.5 Hz for H-11a and H-11s respectively. Knowing the coupling constants of H-11a and H-11s helped with the assignment of these protons to 1.23 and 1.43 ppm respectively. The assignment of H-11a and H-11s is instrumental to the assignment of C-11 to 28.07 ppm as both protons showed HSQC correlation with C-11. The assignment of C-11, H-11a, H-11s, C-4, H-4a and H-4s afford dual handles for solving the rest of the structure as the rest of the assignments can be made via various correlations with these pivotal signals. A HMBC correlation of H-3 and H-5 to C-4 assisted with the assignment of H-3 and H-5 to 2.33 and 2.98 ppm respectively. H-1 and H-10 was assigned to 2.85 and 2.53 ppm respectively due to HMBC correlation with C-11. The presence of a proton peak (1.56 ppm) in the ^{1}H NMR spectrum, which integrated to nine protons could, therefore, be assigned to the three methyl groups (H-8') of the *t*-Boc group. The absence of the imide proton (H-3') at about 10 ppm[20] and the presence of the amide proton (H-1') at 6.02 ppm[20] in the ^{1}H NMR spectrum confirmed that the *t*-Boc group had attached to the imide nitrogen (H-3'). C-5' was assigned to 146.28 ppm due the fact that it is positioned in an electron abundant region; it is therefore expected to be more upfield in comparison with C-4' and C-2'. The peak at 173.08 ppm is associated with C-4' since it positioned in electron deficient area; it is therefore expected to be a bit more downfield. Using the same analogy as above, C-2' was assigned to 151.56 ppm.

These values are in reasonable agreement with those obtained for the corresponding mono-Boc protected trishomocubane hydantoin.[40] The C-7' carbon of the Boc group was assigned to 85.44 ppm in the HMBC spectrum due to correlation with the H-8' methyl protons. The quaternary C-8 carbon is easily recognized at 68.07 ppm as it displays no HSQC correlation. It is also expected to be the most downshifted carbon owing to its direct attachment to the electron withdrawing hydantoin ring. Carbons C-7 and C-9 were assigned at 41.60 and 49.03 ppm owing to their direct attachment to the deshielded C-8 carbon. At this point it was not yet possible to distinguish between C-7 and C-9; their corresponding protons are identified at 2.60 and 2.33 ppm from the HSQC spectrum due to correlation to the two carbon atoms. In order to distinguish between C-7 (H-7) and C-9 (H-9) the assignment of H-5 was useful. The H-5 proton at

2.98 ppm is easily recognisable from the COSY correlation with H-4s at 1.66 ppm. Both H-7 and H-9 are HMBC correlated to C-8, and H-5 is also COSY correlated to H-9 at 2.33 ppm. The rest of the assignments were based on the previously reported NMR elucidation of PCU hydantoin.[19,20] The complete NMR data of **28** is summarised in **Table 2**.



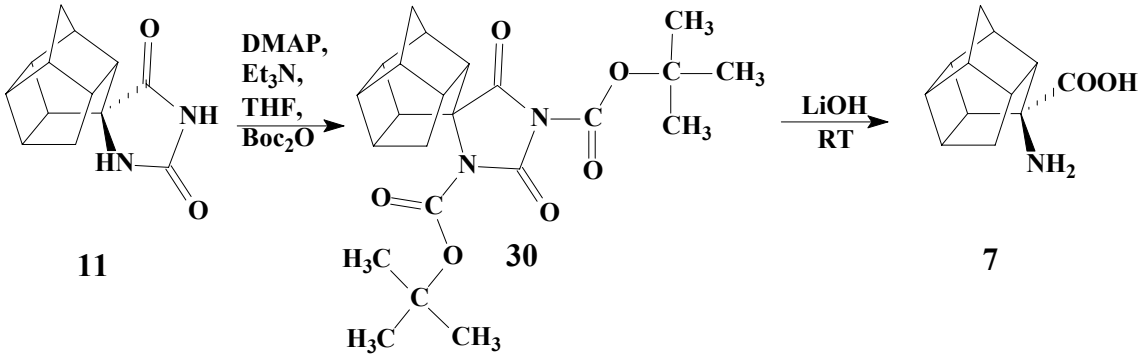
28

Table 2: NMR data[a] for the mono-Boc protected hydantoin (28)

Atom Number	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)
1	**2.85**		**35.88**
2	**2.66**		**44.44**
3	**2.33**		**46.46**
4_a	**1.66**	**10.91**	**34.26**
4_s	**1.27**	**10.91**	
5	**2.98**		**42.43**
6	**2.77**		**41.49**
7	**2.60**		**41.60**
8			**68.07**
9	**2.33**		**49.03**
10	**2.53**		**43.18**
11_a	**1.23**	**3.30**	**28.04**
11_s	**1.43**	**12.5**	
1'	**6.40**		**29.15**
2'			**145.93**
4'			**171.65**
7'			**84.91**
8'			**27.61**

[a]400 MHz for 'H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$

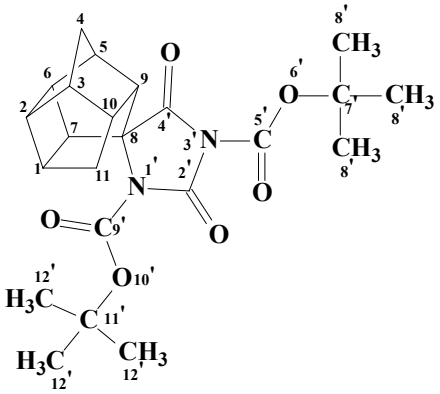
Similar to the approach by Raasch *et al*[39,40,41]a method by Hammer *et. al* [42] was used to synthesise the novel bis-Boc protected PCU hydantoin (30). Hammer's method is similar to Rebek's method, except triethylamine was added to the reaction.



Scheme 11: Synthesis of PCU amino acid (7)

The NMR data of the mono-Boc protected PCU hydantoin (**28**) were used to elucidate the bis-Boc derivative (**30**). The successful synthesis of the bis-Boc protected PCU hydantoin was first evident from the infrared spectrum with the presence of four carbonyl absorption bands at 1724, 1751, 1765 and 1806 cm^{-1}.

The aim of synthesising the bis-Boc protected hydantoin (**30**) is to improve the yield of the PCU amino acid. In this regard the bis-Boc protected hydantoin was subjected to LiOH hydrolysis to obtain an improved yield of amino acid, but the amino acid was contaminated with salts and di-tert-butyl imidodicarbonate (Boc_2NH) so the isolation of the amino acid proved to be difficult. A one pot procedure was used for conversion of bis-Boc protected hydantoin (**30**) to the Fmoc PCU amino acid (**31**). The absence of the amide and imide hydrogens of the hydantoin ring at about 6 and 10 ppm, respectively, in the proton NMR spectrum confirmed bis-Boc protection. The correct molecular ion peak of m/z 431 $[M+H]^+$ in the mass spectrum also confirmed formation of the bis-Boc protected PCU hydantoin (**30**).



30

Table 3: NMR data[a] for bis-Boc protected hydantoin (30)

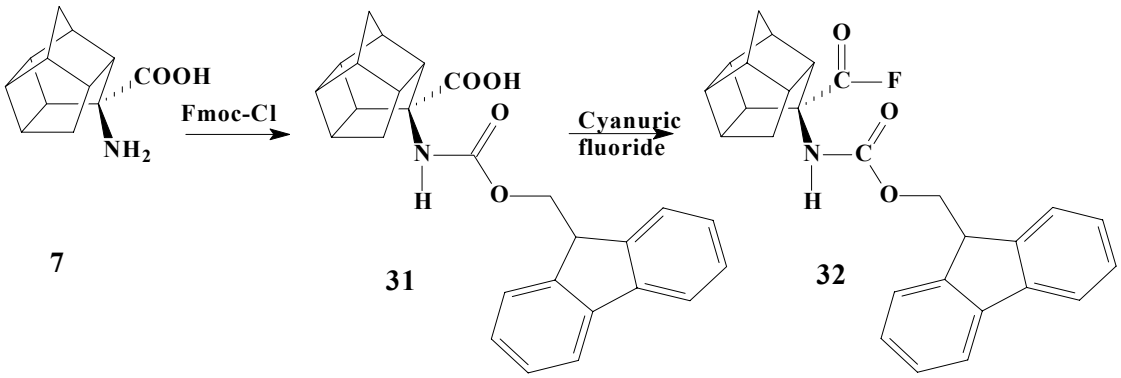
Atom Number	^{1}H (ppm)	*J* (Hz)	^{13}C (ppm)
1	2.82		34.40
2	2.62		41.42
3	2.27		43.44
4_a	1.24	10.40	34.40
4_S	1.67	10.40	
5	2.94		42.70
6	2.77		41.06
7	2.60		41.88
8			46.43
9	2.26		49.29
10	2.50		42.69
11_a	1.26	4.03	29.15
11_s	1.40	13.55	
2'			145.93
4'			171.65
5'			149.71
7'			84.91
8'	1.543		27.61
9'	1.519		149.80
11'			86.10
12'			27.73

[a]400 MHz for 'H NMR and 100 MHz for ^{13}C NMR in CDCl3

The presence of two methyl peaks in the proton NMR spectrum which integrate to nine protons (H-12') is typical of the Boc functional groups. The ^{13}C NMR spectrum exhibits four carbonyl groups. Two-dimensional NMR techniques were essential for the full elucidation of **30**. H-12' and H-8' were assigned to 1.543 and 1.519 ppm owing to HSQC correlation with C-12' and C-8' respectively. The assignments for the bis-Boc hydantoin are presented in **Table 3**.

To overcome the difficulties mentioned above, the cleavage reaction mixture was extracted with ether to remove Boc_2NH while the amino acid (**7**) stayed in the aqueous layer as the lithium salt. Fmoc-Cl was added to the reaction mixture while the pH was adjusted to 6.5 and a quantitative yield of Fmoc PCU amino acid (**31**) was obtained. Evidence of the successful synthesis of the Fmoc PCU amino acid (**31**)[43] was obtained from MS (correct molecular ion peak of m/z 431 IR and NMR data).

The attempted coupling of the sterically hindered PCU amino acid to non-natural peptides is discussed on the next chapter (**Chapter 3**). In order to improve the chances of a successful coupling of the PCU amino acid to a peptide the more active acid halide (**32**) is required. The use of the relatively stable acid fluorides has been reported to ensure successful coupling of sterically hindered amino acids.[44,45] The application of acid chlorides has been introduced but it has shown a lot of disadvantages due to the fact that N-protected amino acid chlorides are relatively unstable due to their high reactivity and sensitivity to hydrolysis.[46,47] The preparation of stable Fmoc protected trifunctional amino acid chlorides showed similar difficulties.[48] Acid fluorides exhibit sufficient reactivity partly due to the smaller size of the fluoride leaving group when compared to acid chlorides.[47] It was therefore decided to synthesise the Fmoc PCU amino acid fluoride (**32**).[43] The synthesis involved the mixing of Fmoc PCU amino acid, cyanuric fluoride and dry pyridine in dry dichloromethane at room temperature.[43,49] The removal of the organic solvent and recrystallisation in hexane/dichloromethane resulted in the formation of the novel Fmoc PCU amino acid fluoride (**32**).[43]

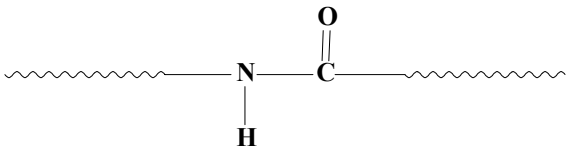


Scheme 12: Synthesis of Fmoc PCU amino acid flouride (32)

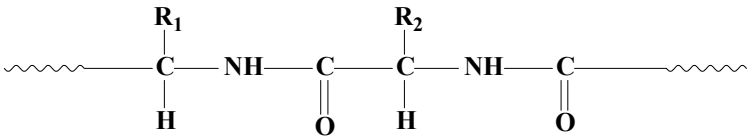
Acid fluorides are stable and can be stored for up to six months under normal conditions. A further benefit of acid fluorides is the absence of oxazolone formation as coupling is performed in the presence of a base.[50] The acid fluorides have proven to be effective in the coupling of sterically hindered amino acids such Aib into short peptides.[47]

3. SOLID PHASE PEPTIDE SYNTHESIS (SPPS)

Naturally occurring peptides are known as biopolymers or proteins. Proteins are basic constituents of all living organisms.[51] Their central role was recognised in the early 19th century when the name of these molecules was coined from the Greek word, Proteios, meaning "holding the first place".[52] Proteins are natural polymers (**34**) built from naturally occurring α-amino acids and the backbone of the protein consists of a continuous amide (**33**) chain.

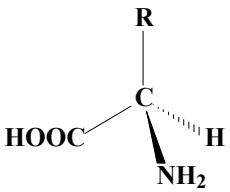


33 Amide



34 Polyamide

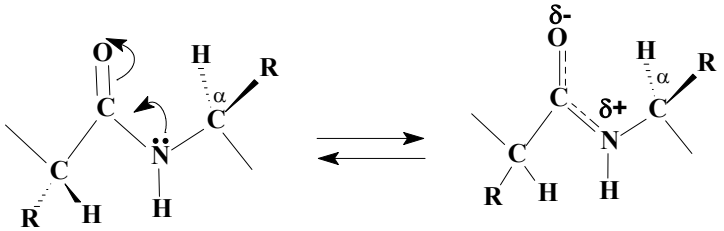
The twenty common amino acids contain at least one chiral centre, except for the achiral glycine (H_2N-CH_2-COOH).[53] The twenty common naturally occurring α-amino acids have the following general formula (**35**):



35

Since the hydrogen atom always has the lowest priority according to the Cahn-Ingold-Prelog rules, followed by the side chain (**R**-group), acid group and lastly the amine group which possesses the highest priority, most of the twenty common naturally amino acids have the (**S**)-configuration.[54] Cysteine is only exception as the side chain contains a sulphur atom, which has a higher priority than the oxygen on the acid function.

The covalent amide bond that joins amino acids together in a condensation reaction is called a peptide bond (**36**).[55] The peptide bond (**36** and **37**) is formed between the α-amino group of one amino acid and the α-carboxyl group of another amino acid. The bond has an unusual property that has a marked effect on the rigidity of a polypeptide chain and consequently on the folding of the polypeptide chain. It has partial double bond character (**36** and **37**), which is caused by delocalization of the nitrogen lone pair which induces partial double bond character to the C-N bond.

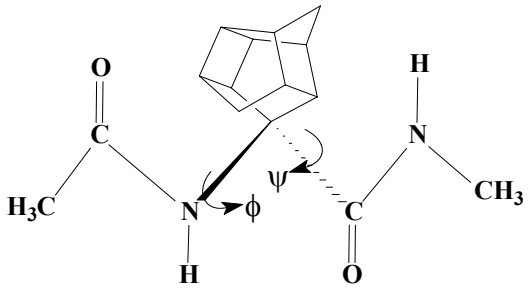


36 **37**

Scheme 13: Peptide bond

The consequence of this arrangement is that the peptide bond is relatively rigid with the hydrogen atom in a *trans* position with respect to the carbonyl oxygen. The net result is that the six atoms around the peptide bond all lie in a plane i.e. the peptide bond "freezes" 6 atoms in a planar state because the C-N bond exhibits partial double bond character. This means that free rotation in peptides is under normal conditions only possible at the bonds adjacent to the peptide bonds. These bonds are defined by the *phi* (ψ) and *psi* (ϕ) angles[14,56] (**38**). The amount of rotation possible and therefore the values of ψ and ϕ depend on the particular side chain (**R**-group) of the amino acids that are joined together. This free rotation gives rise to unique conformational structure of proteins which is an important prerequisite to understanding conformational characteristics of peptides.[14,16,56] The accessible conformational space of an amino acid residue can essentially be characterized by its potential energy map, often referred to as the Ramachandran map.[57] These maps are generated from systematic rotation of the backbone torsion angles, ϕ and ψ (**38**) defined by the N-C and C-C bonds, respectively. Glycine is the most flexible amino acid residue, accessing more than 60% of the conformational space.[58] In contrast, proline is the only natural amino acid residue with its accessible

conformational space considerably reduced.[59] Biopolymers or peptides are considered to be some of the most important compounds used as pharmaceutical drugs.[14,60]



38

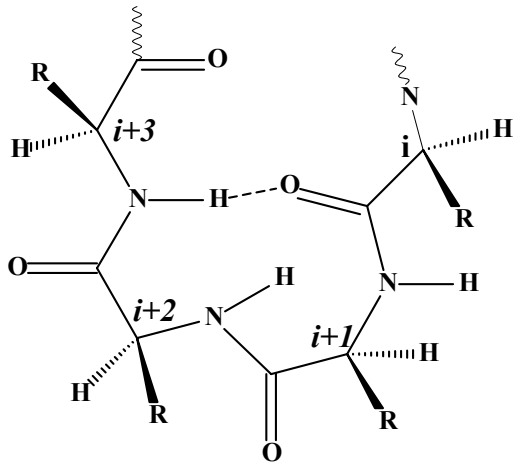
Figure 3: *Phi* (ψ) and *psi* (ϕ) angles[14]

Each specific receptor site of viral or bacterial affected areas possesses a certain 3-dimensional structure which interacts with the pharmaceutical drug.[61] The mechanism of drug and receptor interaction is sometimes called the key and lock, or hand and glove mechanism. One of the most relevant aspects of synthesizing peptides is therefore to combine a limited set of amino acids in a well defined sequence. During the synthesis of the peptide, the peptide molecules arrange themselves into a conformational folder called a foldamer a name which was first coined by Gellman.[60] The structural conformation, such as α-helix, β-sheets and β-turns of the peptide, is an important fixture for designing the best synthetic proteins[62] and the three dimensional structures also serve as the backbone when interacting with target or receptors sites.[61]

Without these conformational structures, it is quite difficult to make general useful rules about the structure and functions of peptides. It is therefore not surprising that research to determine the driving force for the folding process or for the formation of the secondary and tertiary structure of proteins has been the aim of many researchers.[14,16,63] If this secret is revealed it might be possible to predict the structural functions of peptides. Studies have revealed that β-turns **(39)** are the most predominant structural conformations that are used in determining the proper functions of the protein chains.[55] These conformational motifs occur to a great extent in globular proteins and in the

membrane-active, channel-forming peptide antibiotics.[64] The intramolecular hydrogen bonding adopted by an amide group depends most on the steric hindrance of the R-group.

β-Turns (**39**) constitute a significant secondary structural component within peptides and proteins. These conformations differ by the orientation of the amide bond connecting their *i+1*, *i+2* and *i+3* residues.[14]



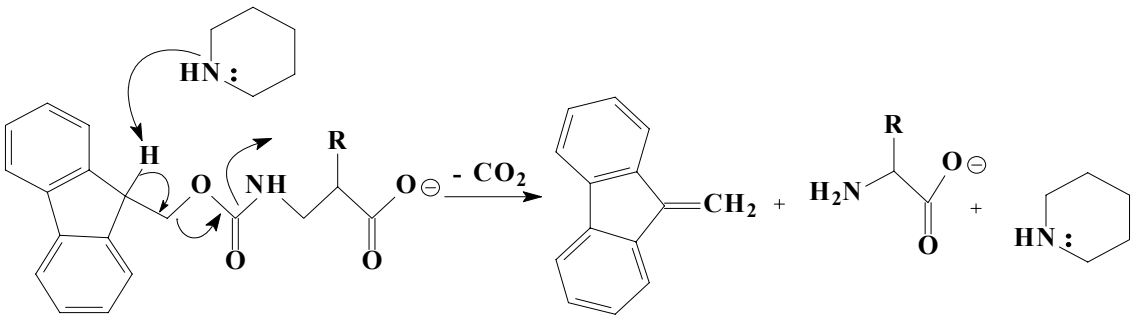
39

Figure 4: A typical β-turn[56]

The β-turns (**39**) comprise about 25 % of all residues in proteins and also are the most important motif for folding of proteins to produce their compact structure.[12,13,14] The criteria for defining a β-turn are widely accepted.[56,65,66]

The first synthetic peptide was introduced by Emil Fischer.[52] Peptide synthesis made use of solution chemistry in the early stages of peptide research. Solution phase peptide synthesis encountered problems with solubility and purification. The versatile solid phase peptide synthesis (SPPS) was first introduced by Merrifield in 1963.[67] Solid phase peptide synthesis strategy with the temporal base labile α-amino protecting group (Fmoc) was introduced by Carpino in 1972.[68] General speaking in Fmoc SPPS, the α-amino group is protected by Fmoc and the side chain functional groups are protected by

the acid labile *t*-butyl type protecting group. Fmoc based SPPS provides an alternative method to the *t*-Boc SPPS and offers the advantage of milder acidic cleavage processes during the deprotection of the Fmoc group. The development in Fmoc SPPS can be summarized in the following categories: solid support, linkers, attachment of the first residue, protecting groups, Fmoc deprotection, coupling reagents, monitoring, cleavage and removal of the protecting groups, peptide evaluation and peptide modification.[69] The mechanism for cleaving the Fmoc group in the presence of piperidine is highlighted below.



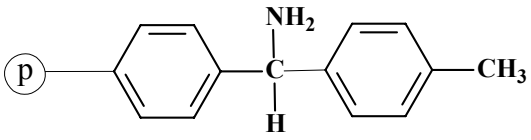
40 **41** **42** **43**

Scheme 14: Deprotection mechanism with piperidine

SPPS requires a well solvated gel to allow the reactions to take place between reagents in the mobile phase and functional groups on the chains attached to the resin. The first polyamide resin was introduced by Atherton[70] under the concept that the solid support and the peptide backbone should be of comparable polarities. Recent developments make use of resins based on grafting of polyethylene glycol (PEG) to low crossed linked polystyrene which led on the development of resins such as Tentagel.[71] 4-Methylbenzhydrylamine resin (MBHA, 0.7 mmol NH_2/g , **44**) has shown excellent swelling capacity and superior performance especially when manual peptide synthetic procedures are employed.[40]

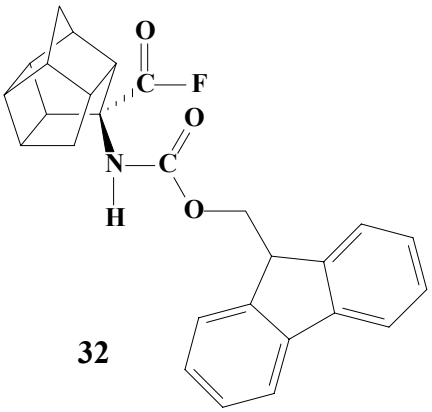
The function of the linker is to provide a reversible linkage between the peptide chain and the solid support, and to protect the C-terminal of the α-carboxylic group. The linker should be stable to the reaction conditions employed and should be cleavable (to

release the product) without destroying the synthesised peptide.[72,73]



44

There has been much success with the use of (*p*-[(**R**,**S**)-α-[1-(9H-fluoren-9-yl)methoxy-formamido]-2,4-dimethyl-benzyl]-phenoxyacetic acid (FmocAM linker, **45**) as it is stable towards basic conditions that are used during the decoupling processes.[72,73]



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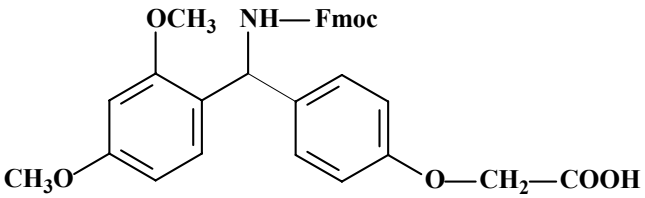
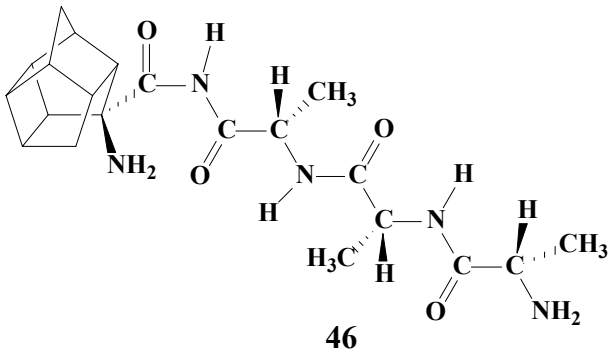


45

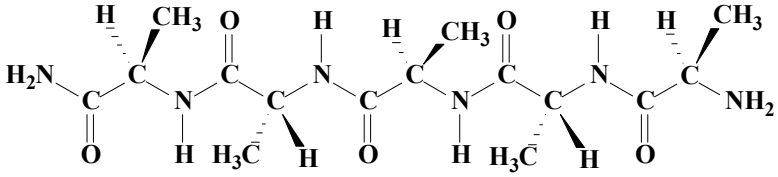
With the fmoc PCU amino acid fluoride (**32**)[43] (see **Chapter 2**), an attempt was made to synthesise the proposed tetrapeptide (**46**)**.** This tetrapeptide (**46**) would be the first step towards verifying the computational predictions by Bisetty.[14]



46

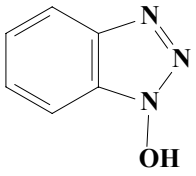
As mentioned above, the synthesis of peptides involves a series of steps therefore a number of peptides were synthesised using SPPS in order to gain insight and hands-on experience with SPPS techniques. The first attempted peptide was the pentapeptide

(ala-ala-ala-ala-ala, **47**). The synthesis of **47** required attachment of the linker **45** to the resin followed by the successive attachment of five alanine amino acids.



47 **Penta-peptide**

The synthesis was performed using the 4-methylbenzhydrylamine resin (**44**) in DMF. Coupling of the linker was achieved by the addition of the *in situ* coupling reagents 1-hydroxybenzotriazole (HOBt, **48**) and the dehydration agent diisopropyl carbodiimide (DIPCDI - **49**) in DMF.[74]



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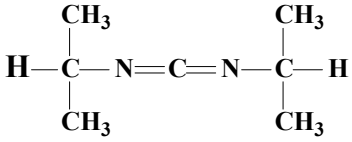
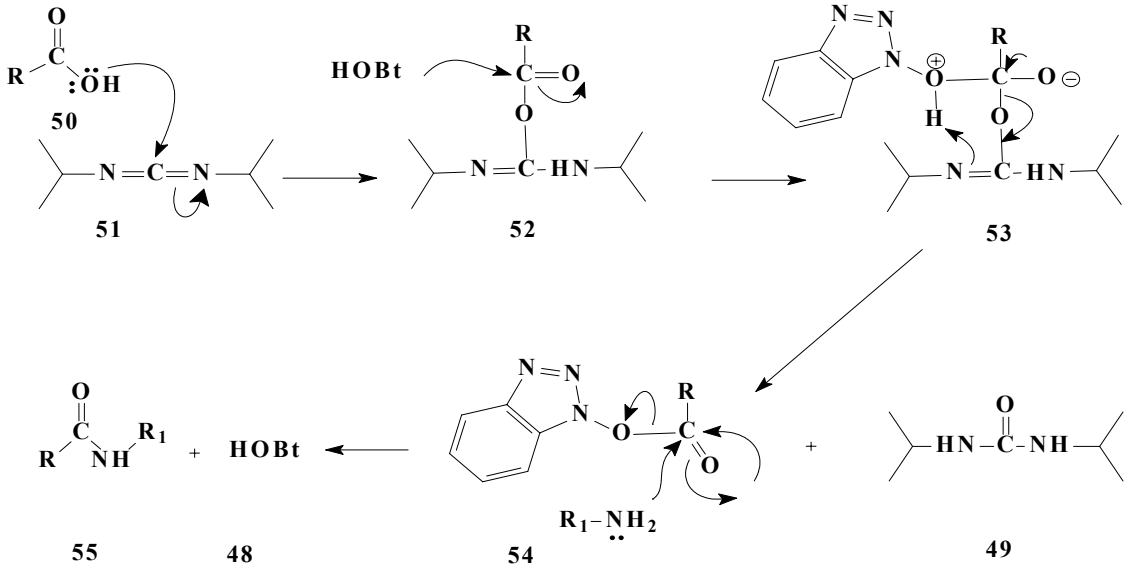


49

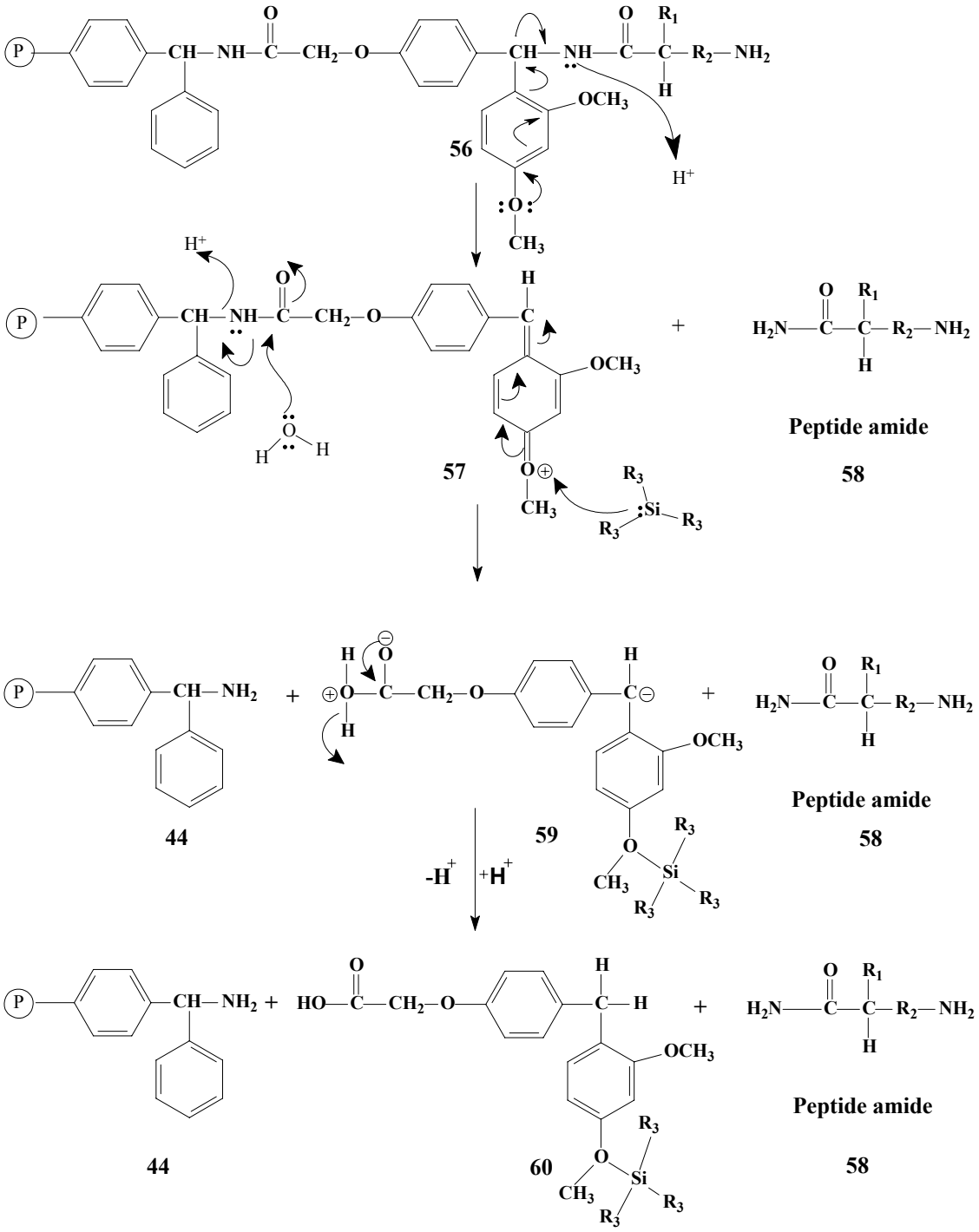
The Fmoc group of the linker was removed by treatment of the resin with 20% piperidine in DMF.[75] The removal of the Fmoc group was confirmed by a positive Kaiser test.[76] This was followed by the successively coupling of the five alanine "layers" in the presence of **48** and **49**. The outlined mechanism (**Scheme 15**) shows that during the synthesis of peptides, the *in situ* reagent **49** acts as the dehydration agent which leads to the formation of urea. It also activates the acid functional group of the incoming amino acid. HOBt (**48**) acts as a catalyst (**Scheme 15**).



Scheme 15: Dehydration mechanism with DIPCDI and HOBt

The excess reagents were removed by washing with DMF and isopropanol. The pentapeptide (**47**) was prepared for cleavage by washing successively with dichloromethane, methanol and diethyl ether, followed by drying *in vacuo.*[77] The cleavage mixture of 95 % ($^{v}/_{v}$) trifluoroacetic acid, 2.5 % ($^{v}/_{v}$) water and 2.5 % ($^{v}/_{v}$) triisopropylsilane was subsequently added.[77] Triisopropylsilane serves as a carbocation scavenger. The resin (**44**) was removed by filtration, the filtrate was centrifuged followed by the application of nitrogen gas to remove most of the TFA.

Diethyl ether was subsequently added to precipitate the peptide from the solution. Decanting the diethyl ether after separation through centrifuging served to separate the linker and triisopropylsilane **(60)** from the peptide.[77] As it can be seen in the cleavage mechanism (**Scheme 16**), a peptide amide (**58**) is formed when the linker **45** is employed. Triisopropylsilane reacts with the linker to form **60** which is soluble in diethyl ether and it is therefore decanted while the resin is filtered out. Triisopropylsilane is therefore called a scavenger as it is assisting with the removal of unwanted and reactive carbocation side-products during the cleavage process.

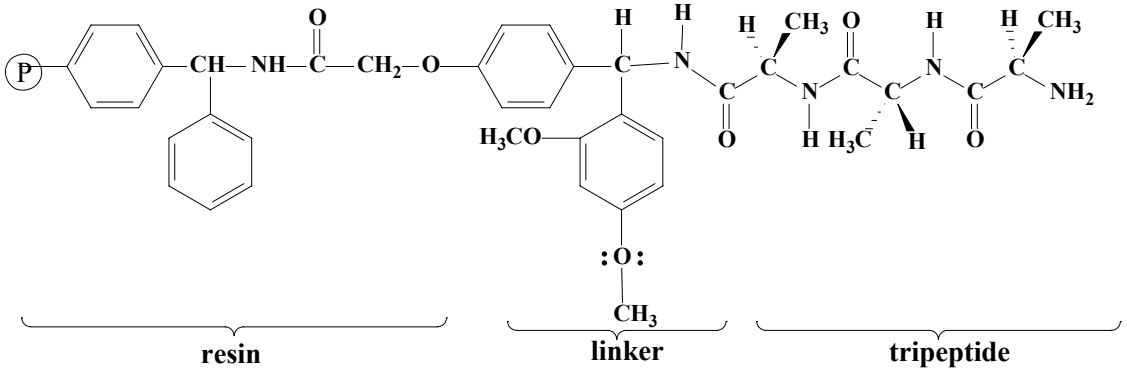


Scheme 16: Mechanism for cleavage of peptide

The successful synthesis of the pentapeptide (**47**) was verified by IR, NMR and HPLC. It was evident that **47** had been synthesised with the appearance of five carbonyl peaks in the ^{13}C NMR spectrum at 174.1, 172.0, 171.7, 171.6, 169.3 ppm. The appearance of the expected molecular ion peak of m/z 372 $[M+H]^+$ in the mass spectrum also

confirmed the formation of the pentapeptide. Further evidence for the formation of the pentapeptide (**47**) was obtained from the presence of five carbonyl peaks in the IR spectrum (1703, 1683, 1663, 1630, 1545 cm^{-1}). The five carbon peaks in ^{13}C NMR at 18.6, 18.4, 18.3, 18.2 and 17.4 ppm were associated with five methyl groups present, one for each alanine. The purity of **47** was also determined with High Performance Liquid Chromatograph (HPLC) which gave two peaks. The first peak at the retention time (RT) of 5.85 min. corresponds to **47** the purity was calculated to be 94.2% and the second unidentified peak appeared at 10.3 min.

From **Scheme 16** it can be concluded that **46** and **47** are the expected peptides when the synthesis is done in the presence of the linker **45.** The synthesis of the proposed Cage tetrapeptide (**46**) involved the synthesis of resin-bound tripeptide (**61**) following by the coupling method presented above. A small amount of **61** was cleaved from the resin to verify the purity of the tripeptide with HPLC analysis[b] only one peak was obtained indicating 100% purity. The tripeptide peak appeared at 3.52 min.



61 Resin bound tripeptide

The Fmoc PCU amino acid fluoride (**32**) was added to the resin-bound tripeptide along with DMF and pyridine as a fluoride ion scavenger.[49] This was necessary since hydrofluoric acid is effective in cleaving MBHA linkages.[78] The successful addition was confirmed by a negative Kaiser test. The Fmoc group was removed by addition of 20 % (v/v) piperidine in DMF.[77] A positive Kaiser test was obtained. The cage tetrapeptide was prepared as described above. The purity of the tetrapeptide (**46**) was

[b] The details of the HPCL conditions are provided in the experimental section.

confirmed using HPLC analysis. The HPLC spectrum clearly reveals that the PCU amino acid was not completely coupled to the tripeptide as it reveals a peak at 3.61 min. which represents the presence of tripeptide. The tetrapeptide (**46**) peak appeared at 14.9 min and the calculated purity of **46** was 67.6 %. Full elucidation of the tetrapeptide was not achieved as an effective separation of the peptides was not achieved with the limited amounts available. The proton NMR analysis of the tetrapeptide was performed and confirmed the presence of the PCU amino acid. NMR analysis of the peptide confirmed the removal of the Fmoc protecting group. The IR, proton NMR and HPLC were used to verify the structure of the tetrapeptide. The presence of the four carbonyl peaks at 1752, 1677, 1622, 1547 cm-1 in the IR spectra confirmed that the tetrapeptide was successfully synthesised. The molecular ion peak of m/z 419 $[M+H]^+$ in the mass spectrum also confirmed the formation of the tetrapeptide (**46**). The proton NMR analysis clearly indicated three methyl groups which were indicating the presence of three alanines. The intensities of the proton peaks are in agreement with the cage peaks, indicating that the tripeptide was in fact coupled to the cage amino acid.

The pentapeptide (**47**) and tetrapeptide (**46**) were successfully synthesised according to spectrometric results given. The tetrapeptide proved difficult to purify, and consequently a full structural elucidation by NMR techniques was not possible. It is of great importance and interest that further study is conducted to synthesise the peptide in purer form or to purify the peptide using preparative HPLC.

4. COMPUTATIONAL CHEMISTRY

4.1. Introduction

The acetylation of the PCU hydantoin (see **Chapter 2**) initiated the computational investigation as the distribution of the products obtained were different to results obtained with basic hydantoin systems.[79,80,81] Computational chemistry can provide one with energetic data about the energy barriers involved between reactants and products, as well as the relative energies of the intermediates and products.[82] The energy barriers between reactants and products provide insight about the kinetics of the reaction and the relative energies of the products and intermediates provide insight about the thermodynamics of the reaction. When two or more competing reactions are possible, one might be able to use a computational model to determine which pathway will be kinetically and/or thermodynamically favoured. The most difficult part of this investigation is to determine the energy barriers involved in the reaction. In order to determine the energy barrier involved, one has to find the transition state structure, which connects the reactants to the products. More information about this aspect will be provided below.

Computational chemistry can also provide valuable spectroscopic (IR, UV, NMR) data of structures under investigation. Another application is to calculate the energies and shapes of various orbitals (such as the HOMO and LUMO) and electron densities of molecules. There are two broad areas within computational chemistry devoted to the structure of molecules and their reactivity: *molecular mechanics* and *electronic structure* theory. Both fields involve the same basic types of calculation used in this investigation:

- Computing the energy of a particular molecular structure. Properties related to the energy may also be estimated.
- Performing geometry optimisations, which locate the lowest energy molecular structure nearest to the specified starting structure.
- Computing the vibrational frequencies of molecules.

Molecular mechanics simulations use the laws of classical physics to predict the

structures and the properties of molecules.[82,83] There are many types of methods of calculation. Each one is characterised by a particular force field. Force fields have the following components:[83]

- A set of equations defining how the potential energy of a molecule varies with the location of its components.
- A series of atom types which define the characteristics of an element within a specific chemical context.
- One or more parameter sets that fit the equations and the atom types to the experimental data. The parameter sets are the force constants which are used in the equations to relate atomic characteristics to energy components and to the structural data such as bond length and angles.
- Each force field achieves good results only for molecules related to those for which it was parameterised.

Molecular mechanics calculations do not explicitly treat the electrons in a molecular system but perform calculations based on the interactions among the nuclei. The electronic effects are implicitly included in the force field through parameterisation.

This approximation makes the molecular mechanics computations quite inexpensive with respect to computing time. However, the approximation also carries several limitations, the most important of which are:[84]

- *Molecular mechanics* methods cannot treat chemical problems where electronic effects predominate because it neglects the presence of electrons
- *Electronic methods* use the laws of quantum mechanics rather than classical physics as the basis for their computations. Quantum mechanics state that the energy and other related properties of a molecule may be obtained by solving the Schrödinger equation.

There are two classes of electronic structure methods:[82]

- *Semi-empirical methods* such as AM1, MINDO/3 and PM3 which are implemented in programs like MOPAC, AMPAC, HyperChem and Gaussian. These methods use parameters derived from experimental data to simplify the computation through quite severe approximations.
- *Ab initio* methods, unlike molecular mechanics or semi-empirical methods, do not use experimental parameters such as bond lengths, angles etc. in their calculations.[82] Instead computations are based on the laws of quantum mechanics, the first principle which is referred to the name *ab initio* and is based on the values of a small number of physical constants such as the speed of light, Planck's constant, the masses and the charges of nuclei and electrons.
- *Semi-empirical* and *ab initio* methods differ in the trade-off made between computational cost and accuracy of results. Semi-empirical calculations are relatively inexpensive and provide reasonable qualitative descriptions of molecular systems and fairly accurate prediction of energies and structures for systems where good parameter sets exist. Semi-empirical methods are therefore not well equipped to deal with most novel transition states as no parameters for these systems exist. In contrast *ab initio* computations provide high quality quantitative predictions for a broad range of systems.

Density functional theory (DFT)[85] is the third class of electronic structure methods which has become very popular recently. It is similar to *ab initio* methods and it requires about the same amount of computational resources as Hartree-Fock theory which is the least expensive *ab initio* method. The DFT methods are attractive because they approximate the effects of electron correlation where electrons in a molecular system react with each other's motion in an attempt to keep out of each other's way. DFT methods only approximate the effect of electron correlation as the derivation of suitable formulae for the exchange correlation term depends on a solution to a function which is not exactly known.[85]

DFT methods are based on the theory by Hohenberg and Kohn[86,87] in which they demonstrated that the ground state energy of any molecule can be described in terms of

the total electron density which means that each molecule has an unique functional form which exactly determines the ground state energy and electron density of the molecule. The Hartree-Fock calculations consider this effect only in an average sense.[88] These approximations cause Hartree-Fock results to be less accurate for some types of systems. Thus, DFT methods can provide the benefits of some more expensive *ab initio* methods (electron correlation methods such as MP2) at essentially the cost of a Hartree-Fock calculation.[89] The Gaussian[90] software offers the entire range of electronic structure methods. This study relies on the application of DFT methods as they provide the most reliable ways for doing calculations at a reasonable level of theory. DFT methods have disadvantages as the precise function is not known and the reason for the relatively good accuracy of result is not exactly known.[85,86,87] The practical problem that theoreticians have with DFT is that one is not able to approach the real solution of the wavefunction, as is the case with *ab initio* methods, by increasing the level of theory and the type of the basis set.[88]

The methods and aspects discussed above [Molecular Mechanics, Semi-empirical, *ab initio* (RHF and MP2) and Density Functional Theory] are commonly called the "level of theory" applied to calculate the geometry and energy of a molecule. Both *ab initio* and DFT are concerned with predicting various properties of atomic and molecular systems. The current investigation depended heavily on transtion state calculations and was limited to RHF and DFT caluations.

The references below discuss important aspects which should be considered when one is using computational methods:

- The Schrödinger equation[88]
- The Born-Oppenheimer approximation of the Schrödinger equation.[91]
- The Hartree-Fock approximation.[88]
- Linear Combination of Atomic Orbitals (LCAO) approximation.[82]
- Roothaan-Hall equations.[82]

4.2. Restricted Hartree-Fock (RHF) vs Unrestricted Hartree-Fock (UHF)

The Hartree-Fock wave function, in which the electron spins are by default paired and also occupy the same spatial orbital, is called a ***Restricted Hartree-Fock*** (RHF) wavefunction. This kind of Hartree-Fock wave function is derived from molecular orbital occupation of electrons which give rise to a wave function of singlet type. ***Unrestricted Hartree-Fock*** wave functions are those that occur when the α-electrons are allowed to differ from those of spin-β-electrons. The difference between these wave functions is that the former method uses a reasonable approximation while the latter is computationally cumbersome but provides superior results for certain system.[83,85]

4.3. Basis sets

Molecular orbitals can be expanded as a linear combination of atomic orbitals and are then called basis functions.[83,85] The basis functions are collectively called basis sets. Basis sets are derived from the following equation [1]:[92]

$$\psi_i = \sum_{\mu=1}^{n} C_{\mu i}\phi_\mu \qquad [1]$$

where, $C_{\mu i}$ = molecular orbital expansion coefficient, and ϕ_μ = basis function of atomic orbital.

There are two ways in which the basis set can be explained.[83] The first is to think of a basis set as the atomic orbital in the qualitative molecular orbital. The second is to think of the basis set as a group of mathematical functions which are designed to give the maximum flexibility to the molecular orbital. However the system must include basis sets that really count for something and poor basis sets must be excluded since they increase the cost of calculation for no gain. There are different kinds of basis sets which are discussed in the following sections.

4.3.1. Minimal basis set[93]

The essential idea about the minimal basis set is that one basis function is selected for every atomic orbital that is required to describe the free atom. Several minimal basis sets which are commonly used are the **STO-nG** basis sets. The most common minimal basis set is called **STO-3G**, where a linear combination of three Gaussian type atomic orbitals (GTO-type) are fitted into Slater-type atomic orbitals (STO).[88] The individual GTOs are called primitive orbitals, while the combined functions is called contracted functions. Some commonly used STO-nG basis are STO-4G and STO-6G where STO is fitted onto 4 and 6 GTOs respectively.

4.3.2. Split-valence basis sets[93]

These are the 3-21G basis set where the valence functions are split into one basis set with two GTOs and one with one GTO, the 6-31G basis set where the core consists of 6 GTOs which are not split, while the valence orbitals are described by one orbital constructed from three primitive GTOs and one that is a single GTO.

4.3.3. Double zeta (DZ) basis sets[93]

In these basis sets, every member of the minimal basis set is replaced by two functions. For some heavier atoms DZ basis sets may double the number of minimal basis set orbitals.

4.3.4. Polarisation basis sets[93]

It was argued that the orbital on an atom becomes smaller in a molecule because of the attraction of the other nucleus. However, it is clear that the other nucleus will only distort or polarize the electron density near the nucleus. This is done in the presence of orbitals with more flexibilities and is accomplished by addition of a basis function of higher angular momentum quantum number. **Figure 5** shows that the 1s orbital of hydrogen can be distorted by mixing with an orbital of p symmetry. It is therefore said the orbital has been polarized.

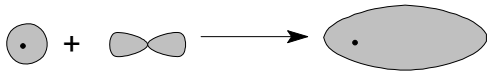


Figure 5: Polarization of a s-orbital

Similarly the p orbitals can be polarized as follows:

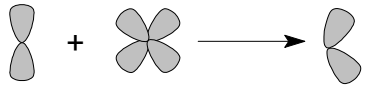


Figure 6: polarization of a p-orbital

These additions of the basis set are called *polarization functions*. The most common polarization basis sets are 6-31G* which adds the d-functions to the atoms and 6-31G** which adds d-function and one type d-function to hydrogen. The modern nomenclature of these basis set has been changed to 6-31G(d) and 6-31G(d,p) respectively. Similarly the basis set can be expanded to 6-31G(3df,pd) which adds 3d-type, 1f-type and one type d-functions. Polarization functions remove some limitations of the basis sets by expansion of the virtual space of the orbital.

4.3.5. Diffuse basis set functions

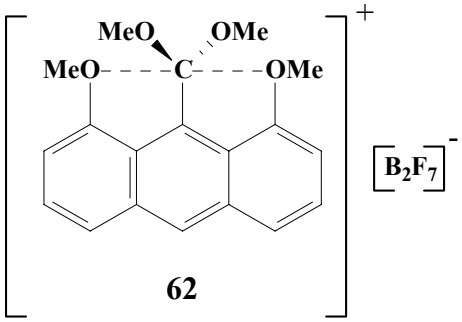
In some cases the normal basis sets described above are inadequate. This is particularly in the case of excited states and in anions where the electron density is more spread out over the molecule (i.e delocalization). To correct this, a model basis function was designed which is more "spread out". This additional "spreading out" of the basis function is called *diffuse functions*.[93]

Diffuse functions are represented as the "+" in the basis set, for example 6-31+G which adds a set of diffuse s- and p-orbitals to atoms. The basis set 6-31++G adds a sets of diffuse s-, p-orbitals to the atoms and a set of diffuse s-function to the hydrogen. *Diffuse functions* can also be used in the presence of polarization functions and the basis sets are then represented as follows: 6-31+G(d), 6-31+G(d,p) and 6-31G(3df,pd) or 6-31G++(3df,pd).

The size of the current problem is similar to that previously studied,[18] a similar basis set [6-31+G(d)] was therefore used. This basis set produces almost the same geometries and relative energies as were obtained when performing[17] these optimisations with the additional polarization functions on hydrogen atoms. Diffuse functions are typically used as a better treatment for cases where negatively charged species are being studied because the ionic radius of an anion is significantly bigger than the corresponding neutral species. In the present case, using diffuse functions on only heavy atoms is justified because the negative charge is mainly located on the oxygen and nitrogen atoms.

4.4. Practical Considerations for Computational Chemistry

Quantum chemical models open a range of possibilities for synthetic organic chemists wishing to anticipate the distribution of the products in kinetically controlled reactions. Experimentally, it has now become possible to examine reaction mechanisms including transition states directly using femtosecond pulsed laser spectroscopy.[94] However, it will be some time before these techniques can be applied to all of the compounds that are accessible computationally. Furthermore, these techniques yield indirect information such as vibrational frequencies rather than a likely geometry for the transition state structure.[84]



62

Synthetic approaches to obtain information about transition-states are also limited to very special cases, such as the static S_N2 transition-state **62** shown above.[95] An X-ray structure of **62** was reported.[95]

A lot of information can be obtained when the results of the kinetically controlled

reaction is compared to the energies of the transition states leading to the formation of different intermediates or products. The observed product will pass through the transition with the lowest energy. One of the interests of chemists is to determine the stability of the products formed. The relative stability of the products is indicated on the potential surface by their relative height with respect to starting materials or reactants (see **Figure 7**).

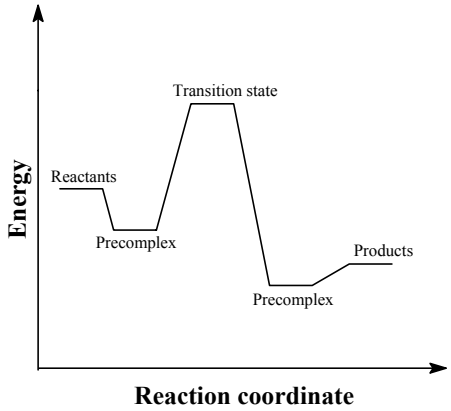


Figure 7: Stages on a simple reaction coordinate[96]

The differences in energies between reactants and intermediates or products represent the thermodynamic nature of the reaction. The most common reaction has the energy of the products lower than that of the reactants. Such reactions could be spontaneous provided that the energy barrier (transition state) between the reactants and products are not too high. In such a case the reaction is called an exothermic reaction (see **Figure 8**). In cases where the free energy of the product is higher than that of the reactant the reaction is said to be endothermic and energy will have to be "pumped" into the system to obtain the endothermic product. The same is true for cases where the energy barrier (transition state or activation energy) is too high (> 15 – 20 kcal mol^{-1})[97] to be overcome at room temperature.

According to the diagram (**Figure 8**) product **C** is more stable than **B,** and **C** is also kinetically preferred as it passes through a transition state with lower energy. The formation of **C** is said to be kinetically and thermodynamically favoured.

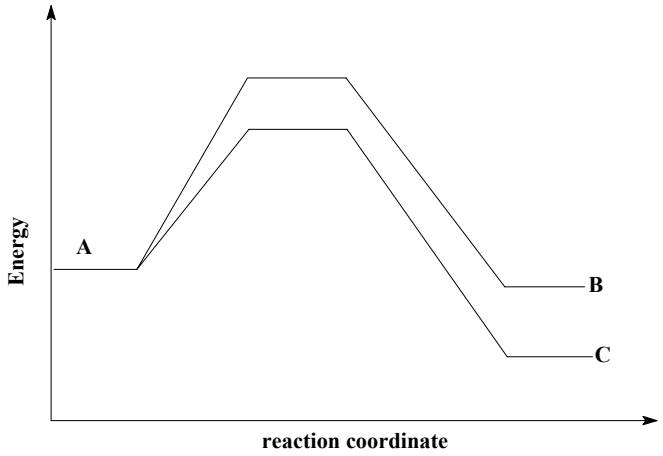


Figure 8: Kinetically and thermodynamically preferred reaction[96]

In some cases the product is only kinetically preferred like product **D** in **Figure 9**.

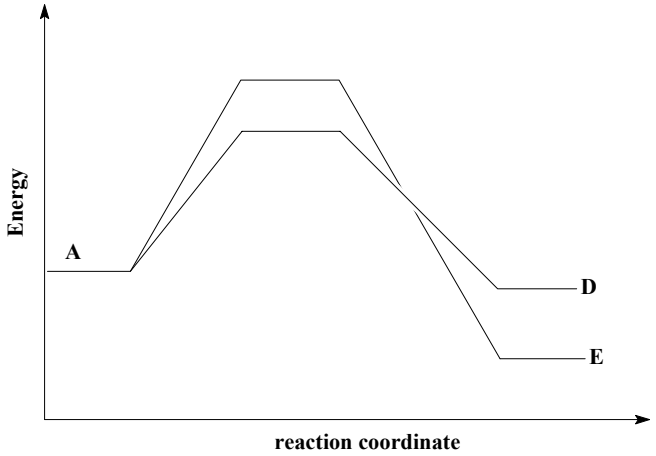


Figure 9: Kinetically preferred reaction[96]

It was hoped that a computational model[17,18] would be able to predict the regioselective protection of hydantoins with anhydrides. Calculations to determine the energies of reagents, transition states and products might shine some light on the mechanism of the reaction especially since regioselective protection of the hydantoins at either N-1' or N-3' is possible (see **Chapter 2 and 5**).

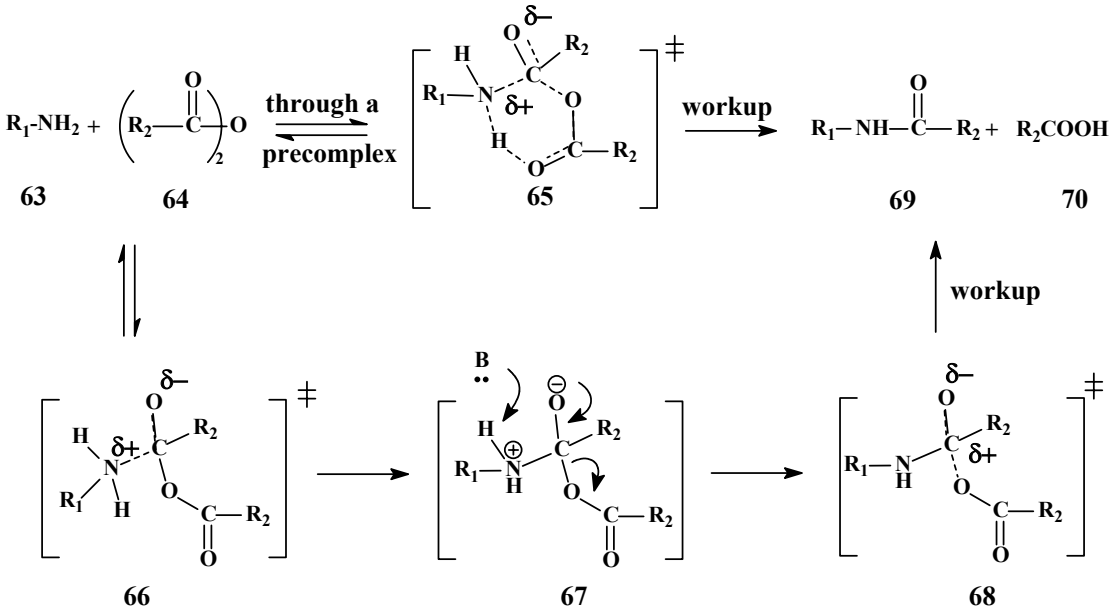
4.5 Computational Considerations and Details

Ab initio gas phase calculations were done with Gaussian 03[90] at the DFT (B3LYP)[98,99,100] level of theory with the 6-31+G(d) basis set. Solvation and catalytic effects were not considered in order to simplify the model. The model was further simplified by using acetic anhydride in the calculations instead of *t*-Boc anhydride. It was previously shown[17] that the model system also holds for sterically hindered anhydrides such as *t*-Boc anhydride.

Geometry optimizations were performed without restrictions in order to locate extrema presented herein (**Table 4)**. Transition states were characterized by a single imaginary frequency which corresponds to the movement of atoms consistent with the expected reaction.

In some cases the animation of the atoms associated with the imaginary frequency might not be clearly associated with the expected transition state. An Intrinsic Reaction Coordinate (IRC) calculation should then be performed to see if the transition will yield the known reagents and products, i.e. the reactants and products are indeed connected through the specific transition.[93] This procedure is unfortunately very expensive in computer time, as a frequency calculation is performed between each forward and backward step. All transition states found in this study were characterised using second-derivative vibrational frequency calculations. A computational model for the regioselective protection of alcohols, amines and lactam nitrogens was recently postulated.[17,18] The model also neglected solvent and catalytic effects and suggested that the protection of OH and NH groups in the "gas phase" proceed through a unique cyclic 6-membered ring transition state (see **Scheme 17**).

The cyclic transition states seem to belong to the same class of pseudopericyclic transition states reported before.[101,102,103] It is beyond the scope of this investigation to determine the similarities and differences between those pseudopericyclic transition states and the cyclic transition states reported herein.



Scheme 17: **Theoretical stepwise (66) vs. cyclic (64) transition states**

The intermediate **67** is not a minimum on the potential energy surface [B3LYP/6-31+G(d)], which illustrates the need for the solvent or a base to remove the proton from the incoming nucleophile. In reality the acyclic route would certainly also occur experimentally, but then almost, if not completely, as a concerted reaction where the solvent (base) would remove the proton from the incoming nucleophile as an effective collision forges bond formation/breaking as suggested in **Scheme 17**. It is expected that the same regional steric factors would be experienced by both the cyclic and acyclic routes, although the cyclic transition state (**65**) is likely to experience an amplified steric effect due to the nature[17,18] of the 3-dimensional structure of the cyclic transition state.

The calculation was successfully applied to the pentacycloundecane cage lactam system.[18] Acetylation of the lactam could potentially lead to four different structural isomers, one of which has two tautomeric forms (See **Figure 10**).

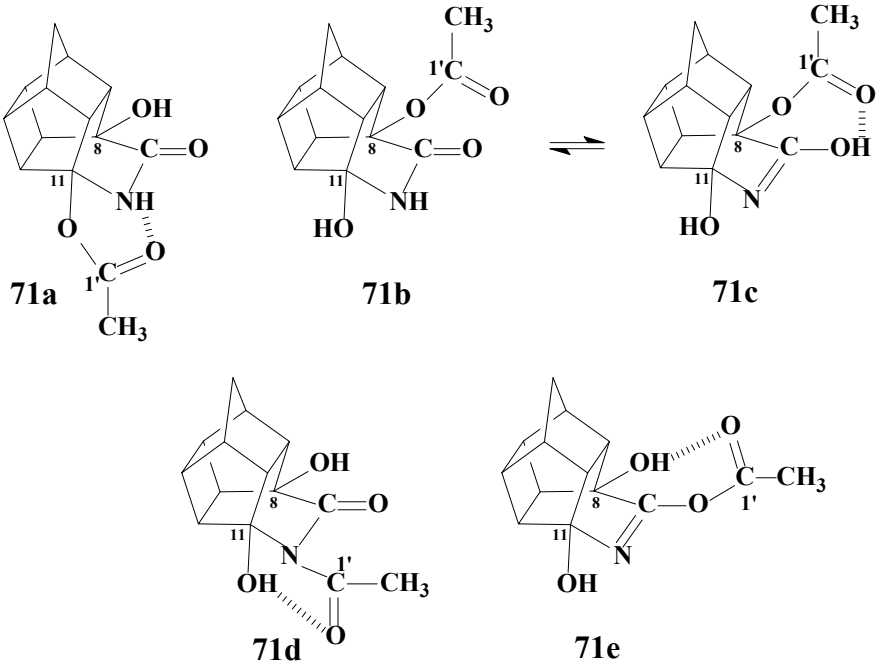


Figure 10: Possible acetylation products of the a δ-lactam[18]

The calculation[18] indicated that **71a** is both thermodynamically and kinetically preferred which correlates with the experimentally observed product. As part of an extended project to synthesise cage amino acid derivatives,[20,39,41,104,105,106] a number of cage hydantoins have been synthesized. The applicability of the computational model was applied to three different hydantoin systems, namely 5-methylhydantoin (**72**), 5,5-dimethylhydantoin (**73**) and a pentacycloundecane cage hydantoin (**11**).

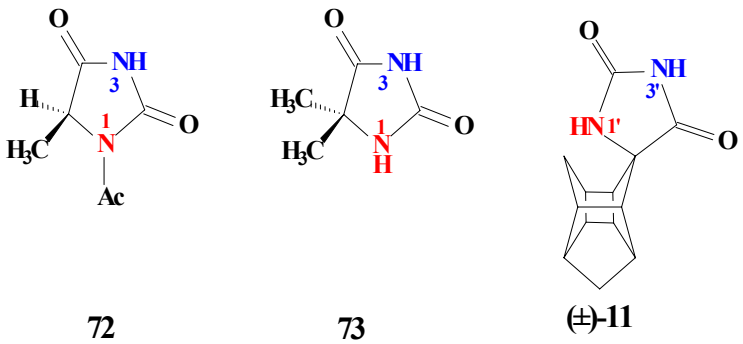
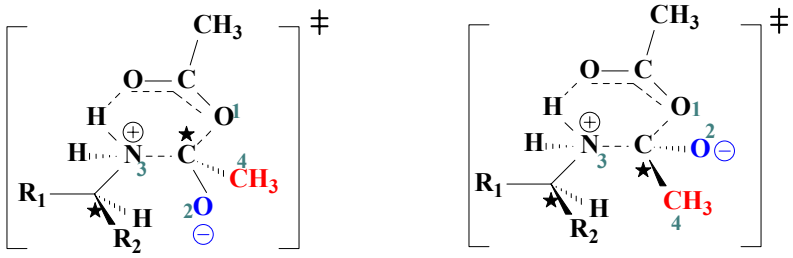


Figure 11: Protection of hydantoins: N-1' versus N-3'

4.6. Synthetic results and considerations

According to Beilstein[107] protection of 5-methylhydantoin (**72**) with acetic anhydride occurs at N-1[79] while protection of 5,5-dimethylhydantoin (**73**) occurs at either N-1[79,81] or N-3.[33,108] On closer inspection of the original papers, it appears[81] as if the initial mono-acetyl protected 5,5-dimethylhydantoins were confused; protection occurs at N-1' while the second product is rather the 5,5-dimethylhydantoin-2-enolacetate.

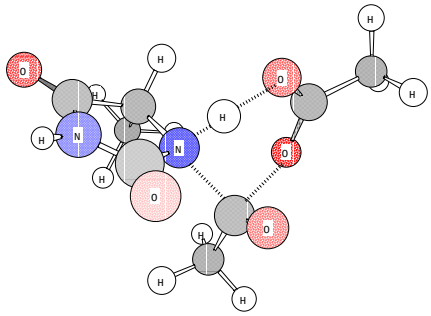
It was also discovered that the mono-Boc protection of **72** and **73** have not yet been reported and attempts to synthesise them will be reported. In a concurrent study,[41] it was found that the trishomocubane hydantoin is selectively protected at N-3'. It appears as if competition between N-1' (more steric hindrance but stronger nucleophile) and N-3' (less steric hindrance but less nucleophilic) influence the course of the reaction. It was previously shown[18] that chiral alcohols and amines form diasteriomeric transition states with anhydrides (see **Figure 12**).



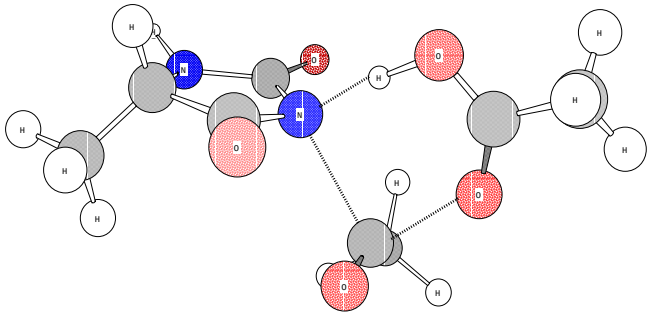
[(R)-74]-TS1 **[(S)-75]-TS2**

Figure 12: Chiral diasteriomeric transition states for a chiral amine.

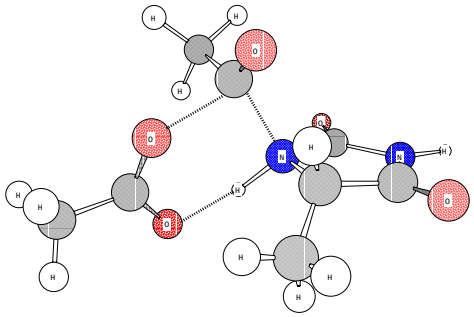
Note that both transition states lead to the same product. In the case of a chiral hydantoin (or lactam) with a non-equivalent "top" and "bottom" side, two more diastereomeric transition states exist (see **Figure 13**).



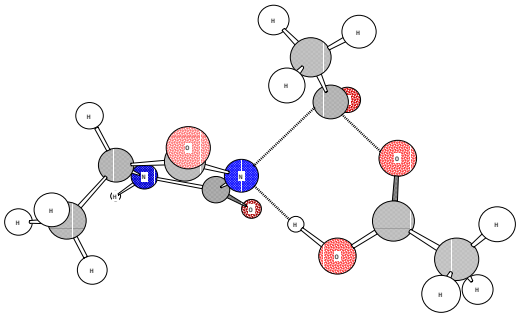
(S,R)-TS-bot-N- 1'



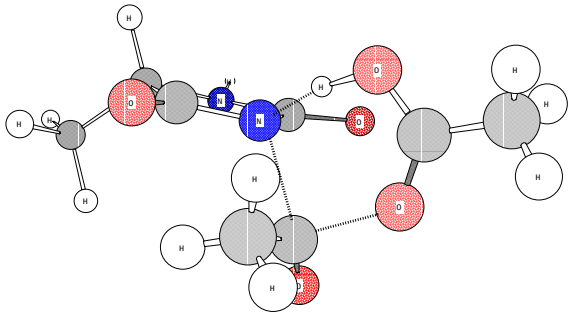
(S,R)-TS-bot-N-3'



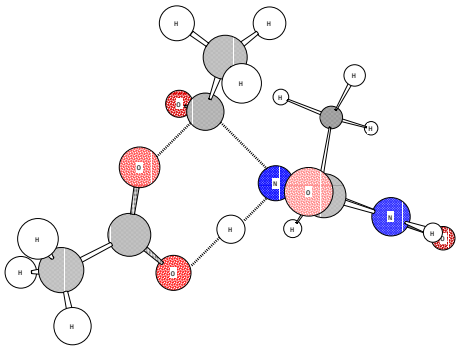
(S,R)-TS-top-N-1'



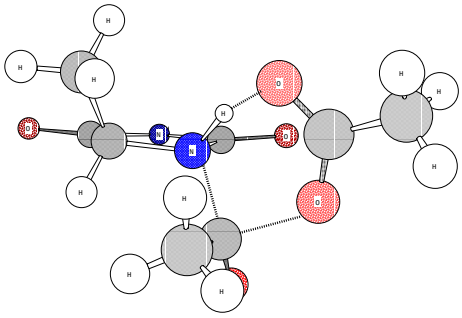
(S,R)-TS-top-N-3'



(S,S)-TS-bot-N-3'



(S,S)-TS-top-N-1'



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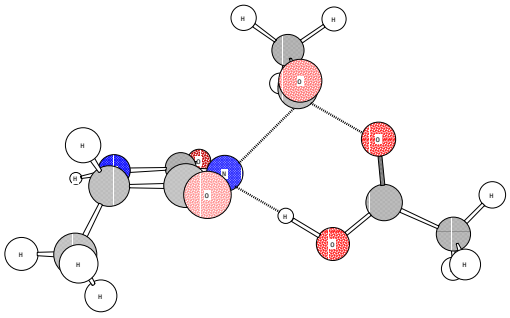
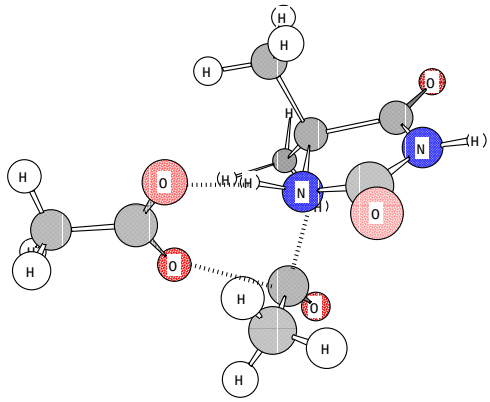


(S,S)-TS-top-N-3'

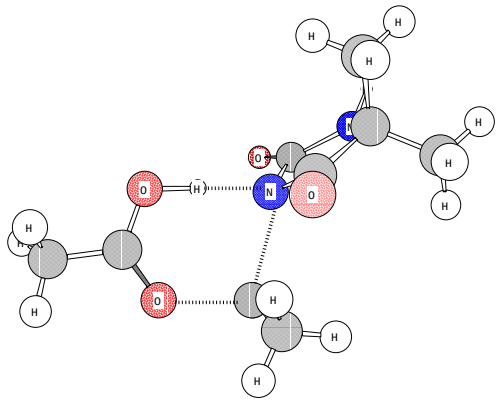
Figure 13: Four pairs of diastereomeric transition states for 5-methyl hydantoin (72) with acetic anhydride [B3LYP/6-31+g(d) optimized][c]

[c] Cartesian coordinates of the structures are available as supplementary material on the CD attached to the thesis.

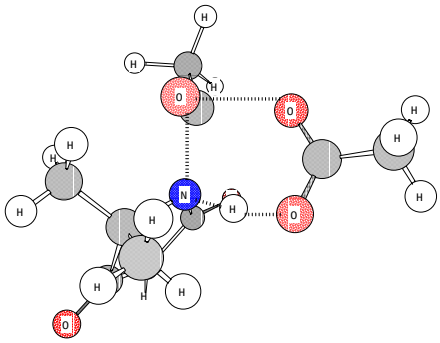
The same holds for transition states leading to the cage hydantoin (**11**). The more symmetric 5,5-dimethyl hydantoin (**73**) has only one pair of diasteriomeric transition states.



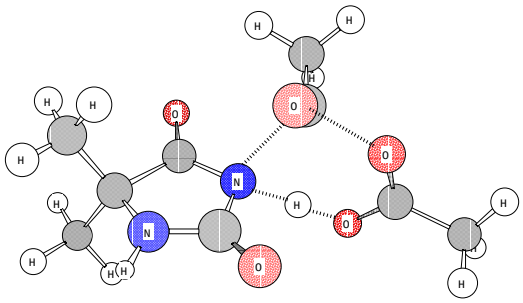
(R)-TS- N-1'



(R)-TS- N-3'



(S)-TS – N-1'



(S)-TS- N-3'

Figure 14: Two pairs of diastereomeric transition states for 5.5-dimethyl hydantoin (73) with acetic anhydride [B3LYP/6-31+g(d) optimized][c].

The three hydantoins (**11**, **72** and **73**) were protected with *t*-Boc anhydride at room temperature under stoichiometric controlled conditions (1:1). The mono-Boc protected hydantoins were isolated and the structures elucidated with normal analytical techniques.

4.7. Discussion of the computational and experimental results

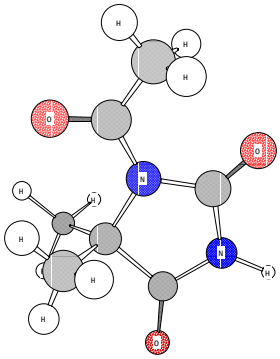
As was the case for the PCU lactam, precomplexes[109] between the hydantoin and acetic anhydride could not be obtained for most of the systems. The computational results for the more symmetric 5,5-dimethylhydantoin (**73**) are presented in **Table 4**.

Table 4: **Relative energies[a] for 5.5-dimethylhydantoin (73)**

	Relative energies (kcal mol-1)			
	(S)-TS – N-1'	(R)-TS- N-1'	(S)-TS- N-3'	(R)-TS-N-3'
ΔE_A	4.5	4.8	7.6	7.6
$\Delta H_{products}$	-21.8		1.8	

[a]Relative to reactants – B3LYP/6-31+G(d)

The same cyclic transition state was obtained for all three hydantoin compounds, both at the N-1' and N-3' position. The experimentally observed product 1-Ac-5,5-dimethyl hydantoin (**76**)[81] is the kinetically and thermodynamically preferred product according to the computational results.



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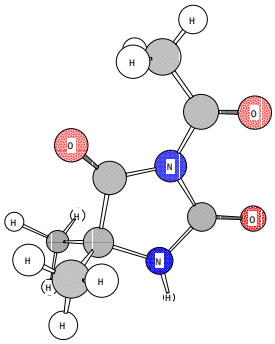

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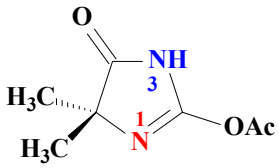

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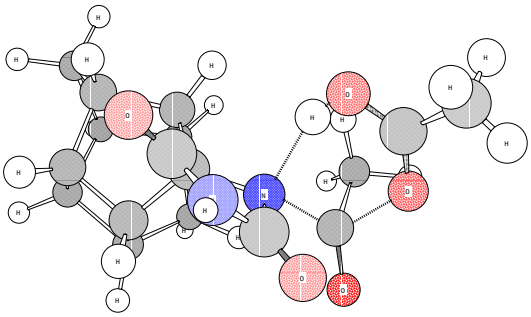
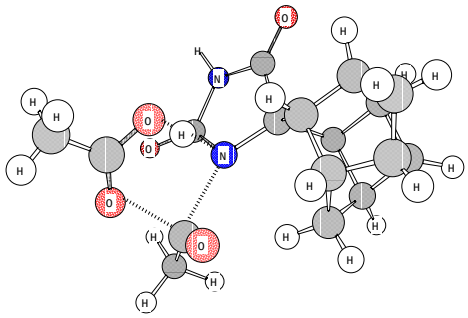
Figure 15: Three possible products for acetylation of 5.5-dimethyl hydantoin (73) with acetic anhydride [B3lyp/6-31+g(d)][d]

The computational results also confirmed the conclusion by Salmon and Kozlowski,[81] namely that upon heating other products such as 5,5-dimethylhydantoin-2-enolacetate (**78**) only the thermodynamically preferred product (1-Ac-5,5-dimethyl hydantoin, **76**) is obtained. They have also found that under thermodynamic conditions, protection at N-1 occurs exclusively. The experiment in the current study was performed at room temperature and according to the ^{1}H NMR spectrum, a small percentage of 3-Ac-5,5-dimethyl hydantoin [**77** (~25%)] had also been formed (see **Chapter 5**).

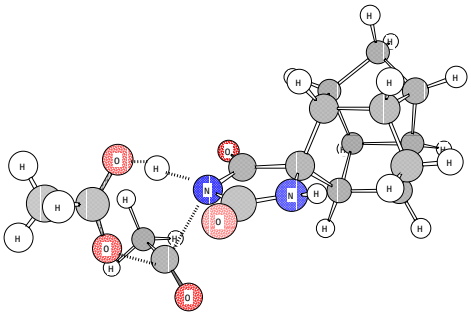
[d] Cartesian coordinates of the structures are available as supplementary material on the CD attached to the thesis.



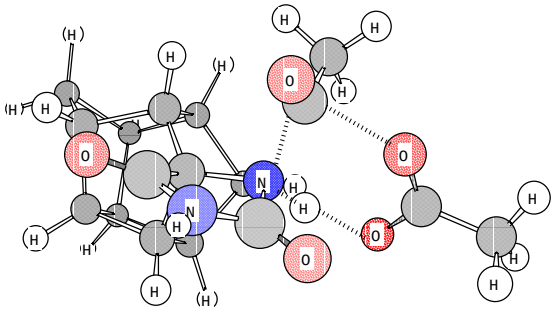
(R,R)-TS-bot-N-1'



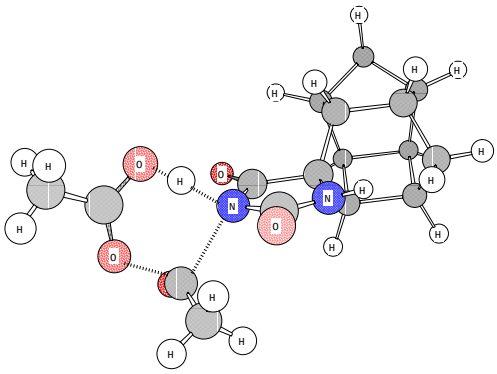
(R,S)-TS-bot-N-1')



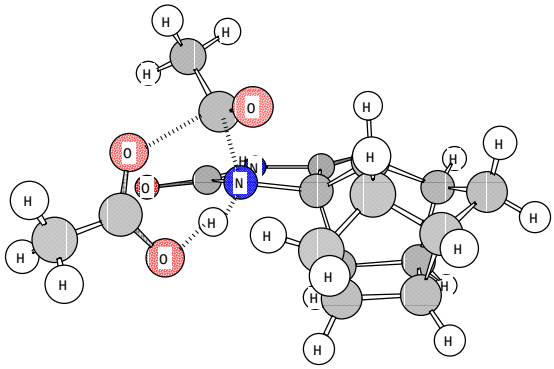
(R,S)-TS-bot-N-3'



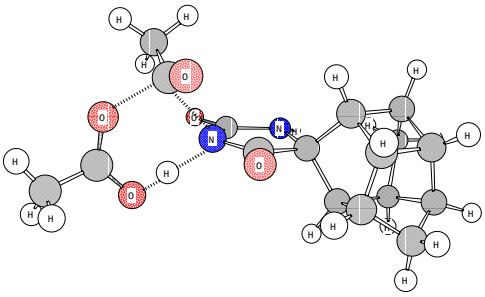
(R,S)-TS-top-N-1'



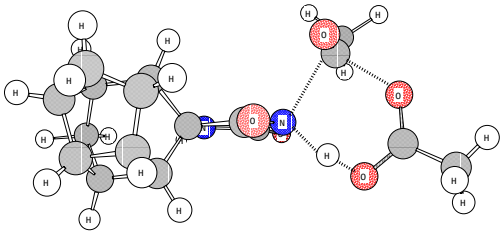
(R,R)-TS-bot-N-3'



(R,R)-TS-top-N-1'



(R,R)-TS-top-N-3'



(R,S)-TS-top-N-3'

Figure 16: Four pairs of diastereomeric transition states for the PCU hydantoin (11) with acetic anhydride [B3LYP/6-31+g(d) optimized].[e]

[e] Cartesian coordinates of the structures are available as supplementary material on the CD attached to the thesis.

The kinetic data in **Table 4** suggests that both N-1' and N-3' should in principle be protected at room temperature as molecules have enough thermal and kinetic energy at room temperature to allow processes requiring between 15 to 20 kcal/mol.[97] However, the rule of thumb[93] is that a difference of about 1 kcal mol^{-1} in activation energy should result in a 90:10 ratio of possible products. The calculated difference of 2.8 kcal mol^{-1} between the transition states indicates a much larger regioselectivity than was obtained experimentally. The discrepancy between the theoretical and experimental results might be due the fact that a smaller anhydride (acetic anhydride) was used in the computational model, while a larger anhydride (*t*-Boc anhydride) was used in the actual experiment (see **Chapter 6**). Furthermore kinetic data represent only part of the whole picture as entropy is also playing a role. The calculated energies for the 5-methylhydantoin (**72**) and PCU hydantoin (**11**) systems are reported in **Table 5**.

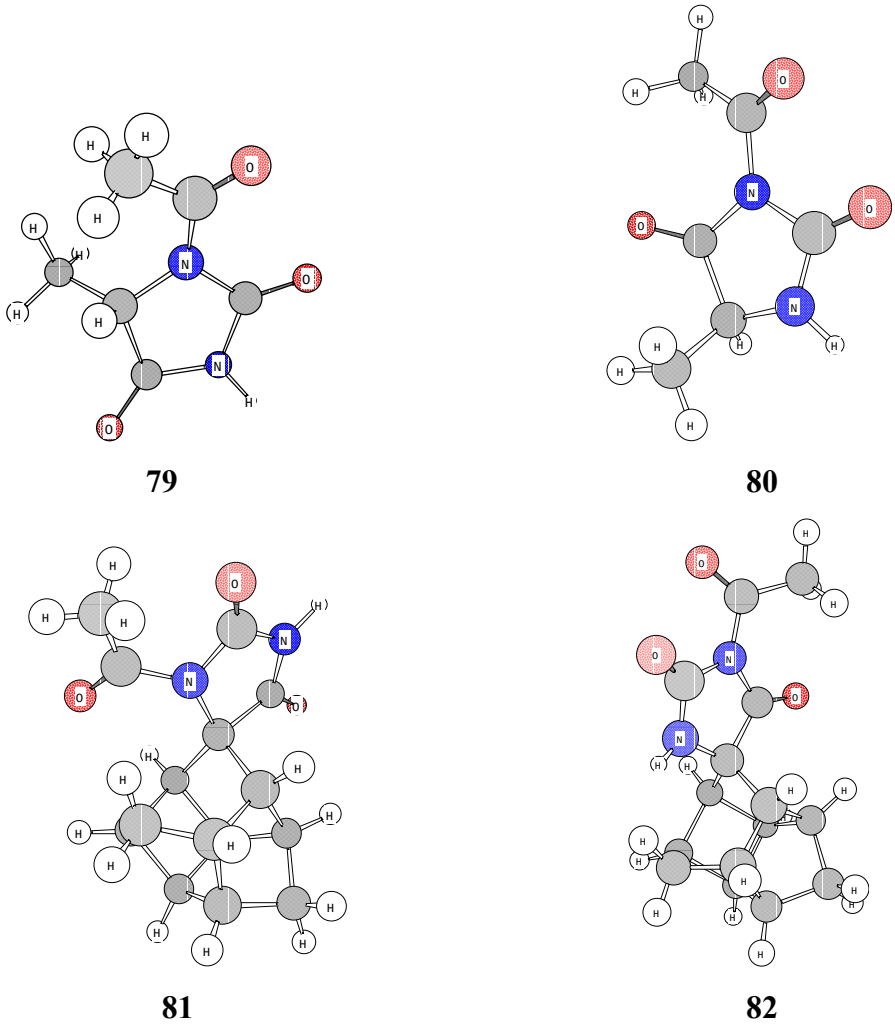
Table 5: **Relative[a] energies of transition states and products [b]**

5-methylhydantoin (11)	**kcal mol^{-1}**	**Pentacycloundecane (PCU) hydantoin (13)**	**kcal mol^{-1}**
(S,R)-TS-top-N-1'	-1.4	(R,R)-TS-top-N-1'	23.0
(S,R)-TS-bot-N- 1'	10.8	(R,R)-TS-bot-N-1'	40.4
(S,S)-TS-top-N-1'	4.6	(R,S)-TS-top-N-1'	24.3
(S,S)-TS-bot-N-1'	3.9	(R,S)-TS-bot-N-1'	35.3
(S,R)-TS-top-N-3'	7.8	(R,R)-TS-top-N-3'	21.5
(S,R)-TS-bot-N-3'	7.8	(R,R)-TS-bot-N-3'	20.5
(S,S)-TS-top-N-3'	7.2	(R,S)-TS-top-N-3'	20.6
(S,S)-TS-bot-N-3'	7.2	(R,S)-TS-bot-N-3'	21.3
Products		Products	
N-1'-Ac (**79**)	-0.1	N-1'-Ac (**81**)	2.4
N-3'-Ac (**80**)	1.1	N-3'-Ac (**82**)	0.4

[a] Relative to reactants – B3LYP/6-31+G(d)
[b] Cartesian coordinates of the structures are available as supplementary material on the CD attached to the thesis.

The calculated relative energies suggest that 1-acetyl-5-methylhydantoin (**79**) is both kinetically and thermodynamically preferred. The kinetic difference is about 8.6 kcal mol^{-1} in favour of protection at N-1'. The experimental was performed at room

temperature and 1-*t*-Boc-5-methylhydantoin (**79**) was exclusively obtained (see **Chapter 5**). The much higher energies for (R,R)-TS-bot-N-1' (40.4 kcal mol^{-1}) and (R,S)-TS-bot-N-1' (35.3 kcal mol^{-1}) is the result of steric repulsion between the incoming carbonyl group and the CH_2 (C-11) group of the rigid cyclohexane boat structure of the PCU hydantoin (see **Figure 16**). It is clear that the larger steric hindrance imposed by the rigid PCU skeleton is forcing protection away from the stronger nucleophilic nitrogen (N-1') towards the less hindered but also much less nucleophilic nitrogen (N-3').



79 **80**

81 **82**

Figure 17: Four products for acetylation of PCU hydantoin (11) and 5-methyl hydantoin (72) with acetic anhydride [B3LYP/6-31+g(d) optimized][f]

[f] Cartesian coordinates of the structures are available as supplementary material on the CD attached to the thesis.

Protection of the PCU hydantoin (**11**) with anhydride occurs at N-3' (see **Chapter 2**). The theoretical results imply that protection at N-3' is kinetically (1.5 kcal mol^{-1}) as well as thermodynamically preferred, which is in agreement with experiment. The energy barrier is just in reach of the available inherent energy at room temperature[97] which was also confirmed by experiment. The reaction was performed at room temperature and 3'-acetyl PCU hydantoin was exclusively isolated.

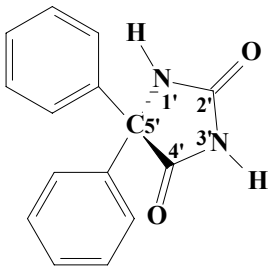
In contrast to common hydantoins, PCU hydantoin is not protected at the stronger nucleophilic N-1' nitrogen, but rather at the less sterically demanding, but much weaker nucleophilic position (N-3').

It appears as if the cage systems lives up to it reputation: "Studies of such systems provide an excellent test for existing chemical theory and thus perhaps furnish the best opportunity for advancing the frontiers of our chemical knowledge."[110]

5. THE SYNTHESIS OF HYDANTOIN DERIVATIVES

5.1 Introduction

During the computational investigation (see **Chapter 4**), it was discovered that the mono- and bis-Boc protected analogues of 5-methylhydantoin and 5,5-dimethyhydantoin have not yet been reported before.[107] The computational prediction in **Chapter 4** suggests that both the mono-Boc species should be protected at the N-1 nitrogen. The purpose of this chapter is to discuss the uses of hydantoins and the synthesis of the novel protected hydantoins in order to test the computational predictions in **Chapter 4**. A brief history of the pharmaceutical applications of hydantoin derivatives is provided below. Hydantoins were first applied as anti-epileptic drugs in the 1950s.[111]



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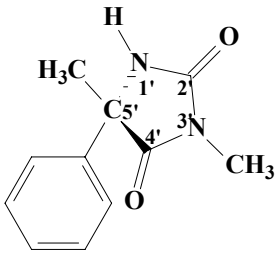

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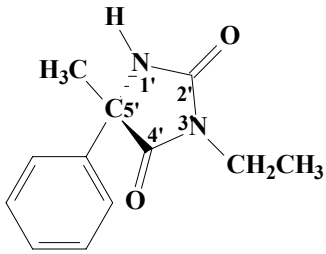

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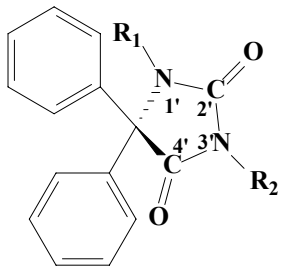
One of the most commonly used anti-epileptic drugs is 5.5-diphenylhydantoin (Phenyntoin, **83**). Other hydantoins such as 5-methyl-5-phenylhydantoin (mephynytoin, **84**) and 3-ethyl-5-phenylhydantoin (**85**) had also been introduced for treatment of epilepsy.[111,112] Merrit *et al* were the first scientists to discover the anticonvulsant activity of the phenyntoin in 1938.[112,113] In 1945 about 700 substances were tested for anticonvulsant activity.[112] Most of the substances evaluated were hydantoins. Some of the characteristics for hydantoins to exhibit promising anticonvulsant activity are:[112]

- the hydantoin must have at least one phenyl group at carbon 5.
- substitution at the N-3' and N-1' positions with alkyl groups increase the anticonvulsant activity.

The first requirement is likely to be necessary for the transport of the drug across cell membranes, especially to reach the CNS and the blood-brain barrier (BBB). A benzene substituent will improve the lypophilic character of the rather polar hydantoin, which is a requirement for the transport of drugs across the cell membrane. The chemical structure of phenyntoin had been modified to extend the anticonvulsant activity. 3-Hydroxyphenyntoin (**86**) did not show any positive activity.[112] Substitution of the N-3' hydrogen with an OH (**86**) group showed remarkable anticonvulsant activity. Samour *et al*[114] evaluated the N-1' substituted derivatives (**88**) which showed low activity as compared to substitution at N-3'.

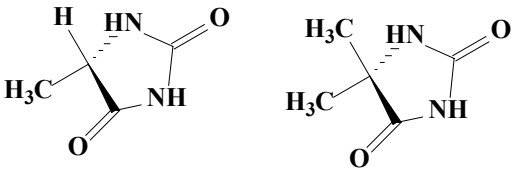


86 R_1=H, R_2=OH
87 R_1=H, R_2=CH_2CH_2OH
88 R_1=CH_2CH_2OH, R_2=H

In **Chapter 2** it was demonstrated that the PCU Cage hydantoin (**11**) is selectively acetylated at the N-3' position. The lack of a phenyl substituent on the α-carbon is not necessarily a major drawback as it was demonstrated in **Chapter 1** that the PCU moiety has shown excellent characteristics to deliver drugs to the CNS and to cross the BBB.[6] The PCU hydantoin could therefore be studied for potential anti-epileptic activity as substitution on N-3', which is required for increased anti-epileptic activity, can be selectively performed.

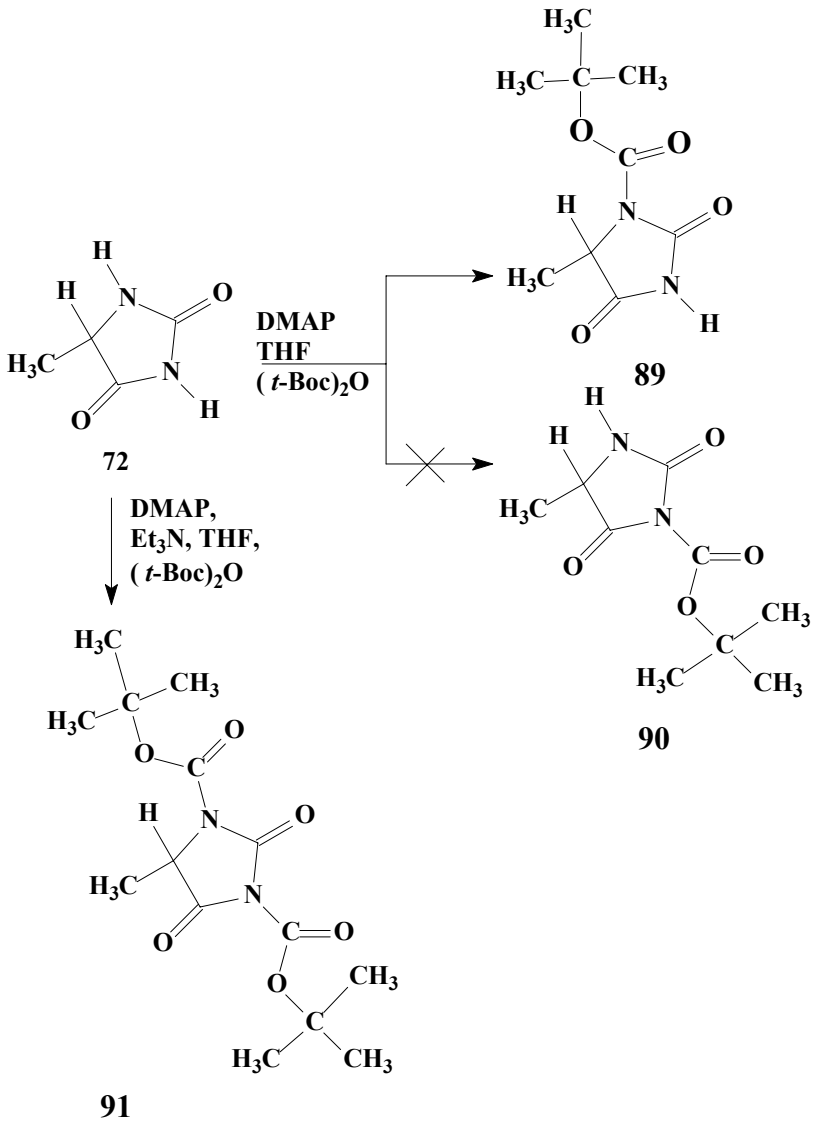
5.2. Results and Discussion

The racemic hydantoins (**72** and **73**) were acetylated with *t*-Boc as in the case of protection PCU hydantoin in **Chapter 2**.



72 73

The novel mono-Boc protected 5-methylhydantoin (**89**) was synthesised using the method by Hammer *et al*.[42]

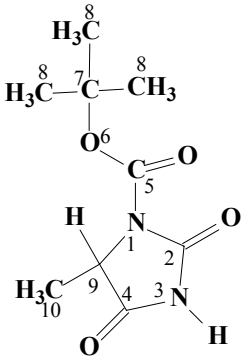


Scheme 18: Synthesis of mono- and bis-Boc protected-5-methylhydantoin

The product (**89**) was characterised with NMR, IR, MS and elemental analysis. A summary of the synthetic scheme is illustrated above (**Scheme 18**). Previous work on

the acetylation of 5-methylhydantoin with acetic anhydride indicated that the protection occurs on the most nucleophilic N-1 nitrogen.[79] When the acetylation was done with *t*-Boc anhydride the NMR elucidation also indicated that the protection had occurred at the N-1 position. It was evident from the IR spectrum that the mono-Boc protection has occurred due to the presence of three strong carbonyl group absorptions at 1800, 1736, 1720 cm^{-1}. Strong absorption band appears at 3288 cm^{-1} in the N-H stretching vibration region.

The mass spectrum shows a molecular ion at m/z 215 $[M+H]^+$ and it is the supportive of a molecular formula $C_9H_{14}N_2O_4$ which corresponds to the mono-protected derivative (**89**).

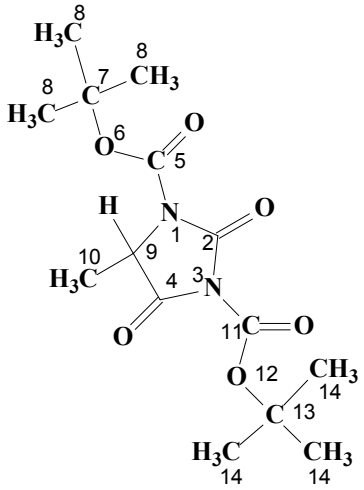


89

It was also evident from the 300 MHz ^1H NMR data that mono-protection has occurred due to the presence of the imide proton (H-3) at about 10 ppm[20], and the absence of the amide proton (H-1) at 6.40 ppm[20] confirmed that the *t*-Boc group had attached to the amide nitrogen (H-1). The presence of a peak at 1.55 ppm is representative of three methyl groups (H-8) and it integrates to nine protons. The three hydrogens (H-10) of the 5-methyl group were assigned to the doublets at 1.53 ppm. This assignment was further confirmed from a HETCOR spectrum of the sample which indicates a correlation between H-10 at 1.53 ppm and C-10 at 16.81 ppm. C-8 at 28.01 also shows a HETCOR correlation with H-8 at 1.55 ppm. H-9 which is attached to the hydantoin ring and is assigned to the quartet (4.37-4.44 ppm); H-9 at 4.37-4.44 ppm shows a HETCOR correlation with C-9 at 84.53 ppm. Mono-protection was also confirmed by

the presence of three carbonyl peaks in ^{13}C NMR at 148.21, 151.56 and 171.66 ppm respectively. The peak at 171.66 ppm is associated with C-4 since it is positioned in an electron deficient part of the molecule and it is therefore expected to be downfield. C-5 is assigned to 148.22 ppm due the fact that C-5 is in the electron rich region and it is therefore expected to be more upfield when compared to C-4 and C-2. Using the same analogy as above, C-2 was assigned to 151.56 ppm.

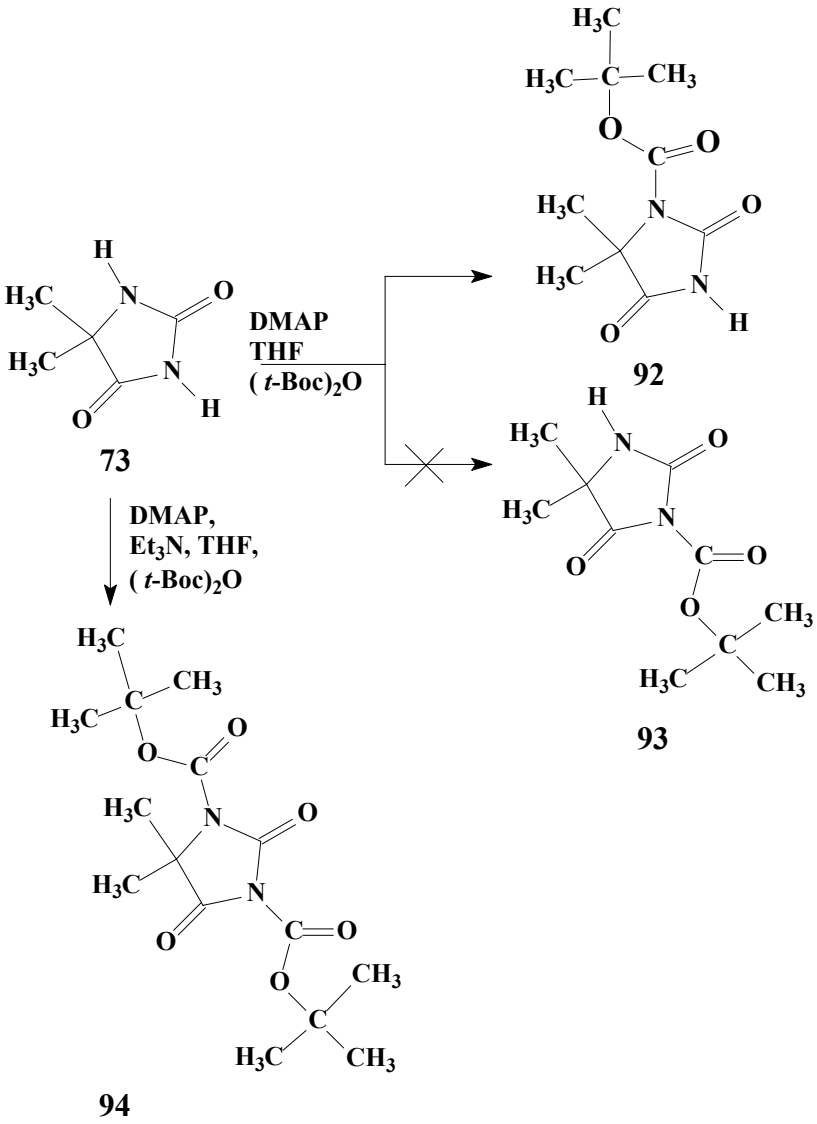
The novel bis-Boc protected hydantoin (**91**) was synthesised via the method of Kubik *et al*[38] which is a modification of the method of Hammer *et al*[42] The method uses excess triethylamine as a base and increases the ratio of di-*tert*-butyl-dicarbonate to obtain **91**.



91

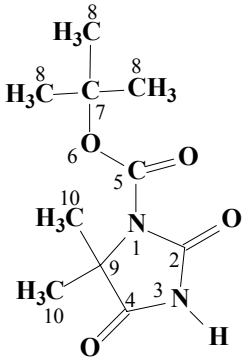
The product (**91**) was also characterised with NMR, IR and elemental analysis. The previous elucidation of mono-Boc protected hydantoin was useful for structural elucidation of the bis-Boc protected derivative. It was evident from the IR spectrum that bis-Boc protection had occurred due to the presence of four strong carbonyl peaks at 1778, 1724, 1736, 1826 cm^{-1} respectively. It was also evident from the ^{1}H NMR data that bis-Boc protection occurred. The two peaks at 1.53 and 1.55 ppm are typical for the methyl protons of two tertiary butyl groups (H-8 and H-14) and each peak integrated to nine protons. Bis-Boc protection was also confirmed by the presence of four carbonyl peaks in ^{13}C NMR spectrum. The mass spectrum shows a molecular ion at m/z 314 $[M+H]^{+}$ which is supportive of a molecular formula $C_{14}H_{22}N_2O_6$. The same

strategy as above was followed to elucidate the rest of the structure and the assignments are provided in the experimental section.



Scheme 19: Synthesis of mono- and bis-Boc protected-5.5-dimethylhydantoin

The novel mono-Boc protected 5.5-dimethylhydantoin (**92**) was synthesised using the same method as described for the synthesis of **89**. It was evident from the IR spectrum that the mono-Boc protection has occurred due to the presence of three strong carbonyl peaks at 1729, 1767 and 1825 cm^{-1} respectively. The strong peak at 3240 cm^{-1} is associated with a N-H vibration frequency.



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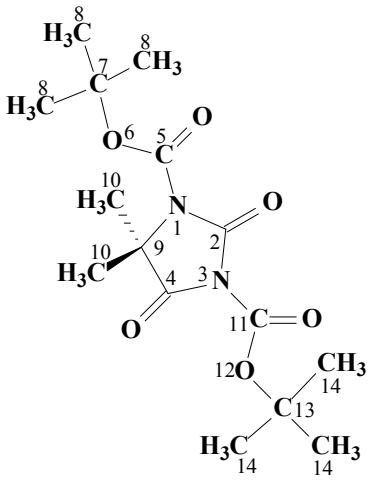
It was also evident from the ^{1}H NMR data that mono-Boc protection has occurred due to the absence of the amide proton (H-1) at about 6.4 ppm[20], and the presence of the imide proton (H-1) at 10 ppm[20] confirmed that the *t*-Boc group was attached to the amide nitrogen (N-1). The peak at 1.55 ppm is characteristic of the three methyl groups of a tertiary butyl group (H-8) and integrated to nine protons. Mono-Boc protection was further confirmed by the presence of three carbonyl peaks in the ^{13}C NMR spectrum at 148.20, 151.92 and 172.51 ppm. The previous ^{13}C NMR elucidation of mono-Boc protected 5-methylhydantoin was useful to assign C-5, C-2 and C-4 to 148.20, 151.92 and 172.51 ppm respectively. The same strategy as before was followed to elucidate the rest of the structure and the assignments are provided in the experimental section (**Chapter 6**).

The novel bis-Boc protected 5.5-dimethyl hydantoin (**94**) was synthesised as described for the synthesis of **91**. It was evident from the IR data that bis-Boc protection occurred due to the presence of four strong carbonyl peaks at 1722, 1741, 1786, 1825 cm^{-1}. It was also evident from the ^{1}H NMR data that bis-Boc protection occurred. The two peaks at 1.553 and 1.551 ppm is characteristic of the methyl protons of two different Boc groups and each signal integrated to nine protons. The protection was confirmed by the presence of four carbonyl peaks in ^{13}C NMR at 145.32, 147.41, 148.33 and 171.39 ppm respectively.



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The same strategy as before was followed to elucidate the rest of the structure and the assignments are provided in the experimental section (**Chapter 6**).

5.3. Conclusion

Four novel compounds were synthesised (**89, 91, 92,** and **94**). The bis-Boc protected hydantoins (**91** and **94**) may be used for an improved synthesis of alanine and amino-isobutyric acid (AIB) respectively via base hydrolysis at room temperature. The PCU hydantoin (**11**) might be a valuable possibility as an antiepileptic drug as it is known[6] that it enables entering the CNS and crossing the BBB. It can also be conveniently modified at N-3', a requirement for the synthesis of more active antiepileptic drug. The experimental results in this chapter verified the computational results in **Chapter 4**. It is clear that the computational model is applicable to correctly predict the regioselective protection of hydantoins with anhydride.

6. EXPERIMENTAL

Melting points were recorded using a Bombay 400 013 instrument from Shital Scientific Industries. All melting points are uncorrected. Infrared spectra were obtained using a Nicolet Impact 410 spectrometer. The one-dimensional NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer, while the two-dimensional NMR spectra were recorded on a Varian Unity Inova 400 MHz spectrometer. The fast atom bombardment (FAB) mass spectra were obtained from a Micromass VG70-70E mass spectrometer, equipped with an In tech FAB gun. The samples were bombarded with xenon atoms (1 mA at 8 keV), with *m*-nitrobenzyl alcohol as the matrix. Electron impact (EI) mass spectra (70eV) were obtained from a Micromass Autospec-TOF mass spectrometer. Elemental analyses were obtained from a Leco CHNS 932 instrument. HPLC analysis was performed using a Waters 600 solvent delivery system, equipped with a Perkin Elmer series 700 autosampler, a Waters 996 photodiode array detector and Millenium software. A Nucleosil 100 C18 column (5 μm particle size, 250 mm x 4.6mm i.d.) was used.

6.1. Synthesis of 5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (14, adduct)[115]

p-Benzoquinone (200 g, 0.54 mol) was dissolved in dry toluene (4 l) and placed in an ice/salt bath within a dark fume hood. Cold, freshly cracked cyclopentadiene (132 ml, 1.96 mol) was added over two hours *via* a dropping funnel. The slow addition and cool temperatures allowed a successful Diels-Alder reaction, without dimerisation of the cyclopentadiene or diaduct formation. The reaction was left to return to room temperature while stirring overnight. The solution was evaporated in a dark fumehood from a flat porcelain dish, yielding yellow crystals of the adduct. The product of this sample was recrystallized from petroleum ether (40-60°C) to yield **14** as yellow crystals. (230g, 74% yield, m.p.77°C). NMR and IR were identical to those of an authentic sample.

6.2. Synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-11-dione (9)[116]

The adduct (200g, 1.15 mol, **14**) was added to a volumetric flask (5.00 l) and dissolved in 10 % (v/v) acetone in a hexane solution (5.00 l). The volumetric flask was exposed to direct sunlight until a colourless solution was obtained. The photodimerization normally takes three to five days in Durban. The absence of the starting meterial was confirmed with TLC (4% hexane/ethyl acetate). The solvent was evaporated *in vacuo* to give a white, microcrystalline solid of **9** (195g, 98%). NMR and IR were identical to those of an authentic sample.

6.3. Synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-11-dione-mono-ethylene ketal (15)[19]

A mixture of the diketone **9** (183.00 g, 1.05 mol), ethylene glycol (81.20 ml, 1.45 mol), *p*-toluenesulfonic acid (6.11 g, 3.21x10^{-2} mol) and 4Å freshly regenerated molecular sieves (2 g) in dry toluene (800 ml) was gently refluxed with stirring in a Dean and Stark trap for four days. The reaction mixture was left to cool and poured slowly into ice-cold 10 % (v/v) aqueous sodium carbonate (1.00 l). The aqueous mixture was extracted with dichloromethane (3 x 500 ml). The combined organic extracts were dried over anhydrous sodium sulphate. The mixture was filtered and the solvent evaporated *in vacuo*. The resulting brown residue was recrystallised from hexane to give **15** as white crystals (170 g, 74 %). NMR and IR were identical to those of an authentic sample.

6.4. Synthesis of 11-hydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one-eth-ylene ketal (16)[30]

The mono-ketal **15** (10.00 g, 4.59x10^{-2} mol) was dissolved in ethanol (100 ml) and placed in an ice-bath to cool. An ethanolic solution of sodium borohydride (3.50 g in 50 ml ethanol) was added, with stirring, over a 10 minute period. The mixture was left to stir for two hours in the ice-bath, and an additional two hours at room temperature. Some sample (1 ml) was withdrawn to confirm complete reduction of the keto functional group using IR spectroscopy. The solvent of the reaction mixture was removed *in vacuo*, and the residue extracted using dichloromethane (50 ml). The

solvent was removed *in vacuo* to leave **16** as a white solid (7.80 g, 78% yield, m.p. 250 °C). NMR and IR were identical to those of an authentic sample.

6.5. Synthesis of 11-hydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one (17)[19]

The hydroxy-ketal (92.5g, 0.42 mol)was placed in an ice-bath to cool at which stage 10 % (v/v) hydrochloric acid (200 ml) was cautiously added. This was left, with stirring, to warm to room temperature for 18 hours. The mixture was extracted with dichloromethane (150 ml) and evaporated *in vacuo* to yield **17** (89.5 g, 96% yield, m.p. 255 °C). NMR and IR were identical to those of an authentic sample.

6.6. Synthesis of *endo*-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-ol (18)[19,75]

A mixture of the hydroxyketone **17** (13.00 g, 7.52x10^{-2} mol) and hydrazine hydrate (23.10 ml, 0.74 mol) in diethylene glycol (200 ml) was refluxed, with stirring, at 120 °C for two hours. The mixture was allowed to cool to 80 °C at which stage excess KOH (12.00 g, 0.21 mol) was added. Excess hydrazine hydrate and water was distilled from the mixture until the temperature reached 185 °C, thereafter, refluxed for a further three hours at 185 °C. The mixture was cooled, diluted with water (300 ml) and extracted with dichloromethane (3x100 ml). The combined organic phases were evaporated *in vacuo*. The yellow residue was steam distilled to yield the alcohol as a white solid with a camphor-like odour (11.2 g, 56.3% yield, m.p. 231 °C). NMR and IR were identical to those of an authentic sample.

6.7. Synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanone (10)[19]

Chromium trioxide (14.00 g, 0.14 mol) was dissolved in deionised water (30 ml) and added to acetic acid (320 ml). The alcohol **18** (10.00 g, 0.0625 mol) was dissolved in acetic acid (100 ml) and added drop-wise to the prepared mixture. The reaction was refluxed at 90 ºC overnight. The successful oxidation (Jones oxidation) of the alcohol was evident through reduction of Cr^{6+} (dark red) to Cr^{3+} (green). The reaction mixture was cooled, diluted with deionised water (1000 ml) and extracted with dichloromethane (800 ml). The organic extract was successively washed with water (2 x 500 ml), a

saturated bicarbonate solution (2 x 500 ml) and water (500 ml). The organic solution was dried, using anhydrous sodium sulphate. The mixture was filtered, and the solvent removed *in vacuo* to yield pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecanone (7.5g, 76%, m.p. 195 °C). NMR and IR were identical to those of an authentic sample.

6.8. Synthesis of PCU-hydantoin (11)[19]

A mixture of the monoketone **10** (1.00 g, 6.25x10^{-3} mol), NaCN (1.00 g, 2.04x10^{-2} mol), $(NH_4)_2CO_3$ (2.00 g, 2.08x10^{-2} mol), ethanol (10 ml) and NH_4OH (15 ml) were sealed in a glass medium pressure vessel. The reaction vessel was sealed in a metal pressure vessel. The reaction vessel was placed in an oil bath and heated at 60 ºC for two hours, 100 ºC for two hours and 120 ºC overnight. The cooled reaction was diluted with deionised water (100 ml) and extracted with ethyl acetate (150 ml). The solvent was removed *in vacuo* to yield the crude hydantion. The product was washed successively with acetone and diethyl ether and thereafter, recrystallised from tetrahydrofuran to yield pure hydantoin (**11**) as a white solid (1.4 g, 98% yield, m.p. 230 °C). NMR and IR were identical to those of an authentic sample.

6.9 General Procedure for preparing mono-*t*-Boc-protected hydantoin

The method was adopted from the literature.[42] A solution of hydantoin (**11**, **72** or **73**) (0.20 g, 2.17x10^{-3} mol), di-*tert*-butyl-dicarbonate (0.71 g, 3.26x10^{-3} mol), 4-dimethyl-aminopyridine (DMAP) (3.00 mg, 2.17x10^{-5} mol) in dry THF (50 ml) was left to stir under a nitrogen atmosphere for 24 hours. The solution was concentrated *in vacuo* to yield the crude product.

6.9.1. Synthesis of mono-*t*-Boc-protected PCU hydantoin (28)

Mono-*t*-Boc-protected PCU hydantoin (**28**) was prepared as described in the general procedure (**§6.9**). Purification was achieved through silica gel column chromatography (dichloromethane) to yield the product (**28**) as a white powder. (0.23 g, 74 %). m.p. 206 °C. IR (KBr) ν_{max} 3305, 1803, 1765, 1718 cm^{-1}. ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 1.24-1.27 (1H, H4a, *J* 10.9 Hz), 1.63-1.66 (1H, H-4s, *J* 10.9 Hz), 1.39-1.43 (2H, H-11a, H11s, *J* 12.5 Hz), 1.54 (9H, H-8'), 2.08 (H-5), 2.77 (H-1), 2.09 (H-3), 2.18 (H-1), 2.64 (H-2), 2.33 (H-9), 2.75 (H-6), 2.35 (H-10), 6.40 (H-1'). ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 27.78 (C-8'), 41.49 (C-7), 28.04 (C-11), 43.18 (C-10), 41.44 (C-2), 49.03 (C-9),

41.60 (C-6), 35.88 (C-1), 68.07 (C-8), 42.43 (C-5), 46.46 (C-3), 34.26 (C-4), 85.44 (C-7'), 152.62 (C-2'), 146.28 (C-5'), 173.079 (C-4'). M.S. $[M+H]^+$ 331 m/z. Elemental analysis. Experimental: C, 65.54, H, 6.41, N 8.27 %. Calculated: C, 65.45, H, 6.67, N, 8.48 %.

6.9.2. Synthesis of Mono-*t*-Boc-protected-5-methylhydantoin (89)

Mono-*t*-Boc-protected-5-methylhydantoin (**89**) was prepared as described in the general procedure (**§6.9**). Purification was achieved through silica gel column chromatography (dichloromethane) to yield the product as a white powder (0.23 g, 74 %). m.p. 121 °C. IR (KBr) ν_{max} 1826, 1778, 1736, 1724 cm^{-1}. ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 1.55 (9H, H-8), 1.53 (9H, H-12), 4.37-4.44 (1H). ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 27.97 (C-8), 55.30 (C-2), 16.96 (C-1), 86.71 (C-7), 148.26 (C-2), 147.34 (C-5), 168.01 (C-4), 84.92 (C-11), 142.26 (C-9). M.S. $[M+H]^+$ 314 m/z. Elemental analysis. Experimental: C, 50.07, H, 6.67, N 12.36 %. Calculated: C, 50.70% H, 6.15% N, 13.14%

6.9.3. Synthesis of Mono-*t*-Boc-protected-5.5-dimethylhydantoin (92)

Mono-*t*-Boc-protected-5.5-dimethylhydantoin (**92**) was prepared as described in the general procedure (**§6.9**). The solution was concentrated *in vacuo* to yield the crude product. Purification was achieved through silica gel column chromatography (dichloromethane) to yield the product as a white powder (0.23 g, 74 %). m.p. 153 °C. IR (KBr) ν_{max} 3240, 1825, 1767, 1729 cm^{-1}. ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 1.55 (9H, H-8'), 1.6 (6H), 11.29 (1H, H-3'). ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 28.01 (C-8), 84.53 (C-2), 16.81 (C-1), 57.16 (C-7'), 152.62 (C-2'), 148.22 (C-5'), 173.079 (C-4'). M.S. $[M+H]^+$ 227 m/z. Elemental analysis. Experimental: C, 53.47, H, 7.36, N 12.36 %. Calculated: C, 52.86, H, 6.65, N, 12.33 %.

6.10. General Procedure for preparing Bis-*t*-Boc-protected hydantoin

The method was adobted from the literature.**38** A solution of hydantoin (**11**, **72** and **73**) (0.20 g, $2.17x10^{-3}$ mol), di-*tert*-butyl-dicarbonate (1.19 g, $5.43x10^{-3}$ mol), 4-dimethyl-aminopyridine (DMAP, 1.3 mg, $1.09x10^{-4}$ mol) and triethylamine (0.35 ml, $2.60x10^{-3}$ mol) in dry THF (50 ml) was left to stir under nitrogen gas for 24 hours. The solution was concentrated *in vacuo* to yield the crude product. Purification was achieved

through silica gel column chromatography (dichloromethane) to yield the product as a white powder.

6.10.1. Synthesis of bis-*t*-Boc protected PCU hydantoin (30)

Bis-*t*-Boc-protected PCU hydantoin (**30**) was prepared as described in the general procedure (**§6.10**) (0.57 g, 98 %). m.p. 227 °C. IR (KBr) ν_{max} 1807, 1765, 1751, 1724 cm^{-1}. ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 1.64-1.67 (H-4s, *J* 10.4 Hz), 1.36-1.39 (H-11s, *J* 13.6 Hz), 1.23-1.24 (H-4a, *J* 10.4Hz), 1.25-1.26 (H-11a, *J* 4.03 Hz), 1.52 (9H, H-12'), 1.54 (9H, H-8'), 2.82 (H-1), 2.77 (H-6), 2.94 (H-5), 2.26 (H-9), 2.62 (H-2), 2.27 (H-3), 2.50 (H-10). ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 27.73 (C-12'), 27.61 (C-8'), 29.15 (C-11), 41.88 (C-7), 49.29 (C-9), 42.69 (C-10), 41.06 (C-6), 34.39 (C-1), 46.43 (C-8), 41.42 (C-2), 43.44 (C-3), 42.69 (C-5), 34.39 (C-4), 86.10 (C-11'), 84.90 (C-7'), 149.79 (C-2'), 149.71 (C-5'), 145.93 (C-9'), 171.65 (C-4'). M.S. $[M+H]^+$ 431 m/z. Elemental analysis. Experimental: C, 63.91, H, 6.70, N, 6.39 %. Calculated: C, 64.19, H, 6.98, N, 6.51 %.

6.10.2. Synthesis of bis-*t*-Boc-protected-5-methylhydantoin (91)

Bis-*t*-Boc-protected-5-methylhydantoin (**91**) was prepared as described in the general procedure (**§6.10**) (0.43 g, 98 %). m.p. 101 °C . IR (KBr) ν_{max} 1826, 1778, 1736, 1724 cm^{-1}. ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 1.55 (9H, H-8), 1.53 (9H, H-12), 4.37-4.44 (1H). ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 27.97 (C-8), 55.30 (C-2), 16.96 (C-1), 86.71 (C-7), 148.26 (C-2), 147.34 (C-5), 168.01 (C-4), 84.92 (C-11), 142.26 (C-9). M.S. $[M+H]^+$ 314 m/z. Elemental analysis. Experimental: C, 53.04, H, 7.43, N 8.94 %. Calculated: C, 53.49, H, 7.05, N, 8.91 %.

6.10.3. Synthesis of Bis-*t*-Boc-protected-5.5-dimethylhydantoin (94)

Bis-*t*-Boc-protected-5.5-dimethylhydantoin (**94**) was prepared as described in the general procedure (**§6.10**). (0.43 g, 98 %). m.p. 115 °C. IR (KBr) νmax 1825, 1786, 1741, 1722 cm^{-1}. ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 1.551 (9H, H-8), 1.553 (9H, H-12), 1.65 (6H). ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 28.03 (C-8), 62.67 (C-2), 23.81 (C-1), 84.67 (C-7), 148.33 (C-2), 147.41 (C-5), 171.39 (C-4), 86.67 (C-11), 145.32 (C-9), 27.73 (C-

12). M.S. $[M+H]^+$ 328 m/z. Elemental analysis. Experimental: C, 53.83, H, 7.25, N 8.81 %. Calculated: C, 54.87, H, 7.37, N, 8.53 %.

6.11. Synthesis of Fmoc PCU amino acid (31)[38]

An aqueous solution of lithium hydroxide (8 mol equivalents) was added to a suspension of **30** (0.2 g, $4.65X10^{-4}$ mol) and left to stir for 24 hours. The resulting light yellow solution was extracted with Et_2O (3 X 50mL) to remove Boc_2NH. The aqueous layer containing the PCU amino acid was cooled in an ice bath and the pH of this solution was adjusted to 6.5 with HCl. This precooled solution was added dropwise to a chilled mixture (ice bath) of 9-fluorenylmethyl chloroformate (0.15g, 5.8 X 10^{-4}mol) in dioxane. A precipitate formed immediately, and the reaction mixture was allowed to warm to room temperature, keeping the pH at 6-6.5 by addition of 10% LiOH. The reaction was left to stir overnight. The dioxane was removed *in vacuo* and the resulting aqueous layer was diluted with deionised water (50 ml) and extracted with diethyl ether (100 ml) to remove unreacted Fmoc-Cl. The aqueous layer was cooled to 10 °C in an ice-bath and acidified to pH 2 with concentrated HCl. The solution was subsequently extracted with ethyl acetate (150 ml). The organic solvent was evaporated *in vacuo* to give the crude Fmoc PCU amino acid derivative which was recrystallised from dichloromethane/hexane to yield white crystals 0.15g, 72%, m.p. 214 °C. The NMR and IR were identical to those of an authentic sample.

6.12. Synthesis of Fmoc PCU amino acid fluoride (32)[43,49]

Cyanuric fluoride (40.50 *u*l, $4.68x10^{-4}$ mol) was added to a suspension of Fmoc PCU amino acid (0.20 g, $4.68x10^{-4}$ mol) and dry dichloromethane (50 ml). Dry pyridine was added (37.80 *u*l, $4.68x10^{-4}$ mol) and the resulting solution was left to stir under nitrogen for 12 hours. The mixture, which now contained a white suspension of water-soluble cyanuric acid was extracted with ice water (40 ml). The organic phase was dried over $MgSO_4$, filtered and removed *in vacuo*. The resulting white solid was recrystallised from dichloromethane/hexane to give the pure acid fluoride as a white solid (0.17 g, 87 %). The NMR and IR were identical to those of an authentic sample

6.13. Coupling of linker to MBHA resin [40]

The MBHA resin (0.50 g, 0.70 mmol NH_2/g) was swelled by adding DMF to the 5ml polypropylene syringe. The FmocAM linker (0.47 g, $8.75x10^{-4}$ mol), DIPCDI (0.14 ml, $8.75x10^{-4}$ mol) and HOBt (0.12 g, $8.75x10^{-4}$ mol) were added at room temperature to the resin in DMF. This was left to stir for 24 hours. Successful attachment was confirmed by a negative Kaiser test.[76] The Fmoc group was cleaved by the application of a 20 % (v/v) piperidine in DMF solution for two hours. Cleavage of the Fmoc group was confirmed by a positive Kaiser test. The Fmoc by-product was removed from the solution by filtration, followed by washing the resin with isopropanol and DMF.

6.12. Washing procedure for solid phase peptide synthesis[77]

The resin was washed with DMF (3 x 10 ml), isopropanol (3 x 10 ml) and DMF (3 x 10 ml).

6.13. Coupling of Fmoc Alanine to the linker[77]

The Fmoc Alanine, DIPCDI (0.14 ml, $8.75x10^{-4}$ mol) and HOBt (0.12 g, $8.75x10^{-4}$ mol) were added at room temperature to the resin in DMF. This was left to stir for 24 hours. Successful attachment was confirmed by a negative Kaiser test. The Fmoc group was cleaved by the application of a 20 % (v/v) piperidine in DMF solution for two hours. Cleavage of the Fmoc group was confirmed by a positive Kaiser test. The Fmoc group was removed from the solution by filtration, followed by washing the resin with isopropanol and DMF.

6.14. Coupling of Fmoc PCU amino acid fluoride to the tripeptide bound resin [43]

The PCU-amino acid fluoride (0.67 g, $1.56x10^{-3}$ mol) and dry pyridine (151.00 *u*l, $1.87x10^{-3}$ mol) was added to the resin in DMF and left to stir for 24 hours. Successful attachment was confirmed by a negative Kaiser test. The Fmoc group was cleaved by the application of a 20 % (v/v) piperidine in DMF solution for two hours. The Fmoc group was removed from the solution by filtration, followed by washing the resin with isopropanol and DMF.

6.15. Cleavage of the tetrapeptide from the resin and linker [77]

The resin was separately washed with dichloromethane (3x10ml), methanol (3x10ml) and diethyl ether (3x10ml) and dried overnight in a vacuum pump. The dry resin was placed in a flask containing the cleavage mixture of 95 % (v/v) TFA, 2.5 % (v/v) water and 2.5 % (v/v) triisopropylsilane. The mixture was left to stir for 12 hours. The resin was removed by filtration and washed several times with TFA. The application of nitrogen gas served to evaporate the TFA. Diethyl ether was subsequently added to precipitate the tetrapeptide as a white solid. Decanting the diethyl ether served to remove the linker from the peptide.

6.16. General procedure for HPLC analysis[77]

HPLC chromatographs of (**46** and **47**) are done from a solvent system which is made of 80 % (v/v) acetonitrile/20 % (v/v) water/0.1 % (v/v) trifluoroacetic acid (solution A) and 100 % water (solution B) gradient system: 80 % solution A and 20 % solution B was changed linearly to 40 % solution A and 60 % solution B at 1.00 ml min^{-1} over 50 minutes.

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109 Refer to reference **17** and **18** for a description of an organizing precomplex that facilitates the structural details of the formation of a six membered cyclic transition state.

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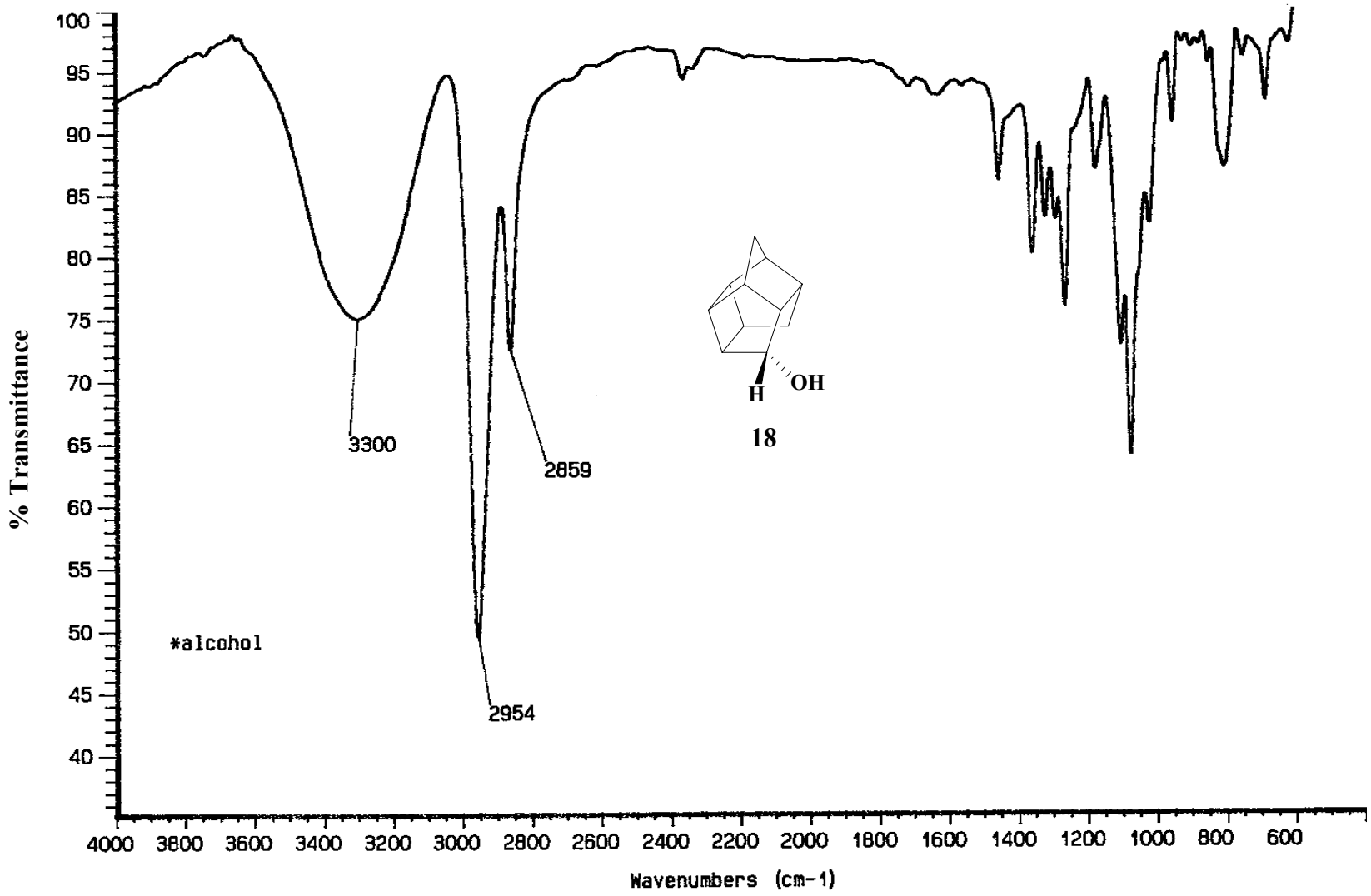
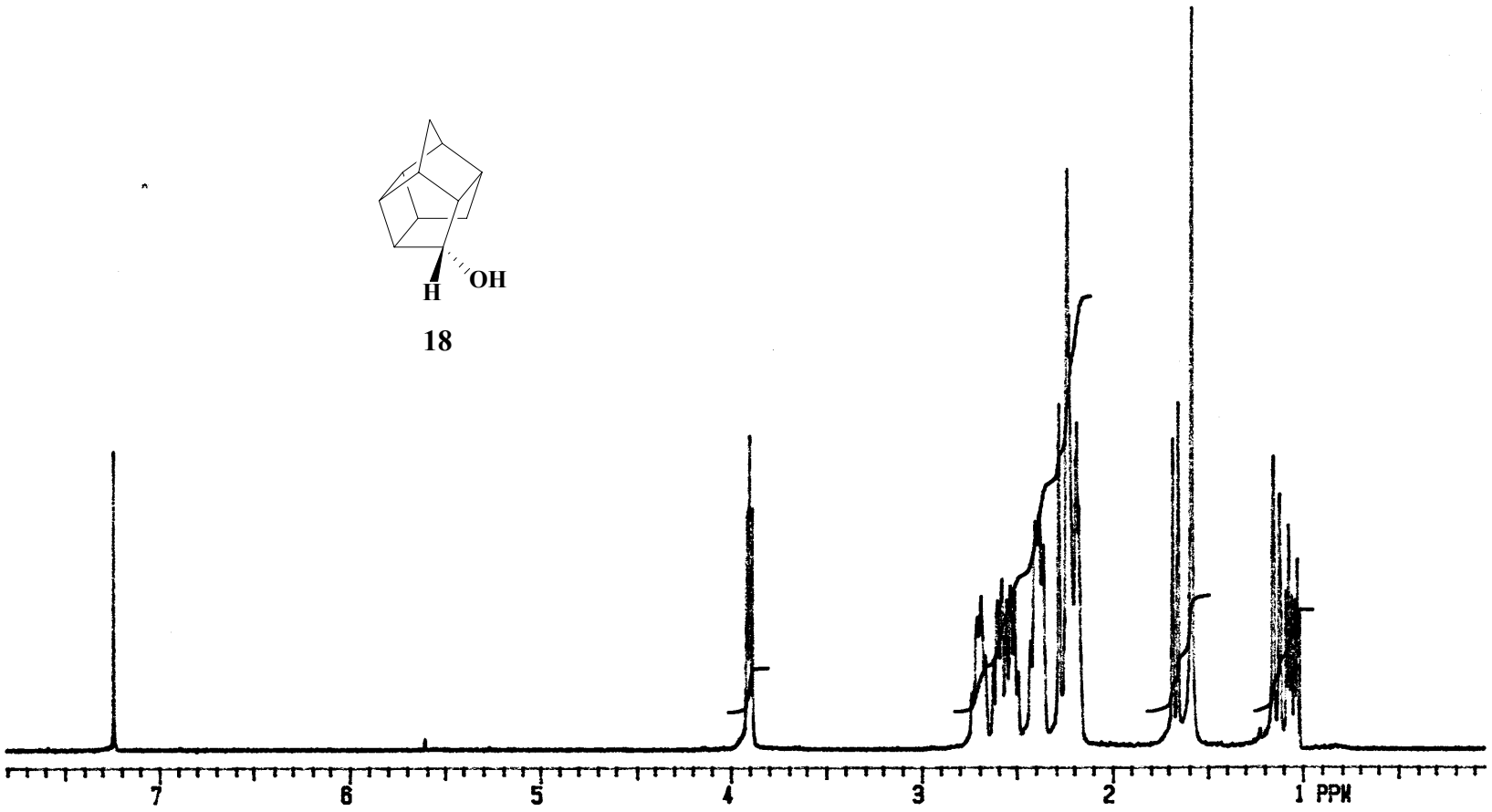
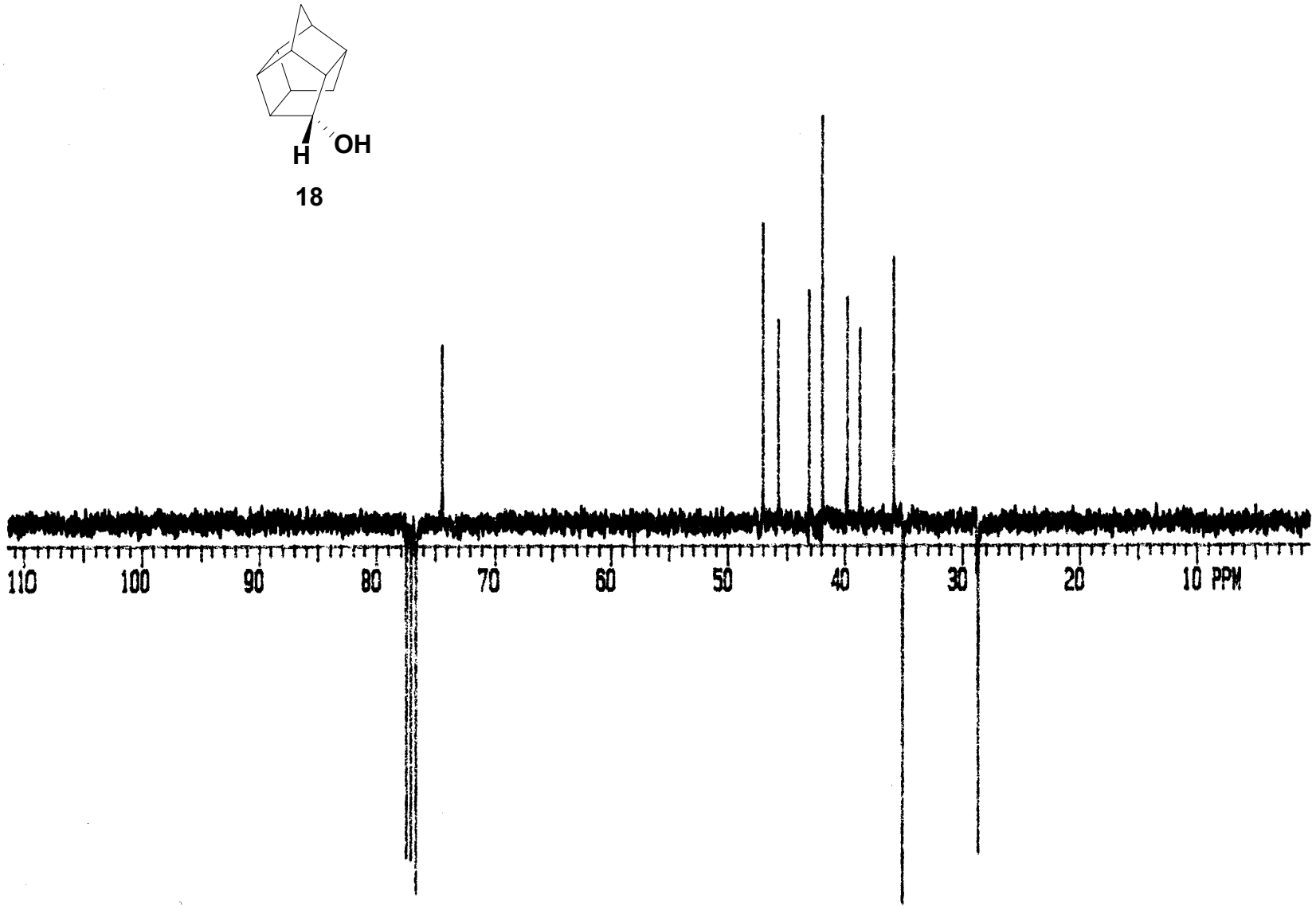


Spectrum 1: Infrared spectrum (KBr) of the *endo*-PCU alcohol (18)

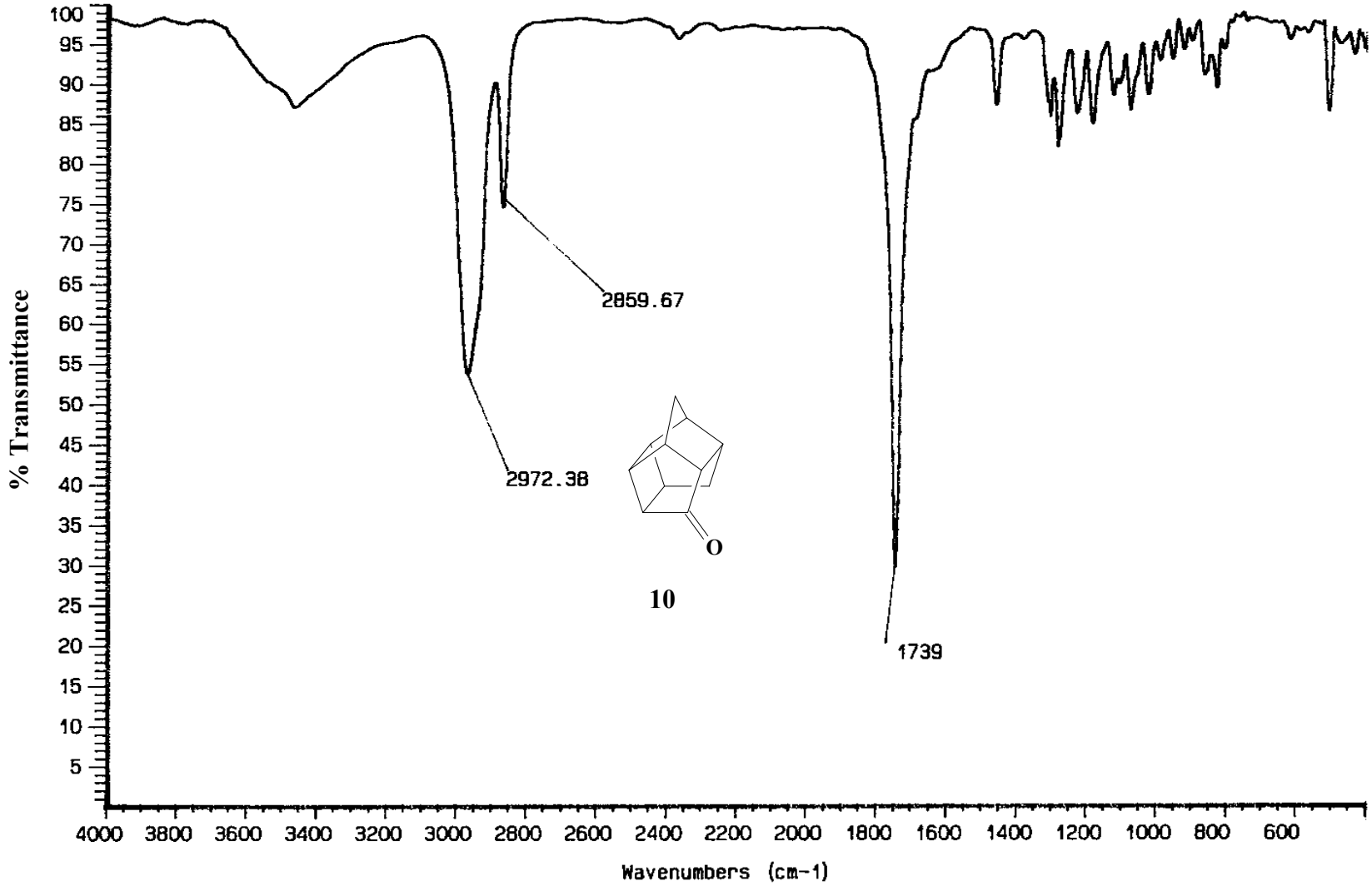


18

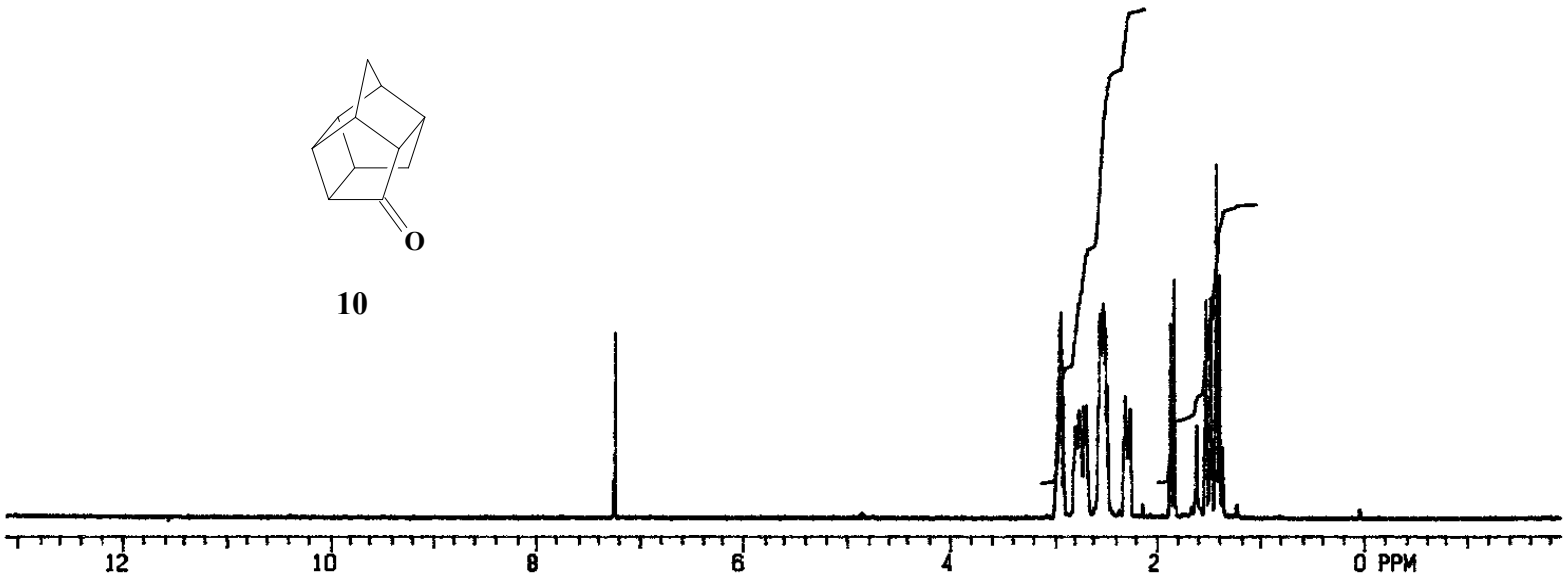
Spectrum 2: ^{1}H NMR spectrum of the *endo*-PCU alcohol (18) in $CDCl_3$



Spectrum 3: ^{13}C NMR spectrum of the *endo*-PCU alcohol (18) in $CDCl_3$

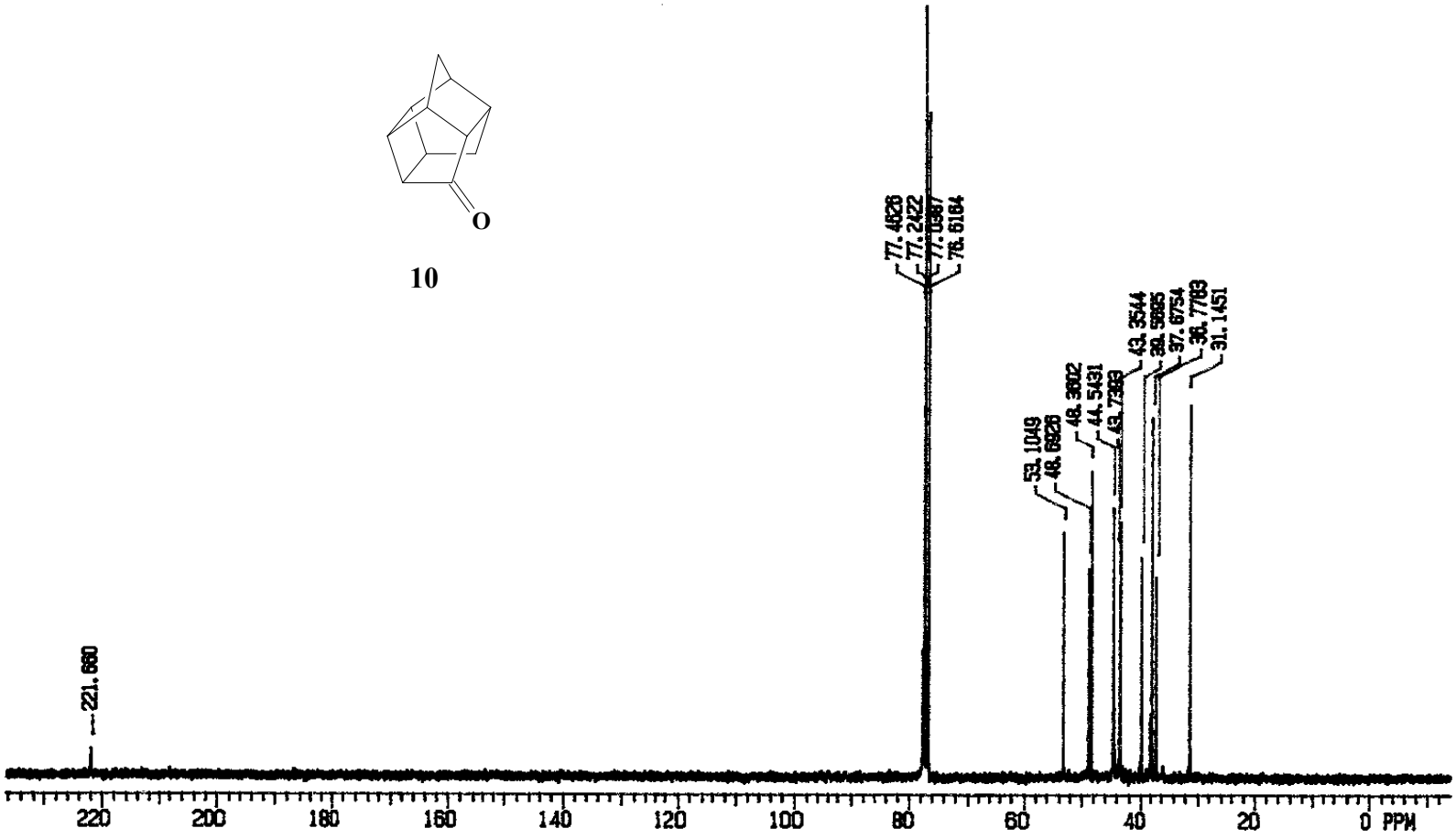


Spectrum 4: Infrared spectrum (KBr) of PCUmonoketone (10)

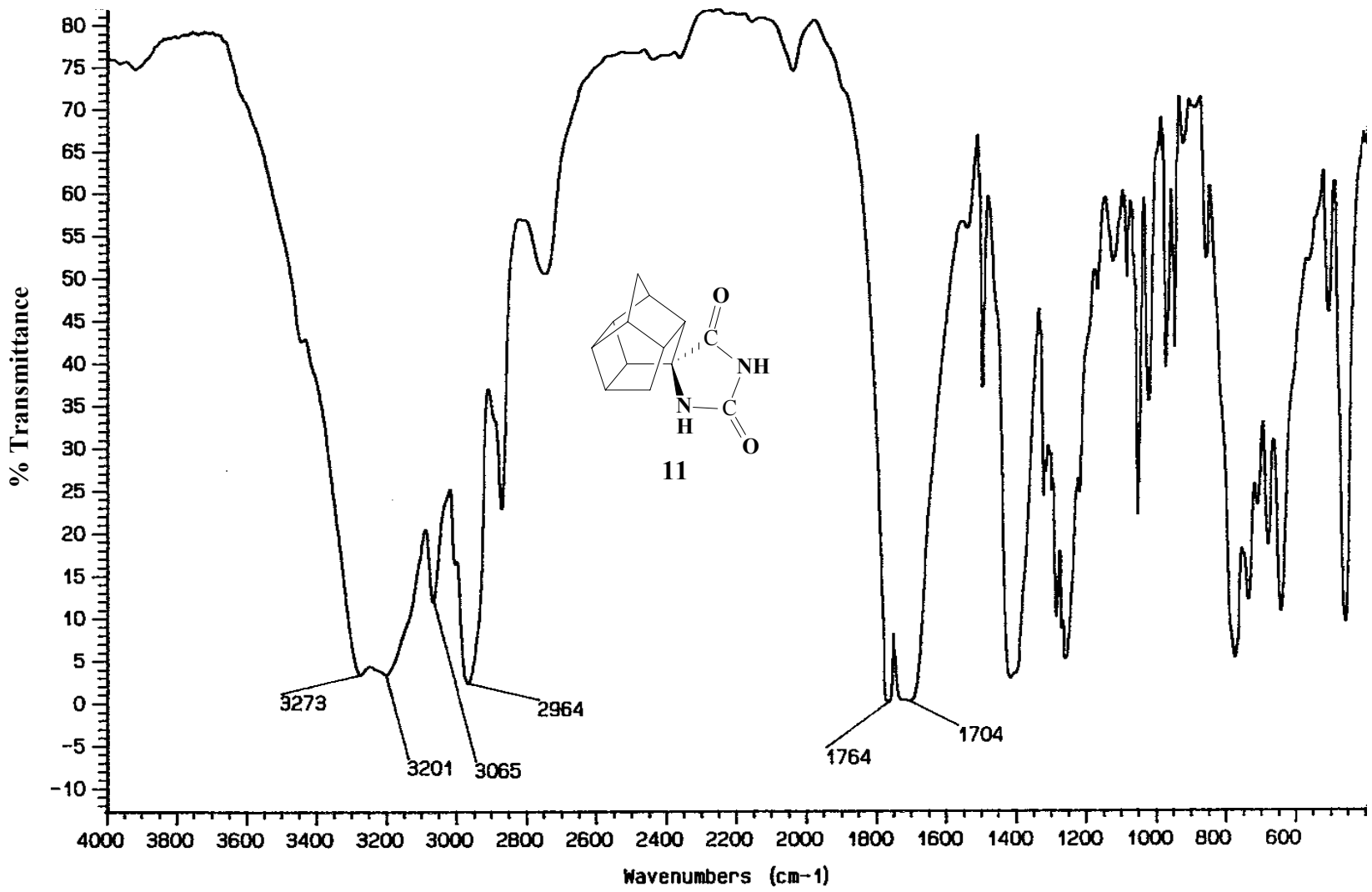


10

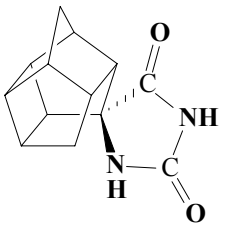
Spectrum 5: ^{1}H NMR spectrum of PCUmonoketone (10) in $CDCl_3$



Spectrum 6: ^{13}C NMR spectrum of PCU monoketone (10) in $CDCl_3$

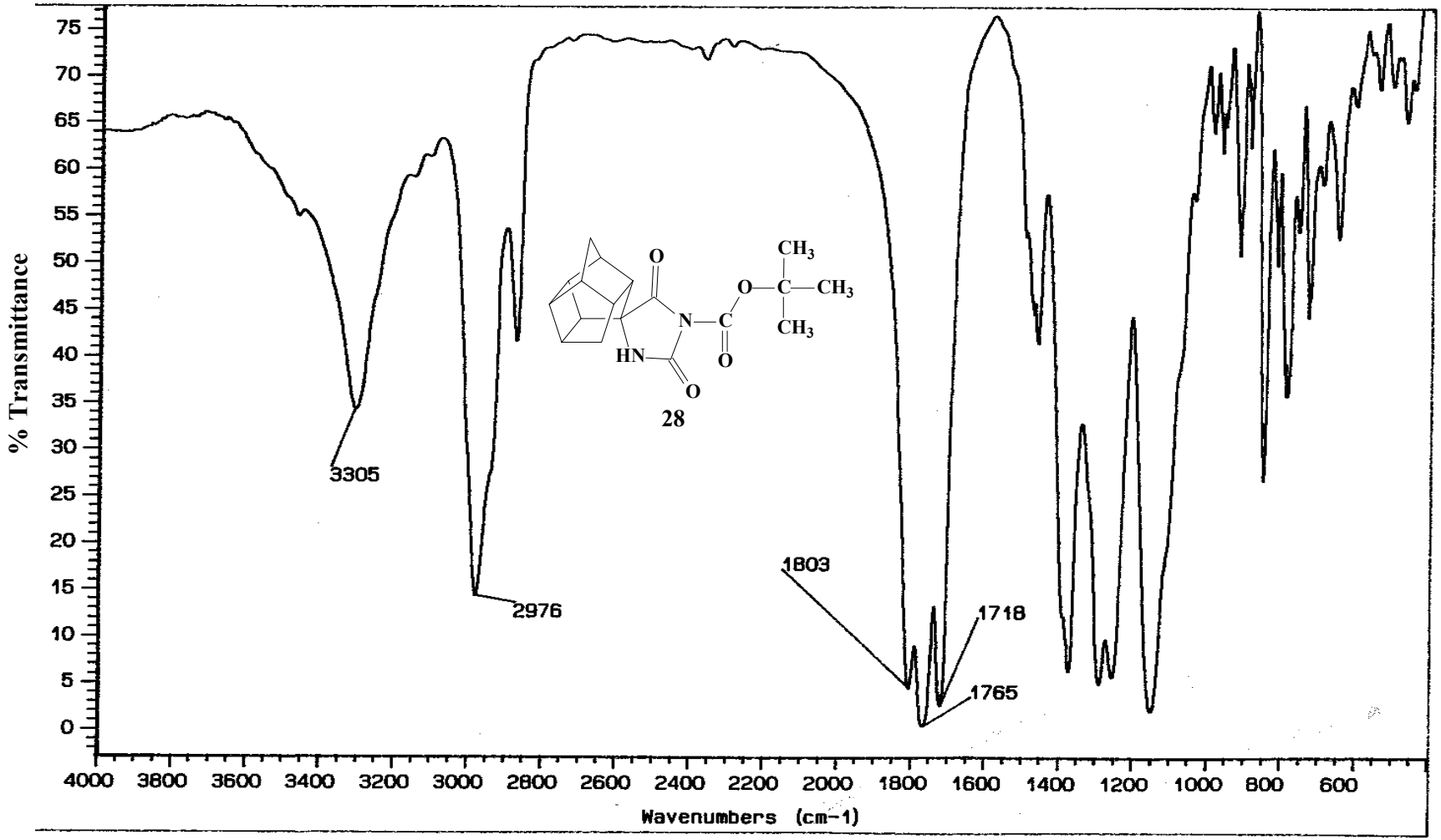


Spectrum 7: Infrared spectrum (KBr) of PCU-hydantoin (11)

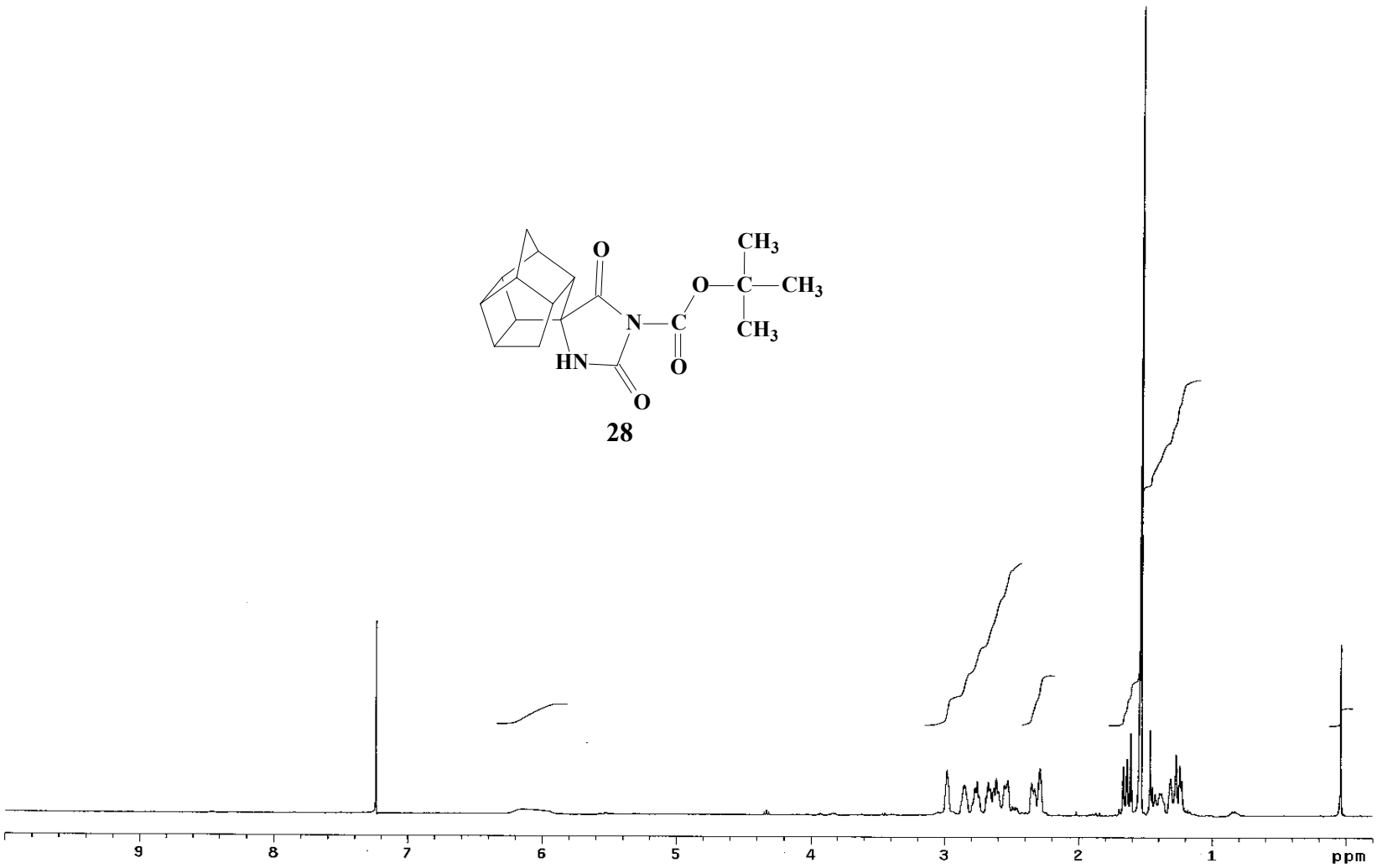


11

Spectrum 7: ^{1}H NMR spectrum of PCUhydantoin (11) in DMSO

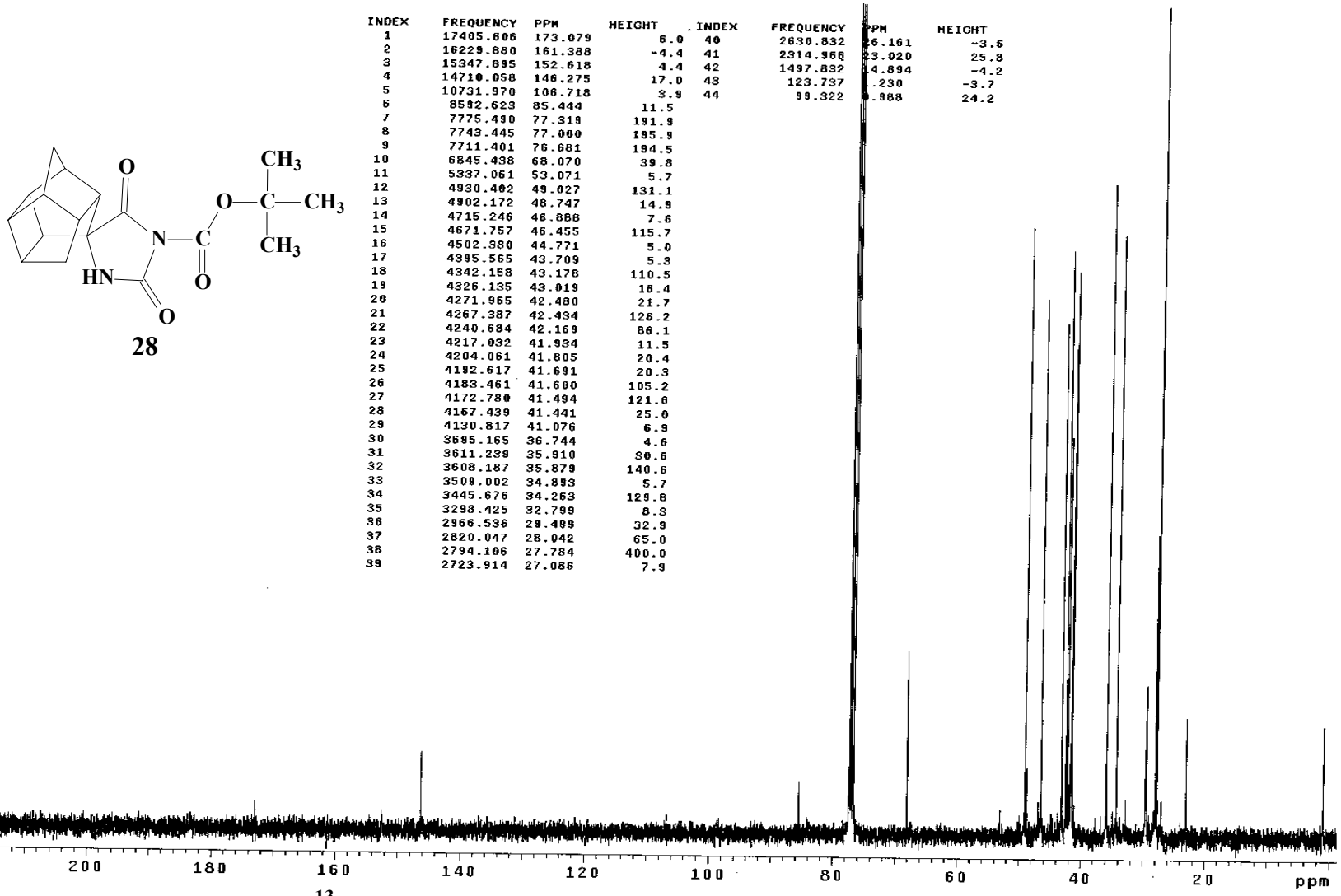


Spectrum 9: Infrared spectrum (KBr) of the mono Boc-PCU hydantoin (28)



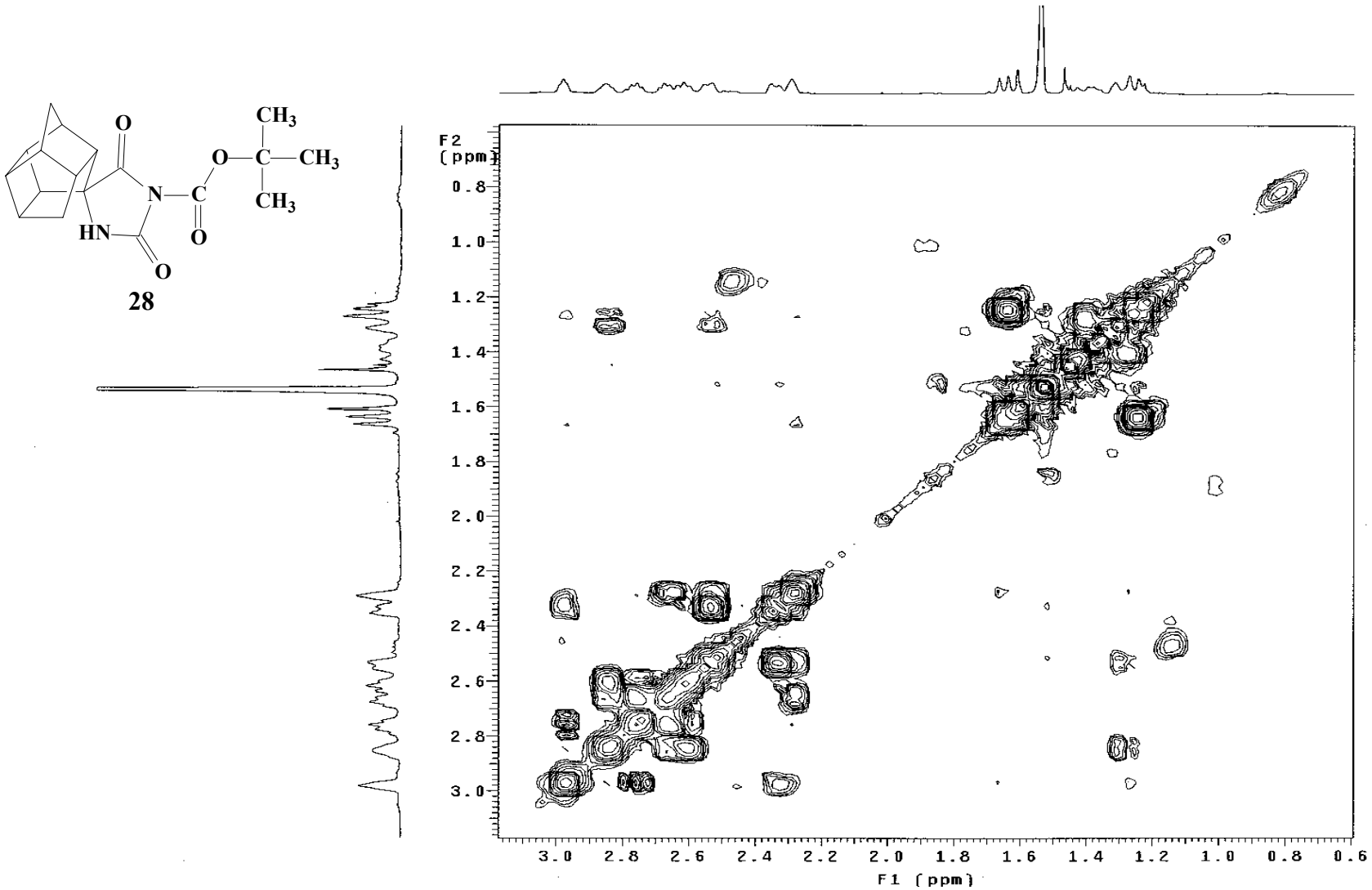
28

Spectrum 10: ^{1}H NMR spectrum of mono Boc-PCU hydantoin (28) in $CDCl_3$

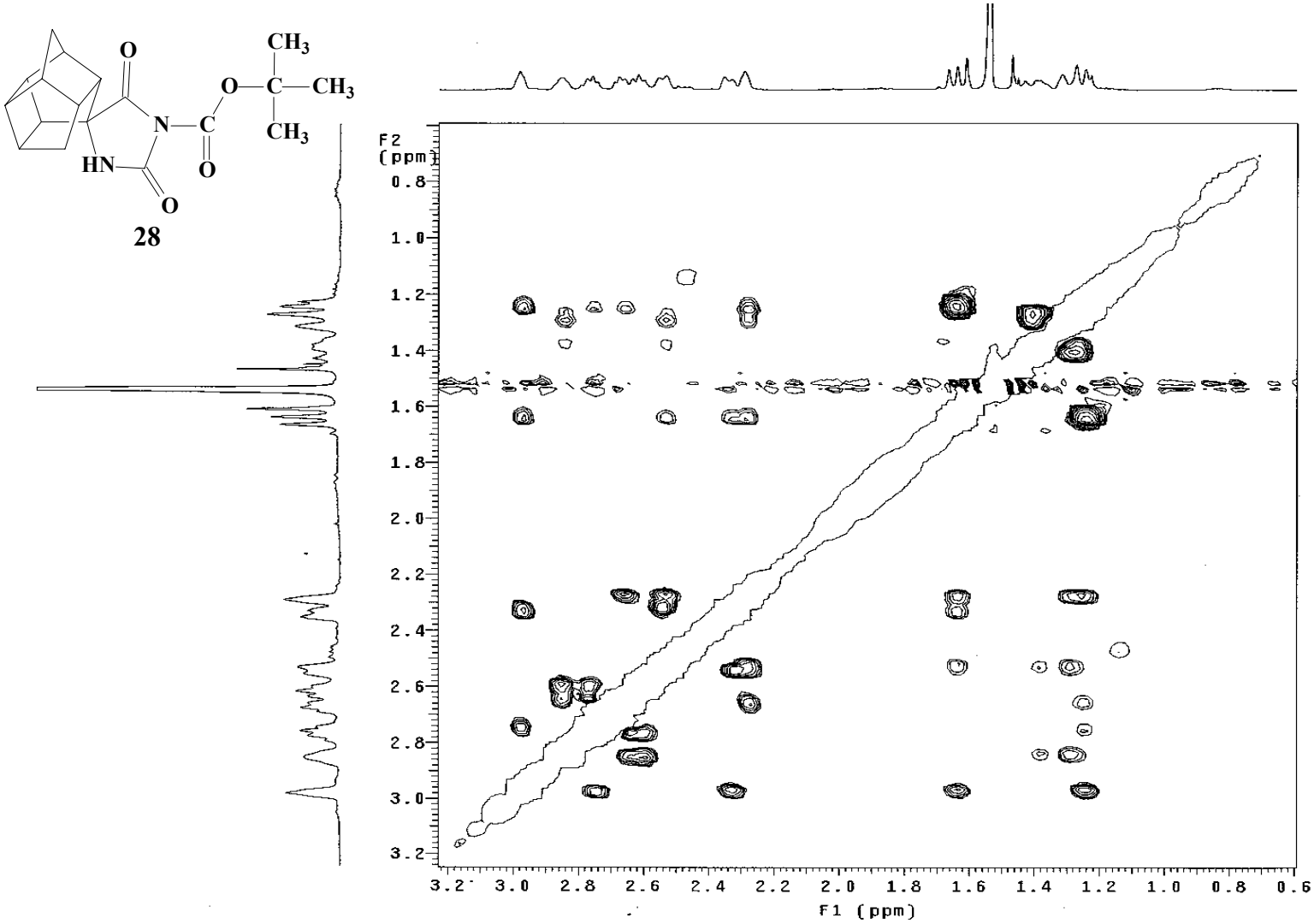


INDEX	FREQUENCY	PPM	HEIGHT	INDEX	FREQUENCY	PPM	HEIGHT
1	17405.606	173.079	6.0	40	2630.832	26.161	-3.6
2	16229.880	161.388	-4.4	41	2314.966	23.020	25.8
3	15347.895	152.618	4.4	42	1497.832	14.894	-4.2
4	14710.058	146.275	17.0	43	123.737	1.230	-3.7
5	10731.970	106.718	3.9	44	99.322	.988	24.2
6	8582.623	85.344	11.5				
7	7775.490	77.318	191.9				
8	7743.445	77.000	195.9				
9	7711.401	76.681	194.5				
10	6845.438	68.070	39.8				
11	5337.061	53.071	5.7				
12	4930.402	49.027	131.1				
13	4902.172	48.747	14.9				
14	4715.246	46.888	7.6				
15	4671.757	46.455	115.7				
16	4502.380	44.771	5.0				
17	4395.565	43.709	5.8				
18	4342.158	43.178	110.5				
19	4326.135	43.019	16.4				
20	4271.965	42.480	21.7				
21	4267.387	42.434	126.2				
22	4240.684	42.169	86.1				
23	4217.032	41.934	11.5				
24	4204.061	41.805	20.4				
25	4192.617	41.691	20.3				
26	4183.461	41.600	105.2				
27	4172.780	41.494	121.6				
28	4167.439	41.441	25.0				
29	4130.817	41.076	6.9				
30	3695.165	36.744	4.6				
31	3611.239	35.910	30.6				
32	3608.187	35.879	140.6				
33	3509.002	34.893	5.7				
34	3445.676	34.263	128.8				
35	3298.425	32.799	8.3				
36	2966.536	29.499	32.9				
37	2820.047	28.042	65.0				
38	2794.106	27.784	400.0				
39	2723.914	27.086	7.9				

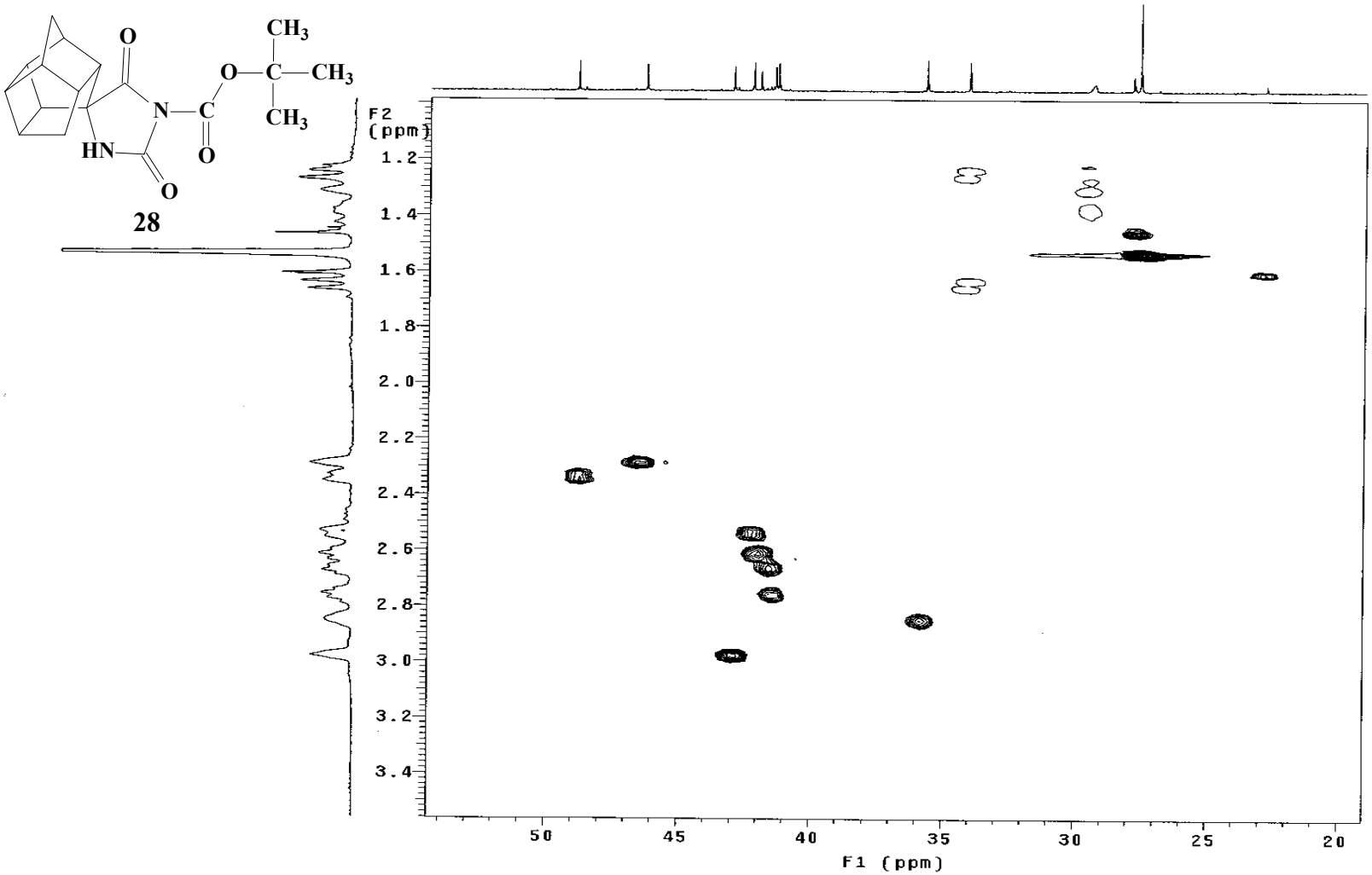
Spectrum 11: ^{13}C NMR spectrum of the mono Boc-PCU hydantoin (28) in $CDCl_3$



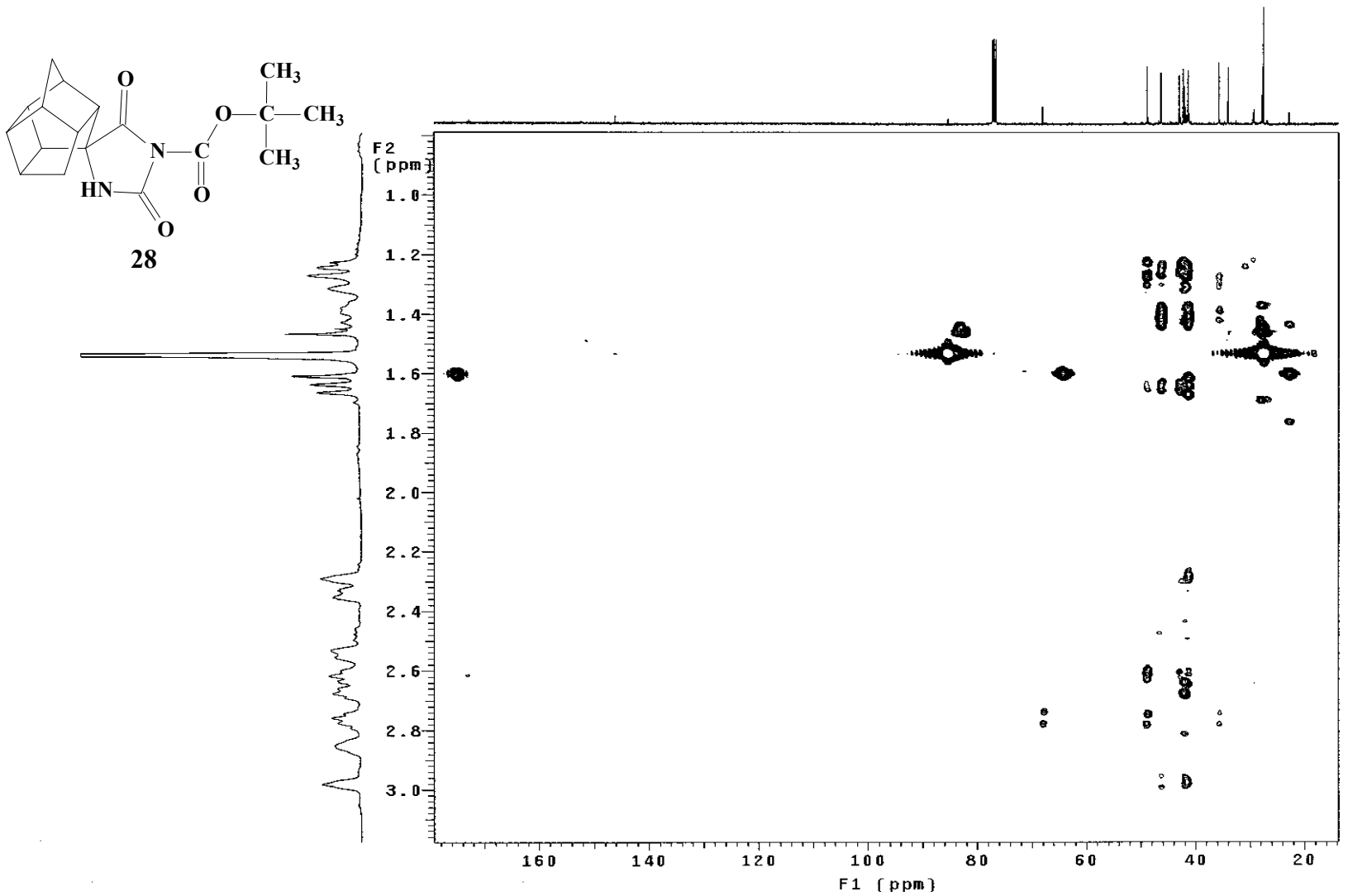
Spectrum 12: COSY spectrum of mono-Boc PCU hydantoin (28) in $CDCL_3$



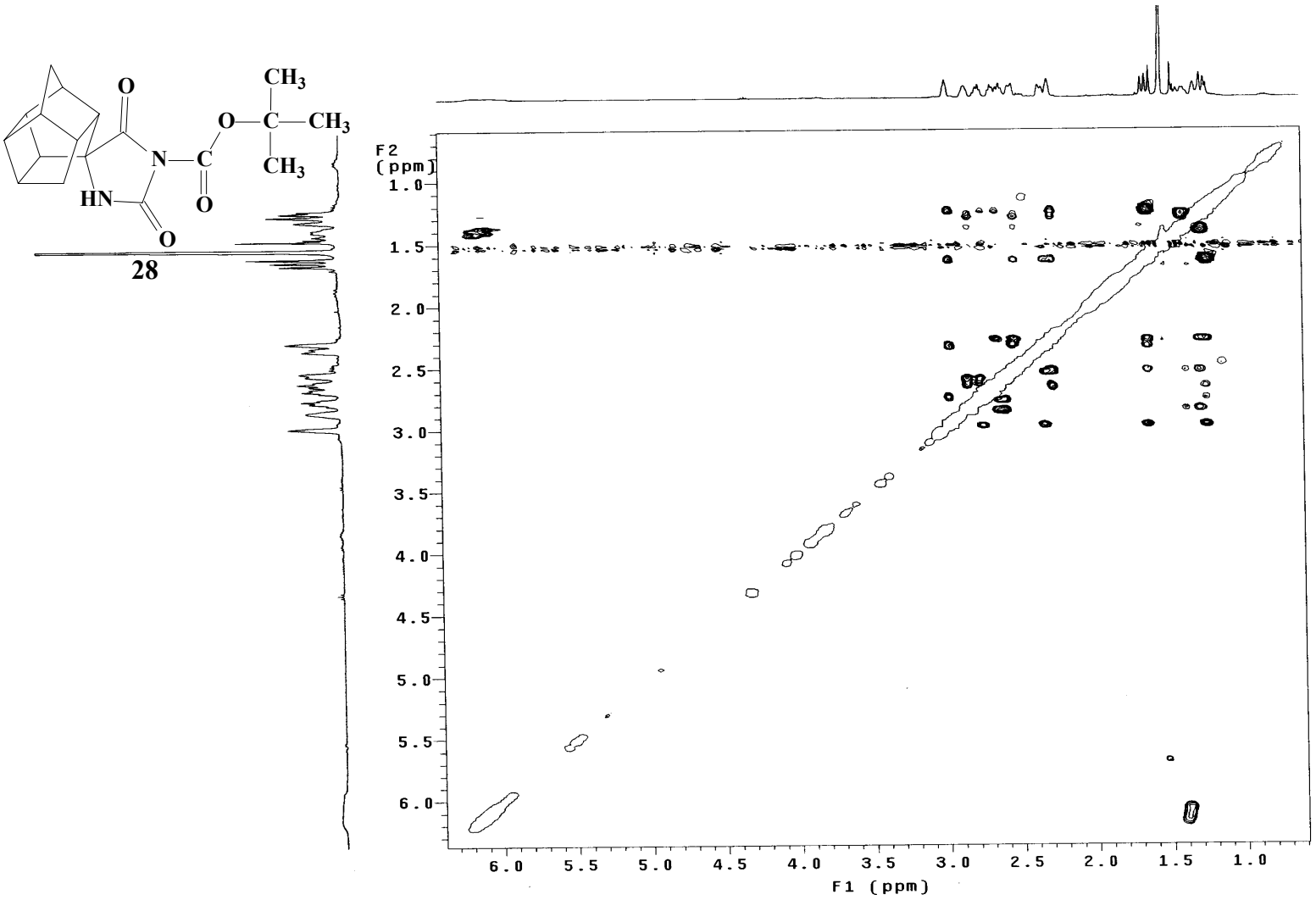
Spectrum 13: NOESY spectrum of mono-Boc PCU hydantoin (28) in $CDCl_3$



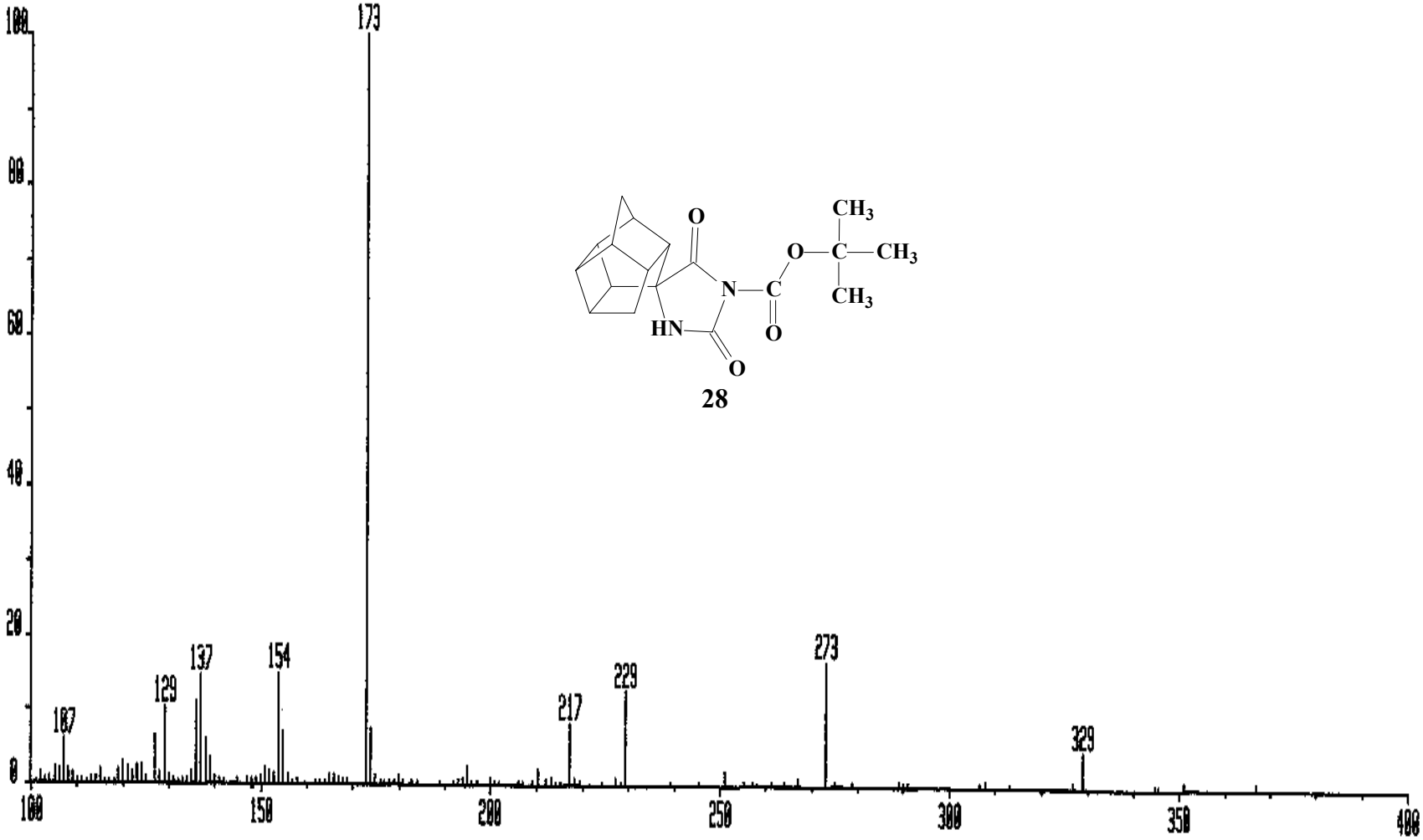
Spectrum 14: HSQC spectrum of mono Boc-PCU hydantoin (28) in $CDCL_3$



Spectrum 15: HMBC spectrum of mono-Boc PCU hydantoin (28) in $CDCl_3$

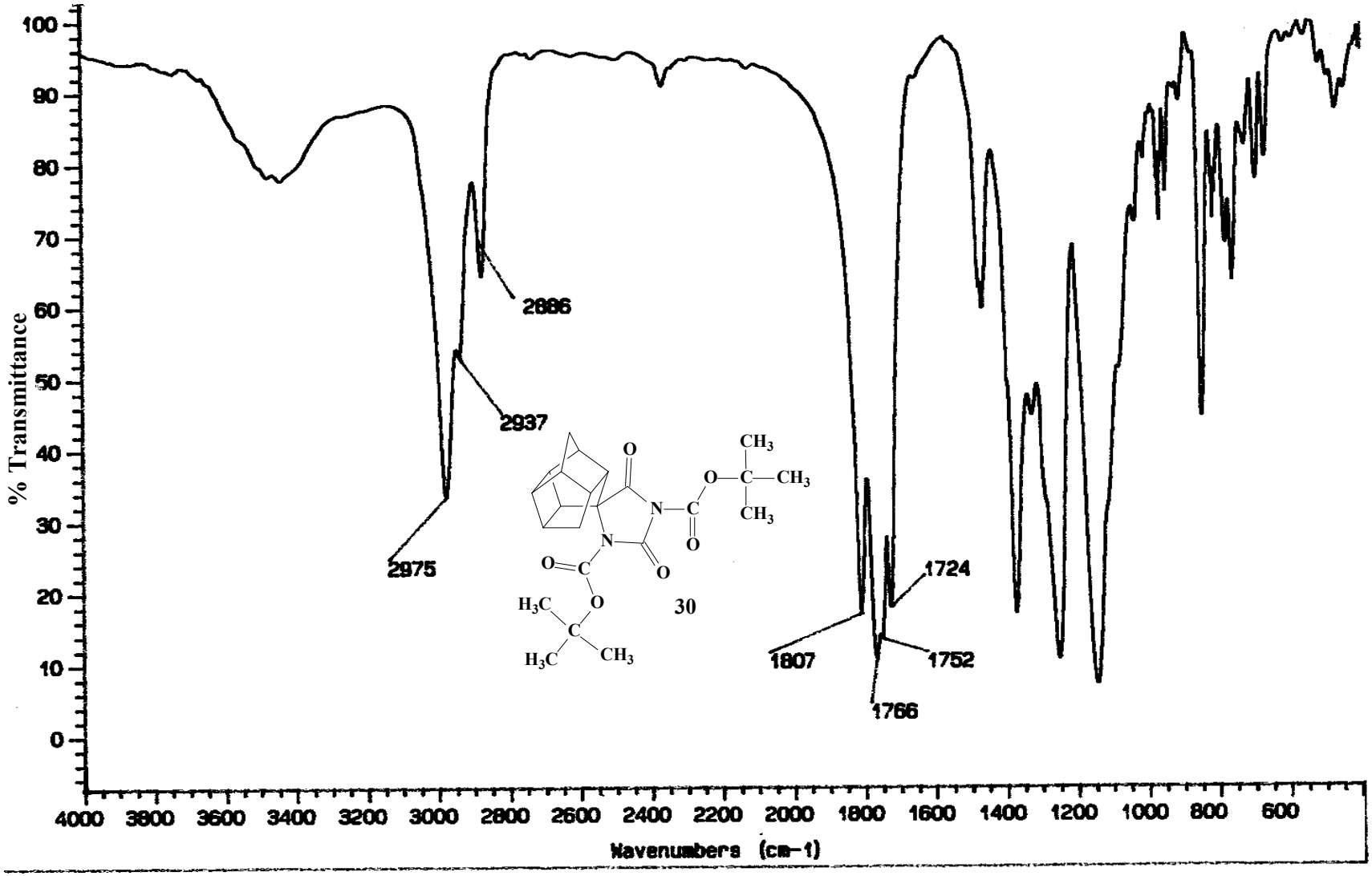


Spectrum 16: NOESY spectrum of mono-Boc PCU hydantoin (28) in $CDCl_3$



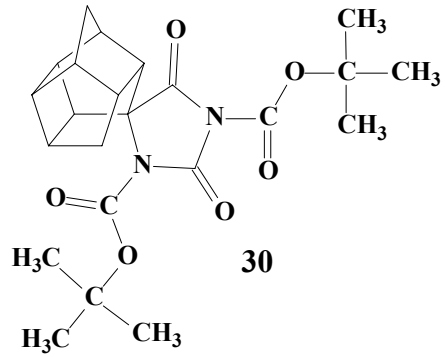
28

Spectrum 18: Mass spectrum (MS-TOF) of mono-Boc PCU hydantoin (28)



Spectrum 19: Infrared spectrum (KBr) of bis-Boc PCU hydantoin (30)

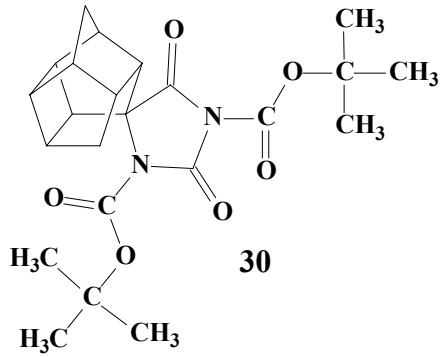
INDEX	FREQUENCY	PPM	HEIGHT	INDEX	FREQUENCY	PPM	HEIGHT
1	2895.755	7.240	36.5	40	433.764	1.085	8.1
2	2895.389	7.240	39.8				
3	1180.199	2.951	4.1				
4	1174.705	2.937	9.4				
5	1168.296	2.921	7.9				
6	1166.831	2.918	7.8				
7	1127.275	2.819	11.3				
8	1123.063	2.808	16.4				
9	1114.822	2.787	5.7				
10	1106.032	2.765	7.6				
11	1099.073	2.748	7.2				
12	1055.305	2.639	4.0				
13	1052.924	2.633	9.1				
14	1051.276	2.629	9.7				
15	1046.148	2.616	13.5				
16	1044.134	2.611	12.7				
17	1042.120	2.606	13.4				
18	1039.922	2.600	13.5				
19	1000.549	2.502	8.7				
20	989.928	2.475	6.9				
21	907.519	2.269	7.9				
22	904.040	2.260	11.5				
23	900.561	2.252	7.1				
24	858.990	2.148	4.4				
25	667.620	1.669	12.8				
26	656.815	1.642	14.5				
27	619.274	1.548	120.7				
28	617.076	1.543	600.0				
29	607.370	1.519	538.4				
30	601.327	1.504	63.5				
31	594.551	1.487	8.2				
32	557.742	1.395	11.6				
33	544.191	1.361	17.6				
34	504.085	1.260	15.0				
35	500.057	1.250	13.4				
36	495.845	1.240	17.4				
37	491.816	1.230	26.1				
38	486.505	1.216	7.7				
39	483.026	1.208	4.9				



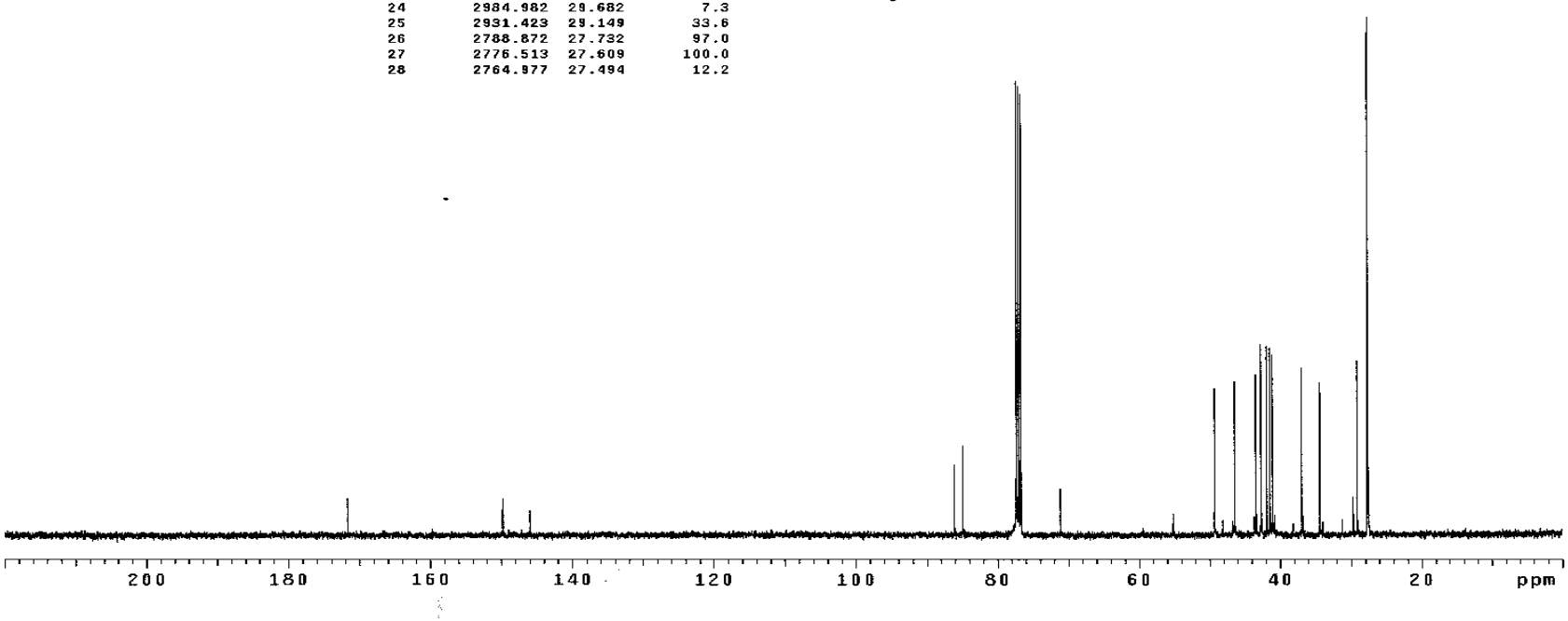
30

Spectrum 20: ^{1}H NMR spectrum of bis-Boc PCU hydantoin (30) in $CDCl_3$

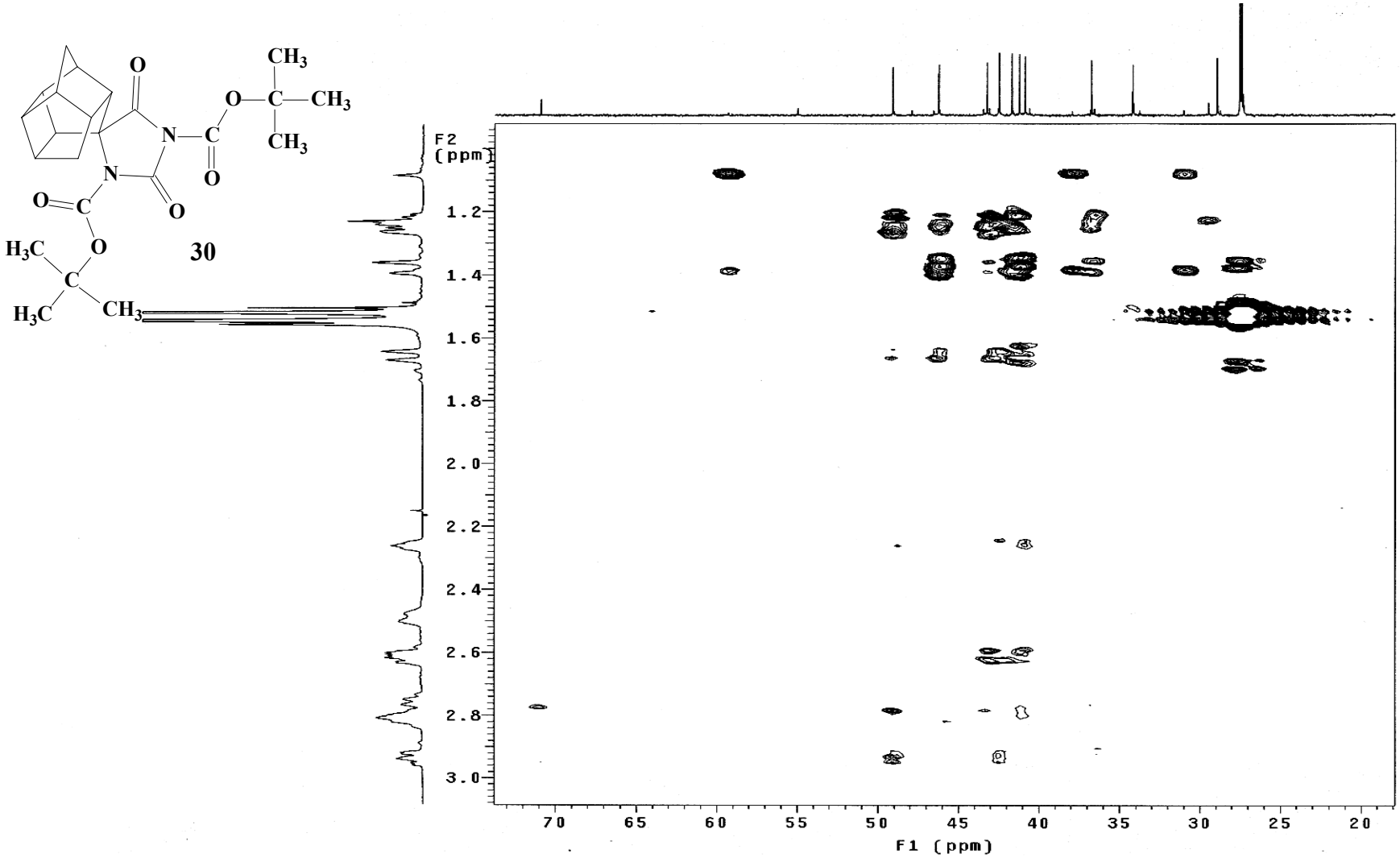
INDEX	FREQUENCY	PPM	HEIGHT
1	17262.247	171.652	7.1
2	15063.843	149.792	7.0
3	15055.604	149.710	3.9
4	14675.744	145.933	4.7
5	8658.973	86.103	13.5
6	8538.671	84.907	17.3
7	7775.657	77.320	87.7
8	7743.521	77.000	86.7
9	7712.209	76.689	85.2
10	7151.073	71.109	9.0
11	5550.061	55.189	3.9
12	4956.789	49.288	28.3
13	4669.216	46.430	29.6
14	4368.460	43.439	31.0
15	4352.804	43.283	3.9
16	4292.653	42.685	36.7
17	4211.902	41.882	36.5
18	4164.935	41.415	36.1
19	4129.503	41.063	34.8
20	4102.312	40.793	3.8
21	3714.213	36.933	32.4
22	3696.685	36.753	3.6
23	3457.952	34.385	29.5
24	2984.982	29.682	7.3
25	2931.423	29.149	33.6
26	2788.872	27.732	97.0
27	2776.513	27.609	100.0
28	2764.977	27.494	12.2



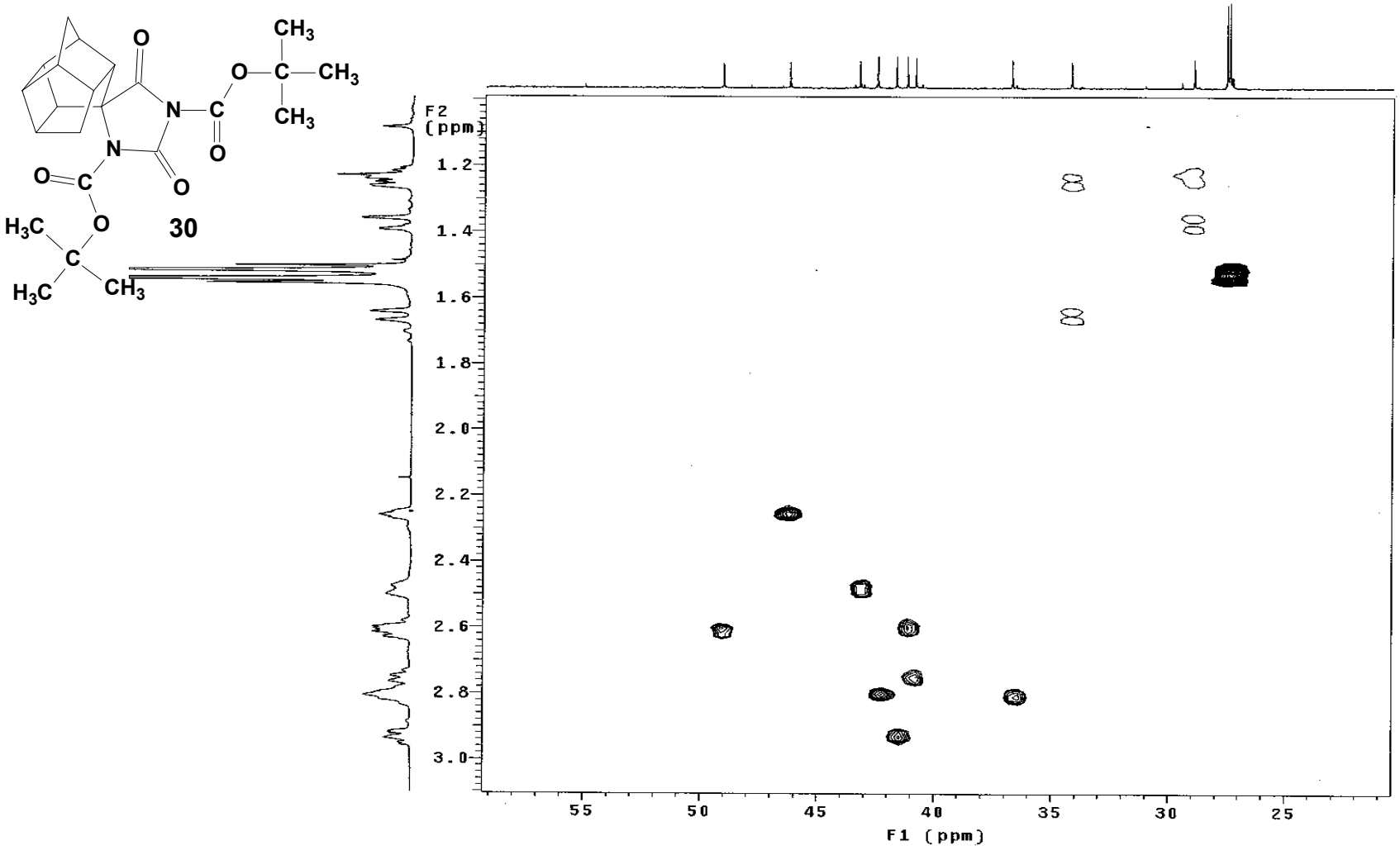
30



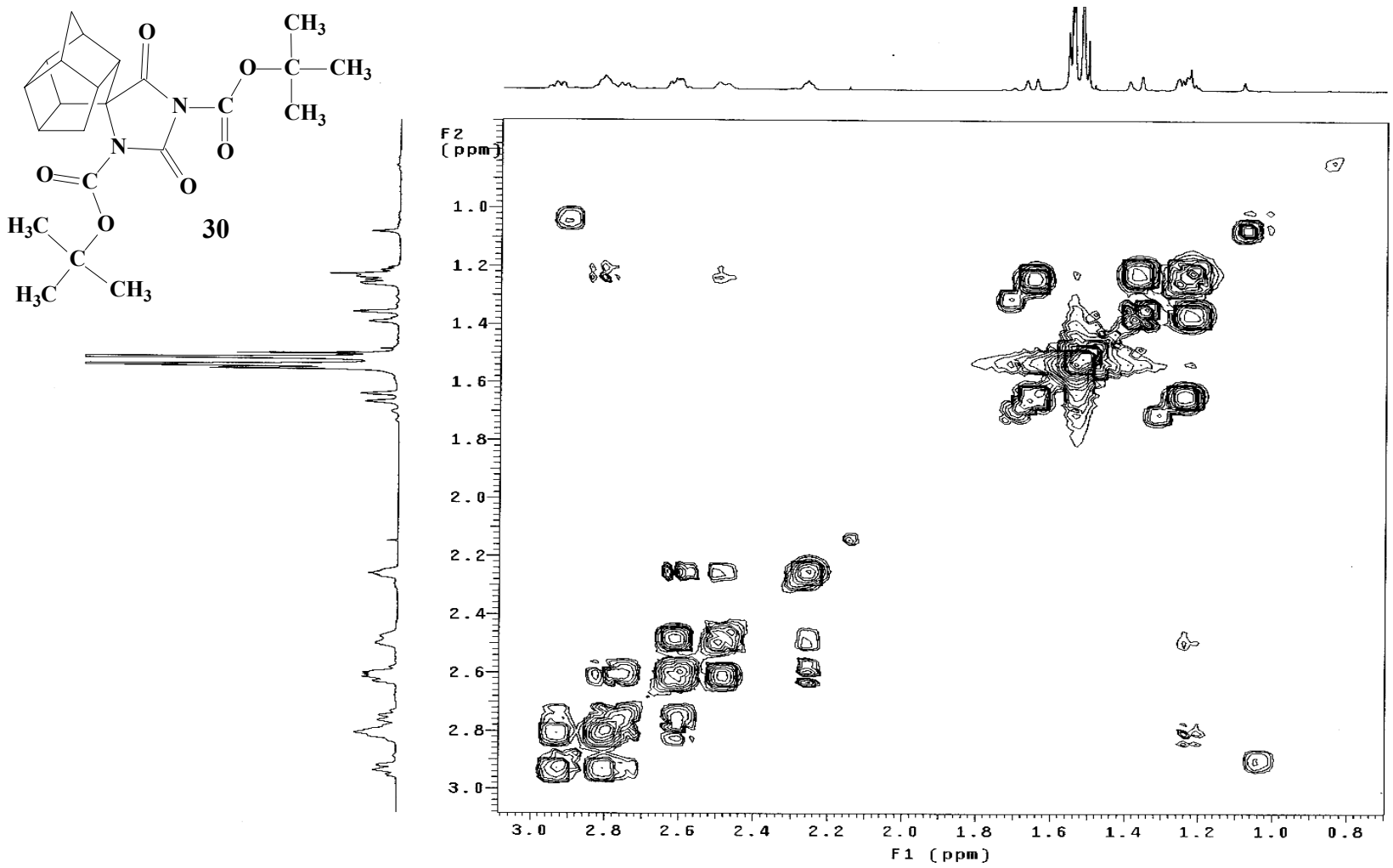
Spectrum 21: ^{13}C NMR spectrum of bis-Boc PCU hydantoin (30) in $CDCl_3$



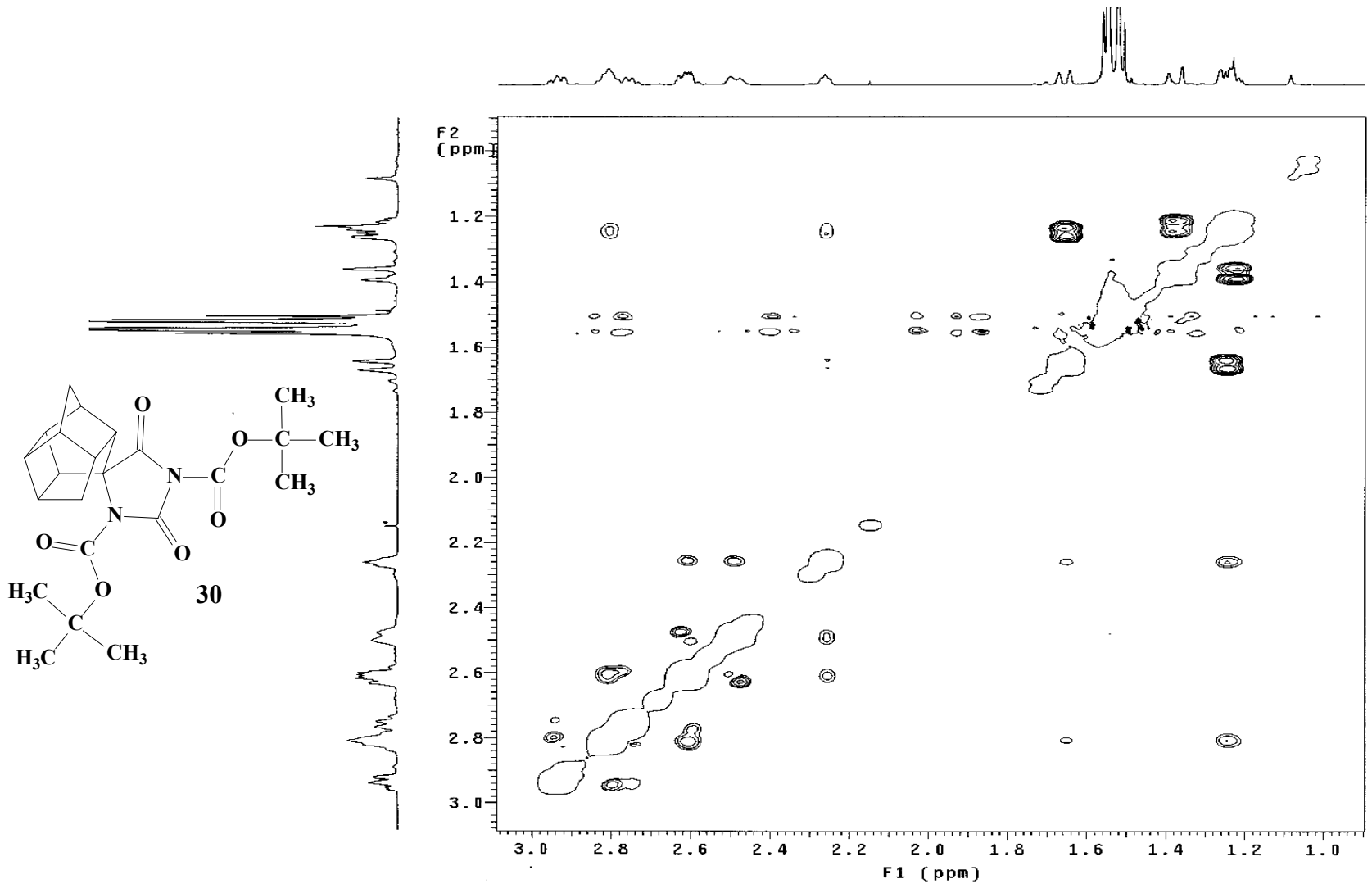
Spectrum 22: HMBC spectrum of bis-Boc PCU hydantoin (30) in $CDCl_3$



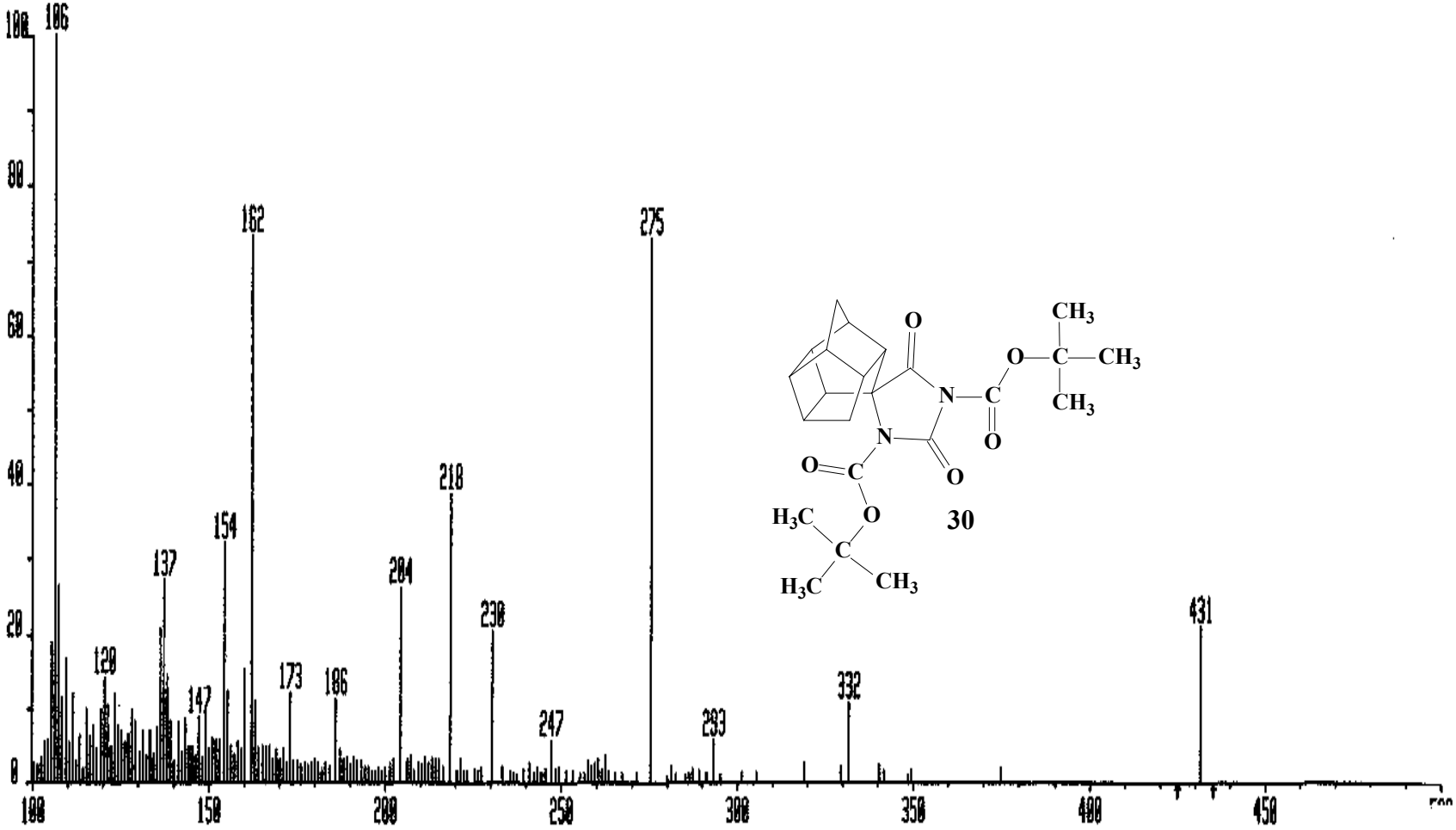
Spectrum 23: HSQC spectrum of bis-Boc PCU hydantoin (30) in $CDCl_3$



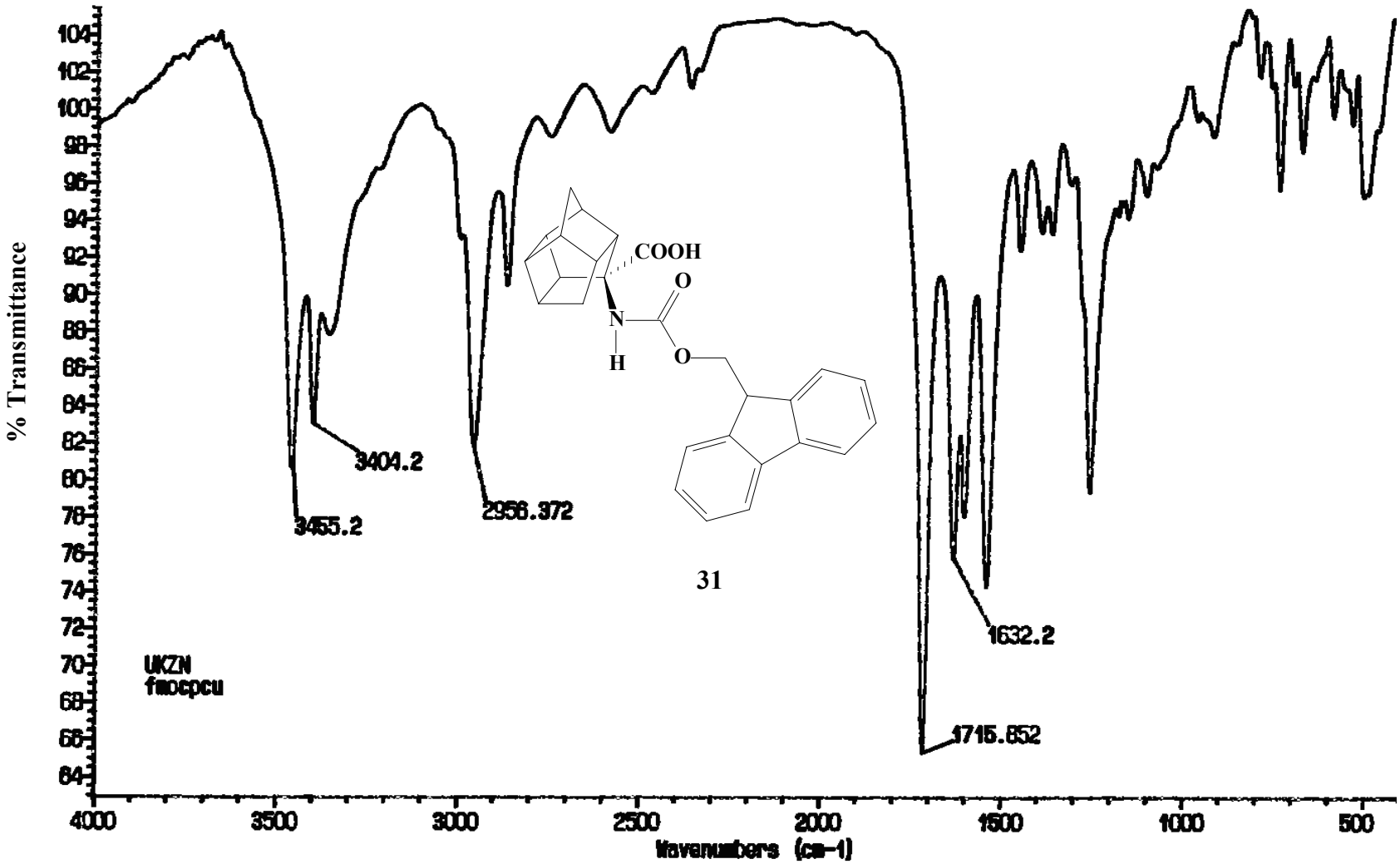
Spectrum 24: COSY spectrum of is-Boc PCU hydantoin (30) in $CDCl_3$



Spectrum 25: NOESY spectrum of bis-Boc PCU hydantoin (30) in $CDCl_3$

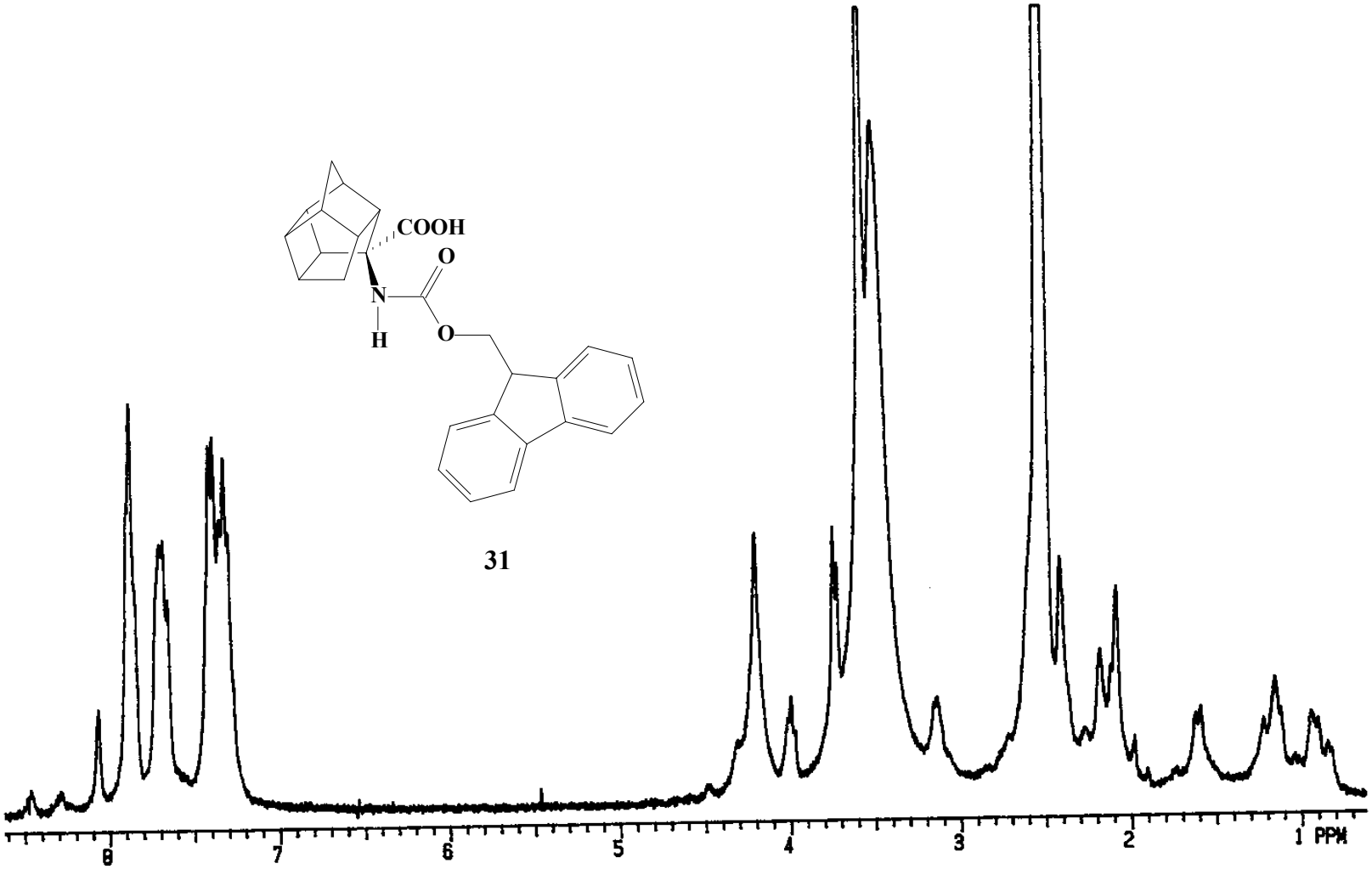


Spectrum 26: Mass spectrum (FAB) of bis-Boc PCU hydantoin (30) in $CDCl_3$



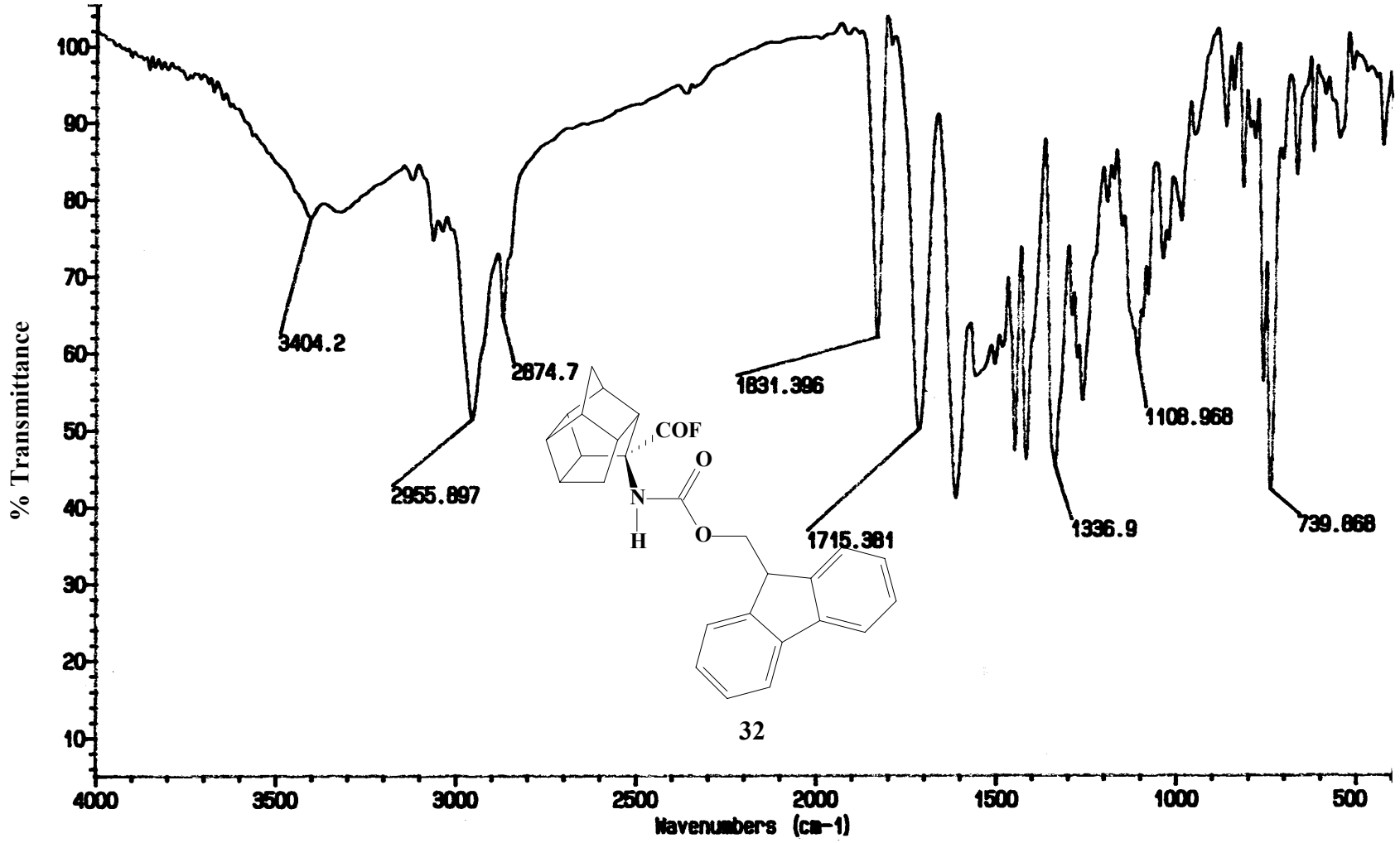
31

Spectrum 27: Infrared spectrum (KBr) of Fmoc PCU (31)



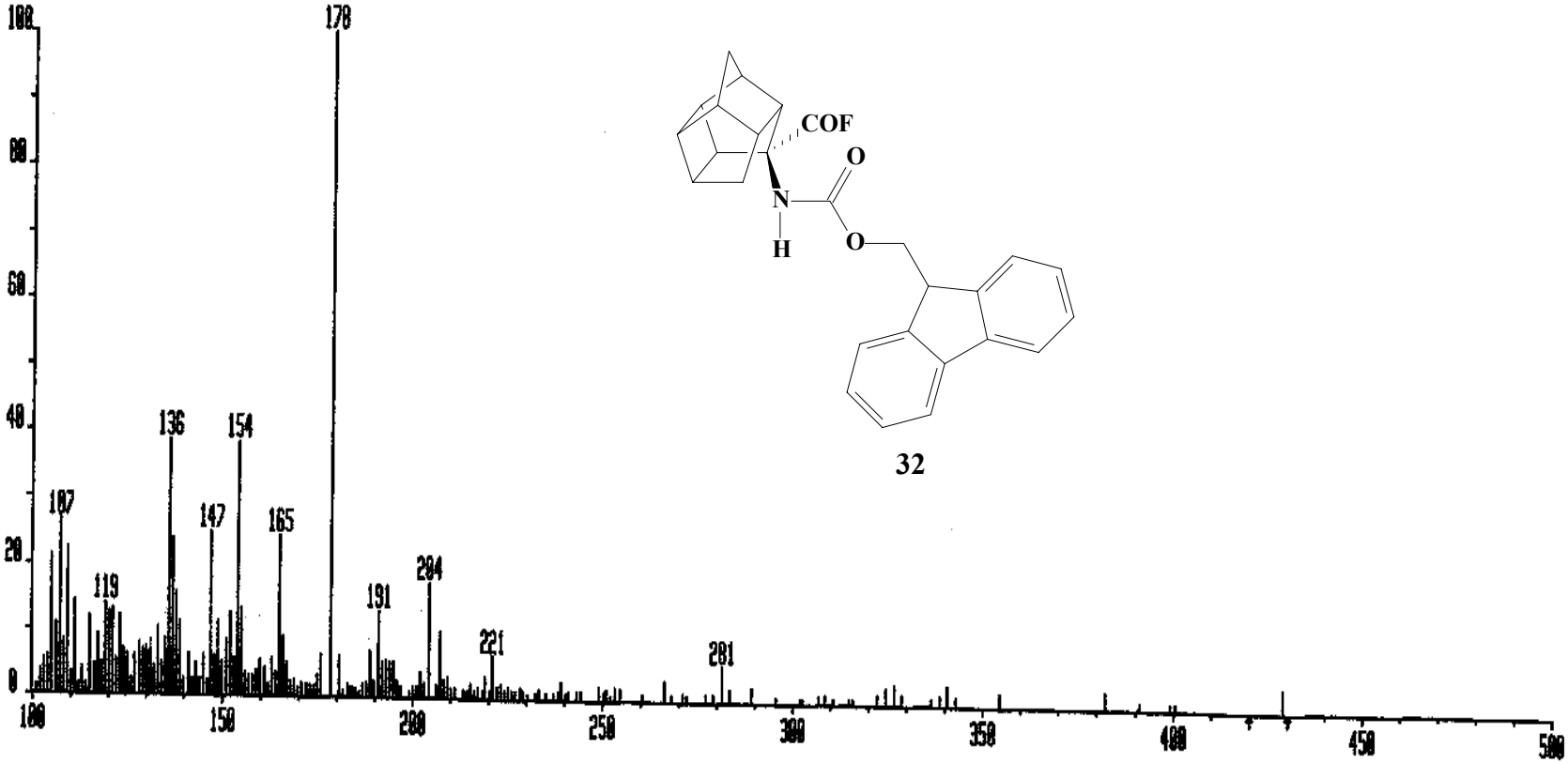
31

Spectrum 28: ^{1}H NMR spectrum of Fmoc PCU amino acid (31) in [$(CD_3)_2SO$]



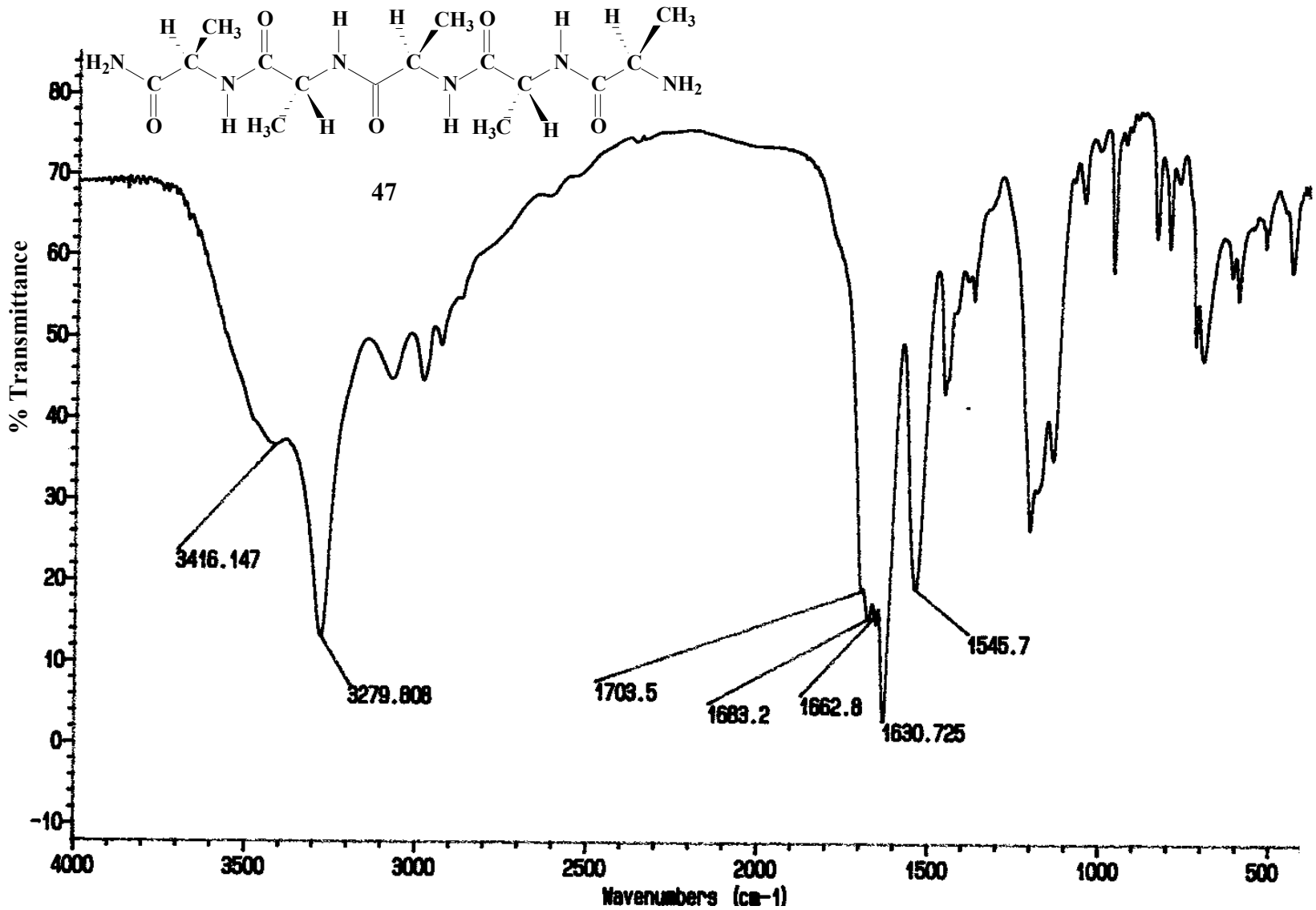
32

Spectrum 29: Infrared spectrum (KBr) of Fmoc PCU Flouride (32)

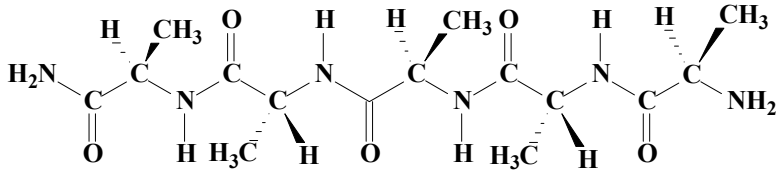


32

Spectrum 30: Mass spectrum (FAB) of Fmoc PCU Flouride (32)

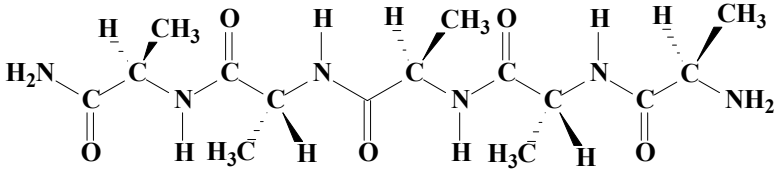


Spectrum 31: Infrared spectrum (KBr) of penta-peptide (47)



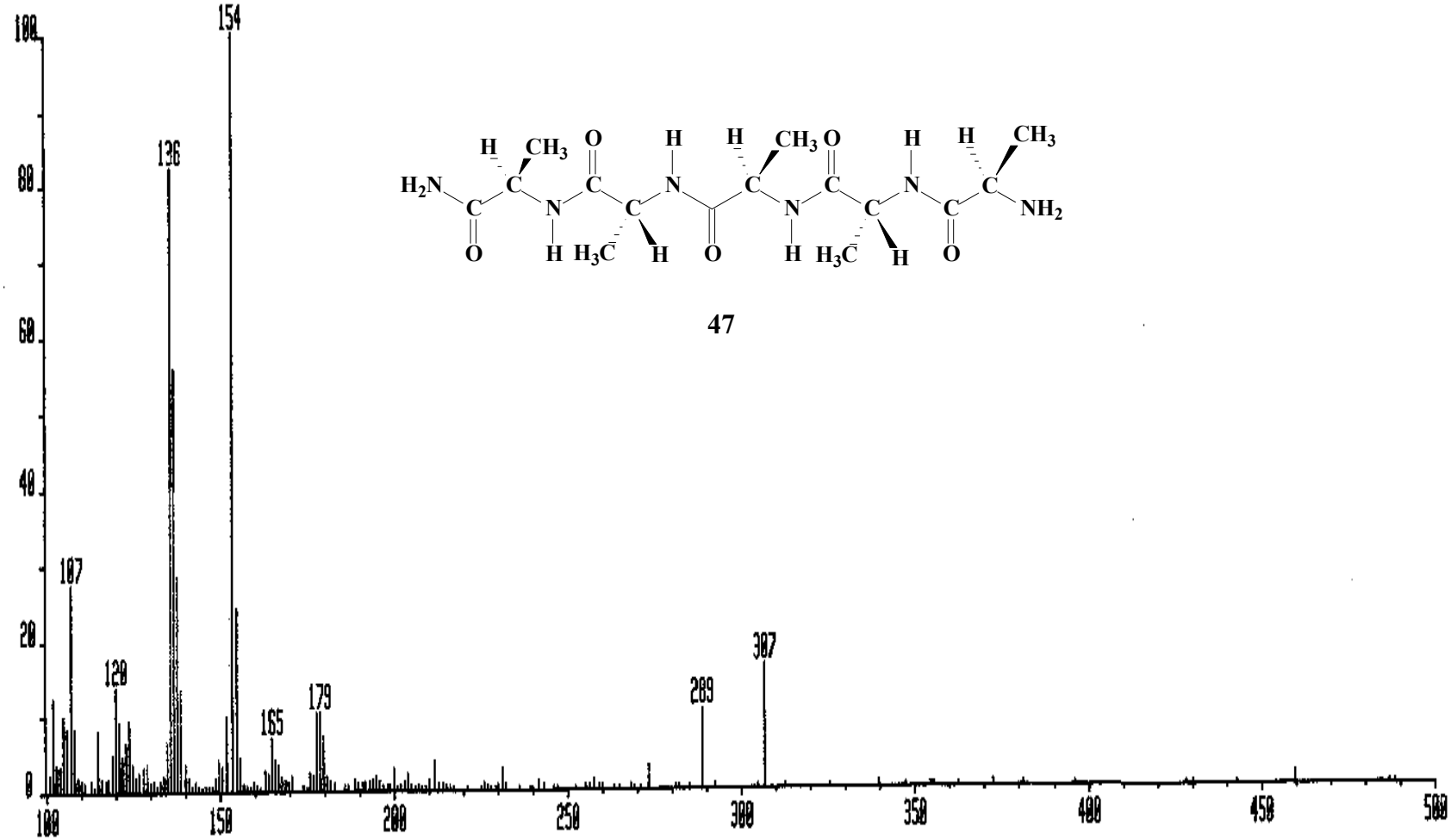
47

Spectrum 32: ^{1}H NMR spectrum of penta-peptide (47) in DMSO



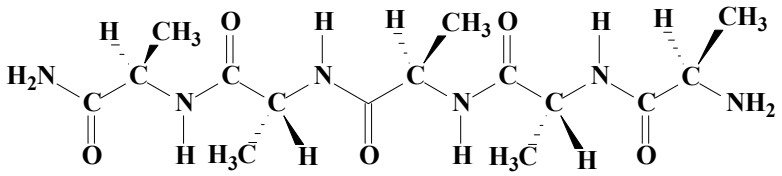
47

Spectrum 33: ^{13}C NMR spectrum of the penta-peptide (47) in DMSO

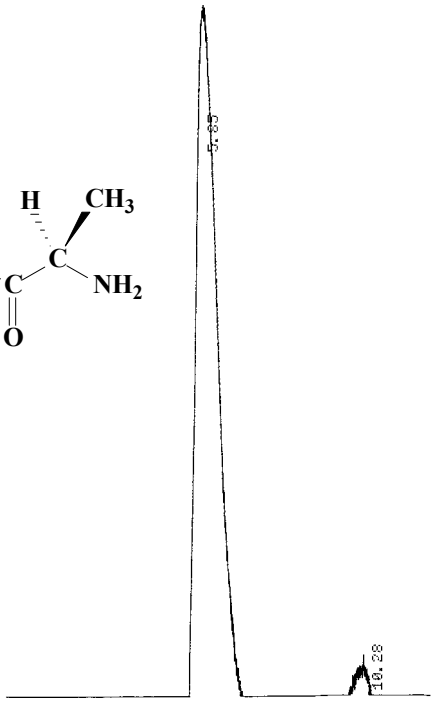


47

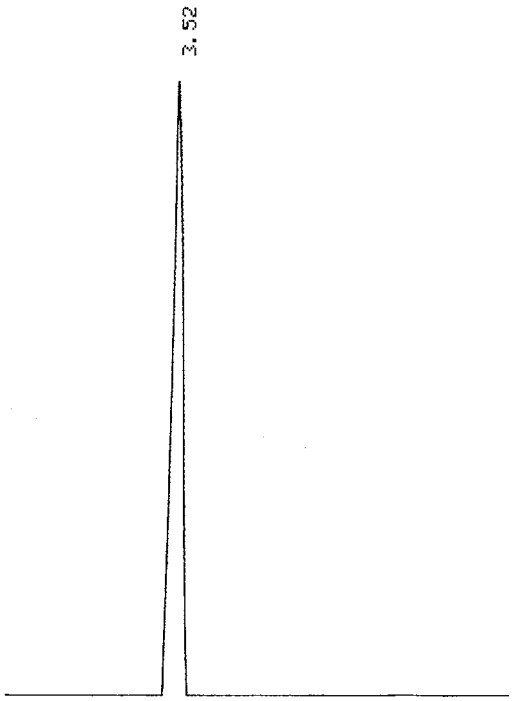
Spectrum 34: Mass spectrum (FAB) of penta-peptide (47)



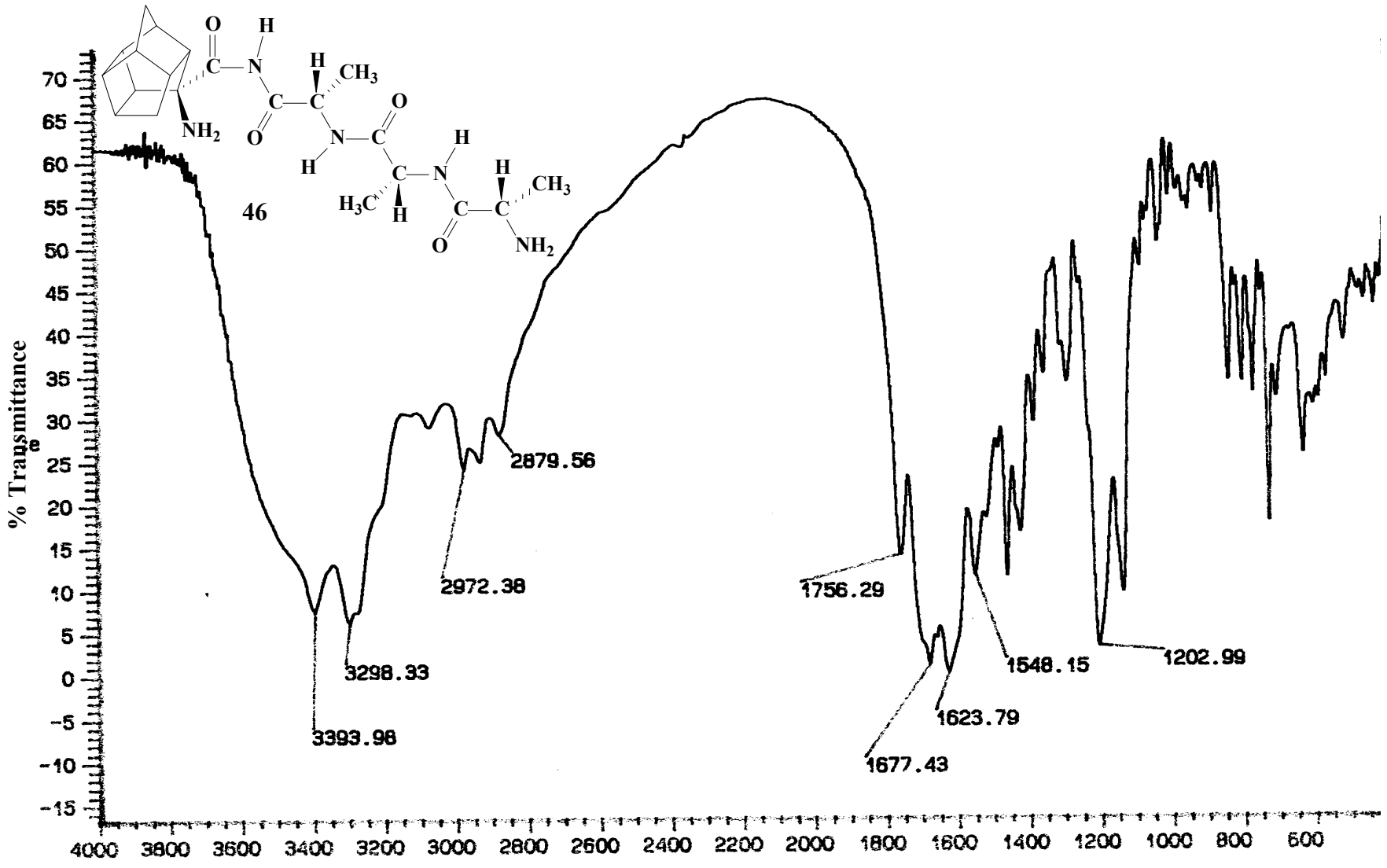
47



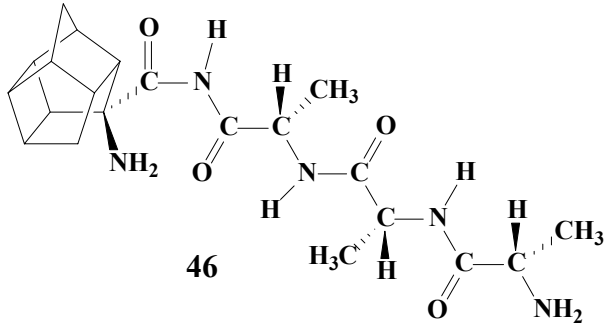
Chromatogram 35: HPLC chromatogram of penta-peptide (47) from an 80 % ($^{v}/_{v}$) acetonitrile/20 % ($^{v}/_{v}$) water/0.1 % ($^{v}/_{v}$) trifluoroacetic acid (solution A) and 100 % water (solution B) gradient system: 80 % solution A and 20 % solution B was changed linearly to 40 % solution A and 60 % solution B at 1.00 ml min^{-1} over 50 minutes.



Chromatogram 36: HPLC chromatogram of tri-peptide from an 80 % ($^{v}/_{v}$) acetonitrile/20 % ($^{v}/_{v}$) water/0.1 % ($^{v}/_{v}$) trifluoroacetic acid (solution A) and 100 % water (solution B) gradient system: 80 % solution A and 20 % solution B was changed linearly to 40 % solution A and 60 % solution B at 1.00 ml min^{-1} over 50 minutes.

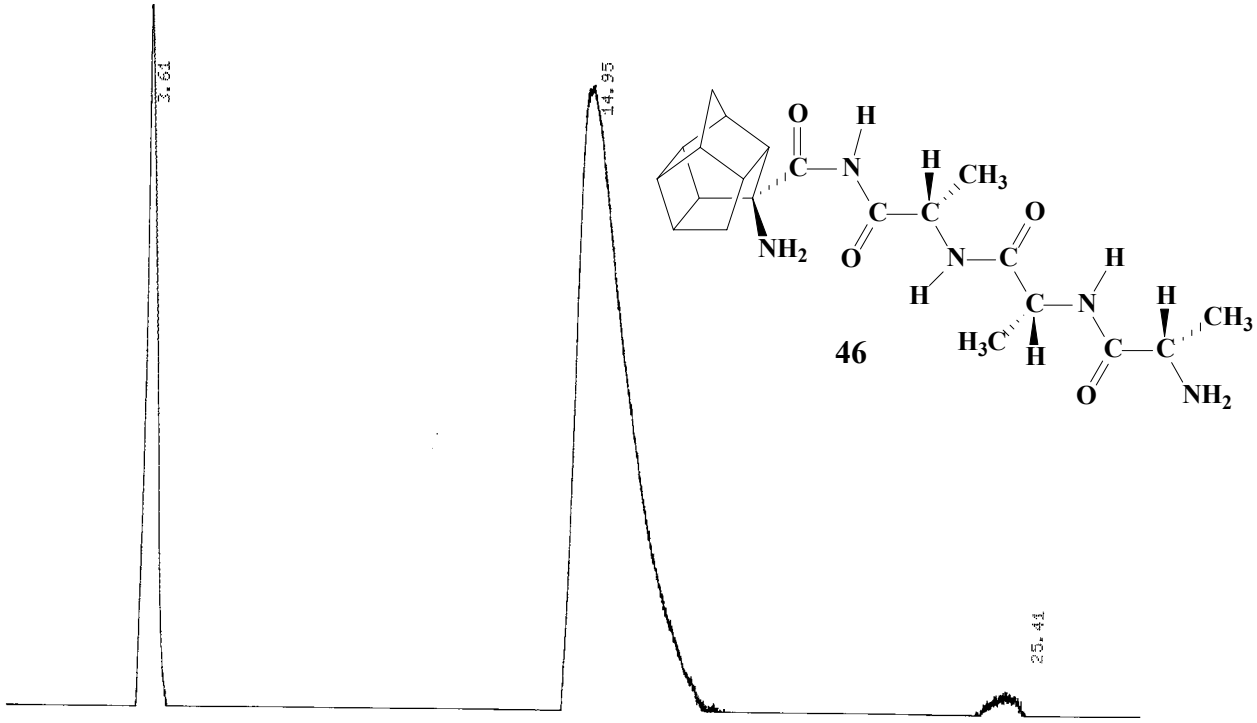


Spectrum 37: Infrared spectrum (KBr) of tetra-peptide (46)

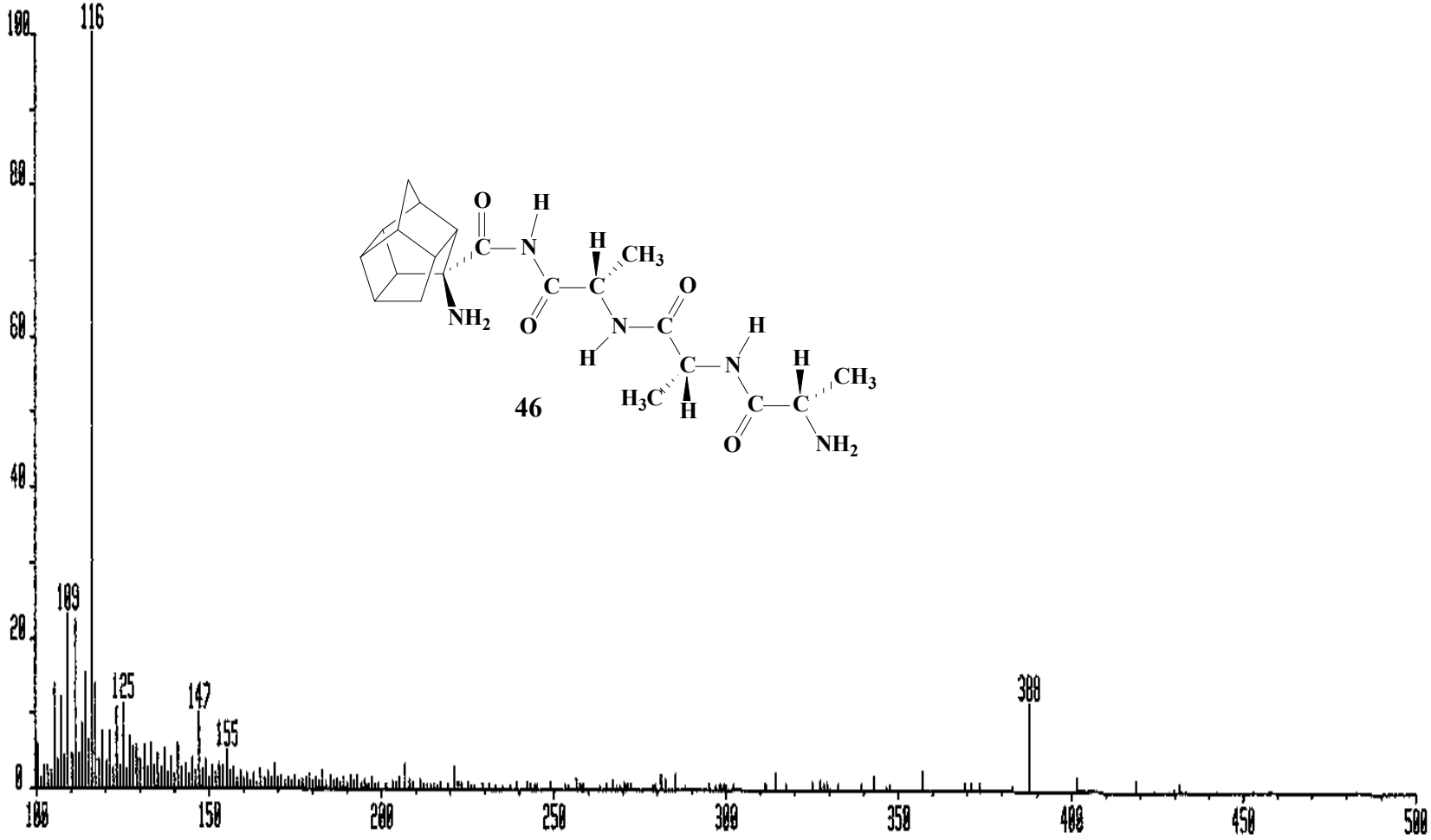


46

Spectrum 38: ^{1}H NMR spectrum of tetra-peptide (46) DMSO

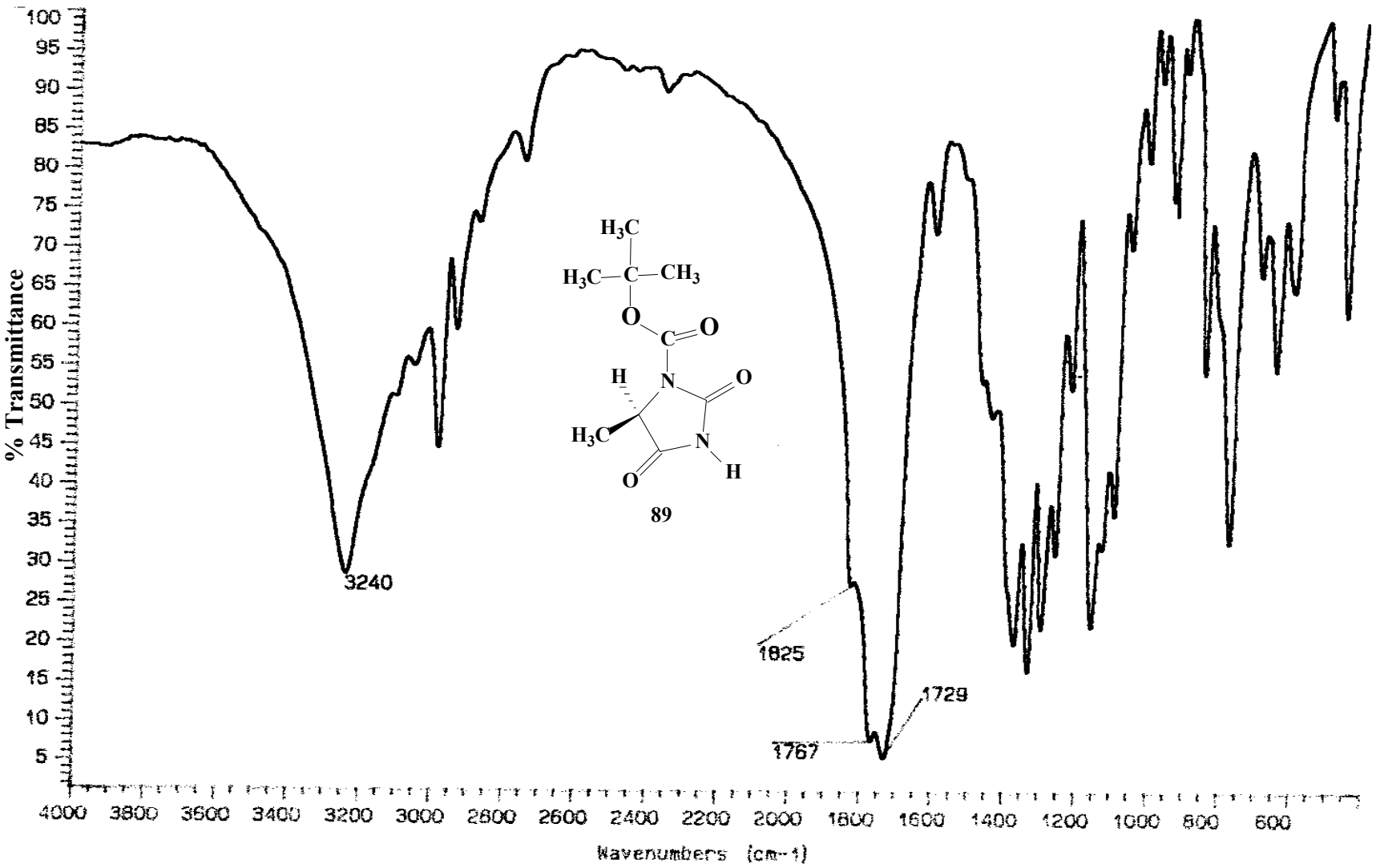


Chromatogram 39: HPLC chromatogram of tetra-peptide (46) from an 80 % ($^{v}/_{v}$) acetonitrile/20 % ($^{v}/_{v}$) water/0.1 % ($^{v}/_{v}$) trifluoroacetic acid (solution A) and 100 % water (solution B) gradient system: 80 % solution A and 20 % solution B was changed linearly to 40 % solution A and 60 % solution B at 1.00 ml min^{-1} over 50 minutes.

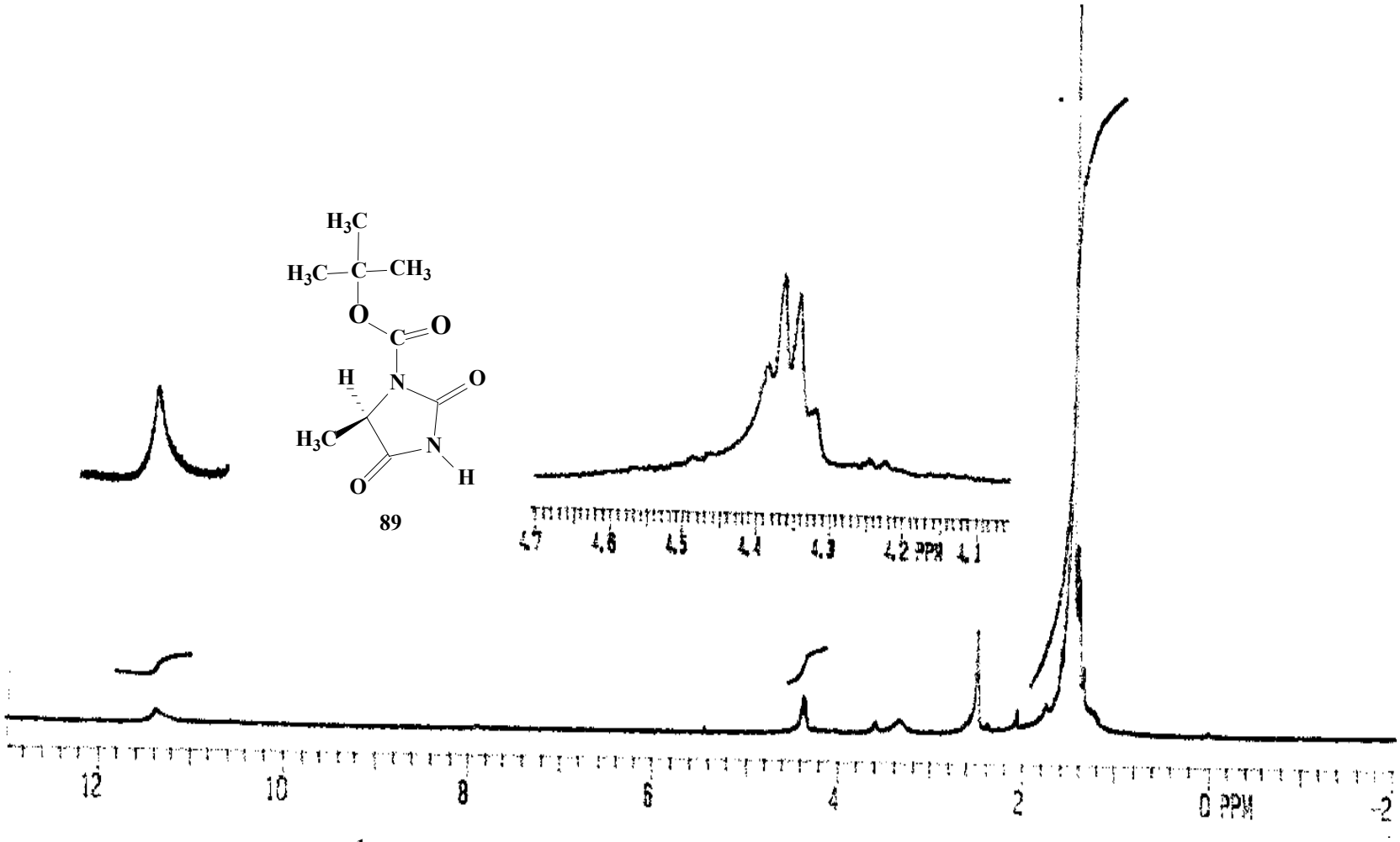


46

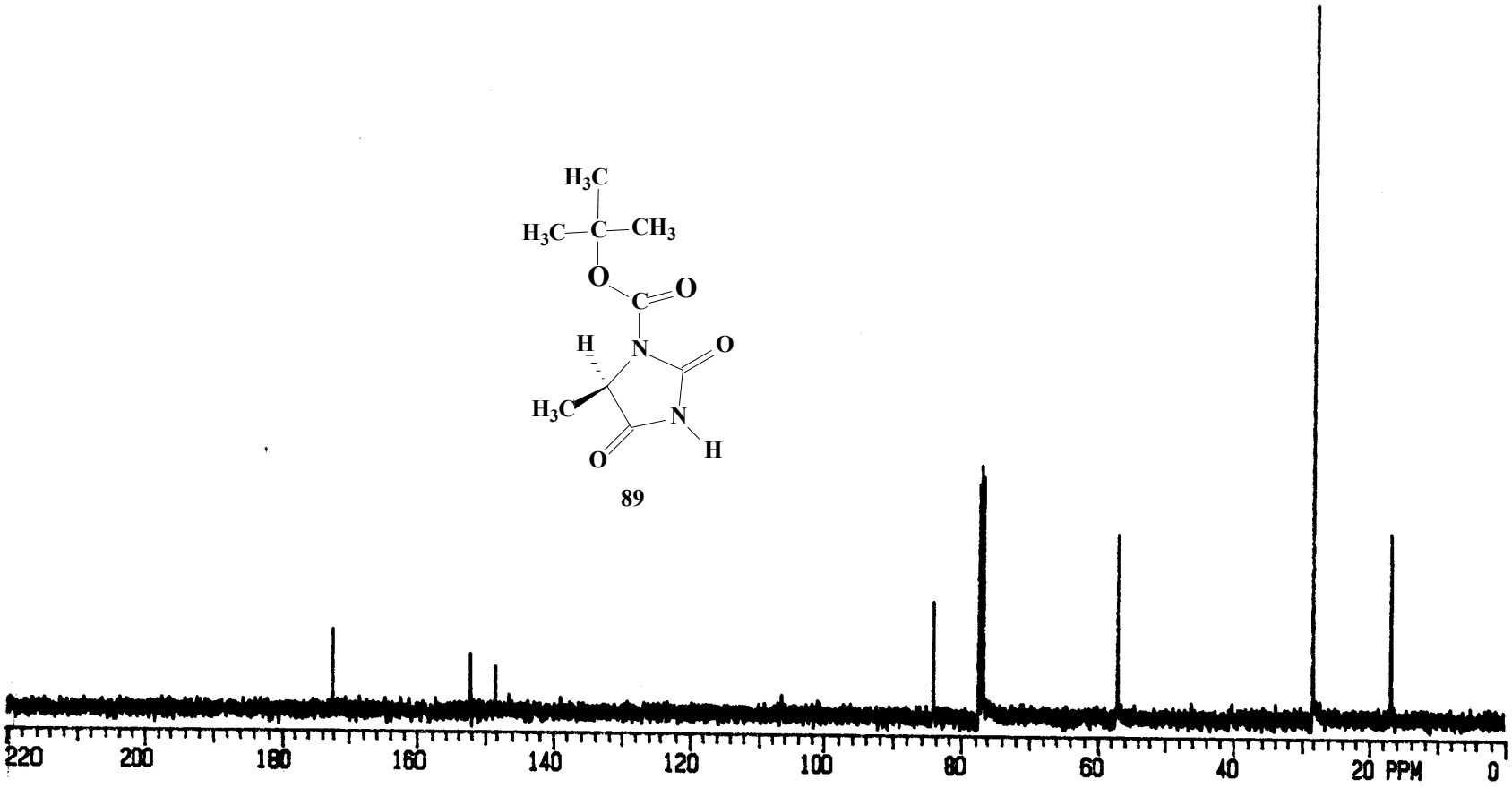
Spectrum 40: Mass spectrum (MS-TOF) of tetra-peptide (46)



Spectrum 41: Infrared spectrum (KBr) of mono-Boc 5-methylhydantoin (89)

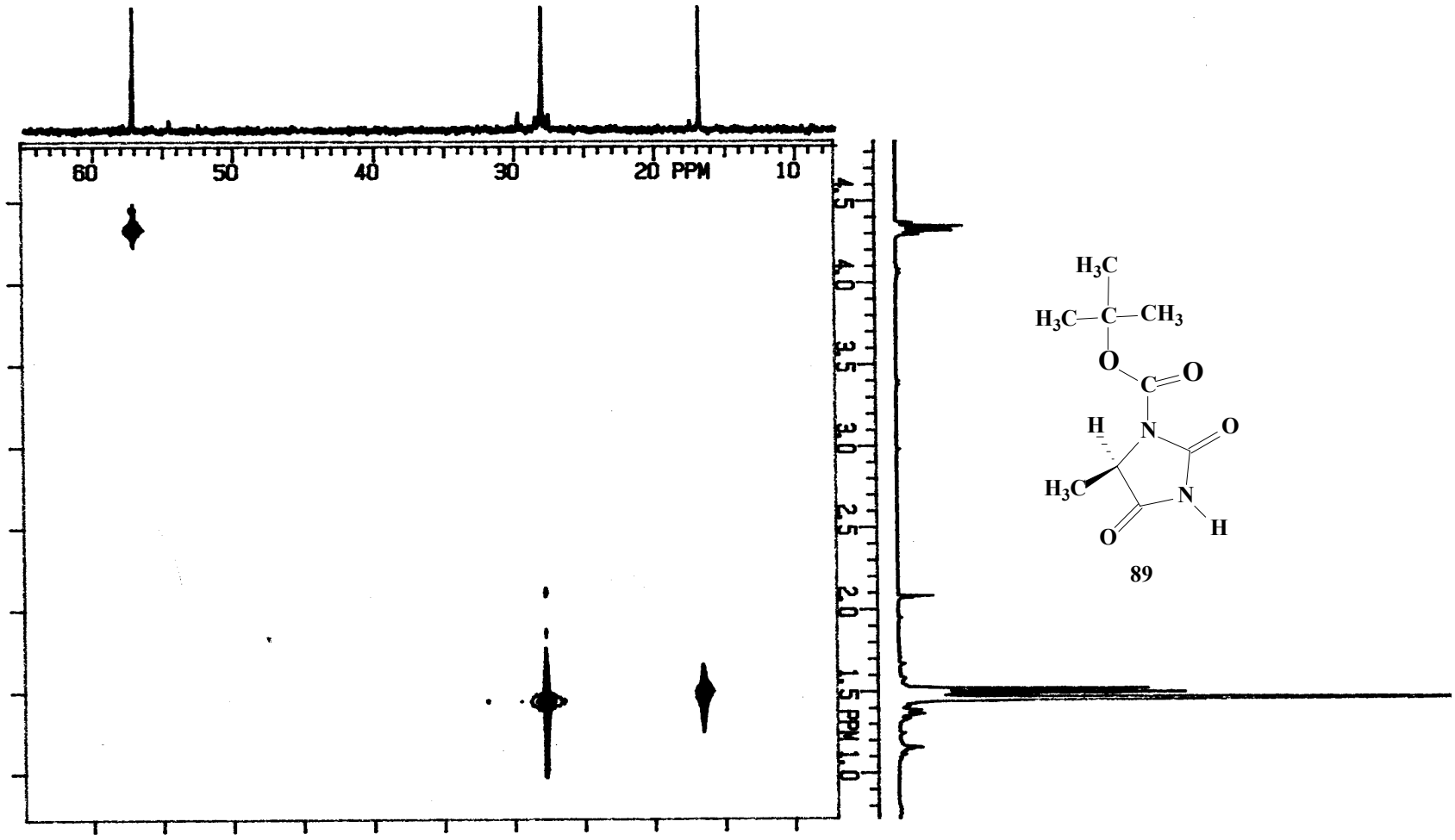


Spectrum 42: ^{1}H NMR spectrum of mono-Boc 5-methylhydantoin (89) in DMSO

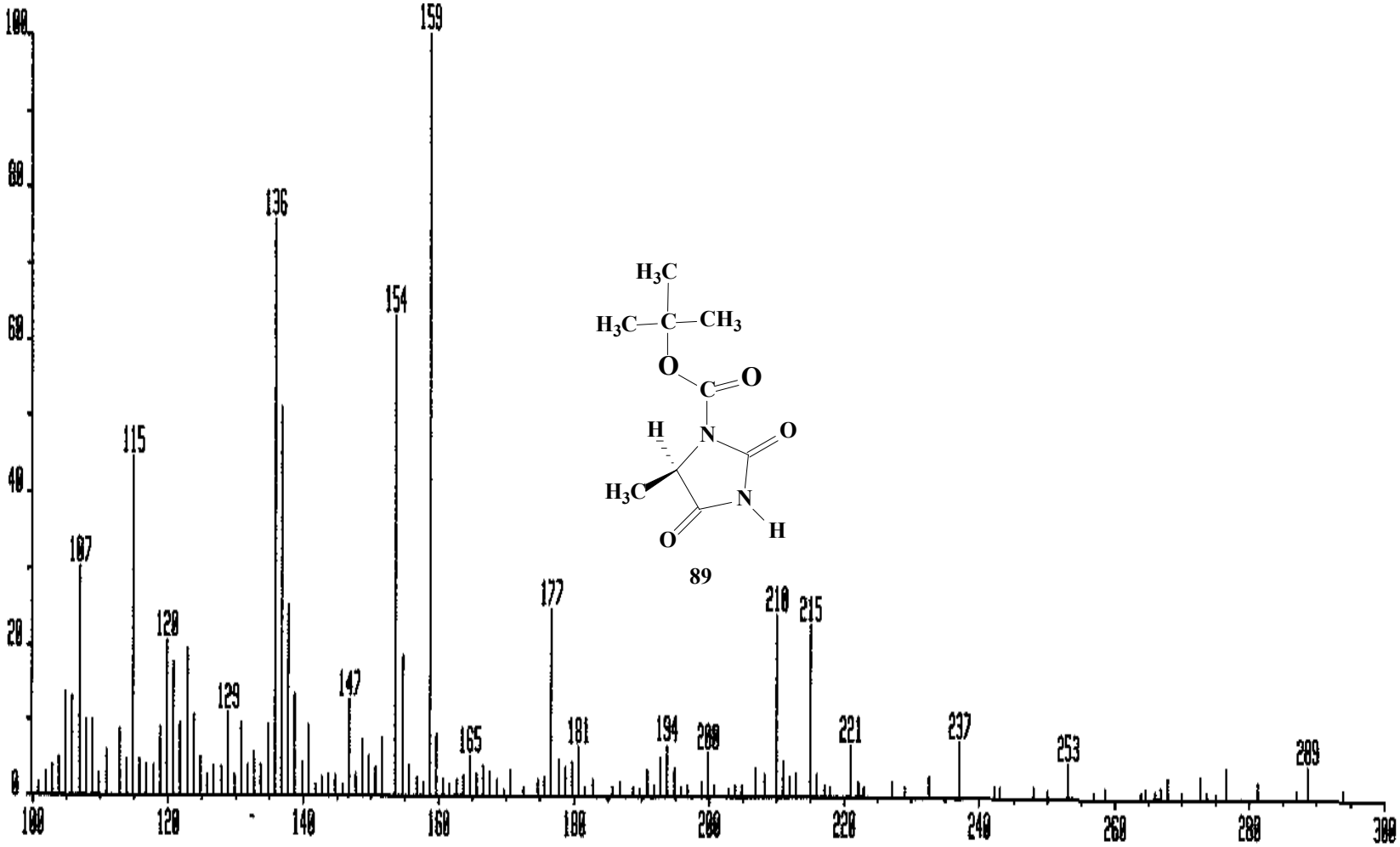


89

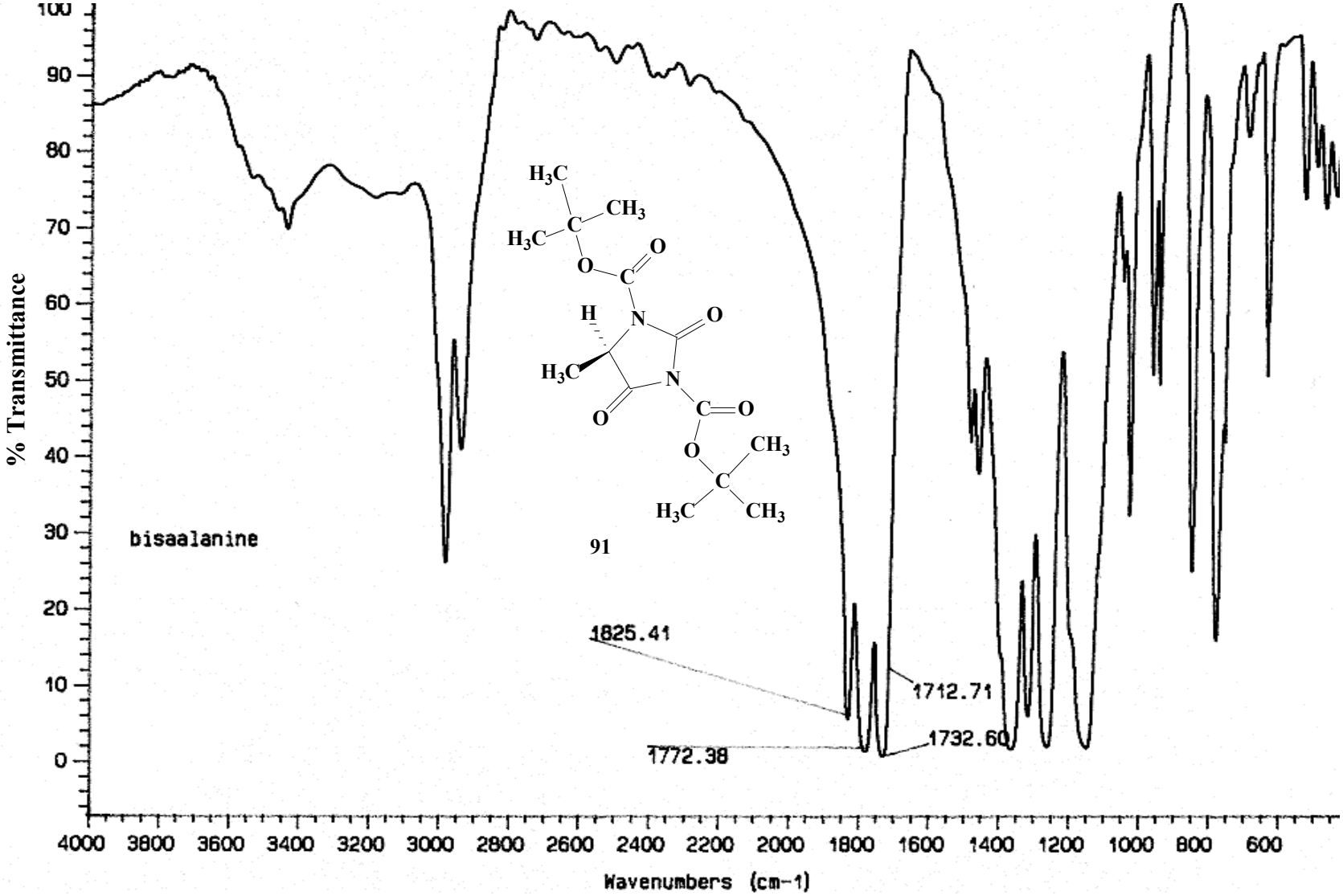
Spectrum 43: ^{13}C NMR spectrum of the mono-Boc-5-methylhydantoin (89) in $CDCl_3$



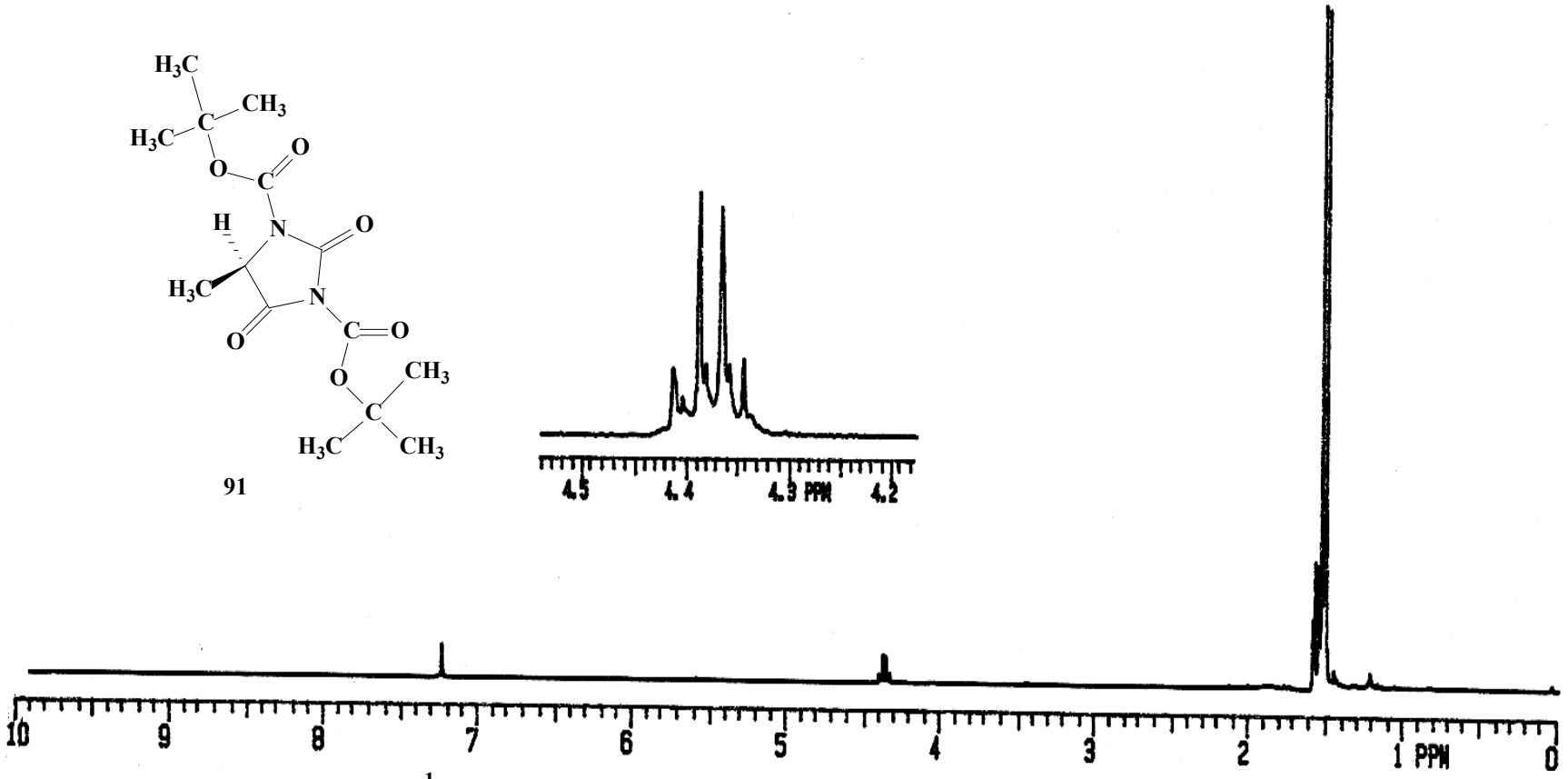
Spectrum 44: HETCOR spectrum of the mono-Boc-5-methylhydantoin (89) in $CDCl_3$



Spectrum 45: Mass spectrum (FAB) of Mono-Boc-5-methylhydantoin (89)

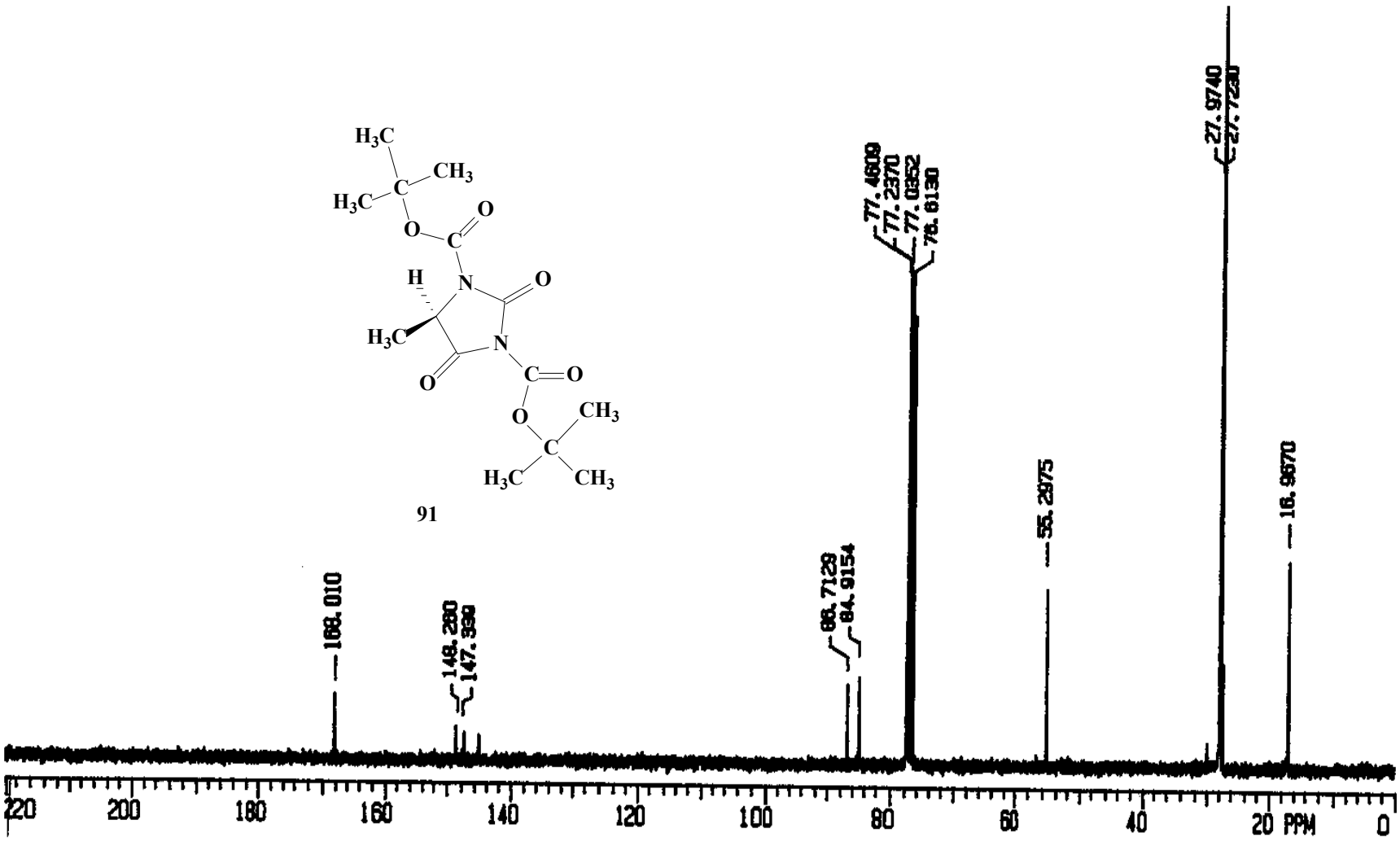


Spectrum 46: Infrared spectrum (KBr) of bis-Boc-5-methylhydantoin (91)

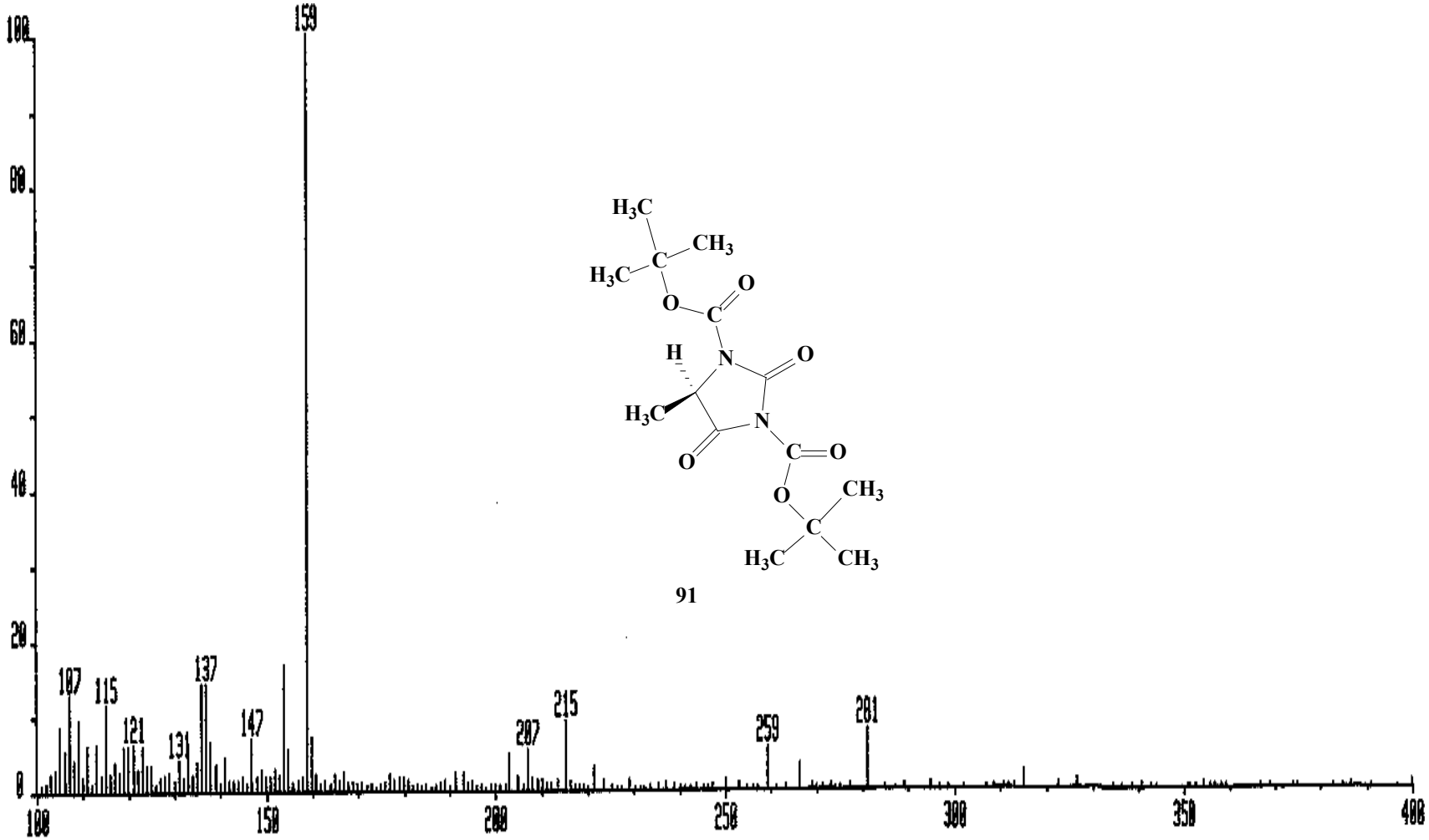


91

Spectrum 47: ^{1}H NMR spectrum of bis-Boc-5-methylhydantoin (91) in $CDCl_3$

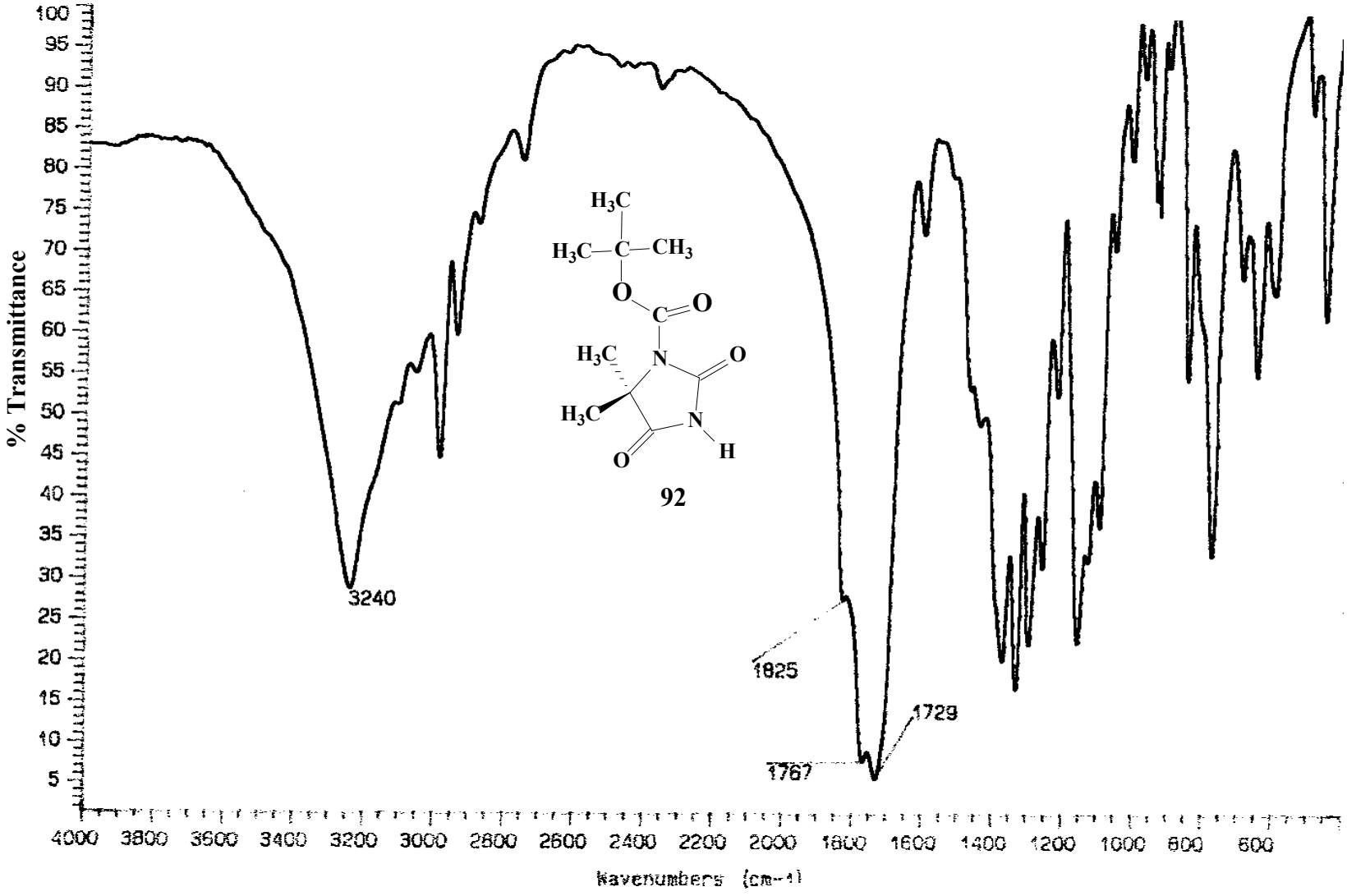


Spectrum 48: ^{13}C NMR spectrum of bis-Boc-5-methylhydantoin (91) in $CDCl_3$

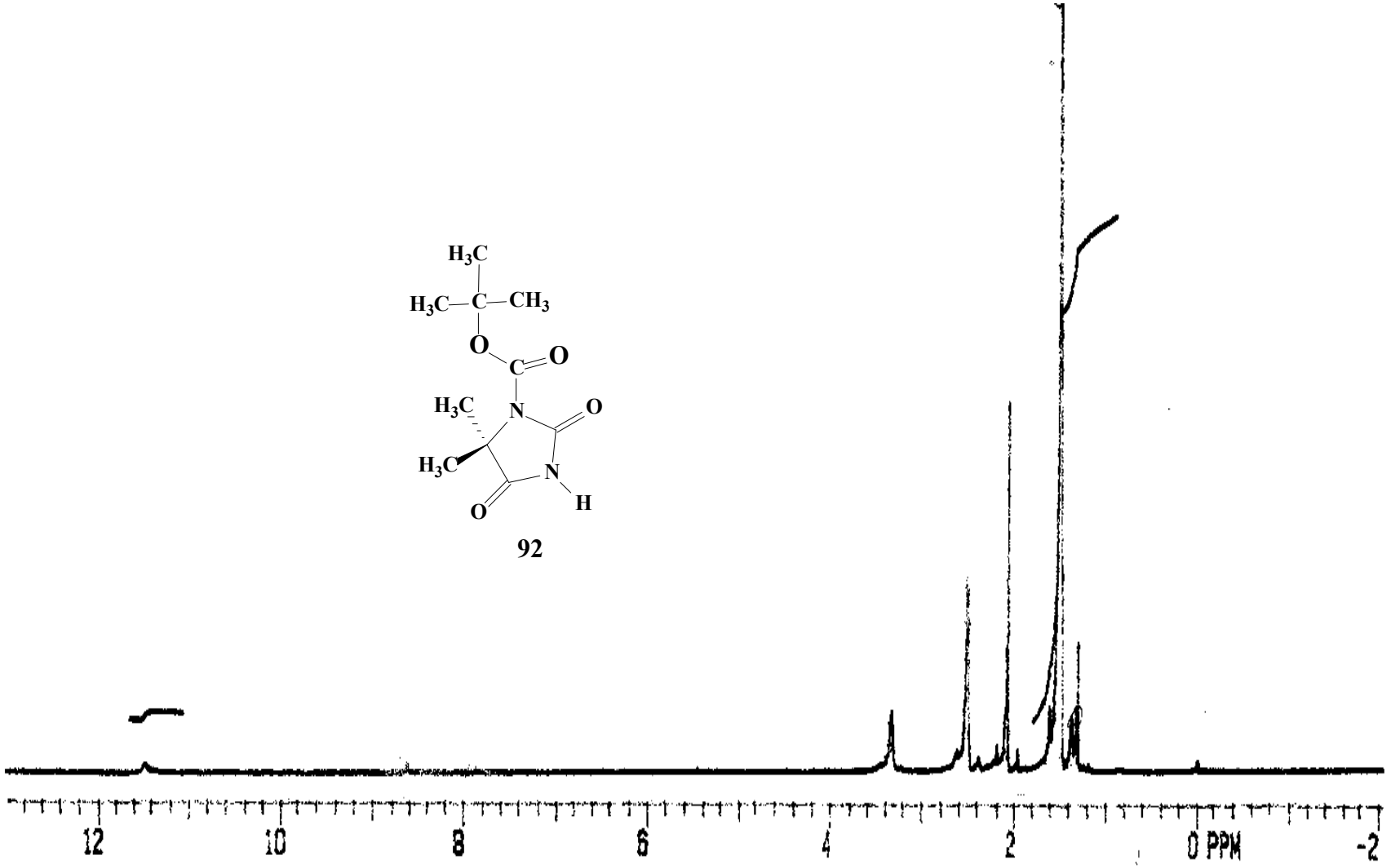


91

Spectrum 49: Mass spectrum (MS-TOF) of bis-Boc-5-methylhydantoin (91)

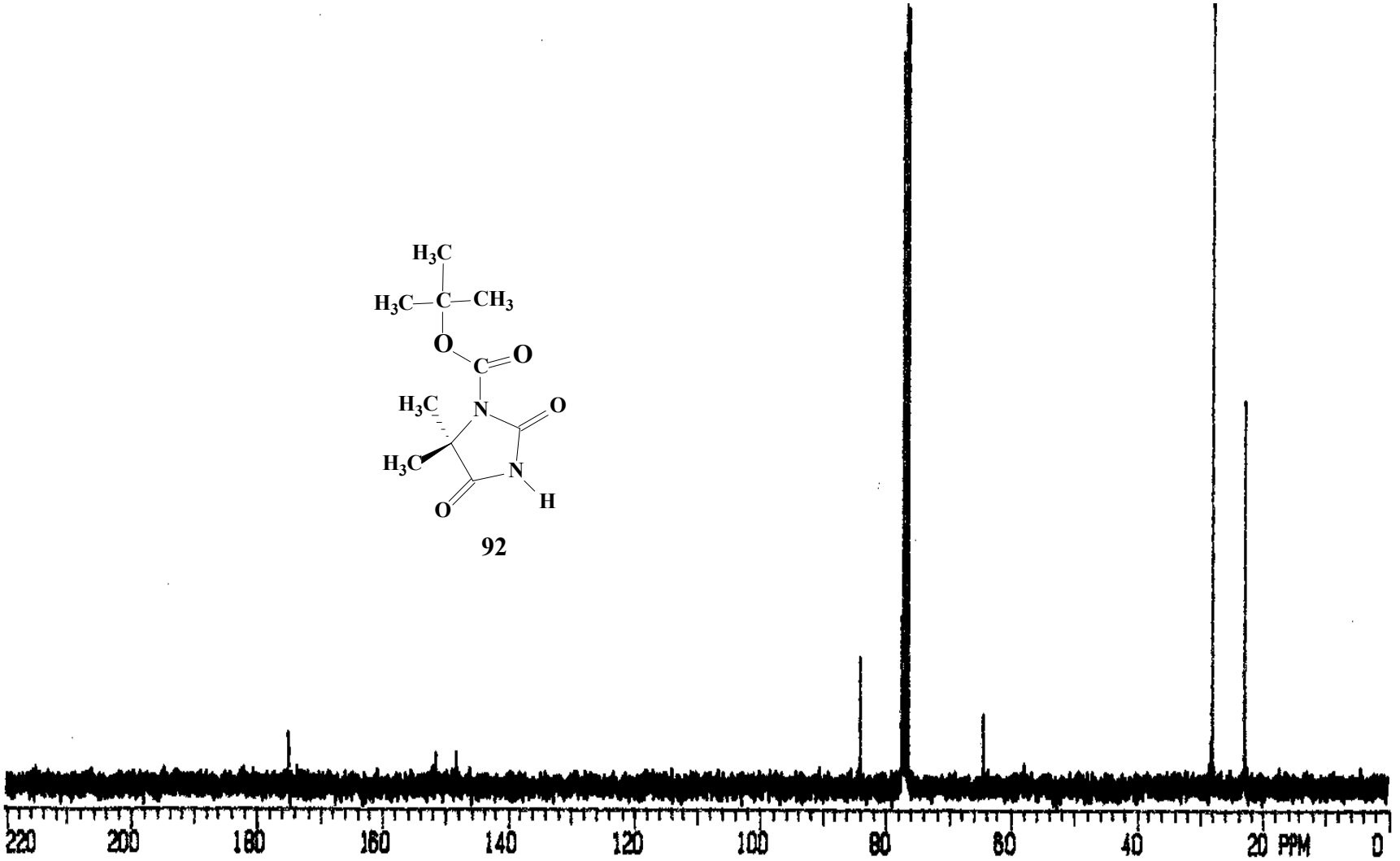


Spectrum 50: Infrared spectrum (KBr) of mono-Boc-5.5-dimethylhydantoin (92)



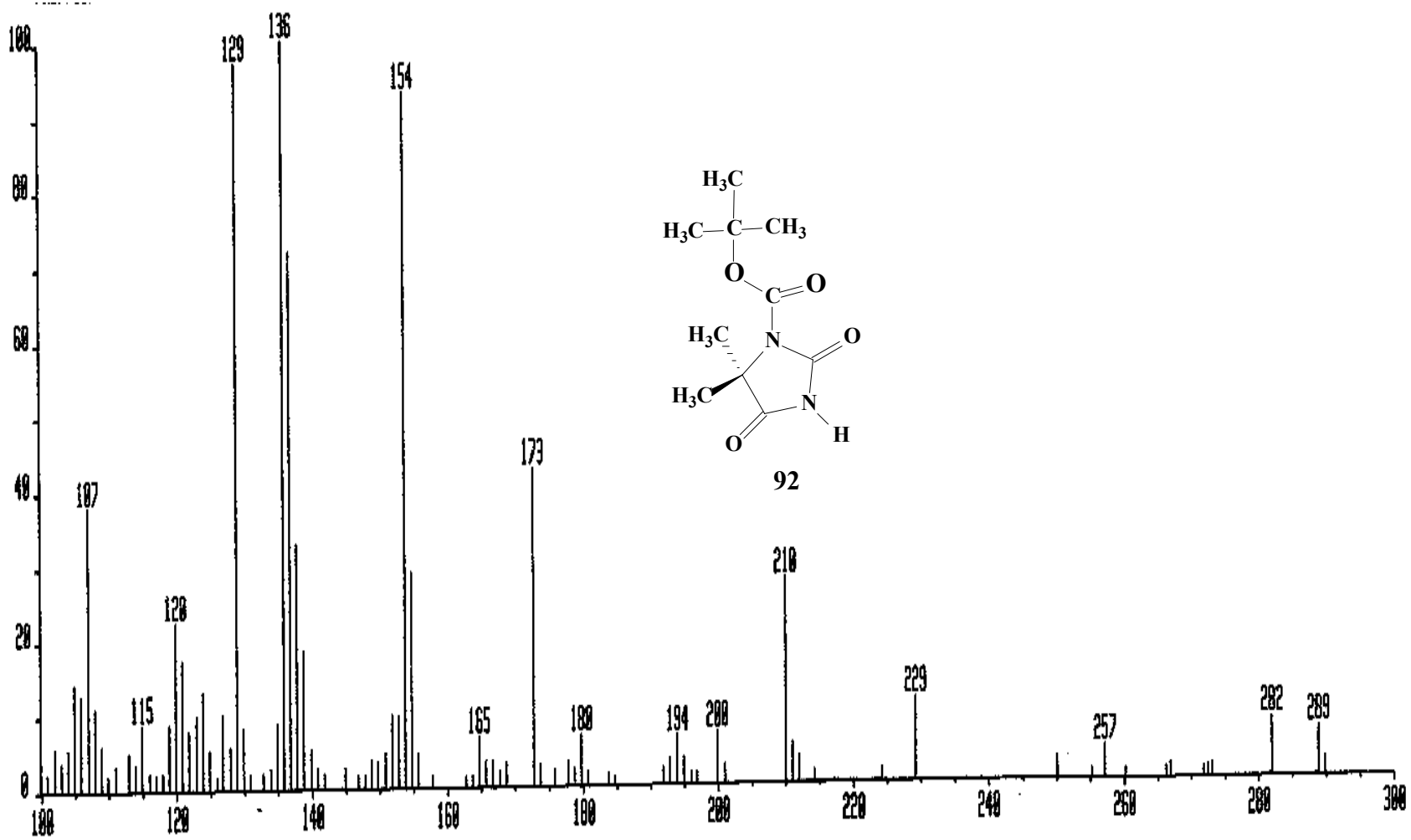
92

Spectrum 51: ^{1}H NMR spectrum of mono-Boc-5.5-dimethylhydantoin (92) in $(CD_3)_2SO$



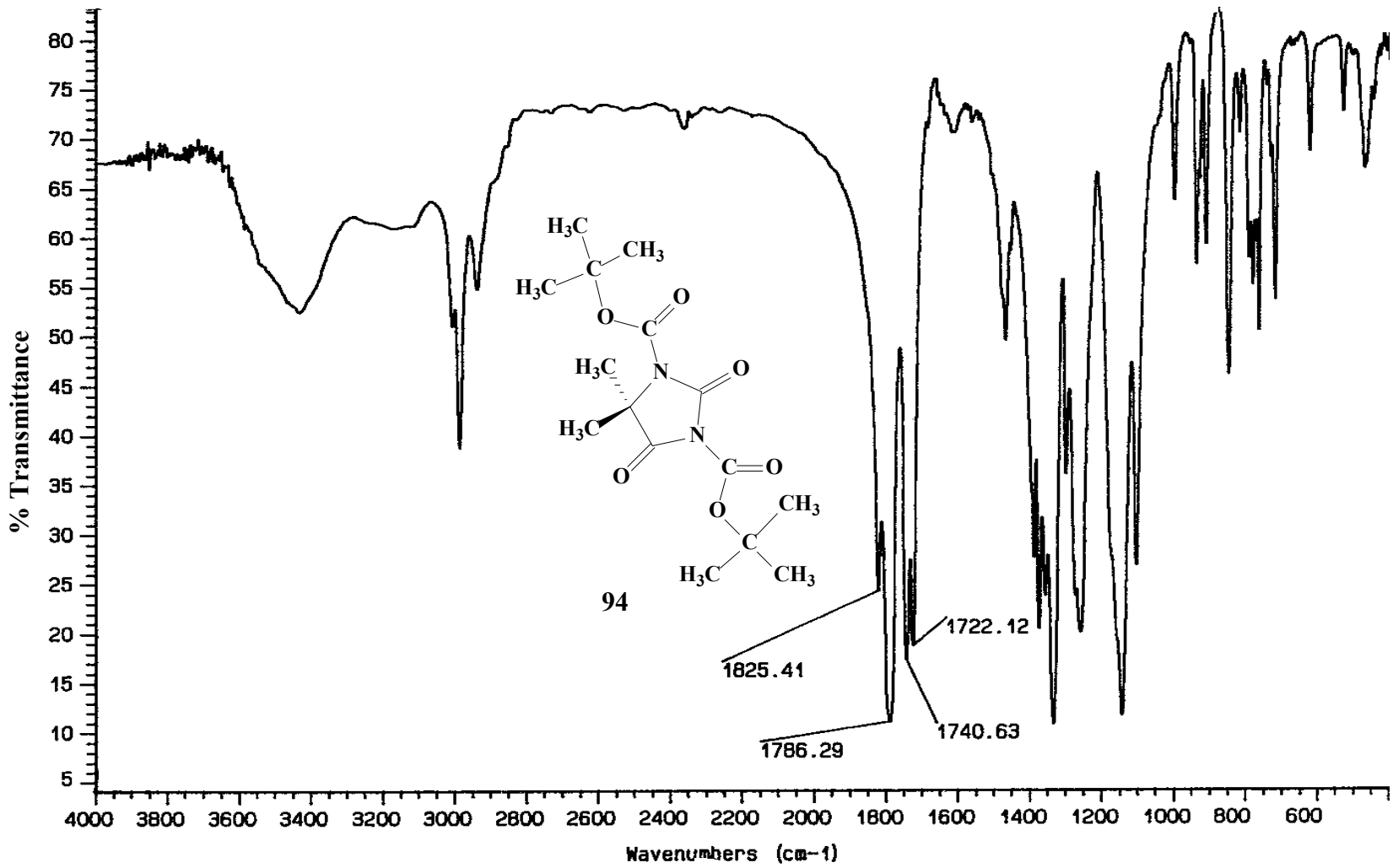
92

Spectrum 52: ^{13}C NMR spectrum of mono-Boc-5.5-dimethylhydantoin (92) in $CDCl_3$

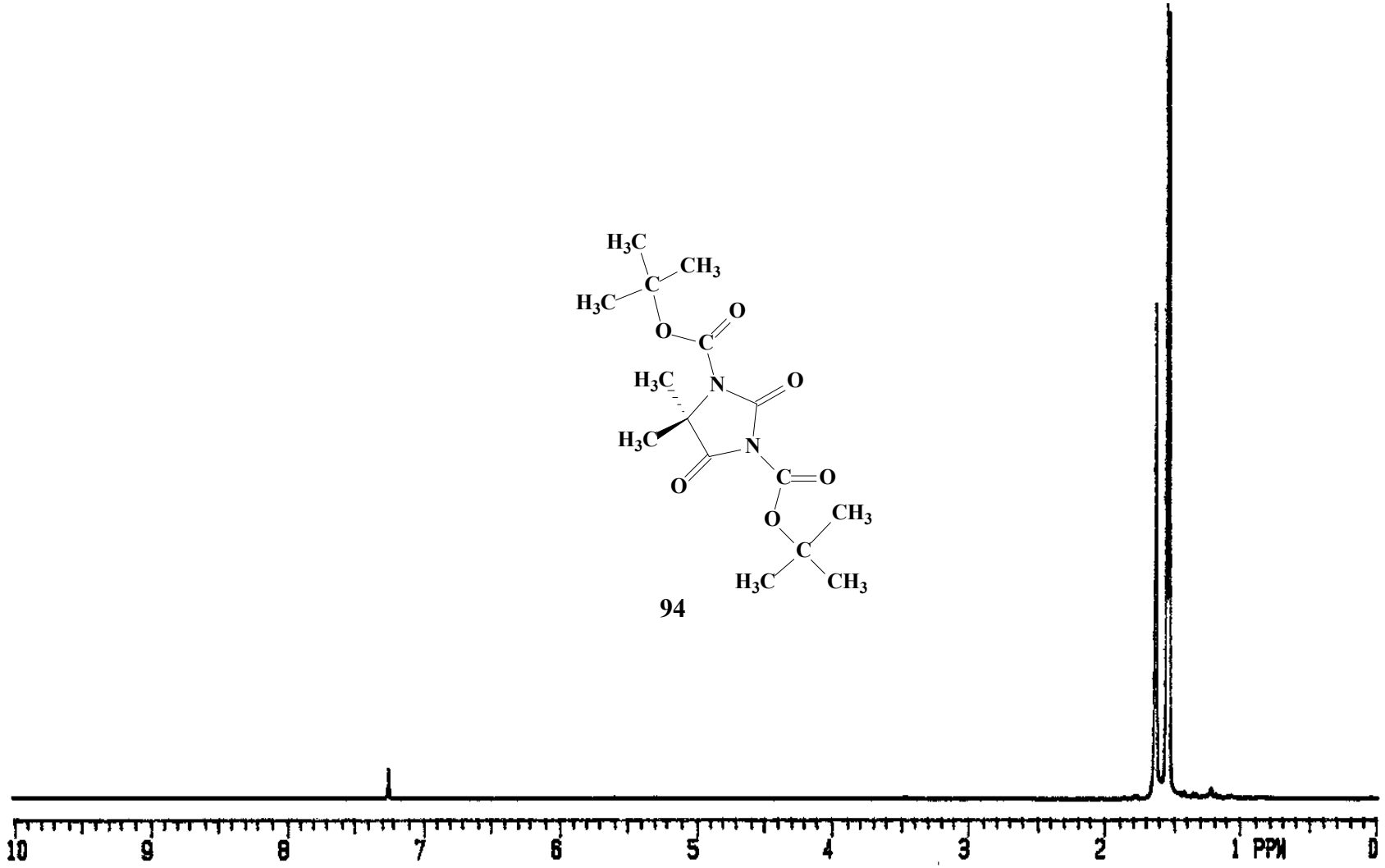


92

Spectrum 53: Mass spectrum (MS-TOF) of mono-Boc-5.5-dimethylhydantoin (92)

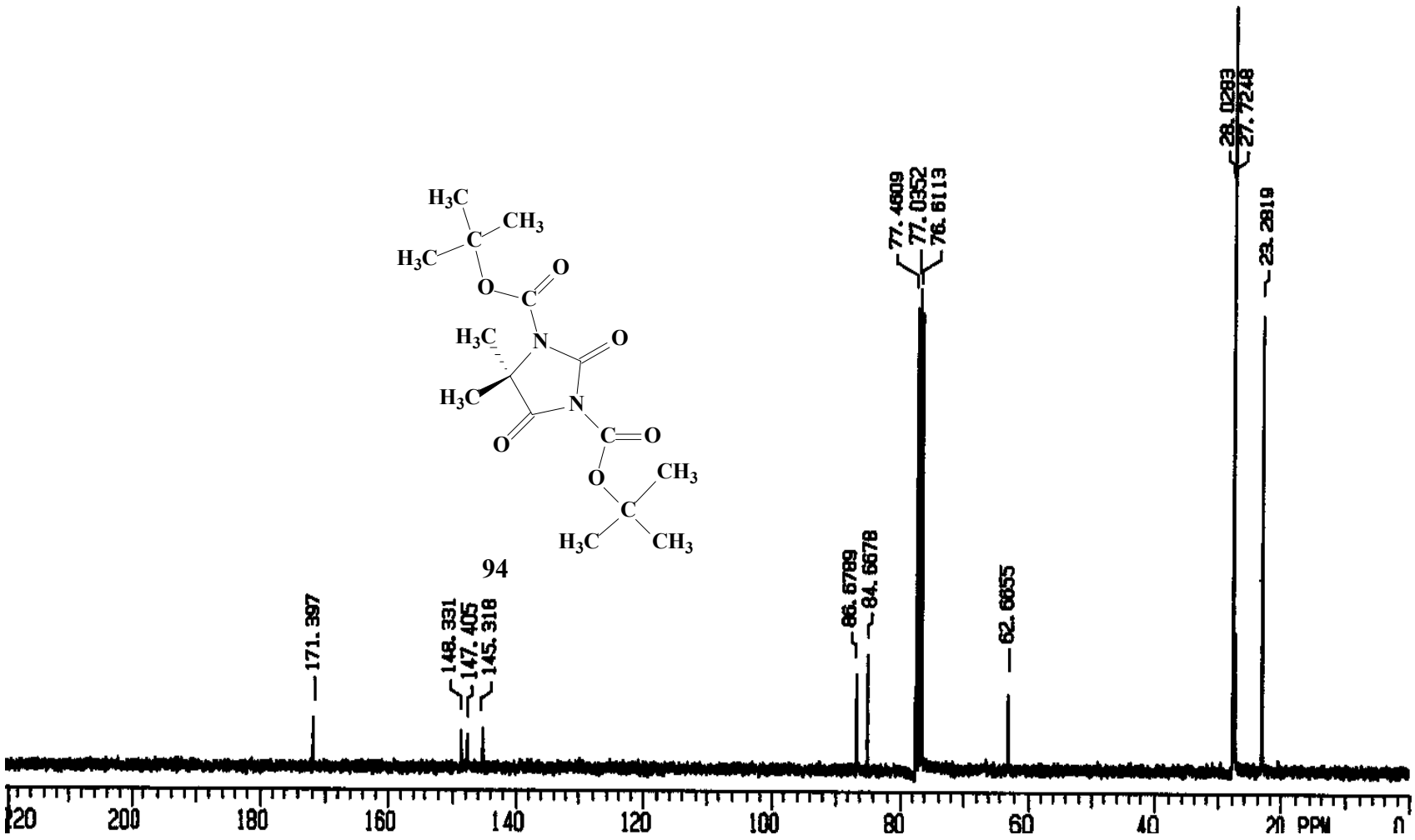


Spectrum 54: Infrared spectrum (KBr) of the bis-Boc-5.5-dimethylhydantoin (94)

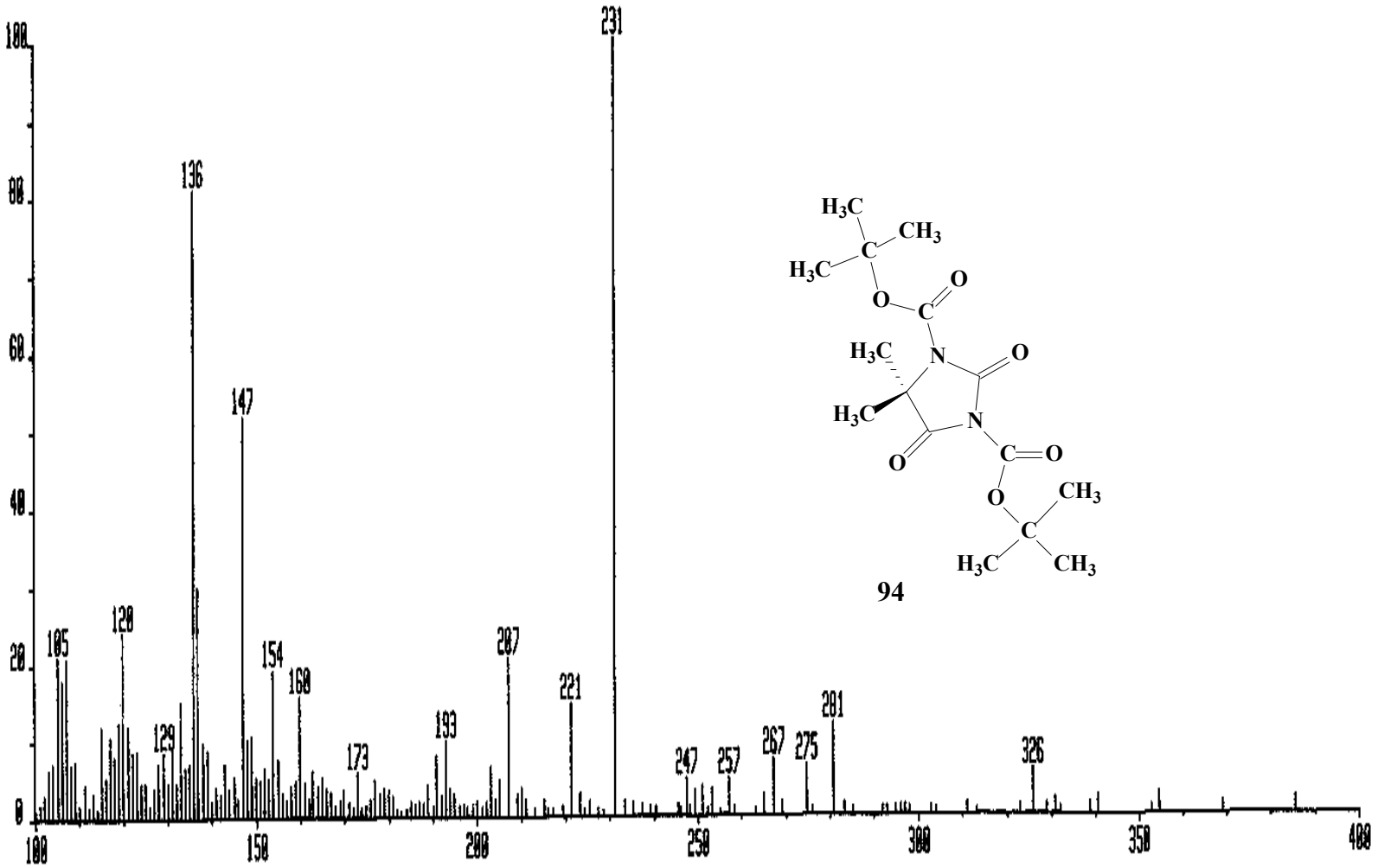


94

Spectrum 55: ^{1}H NMR spectrum of bis-Boc-5.5-dimethylhydantoin (94) in $CDCl_3$



Spectrum 56: ^{13}C NMR spectrum of bis-Boc-5.5-dimethylhydantoin (94) in $CDCl_3$



Spectrum 57: Mass spectrum (FAB) of bis-Boc-5.5-dimethylhydantoin (94)

APPENDIX 2
Cartesian Co-ordinates for all optimized structures

(S)-PCU hydantoin [(S)-11]

#P B3LYP/6-31+G(D) OPT

(HF = -763.7927321a.u.)

0,1
C,-0.1165553282,-0.7388577539,1.8115187816
C,-0.197621714,0.8196621686,1.7646839219
C,-0.1996762651,1.256505886,0.2531869722
C,-0.4586960416,-0.0833259343,-0.4856940932
C,0.4248110756,-1.0331357074,0.3747467488
C,1.9493241827,-0.586526467,0.4905731265
C,2.0484412686,-0.1122660606,1.9741210046
C,1.3011095216,1.2516794639,1.8848990132
C,1.308346502,1.680638841,0.3775863278
C,2.2744823277,0.6982906453,-0.2894295301
C,1.0746278373,-1.0142070841,2.7377992939
N,-1.8853986339,-0.4476972143,-0.357241618
C,-0.3138375869,-0.128462863,-2.0319343602
N,-1.5833779521,-0.3266527502,-2.5337686635
C,-2.5667954555,-0.4786017203,-1.5437582751
H,-1.0466708027,-1.2566860295,2.0619260746
H,-0.9279477999,1.2764960251,2.4382377977
H,-0.8927495103,2.0480893379,-0.0452354115
H,0.3196563713,-2.0789291028,0.0719934428
H,2.6143689619,-1.4229343545,0.2553368574
H,3.0737683882,-0.0554583761,2.3518592822
H,1.5664122495,1.9890773707,2.6468739193
H,1.4927636737,2.7348149605,0.153909708
H,3.3102547083,0.9978236701,-0.0760122416
H,2.1562490443,0.6110266651,-1.3680501968
H,0.8935706498,-0.6899668028,3.7704807821
H,1.3758806219,-2.0691313461,2.750906579
O,0.6832033088,-0.0266847547,-2.722822504
O,-3.7615354786,-0.6186824084,-1.7339414132
H,-2.4093173657,-0.2874661019,0.491851679
H,-1.7859076735,-0.4017293443,-3.5226885559

(R)-PCU hydantoin [(R)-11]

#P B3LYP/6-31+G(D) OPT

(HF = -763.7949808a.u.)

0,1
C,-0.0511857821,-0.6975974632,1.8053759173
C,-0.0778838046,0.8607107003,1.7746344811
C,0.3842080178,-0.9982386811,0.3401677651
C,-0.4686481044,0.0038928078,-0.4913204087
C,-0.1661168086,1.3124777822,0.2788293603
C,1.9315526476,-0.6063325684,0.3546987809
C,2.1447780182,-0.1481047231,1.8311972673
C,1.4401052987,1.2415037059,1.8032413736
C,1.3603981094,1.6909129005,0.3039296585
C,2.2584942385,0.684255772,-0.4231807154
C,1.1883828971,-1.0232944637,2.6478358719
C,-1.9881862673,-0.3109721788,-0.437024194
N,-2.3877073092,-0.5390813786,-1.7354126131
C,-1.3482089264,-0.3932834281,-2.6697750558
N,-0.2572441815,0.003728192,-1.9426022046
O,-2.712681643,-0.3340505724,0.5404163488
O,-1.432915454,-0.5809822958,-3.8700806489
H,-0.9913777052,-1.1605596208,2.1032237014
H,-0.7549379184,1.3255085127,2.4937137303
H,0.2311554074,-2.0371606983,0.0308947477
H,-0.8469187277,2.131303189,0.0329535517
H,2.554221507,-1.4606536999,0.0711663182
H,3.1949826944,-0.1316902034,2.1386256877
H,1.7853879945,1.9614763419,2.5496752197
H,1.5686906485,2.7399411122,0.0777451116
H,3.3129735956,0.943367868,-0.2573840657
H,2.1270446591,0.6450398677,-1.5080436642
H,1.088006227,-0.6994567471,3.6915225693
H,1.4556115763,-2.0877115423,2.6381118748
H,0.6475165532,-0.0438158922,-2.3842090765
H,-3.3390565055,-0.7534342088,-2.0062381946

Mono-Boc PCU hydantoin (28)

#P B3LYP/6-31+G(D) OPT

(HF = -1109.6186101a.u.)

0,1
C,2.548184088,-1.2136255677,-0.2475520649
C,2.822761923,-0.6537480441,1.1816694777
C,2.0275804796,0.0719587521,-0.9559434365
C,1.0801999033,0.7017432883,0.1087715778
C,2.0140696808,0.6765330411,1.3427942644
C,3.3638993132,0.924329401,-1.1484986107
C,4.4463607567,-0.0123608063,-0.5258591332
C,4.1413669536,0.1679259429,0.9913514554
C,3.3367458221,1.5041359619,1.1469356459
C,3.457080308,2.1608272774,-0.2323012929
C,3.9506591153,-1.4295624208,-0.8298816019
C,-0.1742290301,-0.1635266575,0.3745953638
N,-1.284730052,0.5993726132,0.0034889994
C,-0.905795339,1.9065913424,-0.4201700285
N,0.4514977324,1.9736738816,-0.2465410321
O,-0.2086093272,-1.2705567823,0.8687840283
O,-1.6444290085,2.7561228832,-0.8699948706
C,-2.6548402455,0.2141561704,0.1929572759
O,-3.4426663867,0.9114551299,0.7831486877
H,1.8617391683,-2.059529425,-0.2788890931
H,2.7673395253,-1.3903113796,1.9852344031
H,1.5229269975,-0.1140648167,-1.9095213889
H,1.4920361972,0.8444436039,2.2878661464
H,3.5376792315,1.1452955721,-2.2062984711
H,5.4683353407,0.2356900583,-0.8287579785
H,4.979195965,-0.022323586,1.6670958202
H,3.590970042,2.153557815,1.9886401397
H,4.4531904836,2.6107273306,-0.3414597443
H,2.7426071754,2.9659756733,-0.4240442777
H,4.5134827056,-2.2088014369,-0.3004869588
H,3.9465209146,-1.6698501763,-1.900702666
H,0.9327746353,2.7067785214,-0.7449730051
O,-2.8546012159,-0.967801601,-0.3768876047
C,-4.1410321091,-1.7013718509,-0.2145772346
C,-4.4038759964,-1.9558377129,1.272212337
C,-3.8602219246,-3.0102338821,-0.9547437475
C,-5.2661548724,-0.9127582449,-0.8896023646
H,-3.542799142,-2.4510191836,1.7338146183
H,-5.2727626355,-2.6164784954,1.3727452783

H,-4.6125691668,-1.0289777889,1.8109551611
H,-5.459466085,0.0317171182,-0.376695628
H,-6.1839569263,-1.5121904176,-0.8738253484
H,-5.0154709685,-0.7029973316,-1.935384417
H,-3.6182309311,-2.8175913783,-2.0053529291
H,-4.7451922515,-3.6547130698,-0.9154215729
H,-3.0198294903,-3.5414756521,-0.4965230806

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,S)-TS-bot-N-1']

#P B3LYP/6-31+G(D)

(HF=-797.7499694a.u.)

0,1
O,-0.0239072321,-0.1845717638,3.9125928805
C,0.1836734561,-0.1384420387,2.7207006185
C,-0.8478254241,-0.279544729,1.5978045798
H,-1.574931956,0.529658928,1.7120528636
N,1.4100699757,0.0243977832,2.100600785
N,-0.0531200568,-0.0649154896,0.3477343562
C,1.3565924716,0.0013970124,0.7146988668
O,2.2791068715,0.0233482667,-0.0524291898
H,-0.2000809722,-0.8245832861,-0.4662716585
H,2.2892621523,0.1003251455,2.6002818911
O,-0.2922940961,-1.4847954019,-1.7492723549
C,0.0456942818,-0.5651908099,-2.5602101322
C,0.4578443668,-0.9456196041,-3.9653200464
H,0.3131053471,-0.110897199,-4.6549390573
H,1.524386297,-1.2020172799,-3.9535007876
H,-0.0979474802,-1.8264270376,-4.2979471443
O,0.0863663258,0.6724868334,-2.2514743248
C,-0.5065668704,1.3751318941,-0.5150760925
C,-1.9807084352,1.3038054802,-0.821722107
H,-2.3118828481,0.2906422912,-1.0542691531
H,-2.5519345492,1.7063444362,0.0227957936
H,-2.1539238488,1.9463433668,-1.6879659059
O,0.1478321815,2.3347968689,-0.2506439492
C,-1.5586514111,-1.6356060507,1.6339953638
H,-0.8469003881,-2.4585425127,1.509849424
H,-2.0628812483,-1.7511637191,2.5978580155
H,-2.3020669557,-1.7017645408,0.8342989311

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,R)-TS-bot-N- 1']

#P B3LYP/6-31+G(D) OPT=(TS,NOEIGENTEST,GDIIS)

(HF = -797.7390516a.u.)

0,1
C,0.4678811881,-1.3838480372,-0.0213867427
N,0.0765950396,-0.0260097872,0.5113072157
H,-1.0202367296,0.0897667446,0.2325170431
C,0.4045842765,1.6171748556,-0.209676279
O,-0.6016646796,1.0173574993,-1.9040055034
C,-1.8068172962,0.659504678,-1.6823926738
C,-2.8240173444,0.8463190955,-2.7873646641
O,-2.1985897399,0.173053363,-0.5743328261
H,-2.3390136223,0.8497628888,-3.7666018097
H,-3.3131501223,1.8181293667,-2.643879732
H,-3.5932620983,0.0711969812,-2.7376795539
C,0.3181539941,-0.0166009964,1.9405297064
O,0.1253205226,0.8957307154,2.7026343606
N,0.8218409763,-1.268451918,2.281196731
H,1.0446474825,-1.5078409051,3.2411465883
C,0.9332273019,-2.1467930108,1.220923841
H,-0.457024619,-1.8523107924,-0.3777345307
C,1.5122747763,-1.4711775636,-1.1345815961
H,1.1534237233,-0.9780336353,-2.0399024698
H,2.4745305011,-1.0461186064,-0.8340269264
H,1.6698200883,-2.5325921972,-1.3496888606
O,1.3354473734,-3.2889871694,1.2718496417
C,1.7676096261,1.7274489122,-0.8145817569
H,2.5152876749,1.5493057056,-0.0330965303
H,1.9116721441,1.0370373423,-1.6388803821
H,1.8689404229,2.7551386476,-1.174038447
O,-0.2657717378,2.4297984413,0.3170441991

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,R)-TS-bot-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -797.7448029 a.u.)

0,1
C,-0.8554847772,0.404481841,3.7801533356
C,-0.4375853962,-0.6406956847,2.7447771122

N,0.9940396595,-0.6975864143,2.4831373241
C,-0.9693882968,-0.333433451,1.3280798179
N,0.0944878466,-0.3235408851,0.4337431156
C,1.2780335791,-0.6265971458,1.136384947
H,-0.4710644065,1.3937389272,3.5089751201
H,-0.4716992137,0.1442436996,4.7732894449
H,-1.947847005,0.4546556924,3.8299337332
H,-0.8265271766,-1.6272931789,3.0384983989
O,-2.1402370481,-0.1397852923,1.0507351515
O,2.3843819014,-0.7761415525,0.6268303127
H,-0.1373705066,-1.0207456297,-0.8348602232
H,1.6635713687,-1.1321508877,3.1043571519
C,0.0838596038,1.5412503097,-0.778109352
C,1.5313749472,1.8509231824,-0.7799242475
C,-0.2620713803,-0.5531727437,-2.7210456863
C,-0.5331126891,-1.0052063978,-4.1298862804
O,-0.0073359277,0.6596191875,-2.4969639195
O,-0.3233333579,-1.4617244172,-1.8078232247
H,2.1367472805,0.9470906888,-0.8362612733
H,1.7550508521,2.3890501737,0.1472436594
H,1.7181949629,2.5005930136,-1.6415287136
H,-0.2210878414,-0.2425316969,-4.8448812898
H,-1.6105229987,-1.1790377071,-4.2378256819
H,-0.0221318073,-1.9522416869,-4.3248028129
O,-0.9383205169,2.0489346029,-0.5706381289

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,R)-TS-top-N-1']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -797.7584052 a.u.)

0,1
C,-0.8055448118,1.4472746699,0.9618225326
N,-0.1702400947,0.4013940034,0.1810615955
H,-0.8794696962,-0.3858616983,-0.1362207312
C,0.9241640707,-0.6028841706,1.1542562471
O,0.6693419811,-2.1573524478,-0.0830002921
C,-0.4745386261,-2.4740297212,-0.5630189001
C,-0.6246094222,-3.868039825,-1.1376316017
O,-1.4734369518,-1.6945519128,-0.5657134946
H,0.334540207,-4.2428842974,-1.5034222094
H,-1.3737356819,-3.8745562418,-1.9335141012
H,-0.9700737745,-4.5392423004,-0.3411376554
O,-1.5344942954,1.2711656141,1.9071271426

C,0.5748505656,1.0383298042,-0.9471937269
N,-0.4089518419,2.6558780577,0.4231842112
C,0.1826482611,-1.1815365602,2.3207751019
H,0.7377361035,-2.0674256505,2.6394240852
H,0.1778652251,-0.4475123925,3.1331170713
H,-0.8439858709,-1.4462291646,2.0727360288
O,2.0611000137,-0.2713235494,1.0567366094
H,1.6373969246,0.8072939745,-0.8062098106
C,0.1135889181,0.6006334689,-2.3387079476
H,0.6445018147,1.2013247319,-3.0831996994
H,0.3497089162,-0.4526480778,-2.5034918221
H,-0.9631266731,0.7455128194,-2.4736506274
C,0.3831422021,2.535686007,-0.7147379766
O,0.8124544167,3.4502984518,-1.3791941344
H,-0.7189421972,3.5428325844,0.8048198054

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,R)-TS-top-N-3']

#P B3LYP/6-31+G(D) OPT=(TS,NOEIGENTEST,GDIIS)

(HF = -797.7437824 a.u.)

0,1
C,-0.877512106,-0.5929463572,1.2957694926
N,-0.1590185323,0.2131142047,0.4370143298
H,-0.5598105935,0.2445486079,-0.995844195
C,1.8080807476,-0.5276370976,-0.3347703802
O,1.2004656714,-0.8263854726,-2.1582910062
C,0.1652824743,-0.3548417317,-2.6955294538
C,-0.0062354116,-0.4404622894,-4.1872204337
O,-0.7877588884,0.226553313,-2.0465757055
H,0.7282619717,-1.1212379409,-4.6197142415
H,0.1349242029,0.5606199142,-4.6119171502
H,-1.0229619147,-0.7630304403,-4.4292827226
O,-1.2011849623,-1.7587149229,1.0925657271
C,-0.0049863168,1.4896974541,1.0325176705
O,0.4889622118,2.4646235379,0.4906602136
N,-0.5005215072,1.4347719842,2.3238459667
H,-0.715689504,2.3038373189,2.7951346692
C,-1.2210001971,0.1954738698,2.5744895321
H,-0.7983744831,-0.3413306107,3.4348823411
C,-2.7331662282,0.3583762178,2.7686397883
H,-2.9462608808,0.9302358309,3.6794148933
H,-3.1829736055,0.8805949663,1.9166091726
H,-3.2013984746,-0.6267981645,2.8621680727

C,1.7426125525,-1.9291972644,0.1315068348
H,2.4171556456,-2.5112583729,-0.5051179417
H,2.0987257365,-1.9470296247,1.167029347
H,0.7275910406,-2.3223898917,0.0806110068
O,2.5119082235,0.3923308292,-0.3299109327

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,S)-TS-bot-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -797.7438288 a.u.)

0,1
C,0.2629387571,0.2285900124,-3.9006107657
H,-0.4090382878,0.4646578345,-4.7335363821
H,1.0539954975,-0.4328741926,-4.2680124563
H,0.7156742092,1.161488714,-3.5478885286
C,-0.501246337,-0.4613975773,-2.7689885025
H,-0.9571043985,-1.3904391645,-3.1444118665
C,0.4023573782,-0.8354740973,-1.5756020248
O,1.439238735,-1.4772810218,-1.6680676651
N,-1.4862626651,0.3778675753,-2.1044536836
N,-0.142857723,-0.3175655365,-0.4119527451
C,-1.3451321979,0.3650536456,-0.7349367404
O,-2.1104399482,0.8525253151,0.0820148755
H,-0.3046587578,-1.0588403243,0.8362943303
H,-2.3809486165,0.6244144513,-2.5063600487
O,-0.5134651362,-1.396320213,1.8479745202
C,-0.2628479343,-0.4315798818,2.6686418206
C,-0.8112459359,-0.5665293083,4.0595996301
H,-1.8574409488,-0.2369607074,4.041056792
H,-0.7921138903,-1.6126851742,4.3756747999
H,-0.2567684315,0.0642768738,4.7563653441
O,0.3913833682,0.6019200556,2.3622357652
C,1.1579163784,0.9904278562,0.7010186104
C,2.3935085973,0.1626147519,0.7524621857
H,2.1844519641,-0.8755376384,0.9986909278
H,2.8760092778,0.2038667459,-0.227077106
H,3.0424105569,0.6143123757,1.5110217773
O,0.8822682696,2.086902555,0.4150327714

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,S)-TS-top-N-1']

#P B3LYP/6-31+G(D) OPT=(TS,NOEIGENTEST,GDIIS)

(HF = -797.7489578 a.u.)

0,1
C,-0.5646009491,0.9454114212,-1.448347084
N,-0.0032443979,0.0726613143,-0.3653362604
H,-0.859871766,-0.2714022254,0.3623726854
C,2.3178881141,0.5236423948,1.0119235361
C,0.8759819812,0.9234297486,1.0183674503
O,0.3591299112,1.9730771231,1.2251403701
O,0.3042672409,-0.3095809263,2.3588635251
C,-0.8989307825,-0.7321952887,2.3663688034
C,-1.4351317289,-1.3181926906,3.6499206921
O,-1.6677700176,-0.669936482,1.3543185157
H,2.7495865325,0.8580314035,1.9596443602
H,2.8153627741,1.0492286878,0.1886880513
H,2.4409131343,-0.5521510245,0.907409165
H,-2.0259295919,-0.5489261359,4.1626018618
H,-0.61909241,-1.6264877384,4.3067260822
H,-2.0965603454,-2.1610097374,3.4323176802
C,0.5336548907,-1.1096880552,-0.9694622458
O,1.1339130831,-1.99732565,-0.4077051057
N,0.197309516,-1.079133307,-2.3192974743
H,0.4103216023,-1.8483129453,-2.9446375433
C,-0.5234600253,0.0440578665,-2.6880784881
H,-1.6058869938,1.1806742311,-1.2071114845
C,0.2050652655,2.2413571189,-1.7456192978
H,0.113127344,2.9509335167,-0.9236941193
H,1.2675153051,2.0378215693,-1.9231336005
H,-0.2136509686,2.6846750144,-2.6542964876
O,-0.9791765974,0.276927715,-3.7862286433

Transition state for 5-methylhydantoin (73) with acetic anhydride [(S,S)-TS-top-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -797.7447738 a.u.)

0,1
C,-1.4155908901,-0.6175098305,0.6959111083
N,-0.4853213942,0.0421983729,-0.0981392381

H,0.6307581061,-0.7776922547,-0.5925014369
C,1.0997815804,2.3711640416,0.4669057888
C,1.0501888966,1.0598157496,1.1499659199
O,0.9470897933,0.6052054927,2.2119114997
O,2.5776804445,0.247194184,0.2767163646
C,2.5719918811,-0.7765854738,-0.4558576513
C,3.873895155,-1.4261972545,-0.8379056668
O,1.5023473936,-1.3327941869,-0.9152677315
H,2.061012159,2.8295564168,0.7224673834
H,0.2799148071,2.9795894499,0.8631950679
H,0.9954815635,2.2648133663,-0.6124421603
H,4.7181494363,-0.8227234639,-0.5021554051
H,3.9112516967,-1.5676351523,-1.9225106795
H,3.9233184367,-2.4179260407,-0.3737740263
O,-1.1651621451,-1.4105083683,1.5871041273
C,-1.1747094314,0.8267784657,-1.0455884672
O,-0.6460382841,1.481323958,-1.9396061114
N,-2.5245463866,0.7581507602,-0.7853955005
H,-3.1855121746,1.084395458,-1.4777111456
C,-2.8382686228,-0.2070380531,0.2576208275
H,-3.3358406385,0.2803996076,1.1074104649
C,-3.6708525813,-1.4064778207,-0.2056516662
H,-4.6759795137,-1.0898584546,-0.508257968
H,-3.1930447865,-1.9090157726,-1.054174919
H,-3.7663881684,-2.1234146724,0.6159316473

N-1' product (79)

#P B3LYP/6-31G(D) OPT

(HF = -568.6745739 a.u.)

0,1
C,-1.1167476377,-0.0697904736,-0.0677964756
C,-1.8787034838,-0.5090911738,1.1887889254
C,-1.2222072758,1.4534028233,-0.2243204459
N,0.068332605,1.9231501069,-0.1944688264
C,1.0523626678,0.9232337663,-0.0803048726
N,0.3418820583,-0.2994362549,-0.0348812186
C,0.98947753,-1.5554647197,-0.113721377
C,0.0851910524,-2.7687080063,-0.2655147114
H,-2.8976590855,-0.1151394431,1.1318992203
H,-1.9312012559,-1.5965170205,1.2742808341
H,-1.3987355043,-0.1089964247,2.0876485349
H,0.3222933915,2.9006498483,-0.2562031395
H,0.7062631752,-3.5871870229,-0.631954081

H,-0.3252950901,-3.0615831127,0.707088775
H,-0.7508560826,-2.6083971614,-0.9527869883
H,-1.5589061357,-0.5295540089,-0.9592003736
O,2.2378023523,1.1246992239,-0.0458592871
O,-2.2434441959,2.0982215455,-0.3197620447
O,2.1939364469,-1.6605165089,-0.0616422588

N-3' product (80)

#P B3LYP/6-31G(D) OPT

(HF = -568.6717081 a.u.)

0,1
C,-0.974314098,-1.6535876433,-0.0966478251
C,-1.6899605484,-2.3106637438,1.0857409596
C,-1.056251592,-0.1240563477,-0.0368047054
N,0.2502783008,0.3677015823,-0.1423677578
C,1.198533933,-0.7211264874,-0.2741716639
N,0.4594410375,-1.8699068846,-0.1348412593
H,-2.7381923315,-1.9987428527,1.097342606
H,-1.6491786421,-3.4014505013,1.0016624471
H,-1.2214775233,-2.0169903847,2.0300144478
H,-1.4515723764,-1.9698400023,-1.0367716471
O,2.3805961541,-0.6301510902,-0.4879209269
O,-2.0779390988,0.5133308783,0.1007412652
C,0.6598426916,1.7480196672,-0.0520274248
C,-0.406216554,2.7792897089,-0.3359108988
O,1.8002415323,2.0218169334,0.2272256581
H,0.8865435538,-2.7441313026,-0.4063201291
H,0.085513096,3.7525808183,-0.3731124659
H,-0.9216318052,2.5747395177,-1.2790997823
H,-1.171031035,2.7720471282,0.445309022

Transition state for 5.5-dimethylhydantoin (73) with acetic anhydride [R-TS-N-1']

#P B3LYP/6-31+G(D) OPT=(TS,NOEIGENTEST,GDIIS)

(HF = -837.0659616 a.u.)

0,1
C,1.2362313495,-0.8142531663,1.2831078144
N,0.3079543056,-0.2614664473,0.3090613802
H,0.1094348828,-0.9199342654,-0.5433110542
C,1.1373853831,1.0240991857,-0.5608141136
O,-0.2073297873,0.8325423401,-2.1384320143

C,-0.528256846,-0.3209956694,-2.5827311739
C,-1.1547784378,-0.3942094535,-3.9628212532
O,-0.3347020774,-1.3998607348,-1.9429126619
H,-1.6035085743,0.5625137035,-4.240539725
H,-1.8970819741,-1.1963091004,-4.0027610033
H,-0.3692289255,-0.6312222474,-4.6915095343
O,2.2632048204,-1.3929663,1.0234814427
C,-0.986651035,0.0664417413,1.0539547798
N,0.7407762159,-0.5100074176,2.53328917
C,2.290318063,0.4469563208,-1.3295113097
H,2.4735173537,1.1272233861,-2.1647445189
H,3.16987024,0.4295431196,-0.6781535975
H,2.0941889171,-0.5583865488,-1.6972687486
O,1.0101125711,2.1069881523,-0.0960347328
C,-1.9572624036,-1.1228199332,0.8667694646
H,-2.815857477,-0.9866934616,1.5304023711
H,-2.3035961376,-1.1633393256,-0.1687805252
H,-1.4814865763,-2.0809771096,1.1044382172
C,-0.528746077,0.0601715254,2.51760826
O,-1.15349356,0.4146535217,3.4904698117
H,1.2461656427,-0.7386512143,3.3824852173
C,-1.6758545762,1.3833716723,0.680527768
H,-2.6210119201,1.4226961023,1.229614555
H,-1.0820800482,2.2565572479,0.9465521274
H,-1.8770873075,1.4138675955,-0.3919938141

Transition state for 5.5-dimethylhydantoin (73) with acetic anhydride [R-TS-N-3']

#P B3LYP/6-31+G(D) OPT=(TS,NOEIGENTEST,GDIIS)

(HF = -837.0614759 a.u.)

0,1
C,-0.4410795881,0.7708731404,-1.1626206386
N,-0.0221306006,-0.1818352811,-0.256775116
H,-0.9202762511,-0.5283035491,0.8659841852
C,1.4311849727,0.4153355391,1.3323894851
O,0.1985942472,0.205851718,2.8182984775
C,-0.9164847739,-0.3776125628,2.8049151895
C,-1.6129963868,-0.6803017598,4.1031748532
O,-1.5217089411,-0.7604900417,1.7312694881
H,-1.1715402544,-0.1060530495,4.9190375322
H,-1.4994821387,-1.7502509158,4.3155919732
H,-2.682466451,-0.4701917719,4.0142465752
O,-0.9332339884,1.860175655,-0.8868065921
C,0.468606634,-1.3021489976,-0.9719300744

O,0.808472089,-2.3613914587,-0.4699485269
N,0.4999086689,-0.9850576161,-2.3168131915
H,0.5631863323,-1.7425191188,-2.9854430882
C,-0.2010068634,0.2652342641,-2.6062487369
C,-1.5509719079,0.0337437946,-3.309663519
H,-1.3898260205,-0.3690719572,-4.3174424833
H,-2.1720933521,-0.6734778985,-2.7490858215
H,-2.0954720995,0.979183324,-3.3987242595
C,1.3483516251,1.8864789614,1.2031452672
H,1.6696180788,2.3114259189,2.1598074666
H,2.0420157096,2.185712154,0.4103959013
H,0.3393330372,2.2122137879,0.9528553624
O,2.2119113156,-0.43941569,1.3822564413
C,0.6728389268,1.2532912722,-3.3928626381
H,0.1729615912,2.2244660546,-3.4645761487
H,1.6426142102,1.3909220452,-2.9030237068
H,0.8540475208,0.8769918869,-4.4068547684

Transition state for 5.5-dimethylhydantoin (73) with acetic anhydride [(S)-TS–N-1']

#P B3LYP/6-31+G(D) OPT=(TS,NOEIGENTEST,GDIIS)

(HF = -837.0663961 a.u.)

0,1
C,0.3169148812,-0.7668350381,1.4881317302
N,0.0075986612,0.0995564063,0.2836158763
H,-0.6057734078,-0.4837385617,-0.5140881927
C,1.7875667024,1.8185495371,-0.8624310915
C,1.3750619621,0.3784333978,-0.8798906672
O,2.0366114406,-0.6081753579,-0.9660152218
O,0.2578015193,0.498652071,-2.4331547658
C,-0.7205577336,-0.3061773519,-2.5831198902
C,-1.2858358213,-0.4757362599,-3.9735846542
O,-1.2256519424,-0.978275112,-1.629748984
H,2.4412408227,1.9755123879,-1.7249231547
H,2.3597443515,2.0024629564,0.0543600455
H,0.9328770009,2.4889057006,-0.920286917
H,-0.8416099227,-1.3730749261,-4.4221876209
H,-1.0394090603,0.3838602165,-4.6005358691
H,-2.3680800826,-0.622594774,-3.9261277618
C,-0.8220954021,1.1935770403,0.7068823802
O,-1.1856803566,2.1259920235,0.0283997199
N,-1.1745582205,0.9607319857,2.0298485343
H,-1.8201798205,1.5636630304,2.5279941931
C,-0.6370576881,-0.2014792106,2.5557441392

C,1.7487549992,-0.5722577031,2.0286351025
H,2.4823434668,-1.0070352981,1.3486258139
H,1.9828361782,0.4887026569,2.1738871438
H,1.8204348598,-1.0698745301,3.0003511144
O,-0.8500463334,-0.6489205399,3.6615988352
C,0.0208561854,-2.2439016824,1.203914027
H,0.154142498,-2.8197649955,2.1243737235
H,-1.0042171232,-2.389335421,0.8488981947
H,0.7084440235,-2.6189282393,0.441085288

Transition state for 5.5-dimethylhydantoin (73) with acetic anhydride [(S)-TS-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -837.0615195 a.u.)

0,1
C,0.3719529774,0.3310815037,-3.6237945486
H,-0.2716065389,0.5884239678,-4.4737466637
H,1.1874655703,-0.3043178266,-3.9832768861
H,0.7959833202,1.2577030296,-3.2232008394
C,-0.4374098723,-0.4088016569,-2.5479167104
C,0.4572680099,-0.7472850819,-1.3295616406
O,1.4837406003,-1.4098156645,-1.3935373766
N,-1.4194352277,0.4588149967,-1.9011301501
N,-0.0826668901,-0.183514661,-0.1854483141
C,-1.2814353136,0.4944809301,-0.5339634542
O,-2.0440642786,1.0135363162,0.2662129712
H,-0.2409848293,-0.8963141532,1.0676338124
H,-2.3100205508,0.7023550553,-2.3150785387
O,-0.4337610804,-1.2343846721,2.0875887685
C,-0.1441835094,-0.2792368311,2.9053969896
C,-0.6426113775,-0.4204461909,4.3151019176
H,-1.6925621125,-0.1034317713,4.3352615041
H,-0.6005039054,-1.4667047411,4.6290511715
H,-0.0699541089,0.2151394175,4.992495112
O,0.5092993991,0.7503332791,2.5840011212
C,1.2176996634,1.1535372335,0.891987713
C,2.4709724168,0.3524872289,0.9171197243
H,2.2872597762,-0.6924909085,1.1537573774
H,2.9387830243,0.4156146728,-0.0685931128
H,3.1209478497,0.8102338162,1.6709665188
O,0.9093058664,2.2429452502,0.6143215242
C,-1.0701806352,-1.6946824799,-3.109038253
H,-0.2895792431,-2.3667587764,-3.4793573258
H,-1.6457643466,-2.2203311458,-2.3393204903

H,-1.743347292,-1.4539469907,-3.9412288861

N-1' product (76)

#P B3LYP/6-31+G(D)

(HF = -608.0288321 a.u.)

0,1
C,-0.7904213042,-0.6880992918,0.0053252111
N,0.5005470822,0.0698104201,-0.0004475033
N,-1.0960920054,1.6346547823,-0.0127162404
C,-1.8158095876,0.4577607513,-0.0033096746
C,0.2880043965,1.4553734196,-0.0113029819
O,-3.0247329084,0.354310283,-0.0022739056
O,1.1052609653,2.3531497688,-0.0182371555
C,-0.9744911895,-1.5166157537,1.2878919081
H,-1.9978127322,-1.9031352645,1.3145469712
H,-0.2705841443,-2.3506145819,1.3028785863
H,-0.8156187588,-0.9007907513,2.1801851216
C,-0.9745566217,-1.5355991845,-1.2648517841
H,-0.2702269239,-2.3693785655,-1.2677009719
H,-1.9976894558,-1.9229791586,-1.2854301818
H,-0.8162647807,-0.9329467466,-2.1661944135
C,1.7528497065,-0.5772931422,0.004417216
C,3.0045365156,0.2681139761,-0.0014849614
H,3.0455895359,0.9147253501,-0.882870903
H,3.8541733648,-0.4169072109,0.0047431867
H,3.0442929479,0.9293344041,0.8690207387
O,1.789824442,-1.7974280655,0.0133104342
H,-1.5105360757,2.5593355701,-0.0195365127

N-3' product (77)

#P B3LYP/6-31G(D) OPT

(HF = -607.9889642 a.u.)

0,1
C,1.6685267436,-0.1088594031,-0.2270049176
C,2.6560820029,-0.5625083555,0.8593984412
C,0.3294626007,-0.8466835582,-0.0551108358
N,-0.6719374608,0.1168316907,0.1044373194
C,-0.1108346065,1.4524078862,0.0374178759
N,1.2455395645,1.2743517705,-0.0486862141
H,2.8273702076,-1.6399239458,0.7814202157

H,3.6140132503,-0.0445500801,0.7393506614
H,2.265598387,-0.3385190572,1.8565431121
O,-0.7201133557,2.49236361,0.0303261326
O,0.2012758095,-2.0527724958,-0.0512120758
C,-2.0674950056,-0.1282312892,0.3735223844
C,-2.5918905695,-1.4902895651,-0.0149343409
O,-2.7463833551,0.7343148928,0.8724180533
H,1.8133606371,2.0668231295,-0.3150054086
H,-3.6758203362,-1.4683730013,0.1081133755
H,-2.3285470789,-1.7420030063,-1.0465684308
H,-2.1558234896,-2.2686812173,0.6169539795
C,2.2240961793,-0.3762110736,-1.6377757866
H,3.171743034,0.1562713082,-1.7773676142
H,2.4051787504,-1.4467258477,-1.7707866128
H,1.521795054,-0.0415984148,-2.4082448185

Transition state for PCU hydantoin (11) with acetic anhydride [(R,R)-TS-bot-N-1']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4573257 a.u.)

0,1
C,-2.9700235363,0.929399094,0.3363146975
C,-2.5765608719,0.8781431126,-1.173358062
C,-1.2774193456,0.0188059435,-1.0893264622
C,-0.5600097291,0.6217849468,0.1310933152
C,-1.7043799707,0.5432589758,1.1923522546
C,-1.8652422752,-1.4426281414,-0.7945104942
C,-3.4074443402,-1.1901880951,-0.784483593
C,-3.574209493,-0.4894066899,0.5970641974
C,-2.324532173,-0.8730426119,1.451544397
C,-1.6284773486,-1.9551988257,0.6412005105
C,-3.6200379431,-0.058854764,-1.7918280621
C,-0.23907815,2.1492053288,0.0894255343
N,0.8543146965,0.0978298419,0.4253586906
C,1.4612834316,1.1179358804,1.2957703353
N,0.8411563145,2.3075798733,0.9439620113
O,-0.8327614334,3.0610013203,-0.4425058241
O,2.339330719,0.9766132365,2.0997364021
O,2.4866607897,0.4605329817,-1.5996806535
C,3.5033148755,-0.0641606095,-1.0447112578
O,3.4406803599,-0.8035536837,-0.0095181922
C,1.6540233296,-1.5831834366,0.6945090876
C,1.4748544612,-2.4125834067,-0.5442752907
O,1.7926292654,-1.8733092392,1.8236924088

C,4.8712895932,0.1951789104,-1.6487610352
H,-3.5381323027,1.8107598419,0.6399340887
H,-2.4423858319,1.8494415992,-1.6443116109
H,-0.6712514896,0.0442577096,-1.9995496949
H,-1.5122965389,1.1339071299,2.0919402413
H,-1.5525506561,-2.1458502163,-1.5723616139
H,-4.0009548814,-2.099730432,-0.9182601797
H,-4.5673436178,-0.5599535256,1.0476298357
H,-2.4751920674,-1.1070961272,2.5084461827
H,-3.3877573052,-0.3426855917,-2.82599155
H,-4.6331108609,0.3618074512,-1.7661406931
H,1.4020105619,0.2536616947,-0.5076277514
H,4.9207142504,-0.2731709243,-2.6390356086
H,5.0130405302,1.2715161249,-1.7912010974
H,5.6639527693,-0.2082071047,-1.015443742
H,-2.1394900864,-2.9194641557,0.7683485504
H,2.3751191201,-3.0260474987,-0.6291749584
H,1.3693894028,-1.8015069057,-1.4392500434
H,0.6096736689,-3.0685507796,-0.4241513135
H,-0.5984601292,-2.0978940831,0.9508306456
H,1.1803076957,3.2098671919,1.2582118371

Transition state for PCU hydantoin (11) with acetic anhydride [(R,R)-TS-bot-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4891006 a.u.)

0,1
C,2.6887992888,-0.742758843,1.3495161368
C,2.4437930448,-1.6778491395,0.1270457245
C,1.9908763775,-0.6337044353,-0.9357998253
C,1.0275452075,0.2896577101,-0.1349138069
C,1.9179149779,0.5949024474,1.0933032946
C,3.3614572674,0.0958434876,-1.3059156862
C,4.3906535791,-0.6485071848,-0.3981862572
C,4.0396105284,-0.0376014504,0.9915625831
C,3.2742878001,1.3043035746,0.7281271955
C,3.4624770739,1.5395419542,-0.7746946468
C,3.8575388717,-2.0823515798,-0.3101856335
C,-0.286745221,-0.4275274671,0.2931925024
N,0.4495477903,1.422946354,-0.8541773225
C,-0.9128401449,1.3232248779,-1.008623638
N,-1.3809956837,0.2433020523,-0.2414984462
O,-0.3633776872,-1.4190498936,0.9995657882
O,-1.6150731021,2.0696560169,-1.6861819003

O,-4.3527067524,-0.1610204704,0.4598289101
C,-4.297524184,-0.9733688897,-0.5018089422
O,-3.2343804442,-1.2095818444,-1.1904536402
C,-2.864093722,0.7034202318,1.335096661
C,-3.1983070262,2.1009958967,0.9772561041
C,-5.5305499638,-1.741119,-0.8949387251
O,-2.560136678,0.0711594295,2.2599795524
H,2.5824927623,-1.2208396124,2.3252258035
H,1.7279569267,-2.4785968716,0.3078204712
H,1.5139477627,-1.0729731518,-1.8181654348
H,1.3720472955,1.0340936872,1.9325851726
H,3.5802384832,0.0037502069,-2.3746346463
H,5.4305067916,-0.5189833185,-0.7148678186
H,4.8472223899,-0.045769792,1.728477291
H,3.5228073192,2.1606013948,1.3613019435
H,2.7762160734,2.2677574255,-1.2156982628
H,4.474683981,1.9218417177,-0.9659086127
H,3.8819806831,-2.6154579881,-1.269370989
H,4.3755710951,-2.6928595818,0.4405979445
H,-2.4091473646,-0.597809473,-0.8191315543
H,-3.2269360907,2.2450991609,-0.1021723205
H,-2.4312059116,2.746589594,1.4177787089
H,-4.1725570254,2.3215664671,1.4262008356
H,-6.4041551002,-1.367955178,-0.3588020304
H,-5.6828256326,-1.6684015403,-1.9760825246
H,-5.377999717,-2.7993715574,-0.6528572291
H,0.9553253134,1.9820605193,-1.5246742943

Transition state for PCU hydantoin (11) with acetic anhydride [(R,R)-TS-top-N-1']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4850734 a.u.)

0,1
C,2.8914793938,0.1126202645,-0.9257386455
C,2.9717908703,0.460176465,0.5906872837
C,1.5179929585,0.0956586592,1.0439910058
C,0.6577519918,0.7080074973,-0.1015098244
C,1.3803738826,0.0788549531,-1.3304808636
C,1.5588892054,-1.4993380877,1.0319675619
C,3.0200144045,-1.8009860791,0.5815249799
C,2.9289117084,-1.4517204973,-0.9345755061
C,1.4110427483,-1.4963478586,-1.3232225198
C,0.7361418645,-2.1236524306,-0.1014776671
C,3.8451417875,-0.6574753975,1.1729998399

C,0.7901098758,2.2455913036,-0.2382292742
N,-0.8619893421,0.5414735122,-0.1296931338
C,-1.4116723764,1.7302801998,-0.7547382644
N,-0.4355161291,2.700373484,-0.7055164736
O,1.749121104,2.9671937832,-0.067824466
O,-2.52663073,1.8492226382,-1.2009959747
C,-1.6321828851,0.2173235324,1.4235285173
O,-3.2941744156,-0.5964182319,0.5612051301
C,-3.2253248243,-1.2399674341,-0.5309781258
O,-2.177222135,-1.2937662007,-1.2554818772
C,-2.3657108262,1.413578769,1.9563574396
C,-4.4650438928,-1.9609505335,-1.0153211604
O,-1.0912868854,-0.6474309082,2.0323225012
H,3.5823384392,0.6639590955,-1.567364524
H,3.2734297129,1.4817223492,0.8104708481
H,1.260953036,0.4868648901,2.0304048625
H,1.0991749242,0.5342615569,-2.2848614638
H,1.310061113,-1.8909341745,2.0205861463
H,3.345254424,-2.8217370922,0.8043647868
H,3.6534627674,-1.9502058129,-1.5836680967
H,1.1405005298,-1.944192915,-2.2823868174
H,-0.3387294227,-1.978512668,-0.0338727678
H,0.9048786469,-3.2093678795,-0.1154145692
H,3.8708361585,-0.6611815852,2.2701147441
H,4.8771114164,-0.6187980455,0.8011372655
H,-1.3166717331,-0.3566770424,-0.706094583
H,-3.0147613221,1.8773571688,1.2172408044
H,-1.6279778059,2.136001007,2.3283034908
H,-2.9702853231,1.0637879366,2.7964546839
H,-5.1592426339,-2.1402125505,-0.1913512468
H,-4.9625612226,-1.3320737453,-1.7639398522
H,-4.1898911629,-2.9024542875,-1.4993925016
H,-0.5920330671,3.6491362242,-1.026775124

Transition state for PCU hydantoin (11) with acetic anhydride [(R,R)-TS-top-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4874026 a.u.)

0,1
C,-2.8433000813,0.6035921456,1.3893814814
C,-2.6167120877,1.5144688143,0.1454676288
C,-1.9942349501,0.4840794882,-0.8436255598
C,-0.9949411999,-0.3086408853,0.0496165953
C,-1.9262539072,-0.6547021985,1.2375346136

C,-3.2609776566,-0.3897304881,-1.265388654
C,-4.4140860148,0.2746579354,-0.4508685543
C,-4.0901202866,-0.2498057721,0.9805189146
C,-3.1780064527,-1.5145934073,0.8163200942
C,-3.2519771012,-1.8161345337,-0.6863995223
C,-4.0339954649,1.7571297018,-0.3889932953
C,0.2150085493,0.5526465197,0.518490741
N,-0.2674836474,-1.4036959463,-0.582232837
C,1.0937558667,-1.3132015642,-0.44934899
N,1.4011308082,-0.0742896018,0.164314375
O,0.1434290579,1.616501358,1.1185645215
O,1.918477742,-2.149503194,-0.7868188803
O,3.4944742091,-0.4158979792,1.5225354999
C,4.4221924601,-0.2839035035,0.6365039916
O,4.2543448234,0.276123289,-0.4818814428
C,2.6737656009,1.0585482148,-1.1084369827
C,5.7699837184,-0.8556763293,0.9717642586
O,2.4958448741,0.7047564129,-2.2068739594
C,2.7045435146,2.3647281715,-0.3938698267
H,-2.8498720343,1.1238147802,2.3493768702
H,-1.9998290163,2.3912737656,0.3360854653
H,-1.5073852196,0.9331178722,-1.7150008956
H,-1.3952823629,-1.0082143257,2.1257190527
H,-3.4174669587,-0.3569085528,-2.34807062
H,-5.4140059167,0.0282539619,-0.8218896361
H,-4.9383544265,-0.3012065361,1.6683457322
H,-3.3790757751,-2.3695845528,1.4677747978
H,-2.4778793348,-2.4798344573,-1.0804612901
H,-4.2100059536,-2.303549768,-0.9141197961
H,-4.0522598569,2.2513639,-1.3688771551
H,-4.6558499924,2.3371198649,0.3051247885
H,2.5250002835,-0.2096777899,1.0464760069
H,6.5491208653,-0.3891490185,0.3665537916
H,5.7448054641,-1.929374924,0.7484659723
H,5.9777401407,-0.7373606139,2.0384049928
H,3.5522102557,2.926115166,-0.8017808956
H,2.8073759462,2.2441440718,0.6817681858
H,1.7718533416,2.894122597,-0.6041540451
H,-0.6668022686,-2.2951795522,-0.8305196042

Transition state for PCU hydantoin (11) with acetic anhydride [(R,S)-TS-bot-N-1']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4654007 a.u.)

0,1
C,3.1046171506,0.753398407,-0.2723819399
C,2.7003416032,0.4825382741,1.2087503161
C,1.3041586659,-0.1749986764,0.9954682694
C,0.6481727122,0.7119238748,-0.0888859171
C,1.8046608879,0.695993174,-1.1535214341
C,1.6987407316,-1.6236046512,0.4410664078
C,3.2599487096,-1.5727772546,0.4451354009
C,3.5191441058,-0.6630262049,-0.7929966637
C,2.2302744355,-0.7195346271,-1.6756826401
C,1.3949678105,-1.8306382053,-1.0548109354
C,3.6133684921,-0.6744191031,1.6325456484
C,0.5262569828,2.2313437926,0.248770242
N,-0.7599193833,0.3699769044,-0.4843633006
C,-1.4098627883,1.538640912,-0.7976335606
N,-0.6195282968,2.6310299557,-0.3946177138
O,1.2878678761,2.9705939387,0.8473796242
O,-2.5379235026,1.6886845287,-1.2704694574
O,-2.2185331753,0.0588690555,1.6895310813
C,-3.3706818456,-0.3647328162,1.2584265939
O,-3.5398929152,-0.8539474245,0.1187821988
C,-2.0195703439,-1.4848106074,-0.8884909308
O,-1.5665023938,-2.3691185674,-0.2830453172
C,-4.5222246605,-0.2213636651,2.210714159
C,-2.4781191654,-1.1544550346,-2.2534243164
H,3.7883727885,1.5919369476,-0.4200176633
H,2.6916734171,1.3653379014,1.8448779706
H,0.7088586207,-0.2433501485,1.9118305034
H,1.6899152184,1.4602044987,-1.9277214633
H,1.2862525994,-2.4096181246,1.0808866854
H,3.7327780083,-2.5594286516,0.4039375598
H,4.4956235749,-0.7801545206,-1.2709207443
H,2.3589602152,-0.7814897108,-2.7605615784
H,3.3421203574,-1.107640461,2.6040992268
H,4.6730729364,-0.3892494965,1.6630427754
H,-1.5407252791,0.1069903363,0.8793254824
H,-4.795710272,0.8384716488,2.2727453139
H,-5.3808381911,-0.7962347355,1.8615521436
H,-4.2208000067,-0.5455963509,3.211313387
H,-2.8281559328,-0.1230612027,-2.292937858

H,-1.6282806789,-1.3065561986,-2.9261508077
H,-3.282875149,-1.8580794066,-2.4996809504
H,-0.970860193,3.5808446386,-0.3884512838
H,0.346842327,-1.7706366761,-1.3217367774
H,1.7646213818,-2.8172560869,-1.3682820551

Transition state for PCU hydantoin (11) with acetic anhydride [(R,S)-TS-bot-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4878114 a.u.)

0,1
C,2.8309166403,-1.2781911218,0.6969941997
C,2.6333388282,-1.3418628714,-0.8477558136
C,2.023602471,0.0669564888,-1.1089624635
C,1.0039343715,0.2342563229,0.0556244815
C,1.9115511849,-0.1401557527,1.2526755903
C,3.2896896132,1.0249299124,-0.9430129143
C,4.432586147,0.0127918297,-0.6187285289
C,4.0817720303,-0.3506915548,0.8558452858
C,3.1666374644,0.7949915638,1.4096769828
C,3.2607405258,1.8845464319,0.3364973092
C,4.0611765801,-1.2507126019,-1.40175263
C,-0.2042574928,-0.7410793385,-0.0417586125
N,0.2785820509,1.5000179555,0.1189255987
C,-1.0684228448,1.3628267211,-0.1123159034
N,-1.3832963574,-0.0165200295,-0.1291382961
O,-0.1347171854,-1.9625898756,-0.0083873933
O,-1.8749558674,2.2661523627,-0.2772078117
O,-4.3027102521,0.0062709204,0.3516221655
C,-4.3545422771,0.0015851958,-0.9088663719
O,-3.3581269247,-0.3016078846,-1.6702514991
C,-2.8197534029,-0.42877053,1.4064244014
C,-5.6370605798,0.3862545487,-1.5889000311
O,-2.7013411537,0.3874697358,2.2319244979
C,-2.8630349803,-1.9159754985,1.3603930718
H,2.8207903178,-2.2449671882,1.2043391036
H,2.017233275,-2.1723830247,-1.1907294164
H,1.558378885,0.177220364,-2.0939978267
H,1.3597017811,-0.3354712359,2.175840998
H,3.4678164871,1.6015577023,-1.8563540989
H,5.4371571328,0.4196174782,-0.771967443
H,4.9181720751,-0.6980218933,1.4682677048
H,3.3491551812,1.1395778276,2.4311270158
H,2.4826008656,2.6505243279,0.3900149687

H,4.2172049843,2.4168633106,0.4314507225
H,4.0989481057,-1.1155211935,-2.4904190073
H,4.6755256208,-2.1213733689,-1.1382129496
H,-2.4407754226,-0.2845602046,-1.070564527
H,-6.4855296832,0.2584424945,-0.9145782739
H,-5.56443972,1.4446174739,-1.8681888645
H,-5.7712891246,-0.1962013912,-2.5040743577
H,-2.9077404818,-2.2956508333,0.3426033873
H,-1.9618684114,-2.3017428892,1.8429935492
H,-3.7517620912,-2.2209819713,1.9240146584
H,0.695285761,2.3982081901,-0.0741444558

Transition state for PCU hydantoin (11) with acetic anhydride [(R,S)-TS-top-N-1']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4829379 a.u.)

0,1
C,2.8689076823,0.2657707233,-1.0383212975
C,2.9728259785,0.5477415838,0.4898075151
C,1.5567793545,0.0775132654,0.9628357703
C,0.6331093794,0.6816427673,-0.1247158607
C,1.3500213287,0.1569509039,-1.4043290043
C,1.6857062235,-1.5118131818,0.8715762527
C,3.1513414668,-1.7040730429,0.3733441369
C,3.0014002102,-1.291363848,-1.1219669796
C,1.4813654409,-1.4108964052,-1.478420128
C,0.8737922635,-2.1357957816,-0.276427276
C,3.9243616535,-0.5414953971,0.9975728764
C,0.6432337848,2.2311441708,-0.1948132024
N,-0.8747181296,0.4221711159,-0.0962266872
C,-1.4854568365,1.56326185,-0.8247337084
N,-0.5843356998,2.5936483959,-0.7274626969
O,1.5355611299,3.0112355017,0.0516856511
O,-2.5518230133,1.5595304348,-1.3709937505
C,-1.568221714,0.4602647037,1.4457810376
O,-3.3494811945,-0.3362713763,0.6982463876
C,-3.3630603119,-1.1932668429,-0.2414185822
O,-2.3231542961,-1.5743414589,-0.8691600916
C,-4.7062437173,-1.7635780798,-0.6542194907
H,3.505085913,0.8874588368,-1.6717191966
H,3.2130605382,1.5753380879,0.7522116563
H,1.3174229593,0.4239945548,1.9708140029
H,1.0130785788,0.6399030498,-2.3258762254
H,1.5006419249,-1.9729868071,1.8461631593

H,3.5398477025,-2.7130637896,0.5403380614
H,3.7385408188,-1.7157099189,-1.8079518681
H,1.2143032146,-1.8296247351,-2.4514679852
H,-0.2109775393,-2.0699519267,-0.2054875623
H,1.1119042029,-3.2062154161,-0.3414212952
H,3.9825844681,-0.592113536,2.0921322159
H,4.9409252717,-0.4275882248,0.6007591464
H,-1.2906548685,-0.5007136744,-0.524562538
H,-5.420859247,-1.7208194528,0.1714034667
H,-5.0974043936,-1.1551256408,-1.4791768873
H,-4.5917370296,-2.7893349048,-1.01564931
H,-0.8148124315,3.5416225354,-1.0032420789
O,-1.7947738107,1.5604554005,1.8528887125
C,-1.3137042758,-0.7761520393,2.2619248794
H,-1.2300217929,-1.6766383496,1.6575745417
H,-2.1663708531,-0.873863264,2.9373644624
H,-0.4087586198,-0.6353041189,2.8614230176

Transition state for PCU hydantoin (11) with acetic anhydride [(R,S)-TS-top-N-3']

#P B3LYP/6-31+G(D) OPT=(CALCFC,TS,NOEIGENTEST)

(HF = -1145.4888806 a.u.)

0,1
C,-2.6539758291,-1.3128197575,-0.9739885455
C,-2.4211982523,-1.5203932515,0.5530094907
C,-1.9864453031,-0.0815349633,0.9655804594
C,-1.015064331,0.3335515846,-0.1779795168
C,-1.890111229,-0.0181169266,-1.4049104623
C,-3.3659388767,0.7175746266,0.9177292614
C,-4.3796070908,-0.3860996511,0.4843949939
C,-4.0114109581,-0.5341138525,-1.0226371964
C,-3.25282565,0.771514022,-1.4465618446
C,-3.4652859507,1.7123267832,-0.2534222073
C,-3.8394390473,-1.6722563137,1.1173028693
C,0.309089609,-0.4878256986,-0.1808722381
N,-0.4489830948,1.6777552357,-0.1136135434
C,0.9214834605,1.6998882717,-0.155137492
N,1.3975252769,0.3762571657,-0.1224796257
O,0.4001294622,-1.701840883,-0.2523375117
O,1.6251203681,2.7059010816,-0.1992779042
O,3.3697904756,-0.2521275406,-1.5859310567
C,4.3478638571,-0.5361805207,-0.7978946196
O,4.2899669963,-0.4624104673,0.4593243077
C,2.7208454626,-0.1767806602,1.5400836591

C,5.623881446,-0.9918313342,-1.4525891219
H,-2.5352184765,-2.2091113153,-1.5860465476
H,-1.6998686408,-2.2986713629,0.7973332704
H,-1.5183821331,-0.0223046838,1.9533780889
H,-1.3365267508,-0.0443196252,-2.3475045652
H,-3.597373983,1.1620279437,1.8909705864
H,-5.4243872706,-0.1286686461,0.685744364
H,-4.80863091,-0.9102132871,-1.6693824779
H,-3.4968054667,1.2023800903,-2.4216117493
H,-2.7940019657,2.5737323266,-0.1962827023
H,-4.4826673882,2.1257842769,-0.2902831202
H,-3.8755787415,-1.6659815465,2.2143318373
H,-4.343857731,-2.5783964597,0.7578166824
H,2.4933303604,0.040734025,-0.9962666577
H,6.4361770593,-1.0345006208,-0.7256700222
H,5.8791575957,-0.3196468278,-2.2771840869
H,5.4626639359,-1.9900318121,-1.8764104136
H,-0.9492733323,2.5276061016,-0.3223829962
O,2.3487783273,-1.2069981337,1.9277719631
C,3.0660575125,1.1662675037,2.0621346587
H,3.1778617908,1.8944628574,1.2600090182
H,3.9977545434,1.0600989562,2.6277255423
H,2.2580342158,1.4777211722,2.7325168598

N-1' product (81)

#P B3LYP/6-31+G(D) OPT

(HF = -916.4360935 a.u.)

0,1
C,-0.43067893,-0.6951717103,2.2500437963
C,-0.2247097057,0.8483778465,2.2055595424
C,0.1027622286,-1.0774869218,0.8342254492
C,-0.5403194585,0.0418298218,-0.0735127458
C,-0.099126518,1.2906579939,0.7025941411
C,1.6757149787,-0.9289455557,1.0111964345
C,1.8064362819,-0.4752279539,2.4967424573
C,1.3222229629,1.0017293662,2.3832253389
C,1.4576071822,1.4199967156,0.8780887953
C,2.2541999143,0.2697669936,0.2505169801
C,0.6556524856,-1.1833943498,3.2160338548
C,-2.0616975995,-0.2122533845,-0.0530401008
N,-2.3096786851,-0.9800521361,-1.1828038789
C,-1.2800160922,-0.927236586,-2.1172351782
N,-0.2597269561,-0.1269667364,-1.5435862929

O,-2.8907222136,0.1045769566,0.7724020518
O,-1.3116097842,-1.4372569847,-3.2173346799
C,0.4062827192,0.8290523228,-2.3634398125
C,0.6832848224,0.4435196484,-3.8006272004
O,0.7570134166,1.9012737467,-1.9085517826
H,-1.4505218978,-1.0156968988,2.4627974353
H,-0.8943135968,1.4226502923,2.8486041347
H,-0.1762814655,-2.0840832921,0.5064560651
H,-0.6103149368,2.2071185612,0.4082795108
H,2.1794071702,-1.8773273344,0.7981053231
H,2.8117285789,-0.6061294686,2.9090841593
H,1.6932046084,1.6809509913,3.1552828821
H,1.8412192586,2.4163963199,0.6532309341
H,0.4960092863,-0.8276316585,4.2417749858
H,0.7601491729,-2.2758772822,3.238384419
H,1.3828582198,1.1812810526,-4.1984908465
H,1.0948094223,-0.5654577603,-3.8809677998
H,-0.235123011,0.4566406126,-4.3956021559
H,3.3188795345,0.3793379284,0.4989803351
H,2.1884801776,0.199080364,-0.8341325324
H,-3.2174940133,-1.362155549,-1.4214108756

N-3' product (82)

#P B3LYP/6-31+G(D) OPT

(HF = -916.4392619 a.u.)

0,1
C,0.5888280338,-0.4926123888,2.1559166703
C,0.5711109302,1.0644417344,2.0784129992
C,1.0266388332,-0.8397130942,0.7020373789
C,0.1869187457,0.1438130442,-0.1676818613
C,0.4914337428,1.4724358963,0.5695847503
C,2.5766870374,-0.4565482167,0.7081581119
C,2.7873718798,0.0437477152,2.1721735925
C,2.0912130479,1.4361710308,2.1014690282
C,2.0198273199,1.8416521122,0.5890567357
C,2.9149671154,0.8096242188,-0.1042307115
C,1.8239109066,-0.8012858644,3.0110325267
C,-1.3275281346,-0.1511205964,-0.1187437043
N,-1.7548579284,-0.4271005229,-1.4233048557
C,-0.6518157549,-0.3485461238,-2.344360334
N,0.4152272879,0.096309201,-1.6090623866
O,-2.0403935769,-0.1029770959,0.8643861713
O,-0.6631632785,-0.6544672717,-3.5145343843

C,-3.118395094,-0.6348824616,-1.8497614397
C,-4.043859485,-1.2781963343,-0.8473600124
O,-3.4521783654,-0.307202803,-2.9629317873
H,-0.354173224,-0.9417425424,2.4663019521
H,-0.1056060638,1.5545215428,2.7807806701
H,0.8685693327,-1.8867512373,0.4232898493
H,-0.1830246187,2.2875294128,0.2958231336
H,3.1944015435,-1.3229889848,0.4522904927
H,3.8366886451,0.0625691212,2.4821663634
H,2.4388812225,2.17540524,2.8275377545
H,2.2346604025,2.8822481362,0.3327318081
H,3.9701221463,1.0665180488,0.0599733814
H,2.7878763319,0.744570986,-1.1881605372
H,1.7223064787,-0.4463030668,4.0443342037
H,2.084107131,-1.8671958928,3.0332718595
H,-3.5759983283,-2.1400242436,-0.3613212276
H,-4.9483299816,-1.5818687202,-1.378105212
H,-4.2983036689,-0.566947597,-0.0556687139
H,1.3272641559,-0.0407076144,-2.018257462

APPENDIX 3
Compact disk containing: Electronic copy of this thesis in word and PDF format, Cartesian coordinate and Gaussian output files.