

INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

**Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600**

UMI[®]



Université d'Ottawa • University of Ottawa



National Library
of Canada

Acquisitions and
Bibliographic Services

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale
du Canada

Acquisitions et
services bibliographiques

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-46589-6

Canada

TABLE OF CONTENTS

Acknowledgements	i
List of Figures	ii
List of Schemes	v
List of Tables	viii
Abbreviations and symbols	ix
Abstract	xi

Chapter 1

Preparation of Optically Active Compounds via Dynamic Kinetic Resolution

1.0	Introduction	1
1.1	Synthesis of Asymmetric Piperazine Rings	3
1.3	Use of Dynamic Kinetic Resolution for Piperazine and Other Heterocycle Synthesis	6
1.3.1	Principle of Dynamic Kinetic Resolution (DKR)	6
1.4	DKR of α -Halo [<i>R</i>]-Pantolactone Esters to Form Piperazines and Related Heterocycles	10

Chapter 2

Preparation of Enantiomerically Enriched Compounds Containing Piperazine Rings and Other Heterocycles via Dynamic Kinetic Resolution		13
2.0	Background	13
2.1	Results	14

2.2	DKR of ω -Bromo- α -Iodo alkyl [<i>R</i>]-Pantolactone Esters with Bifunctional Nucleophiles (Preparation of the [<i>R</i>]-Pantolactone Esters)	14
2.3	DKR of [<i>R</i>]-Pantolacto-6-Bromo-2-Iodohexanoate, 20c, with Bifunctional Nucleophiles	17
2.4	DKR of [<i>R</i>]-Pantolacto-5-Bromo-2-Iodopentanoate, 20b, with Bifunctional Nucleophiles	43
2.5	DKR of [<i>R</i>]-Pantolacto-4-Bromo-2-Iodobutanoate, 20a, with Bifunctional Nucleophiles	55
2.6	DKR of (4 <i>S</i>)-1-methyl-3-(6-bromo-2-iodohexanoyl)-2-oxoimidazolidine-4-carboxylate with 1,2-phenylenediamine	57
2.7	Attempted Explanation of Observed Diastereoselectivity	60
2.8	Summary	63
2.9	Experimental	64

Chapter 3

	Applications and Preparations of Benzocyclobutenols and Benzocyclobutenones	89
3.0	Evolution and Use of Benzocyclobutenones and Benzocyclobutenols in Synthetic Chemistry	89
3.1	Synthetic Methods for Generating Benzocyclobutenones and Benzocyclobutenols	93

Chapter 4

Exploration of New Paths to Benzocyclobutenones and Benzocyclobutenols	95
4.0 Benzocyclobutenone Preparation via Halogen-Metal Exchange	
(Background)	95
4.1 Results of Halogen-Metal Exchange in 72, 73, 74	99
4.2 Exploration of Benzocyclobutenol and Benzocyclobutenone Preparation	
via a Benzyne Route	107
4.3 Benzocyclobutenol and Benzocyclobutenone Formation via Reaction of	
Benzyne with Amide, Ketone and Ester Enolates	108
4.4 Attempted Benzyne Generation From <i>o</i>-Iodophenyl Tosylate	110
4.5 Benzyne Generation by Deprotonation of Aryl Halides with Lithium	
2,2,6,6-Tetramethylpiperidide	115
4.6 Benzyne Generation by Deprotonation of Phenyl Triflate with Lithium	
2,2,6,6-Tetramethylpiperidide	129
4.7 Summary	133
4.8 Experimental	135
 References	 154
Claims to Original Research	158

ACKNOWLEDGEMENTS

I wish to give my sincerest thanks to my supervisor, Dr. Tony Durst. His leadership, regular input and constant availability was of extreme importance in my development as an organic chemist.

I thank the members of the Durst group, especially James Jacquith for his constant help and Sasmita for her help on the benzocyclobutenone project. Special thanks go to all my other friends, Sue, Najma, Gianni and especially Chantal for allowing me access to CISTI's extensive library at many occasions.

I would also like to thank Dr. Glen Facey and Raj Capoor for their high-resolution NMR contributions to this work and C. Kazakoff for mass spectral analyses.

Finally, I would like to thank my parents and my sister for all their support during my graduate, as well as, my undergraduate studies. Without their large contribution, this may have not been possible.

LIST OF FIGURES

Chapter 1

Figure 1.0.1	Initial preparation of N-phenylpiperazine	1
Figure 1.0.2	Pharmaceutical candidates containing a piperazine moiety	2
Figure 1.1.1	Formation of diketopiperazine from Aspartame	3
Figure 1.3.1	Dynamic Kinetic Resolution	7
Figure 1.3.2	Asymmetric synthesis of β -hydroxy esters	8
Figure 1.3.3	Stereoselective amination of α -bromo amides	9
Figure 1.3.4	Synthesis of optically active α -amino acids	10

Chapter 2

Figure 2.3.1	^1H -NMR Spectrum of 6,6a,7,8,9,10-hexahydro-5 <i>H</i> -pyrido[1,2- <i>a</i>]quinoxalin-6-one 23	18
Figure 2.3.2	^{13}C -NMR Spectrum of 6,6a,7,8,9,10-hexahydro-5 <i>H</i> -pyrido[1,2- <i>a</i>]quinoxalin-6-one 23	19
Figure 2.3.3	HPLC trace of compound 23 with Chiralcel OB column	22
Figure 2.3.4	^1H -NMR Spectrum of 6,6a,7,8,9,10-hexahydrobenzo[<i>b</i>]pyrido[1,2- <i>d</i>][1,4]oxazin-6-one 26	27
Figure 2.3.5	^{13}C -NMR Spectrum of 3-(3-butenyl)-3,4-dihydro-2 <i>H</i> -pyrido[3,2- <i>b</i>][1,4]oxazin-2-one 29	29
Figure 2.3.6	^1H -NMR Spectrum of compound 31a	32
Figure 2.3.7	^{13}C -NMR Spectrum of compound 31a	33

Figure 2.3.8	¹ H-NMR Spectrum of 1,2,3,4,6,11,12,12a-octahydrobenzo[<i>e</i>]pyrido [1,2- <i>a</i>][1,4]diazepin-12-one <u>32</u>	34
Figure 2.3.9	¹³ C-NMR Spectrum of 1,2,3,4,6,11,12,12a-octahydrobenzo[<i>e</i>]pyrido [1,2- <i>a</i>][1,4]diazepin-12-one <u>32</u>	35
Figure 2.3.10	¹ H-NMR Spectrum of 2-phenylperhydropyrido[1,2- <i>a</i>]pyrazin-1-one <u>34</u>	38
Figure 2.3.11	¹³ C-NMR Spectrum of 2-phenylperhydropyrido[1,2- <i>a</i>]pyrazin-1-one <u>34</u>	39
Figure 2.4.1	¹ H-NMR Spectrum of 5,6,6a,7,8,9-hexahydropyrrolo[1,2- <i>a</i>]quinoxalin -6-one <u>41</u>	44
Figure 2.4.2	¹³ C-NMR Spectrum of 5,6,6a,7,8,9-hexahydropyrrolo[1,2- <i>a</i>]quinoxalin -6-one <u>41</u>	45
Figure 2.4.3	HPLC trace of compound <u>41</u> with [<i>R</i>]-3,5-dinitrobenzoyl phenylglycine propylsilyl column	48
Figure 2.4.4	¹ H-NMR Spectrum of compound <u>42</u>	49
Figure 2.4.5	¹³ C-NMR Spectrum of compound <u>42</u>	50
Figure 2.4.6	¹ H-NMR Spectrum of compound <u>45</u>	53
 Chapter 4		
Figure 4.0.1	2-Hydroxybenzocyclobutenones	96
Figure 4.2.1	Benzyne precursors	108
Figure 4.4.1	Suzuki protocol for benzyne generation	111
Figure 4.4.2	¹ H-NMR Spectrum of 2-(1-hydroxycyclohexyl)-1-[(4-methylphenyl) sulfonyloxy] benzene <u>96</u>	114
Figure 4.5.1	¹ H-NMR Spectrum of 3-(2-iodophenyl)-N-methyl-2-pyrrolidinone <u>102</u>	116

Figure 4.5.2	¹³ C-NMR Spectrum of 3-(2-iodophenyl)-N-methyl-2-pyrrolidinone 102	117
Figure 4.5.3	Iodination of anion with 1,2-diiodoethane	118
Figure 4.5.4	¹ H-NMR Spectrum of N-(2-iodophenyl)-2,2,6,6-tetramethylpiperidine 103	120
Figure 4.5.5	¹ H-NMR Spectrum of compound 108	123
Figure 4.5.6	¹³ C-NMR Spectrum of compound 108	124
Figure 4.6.1	¹ H-NMR Spectrum of N-methyl-5-[(trifluoromethyl)sulfonyl] -2-pyrrolidinone 114	131
Figure 4.6.2	¹³ C-NMR Spectrum of N-methyl-5-[(trifluoromethyl)sulfonyl] -2-pyrrolidinone 114	132

LIST OF SCHEMES

Chapter 1

Scheme 1.1.1	Synthesis of 2-alkyl-4-acylpiperazine Ftsase inhibitor	4
Scheme 1.1.2	Asymmetric hydrogenation of tetrahydropyrazine derivatives	4
Scheme 1.1.3	Solid phase synthesis of a tetrahydroquinoxalin-2-one	5
Scheme 1.4.1	General example of heterocycle synthesis via DKR of α -halo [R]-pantolactone esters with bifunctional nucleophiles	11

Chapter 2

Scheme 2.2.1	DKR approach to heterocycle formation	14
Scheme 2.2.2	Preparation of [R]-pantolactone esters	16
Scheme 2.3.1	Proposed order of displacement in DKR reactions	20
Scheme 2.3.2	Preparation of 23 from 20c and 22	21
Scheme 2.3.3	Proposed intermediates (products) for the reaction of 20c with 24	24
Scheme 2.3.4	Cyclization attempt of compound 28	28
Scheme 2.3.5	Preparation of isomers 31a and 31b	30
Scheme 2.3.6	Formation of the 7-membered ring in 32 from compound 31a	31
Scheme 2.3.7	Preparation of compound 34	36
Scheme 2.3.8	Possible preparation of compound 37	37
Scheme 2.3.9	Formation of the major side product 38	41
Scheme 2.4.1	Preparation of compound 41 from 20b and 40	46
Scheme 2.4.2	Formation of the double elimination product 42	46

Scheme 2.4.3 Formation of compound 43	51
Scheme 2.4.4 Formation of compound 44	51
Scheme 2.4.5 Formation of N-benzyl proline derivatives via DKR process	52
Scheme 2.4.6 Formation of compound 45	54
Scheme 2.6.1 Preparation of starting material 50	59
Scheme 2.7.1 DKR products from nucleophilic substitution of t-butyl pyroglutamate derivatives	61
Scheme 2.7.2 Proposed reaction pathway for the formation of 23 from 50	62
 Chapter 3	
Scheme 3.0.1 Original preparation of benzocyclobutenol and benzocyclobutenone	89
Scheme 3.0.2 Preparation of substituted isoquinolines	90
Scheme 3.0.3 Preparation of 2-substituted indoles	91
Scheme 3.0.4 Preparation of substituted naphthalene derivatives	92
Scheme 3.1.1 2+2 Cycloaddition	93
Scheme 3.1.2 Benzocyclobutenones from acylsilanes	94
 Chapter 4	
Scheme 4.0.1 Halogen-metal exchange approach	95
Scheme 4.0.2 Biehl's Anthrone imine synthesis	97
Scheme 4.0.3 Proposed mechanism for conversion of 67 to 70	98
Scheme 4.0.4 Proposed formation of cyclobutenone ring via intermediate 69	99
Scheme 4.1.1 Preparation of 2-bromophenylacetic acid	100

Scheme 4.1.2 Preparation of 2-(2-bromophenyl)-2-methylpropanenitrile 75	102
Scheme 4.1.3 Ring opening products from the reaction of compound 75	103
Scheme 4.1.4 Functionalized arylmagnesium iodide preparation	106
Scheme 4.1.5 Preparation of 2-iodobenzyl cyanide	106
Scheme 4.2.1 Synthesis of benzocyclobutenones from benzyne and 1,1-dimethoxyethylene	107
Scheme 4.3.1 Proposed benzocyclobutenone synthesis	109
Scheme 4.3.2 Proposed application of products formed from the reaction of cyclic amides with benzyne	110
Scheme 4.4.1 Preparation of 2-iodophenyl tosylate 95	111
Scheme 4.4.2 Reaction of <i>o</i> -iodophenyl tosylate and cyclohexanone with <i>t</i> -BuLi	112
Scheme 4.4.3 Benzyne generation by deprotonation of phenyl halides with LTMP	113
Scheme 4.5.1 Proposed mechanism for the formation of 102	118
Scheme 4.5.2 Hypervalent iodine intermediate	119
Scheme 4.5.3 Proposed formation of compound 103	121
Scheme 4.5.4 Formation of the proposed structure 106	125
Scheme 4.5.5 Proposed mechanism to final product 108	126
Scheme 4.6.1 Preparation of phenyl triflate	130

LIST OF TABLES

Chapter 1

Table 1.4.1	Products of DKR reactions on α -halo [<i>R</i>]-pantolactone esters	11
-------------	--	----

Chapter 2

Table 2.3.1	Solvent effect on the enantiomeric ratio of compound 23	23
Table 2.3.2	Heterocycles prepared via DKR of 6-bromo-2-iodo [<i>R</i>]-pantolactone ester 20c with bifunctional nucleophiles	25
Table 2.6.1	Preparation of α -benzylamino derivatives	58

Chapter 4

Table 4.1.1	Reaction of compound 75 with t-BuLi	104
Table 4.5.1	Reaction of N-methyl-2-pyrrolidinone enolate with benzyne generated from different phenyl halides	128

ABBREVIATIONS AND SYMBOLS

AB d	AB doublet
brs	broad singlet
°C	degrees Celsius
calcd.	calculated
CH₂Cl₂	methylene chloride
cm⁻¹	wavenumber
¹³C-NMR	carbon-13 nuclear magnetic resonance
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DKR	Dynamic Kinetic Resolution
dt	doublet of triplets
EI	electronic ionization
equiv.	equivalents
Et₃N	triethylamine
g	gram
¹H-NMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared

J	coupling constant
m	multiplet
Me	methyl
mg	milligram
mL	milliliter
mp	melting point
M ⁺	parent molecular ion
MS	low resolution mass spectroscopy
NMR	nuclear magnetic resonance
ppm	parts per million
q	quartet
qt	quartet of triplets
rt	room temperature
rx.	reaction
s	singlet
t	triplet
td	triplet of doublets
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography

ABSTRACT

The preparation of enantiomerically enriched bi- and tricyclic heterocycles via a dynamic kinetic resolution protocol is discussed. This methodology was applied to the reaction of ω -bromo- α -iodo alkyl [*R*]-pantolactone esters with a number of bifunctional nucleophiles such as, 1,2-phenylenediamine, which resulted in the formation of bicyclic piperazines. Several other nucleophiles such as 2-aminophenols, also formed the expected heterocycles, but aliphatic 1,2-diamines tended to give elimination rather than displacement products, with the above dihalo esters. The preparation of these heterocycles in a simple three step sequence, starting from commercially available ω -bromo alkyl acids is detailed.

Attempts were made to prepare benzocyclobutenones and benzocyclobutenols via halogen-metal exchange and subsequent cyclization in *o*-halobenzyl cyanide. Finally, the reaction of amide, ester and ketone enolates with a benzyne species generated via reaction of halobenzenes with lithium 2,2,6,6-tetramethylpiperidide at room temperature or below is also discussed. The reaction of amide and ester enolates with benzyne has not been previously discussed in the literature. Surprisingly, reaction of ester or amide enolates with benzyne in the presence of excess iodobenzene afforded substituted iodobenzenes as the major reaction product. These products were obtained by reaction of the enolates with benzyne followed by transfer of iodine from iodobenzene. The results represent the first example in which iodobenzene acts as a positive source of halogen.

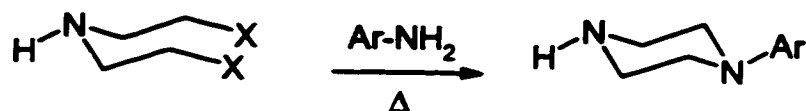
Chapter 1

Preparation of Optically Active Compounds via Dynamic Kinetic Resolution

1.0 Introduction

Piperazine rings began making their appearance back in the 1920's where they were typically symmetrically N-aryl or N-alkylated. In 1933, Prelog published the first synthesis of a mono-substituted piperazine ring, N-phenylpiperazine, by the reaction of aniline and N,N-bis-(2-chloroethyl)amine (figure 1.0.1).¹

Figure 1.0.1 : Initial preparation of N-phenylpiperazine

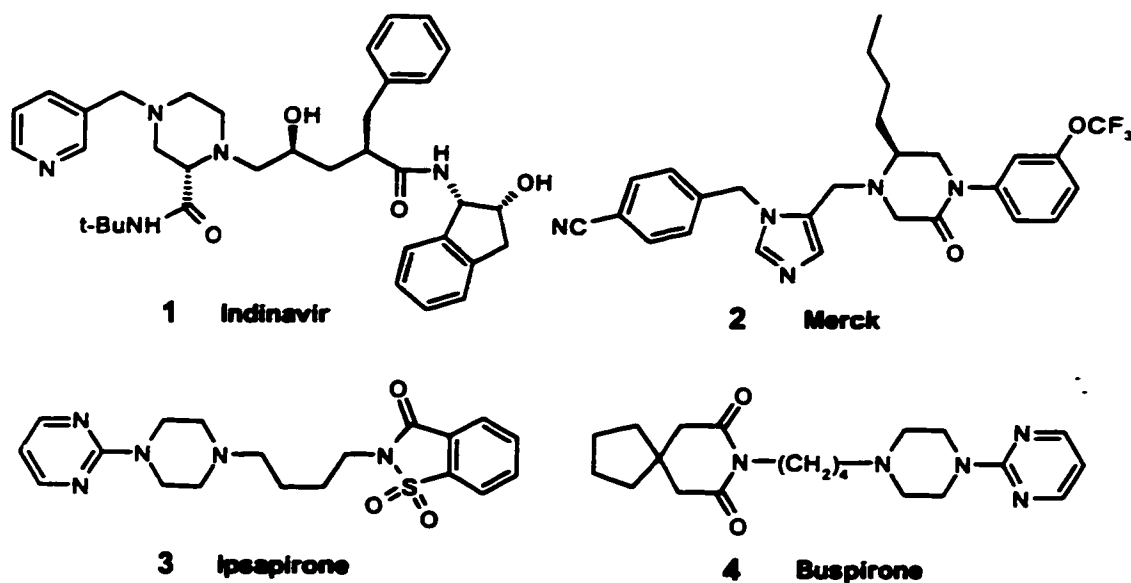


From those early days, the physiological properties of piperazines were already generating interest since they were found to exert, even in small dosages, various physiological effects. These included accelerated pulse and breathing and hypersensitivity to external stimuli.¹

The past few decades have seen the introduction of a number of pharmaceutical compounds which contain five, six, and seven-membered rings such as piperazines, piperidines, imidazoles, benzodiazepines and/or other heterocycles containing in addition to nitrogen, sulfur and oxygen. Compounds containing these heterocycles have important physiological properties, the effects of which range from anti-histamine, analgesic, anti-inflammatory, anti-hypertensive and anti-cancer. Some current examples of promising candidates containing a piperazine moiety include the HIV protease inhibitor Indinavir² 1 and

a compound that blocks farnesyltransferase activity (anti-cancer)³ 2 from Merck, Ipsapirone (antidepressant)⁴ 3 and Buspirone (anxiolytic drug) 4.⁵

Figure 1.0.2 : Pharmaceutical candidates containing a piperazine moiety

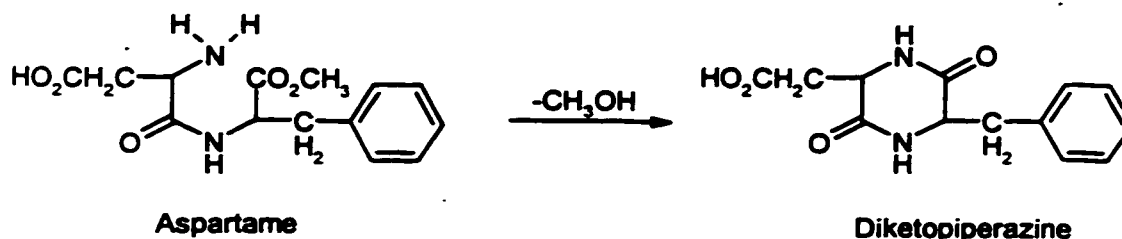


A large number of the piperazines have groups attached only to the nitrogens of the piperazine ring, which often serves mainly as a cyclic linker. In more recent times there has been a greater use of carbon substituted piperazines (e.g. Indinavir 1 and compound 2). This has resulted in a need for methods of synthesis that allow for the generation of specific isomers since physiological properties of different isomers sometimes vary greatly from one to another.

1.1 Synthesis of Asymmetric Piperazine Rings

One area of chemistry, related to piperazines that has received a fair amount of attention in recent years has been the ready cyclization of dipeptides to form diketopiperazines. These have been investigated as a tool in the study of peptides. Their role has been to serve as constrained peptide mimics.⁶ These mimics restrict the motion of the peptide, allowing for easier determination of the conformation of the peptide, as well as, the action of the natural peptide. The study of the different factors that induce this peptide cyclization, which include heat, moisture, and pH has therefore received much attention in recent years. One dipeptide that has been extensively studied for its ready cyclization to the diketopiperazine (figure 1.1.1) is Aspartame.^{7,8,9} In the case of Aspartame, studies have focused on finding ways to prevent this cyclization in order to allow a greater variety of uses for this sweetener. At the present time, it cannot be used for baking since upon cyclization, caused by heating, the compound loses its sweetness.

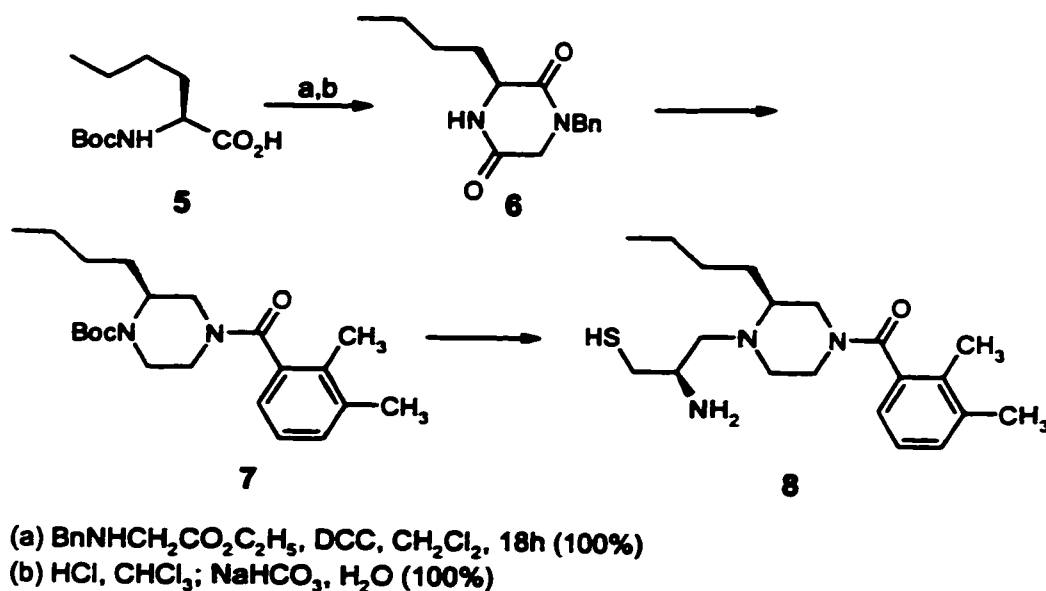
Figure 1.1.1 : Formation of diketopiperazine from Aspartame



When incorporating a specific R-group onto the piperazine ring, the general approach has been to use chiral starting materials, which already have the desired group with the required stereochemistry, such as amino acids. When a specific group is not available, chiral starting materials with a functional group that could later be modified to obtain the desired functionality and stereochemistry have been employed. An example of the former is shown

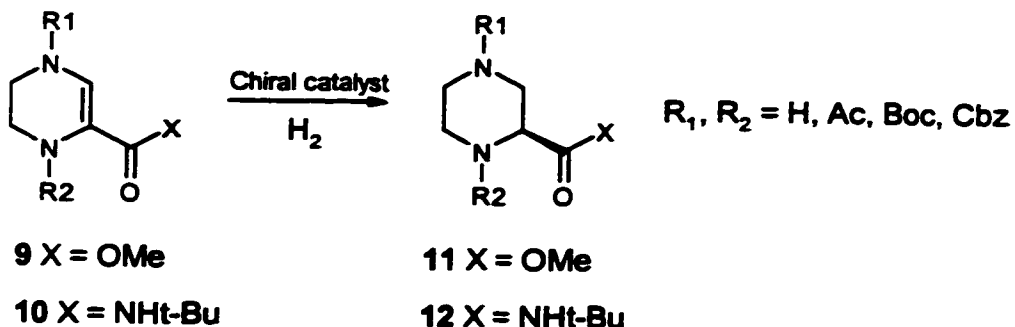
in scheme 1.1.1 for an earlier Merck compound designed to inhibit the activity of farnesyltransferase (Ftase).¹⁰

Scheme 1.1.1 : Synthesis of 2-alkyl-4-acylpiperazine Ftase inhibitor



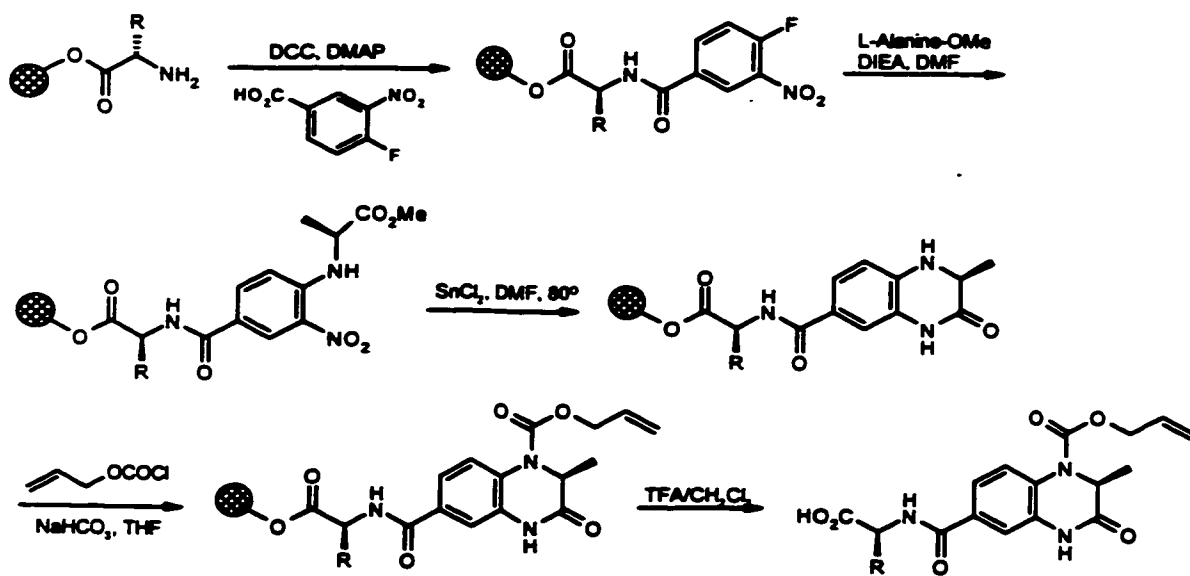
In this synthesis, the optically active piperazine ring was formed by coupling of N-Boc-norleucine **5** with ethyl N-benzylglycinate, followed by N-deprotection and cyclization to the diketopiperazine **6**. Reduction by LiAlH_4 then a sequence of deprotection, protection and acylation give the intermediate **7**. N-alkylation under appropriate conditions affords the Ftase inhibitor **8**. Although using chiral starting materials in the preparation of optically active piperazines is widely used, there have also been examples where chiral catalysts are used to generate the chiral center from an achiral compound, an example² of which is shown in scheme 1.1.2.

Scheme 1.1.2 : Asymmetric hydrogenation of tetrahydropyrazine derivatives



These previous asymmetric piperazine syntheses have been examples of solution phase chemistry. In recent years, we have seen a growing number of reactions being carried out on solid phase. Heterocycle synthesis would not be the exception. Using solid phase chemistry for synthesizing pharmaceutical compounds is a very attractive area since it helps eliminate the tedious purification process needed after a solution phase reaction. In solid phase chemistry, one simply detaches the final product from the resin and you have, usually, a clean product. The following is an example of solid phase synthesis for tetrahydroquinoxalin-2-ones (scheme 1.1.3).¹¹

Scheme 1.1.3 : Solid phase synthesis of a tetrahydroquinoxalin-2-one



Even though these types of synthetic pathways to optically active piperazines are very effective, they require the use of pure and optically active starting materials and can be somewhat lengthy.

In order to eliminate the need for optically active starting materials, we opted for a synthetic pathway to piperazines and related heterocycles that takes advantage of dynamic kinetic resolution.

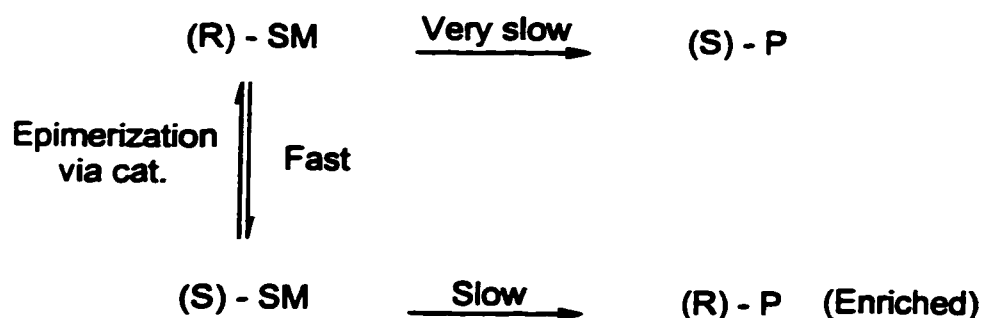
1.3 Use of Dynamic Kinetic Resolution for Piperazine and Other Heterocycle Synthesis

Dynamic kinetic resolution has become a very useful synthetic tool in recent years with the advent of very effective chiral auxiliaries. Development of new auxiliaries, such as, pyrrolidinones¹² and imidazolidin-2-ones^{13,14} has resulted in high levels of chiral induction, as well as, a greater ability to predict the outcome of such reactions.

1.3.1 Principle of Dynamic Kinetic Resolution (DKR)

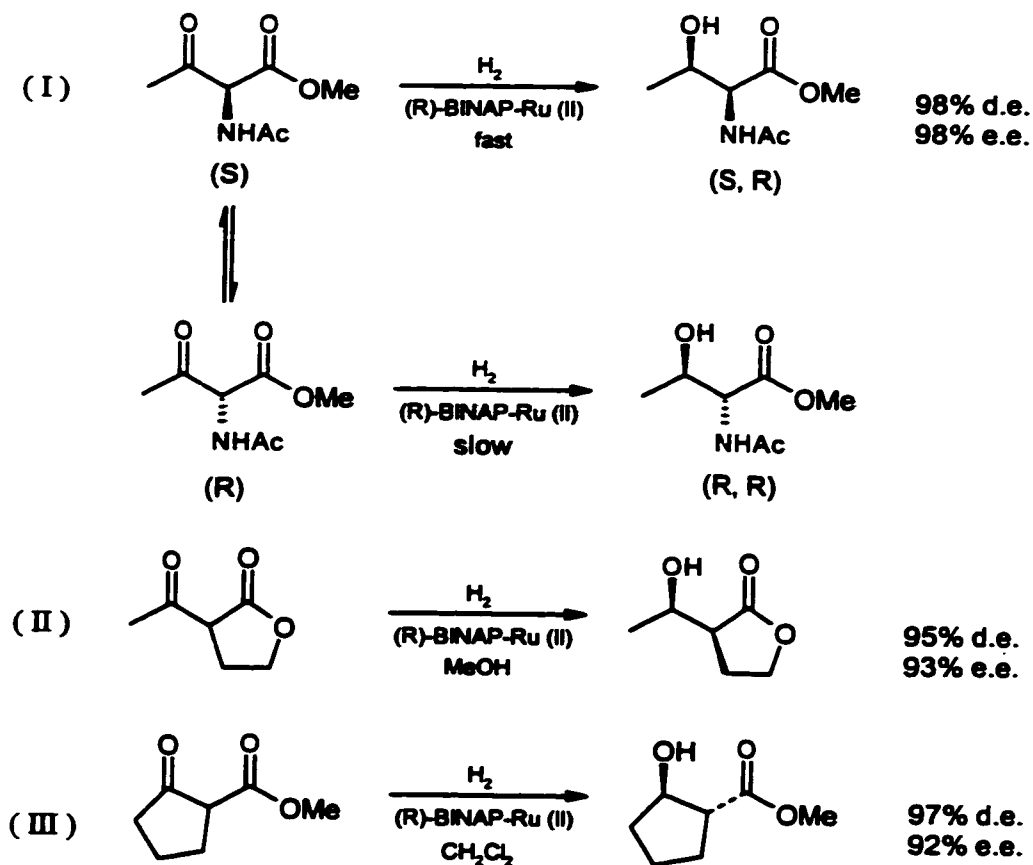
DKR is an evolution of traditional kinetic resolution methods, in that it can, in principle, allow for quantitative conversion of the racemic starting material into a single stereoisomer of the product compared to a maximum 50% yield for classical resolution methods¹⁵. The reason for this is that in the DKR process, in addition to a substantial reaction rate difference between the substrate isomers, one also has *in situ* isomerization of the isomers. This allows both isomers to be converted into one, or mainly, one of the enantiomeric product. This method requires that the rate of epimerization of the starting isomers be fast compared to the reaction leading to the products. Also, the products must be stable under the reaction conditions. Figure 1.3.1 shows a schematic of this process.

Figure 1.3.1 : Dynamic Kinetic Resolution



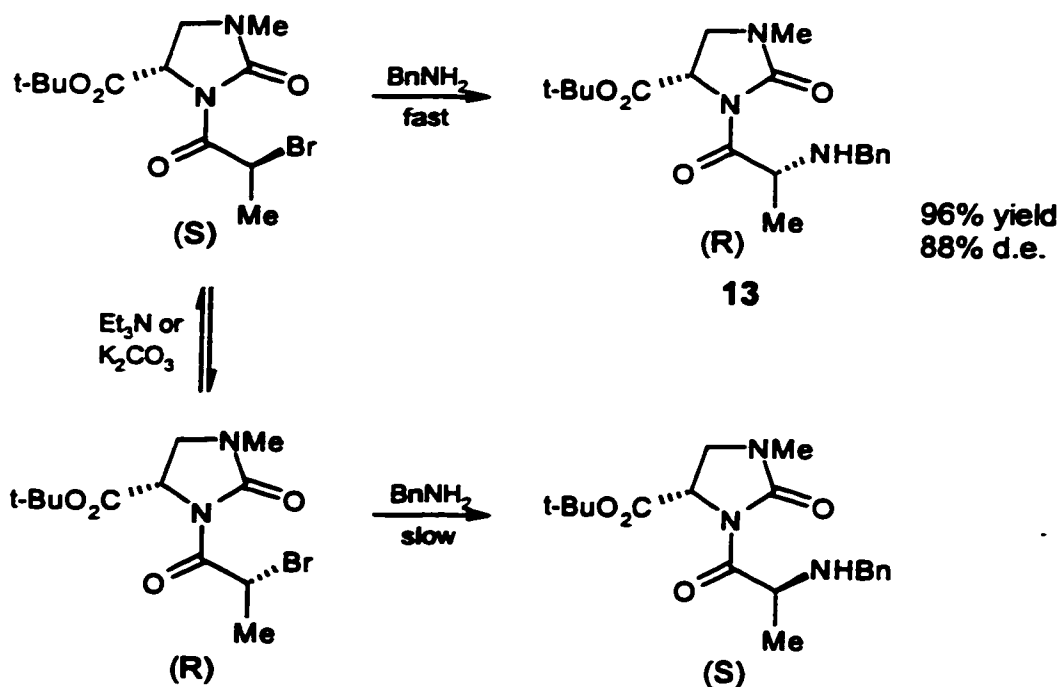
Many organic reactions have been adapted to take advantage of dynamic kinetic resolution in order to obtain products stereoselectively instead of in racemic mixtures. Noyori made an efficient use of DKR for the stereoselective hydrogenation of α -substituted β -keto esters using BINAP-Ruthenium(II) as a chiral hydrogenating agent. Use of this catalyst led to the formation of a series of β -hydroxy esters with high levels of chiral induction (figure 1.3.2).¹⁵

Figure 1.3.2 : Asymmetric synthesis of β -hydroxy esters



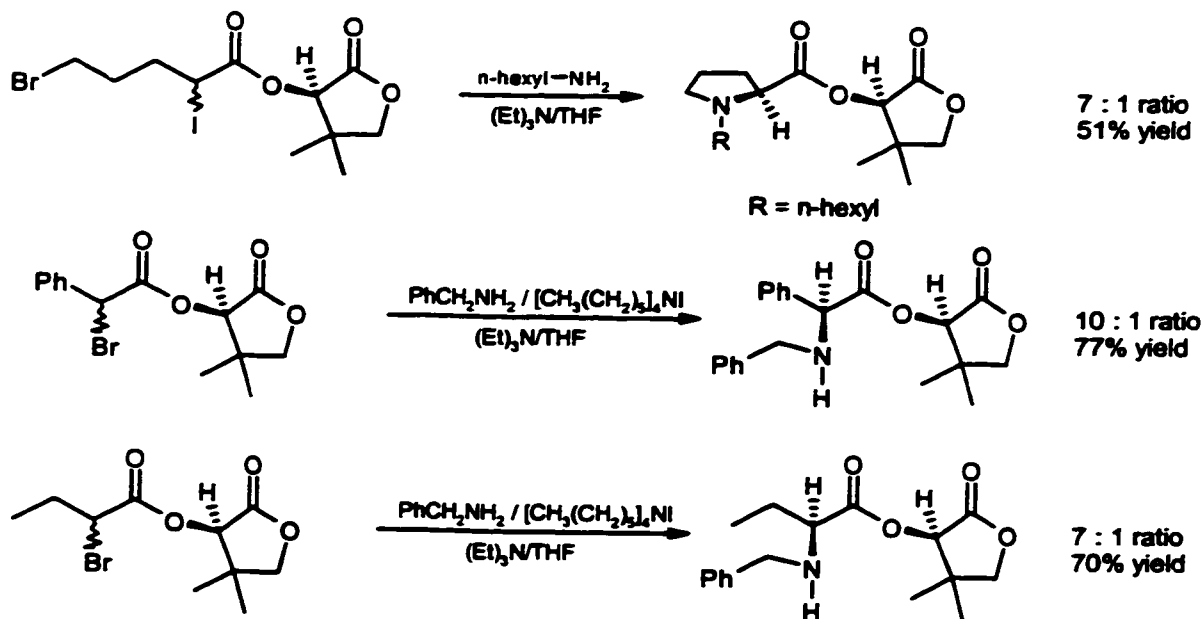
Nunami used the chiral auxiliary, *t*-butyl (4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate, coupled to α -bromo acids, to prepare a series of optically active unnatural α -amino acids.¹⁶ In these reactions, rapid epimerization prior to nucleophilic attack by the benzylamine, led to 13 with 88% diastereomeric excess (figure 1.3.3).¹⁵

Figure 1.3.3 : Stereoselective amination of α -bromo amides



An earlier example of the utilization of chiral auxiliaries in the preparation of novel amino acids was shown by Durst *et al.* They reacted various amines with [*R*]-pantolactone esters of α -haloacids in the presence of tetraalkylammonium iodide to generate enantiomerically enriched α -amino esters (figure 1.3.4).¹⁷ Epimerization of the starting esters prior to nucleophilic attack by the amine is facilitated by addition of I^- to the reaction mixture.

Figure 1.3.4 : Synthesis of optically active α -amino esters



1.4 DKR of α -Halo [*R*]-Pantolactone Esters to Form Piperazines and Related Heterocycles

As shown previously, there are examples^{18,19} in the literature highlighting the use and effectiveness of dynamic kinetic resolution. Recent results in our own labs have shown that DKR is an effective and quick way of producing optically enriched heterocycles such as piperazines. In order to obtain these various heterocycles, α -halo [*R*]-pantolactone esters and acrylates were reacted with a variety of bifunctional nucleophiles such as 1,2-phenylenediamine, 1,8-diaminonaphthalene and 2-aminophenol.²⁰ Scheme 1.4.1 shows the general reaction involved followed by a table of some of the results obtained (table 1.4.1).

Scheme 1.4.1 : General example of heterocycle synthesis via DKR of α -halo [*R*]-pantolactone esters with bifunctional nucleophiles

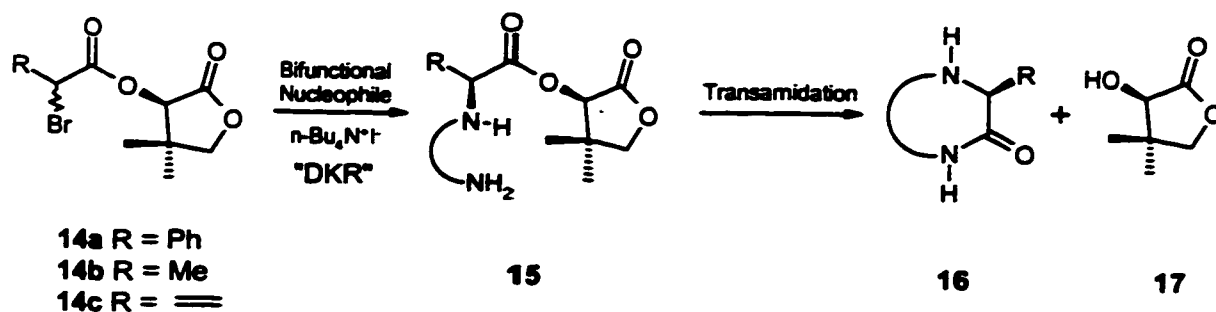
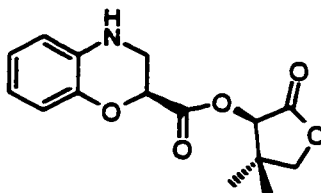
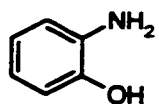


Table 1.4.1 : Products of DKR reactions on α -halo [*R*]-pantolactone esters

Entry	Ester	Nucleophile	Product	Yield(%)	er or dr
1	14a			84	--
2	14a			72	94 : 6
3	14a			45	--
4	14c			34	84 : 16

5

14c



34

80 : 20

Reaction conditions simply involved stirring a solution of the [*R*]-pantolactone ester, *n*-tetrabutylammonium iodide, triethylamine and the diamine or other nucleophile under nitrogen at room temperature. The enantiomeric (er) or diastereomeric (dr) ratios were obtained by chiral HPLC and proton NMR, respectively.

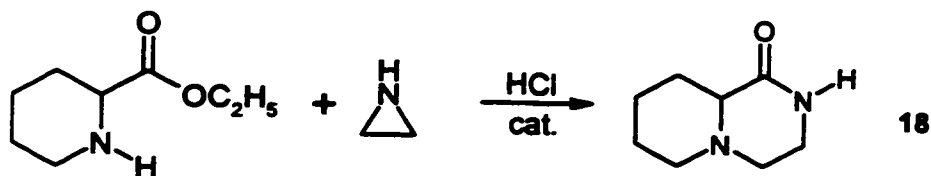
These preliminary results have shown that the use of dynamic kinetic resolution to prepare piperazine rings and other heterocycles seems promising. Hence, the next chapter will focus on the results obtained from the reaction of 5-bromo-2-iodopentanoate and 6-bromo-2-iodohexanoate [*R*]-pantolactone esters with diamines and amino alcohols to form bicyclic and tricyclic piperazines and heterocycles.

Chapter 2

Preparation of Enantiomerically Enriched Compounds Containing Piperazine Rings and Other Heterocycles via Dynamic Kinetic Resolution

2.0 Background

The bicyclic oxo-piperazine **18** was first prepared more than three decades ago. One method of preparation involved treating ethyl 2-piperidinecarboxylate in the presence of a catalytic amount of its hydrochloride, with one equivalent of ethyleneimine.²¹



A number of papers on the synthesis of these types of ring systems were published during the early 1980's, most of which did not take into consideration the stereochemistry at the asymmetric carbons.^{22,23} With the level of interest for these types of compounds growing, syntheses of optically active piperazines began making their appearance in the latter part of the 80's. These however, involved the use of chiral starting materials such as amino acids, which carried the required stereochemistry.^{24,25}

The results presented in this chapter will demonstrate a simple procedure that allowed for the preparation of several piperazines and related heterocycles in enantiomerically enriched form via the use of dynamic kinetic resolution. The use of both (S) and (R) forms of the chiral auxiliary would therefore enable one to prepare such compounds enriched in either isomer.

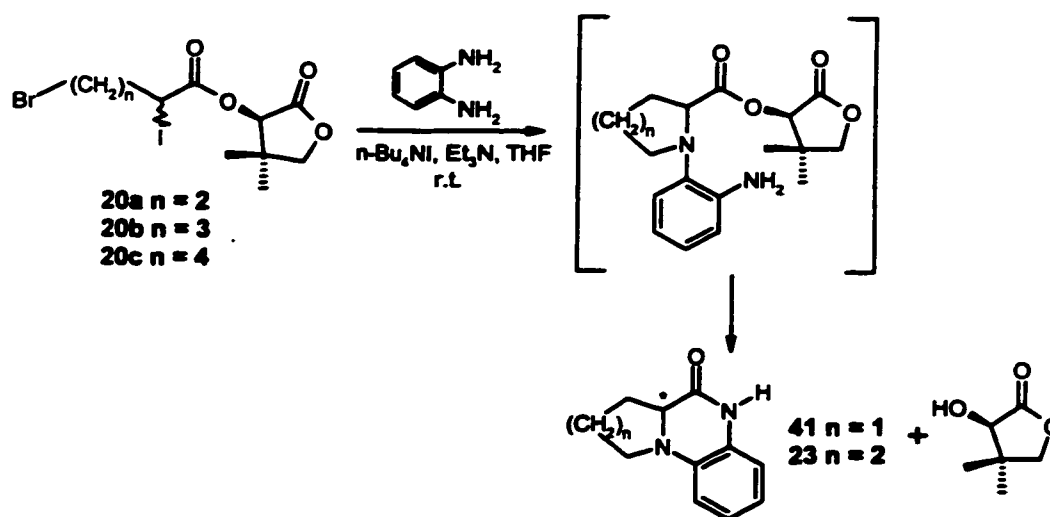
2.1 Results

DKR reactions involving simple S_N2 displacement of α -halo [*R*]-pantolactone esters with mono-functional nucleophiles, such as, benzylamine, dibenzylamine and pyrrolidine (chapter 1) have been described by our group. In this chapter, the DKR of α -halo and ω,α -dihalo [*R*]-pantolactone esters with bifunctional nucleophiles, such as, 1,2-phenylenediamine and 2-aminophenol will be discussed.

2.2.1 DKR of ω -Bromo- α -Iodo Alkyl [*R*]-Pantolactone Esters with Bifunctional Nucleophiles (Preparation of the [*R*]-Pantolactone Esters)

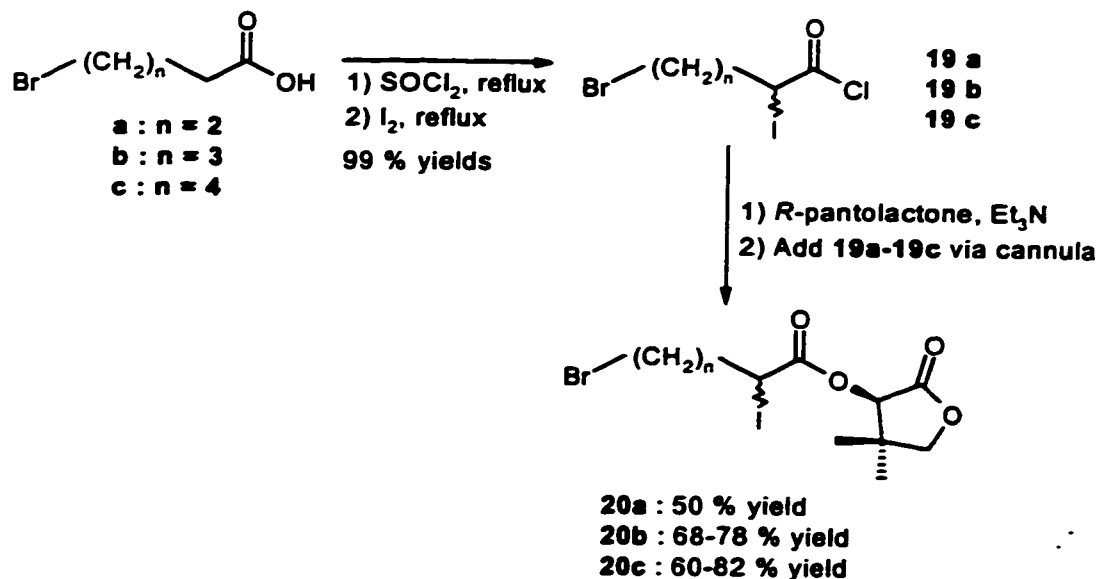
The reaction of a ω -bromo- α -iodo alkyl [*R*]-pantolactone ester (20a-c) with bifunctional nucleophiles should result in the sequential formation of two heterocycles. Scheme 2.2.1 outlines this possibility with 1,2-phenylenediamine as the nucleophile. This nucleophile was chosen in combination with 20c since the product formed is known in the literature and thus, its formation was suitable for determining optimal reaction conditions for this type of process.

Scheme 2.2.1 : DKR approach to heterocycle formation



The first step to these heterocyclic compounds was the preparation of the ω -bromo- α -iodo alkyl [*R*]-pantolactone esters **20a-c**. Three esters were synthesized from their corresponding C4, C5 and C6, ω -bromo acids. The three acids were refluxed in thionyl chloride to generate the acyl chlorides that were converted to the 2-iodo acyl chlorides by addition of iodine and further reflux.²⁶ These reactions proceeded quantitatively to give the three required acyl chlorides as liquids (**19a-c**). Each was confirmed by HRMS, ¹H-NMR, ¹³C-NMR and infrared spectroscopy. The incorporation of the iodide was confirmed with the ¹H-NMR spectrum by the appearance of a triplet integrating for 1H, representing the α -proton of the aliphatic side chain, at 4.98, 4.68 and 4.65 ppm for the C4, C5 and C6 analogs respectively. Preparation of the [*R*]-pantolactone esters was achieved by adding the acyl chlorides dissolved in dry THF, to a solution of [*R*]-pantolactone and triethylamine at 0 °C in THF. Silica gel chromatography produced roughly a 55:45 mixture of diastereomers of esters **20a**, **20b**, and **20c** in yields of 50%, 68-78% and 60-82% respectively (scheme 2.2.2). The diastereomeric ratio was most readily determined by integration of the signals of the remaining alpha hydrogen of the aliphatic chain due to the different diastereomers.

Scheme 2.2.2 : Preparation of [R]-pantolactone esters



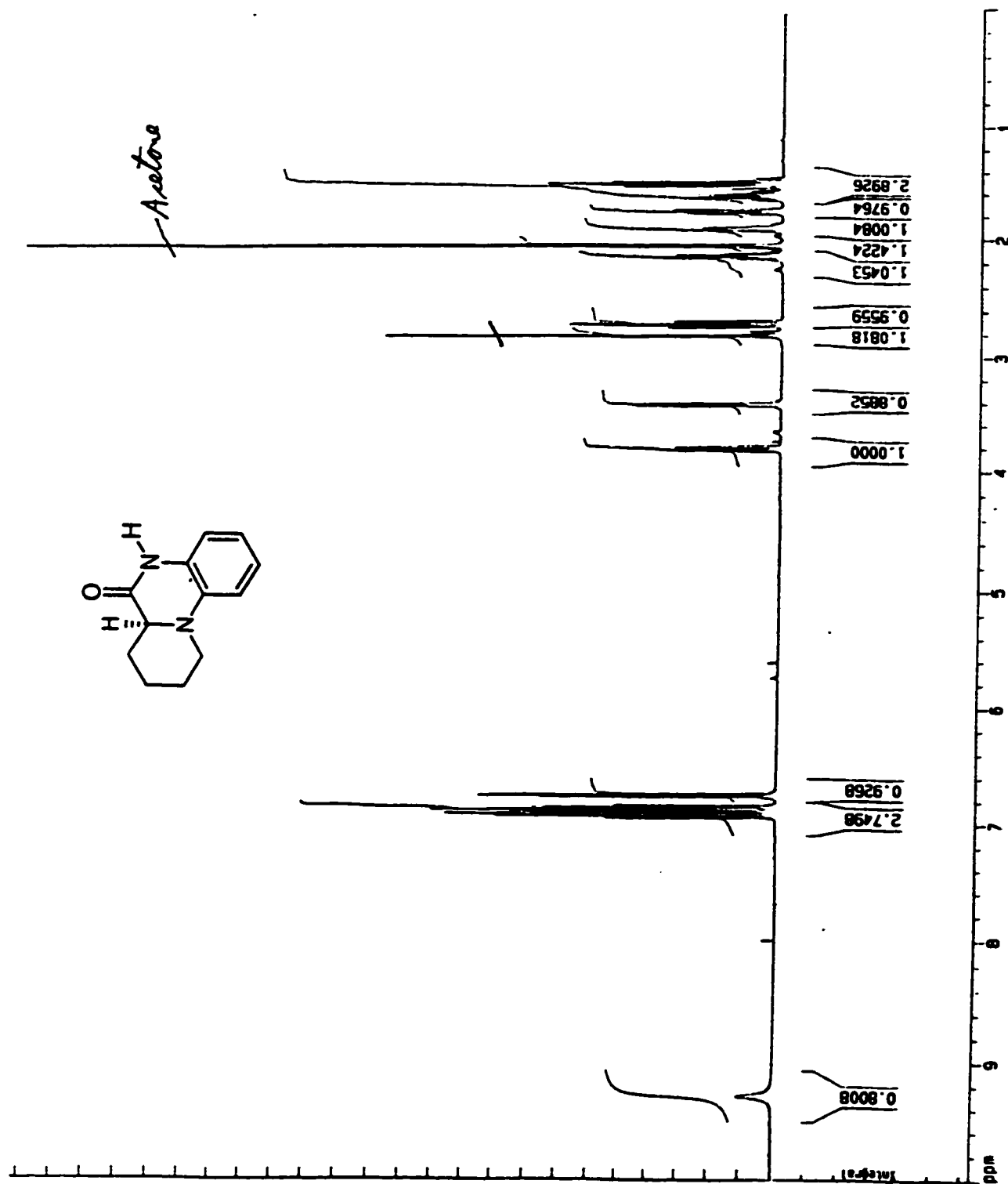
The yields for esters **20a-c** were somewhat lower than expected, possibly because of some ester hydrolysis during purification by silica gel chromatography. All of the [R]-pantolactone was consumed during the esterification step.

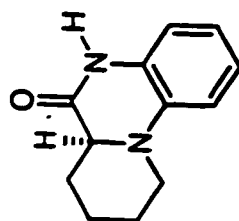
DKR reactions were carried out in anhydrous tetrahydrofuran at room temperature and under nitrogen atmosphere. The different bifunctional nucleophiles were added to solutions of the [R]-pantolactone ester containing 0.1 to 0.5 equivalent of $n\text{-Bu}_4\text{NI}$ followed by the addition of three equiv. of triethylamine. The mixtures were stirred for 19 hours to 8 days followed by an aqueous workup and purification by silica gel chromatography. The long reaction times are attributed to the fact that the TLC's were very unclear and always seemed to show some starting material. The reactions may have been allowed to continue for times much greater than needed. With knowledge of the TLC behavior, when reactions were repeated, they were stopped after much shorter times with the same yields and enantiomeric ratios as those with very long reaction times.

2.3 DKR of [*R*]-Pantolacto-6-Bromo-2-Iodohexanoate, 20c, with Bifunctional Nucleophiles

To a solution of 20c in 5 mL of dry THF and 0.5 equiv. of *n*-Bu₄NI was added one equivalent of 1,2-phenylenediamine (21) followed by addition of 3.1 equiv. of triethylamine. The reaction mixture was stirred at room temperature for 28 h followed by aqueous workup. Purification by silica gel chromatography afforded the desired heterocycle 23 in 54% yield as a yellow solid (mp, 184.0 –185.0 °C, [α]_D = -15.5 ° (c=1.0, CH₂Cl₂)). The structure assignment of the product was made based with the absence of the [*R*]-pantolactone peaks and the presence of the N-H peak as a broad singlet at 8.59 ppm in the ¹H-NMR spectrum (see figure 2.3.1). The spectrum also showed the 4 phenyl protons at 6.97, 6.77 and 6.72 ppm, the alpha proton appeared as a doublet of doublets at 3.53 ppm, and the CH₂ alpha to the nitrogen showed up as triplets of doublets at 3.76 and 2.71 ppm. The 6 protons from the other three CH₂ groups appeared at 2.20, 1.94, 1.73, 1.64 (2H) and 1.49 ppm. The IR spectrum showed the N-H stretch at 3466 cm⁻¹ and the amide carbonyl stretch at 1679 cm⁻¹. The ¹³C-NMR spectrum (see figure 2.3.2) showed the 12 carbon resonances with the carbonyl appearing at 169.7 ppm. The HRMS showed a strong M⁺ ion peak (17.9%) at *m/z* 202.1100 which was in agreement with the calculated value of 202.1106.

The proposed mechanism for the formation of compound 23 and all of the subsequent heterocycles is shown in scheme 2.3.1.

FIGURE 2.3.1: ¹H-NMR SPECTRUM OF 6,6A,7,8,9,10-HEXAHYDRO-5H-PYRIDO[1,2-A]QUINOXALIN-6-ONE 23



INDEX	FREQUENCY (PPM)	HEIGHT
1	169.691	31.1
2	135.516	41.2
3	126.293	41.1
4	124.040	80.0
5	119.319	84.2
6	115.465	77.4
7	112.095	60.0
8	77.450	116.5
9	77.027	119.3
10	76.603	118.0
11	59.724	76.6
12	46.557	68.4
13	26.702	70.0
14	23.726	70.9
15	23.247	73.6

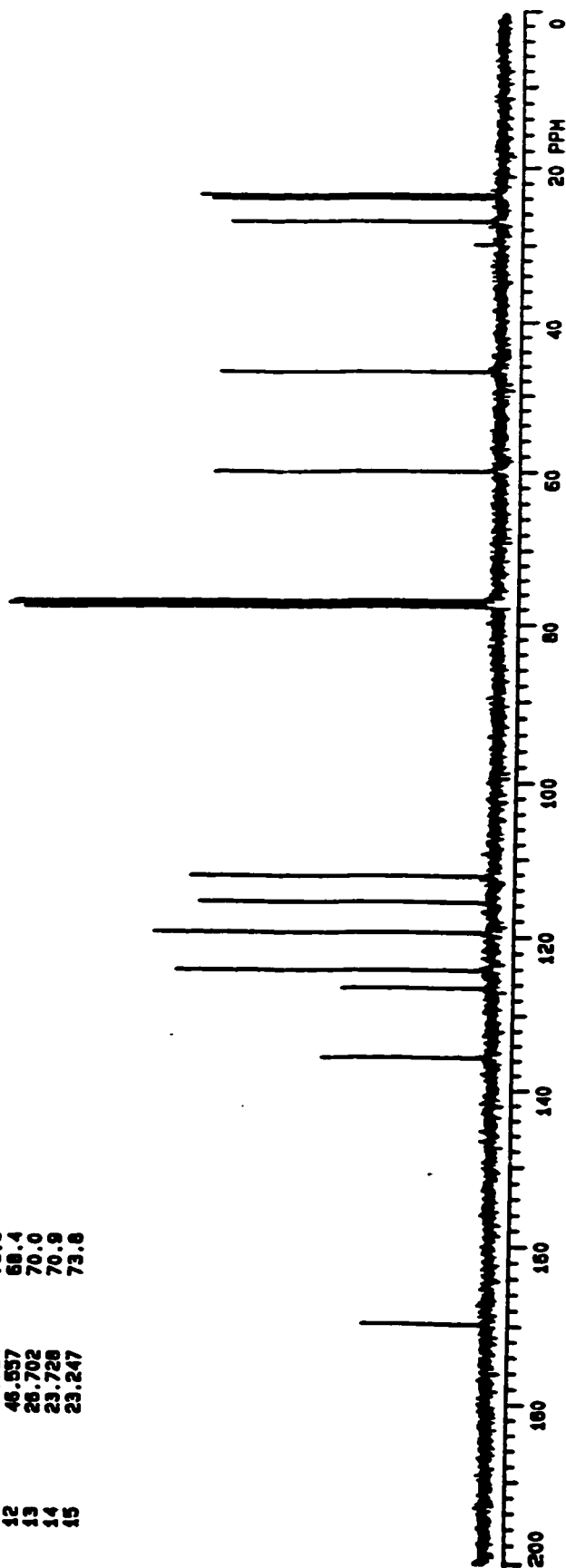
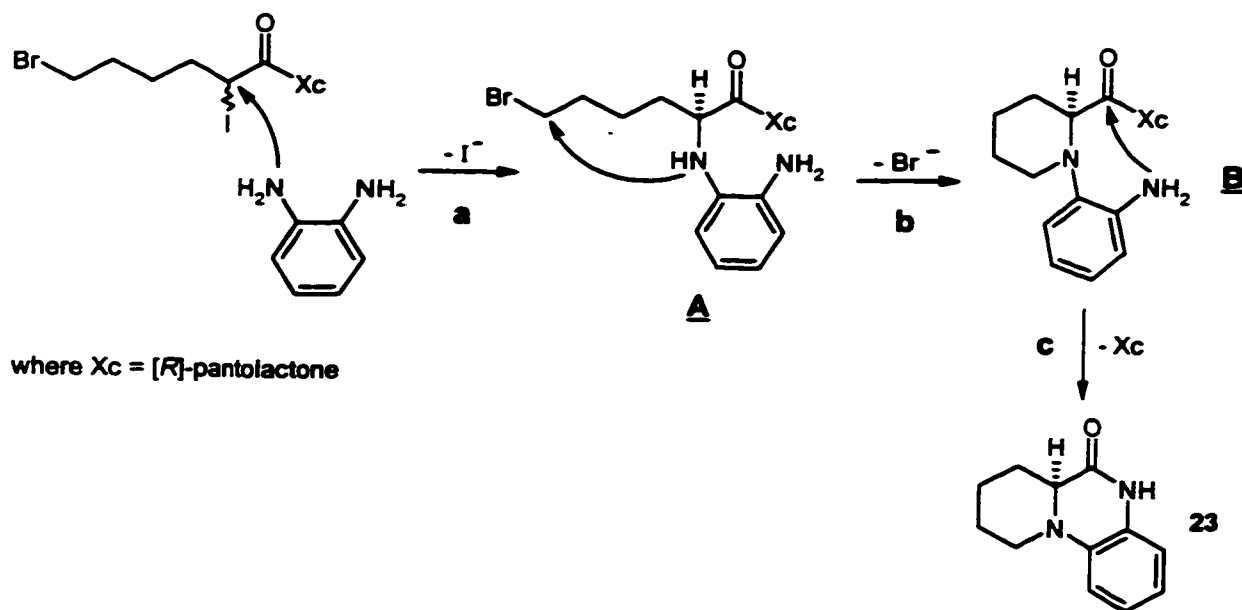


FIGURE 2.3.2: ^{13}C -NMR SPECTRUM OF 6,6A,7,8,9,10-HEXAHYDRO-5H-PYRIDO[1,2-A]QUINOXALIN-6-ONE 23

Scheme 2.3.1 : Proposed order of displacement in DKR reactions

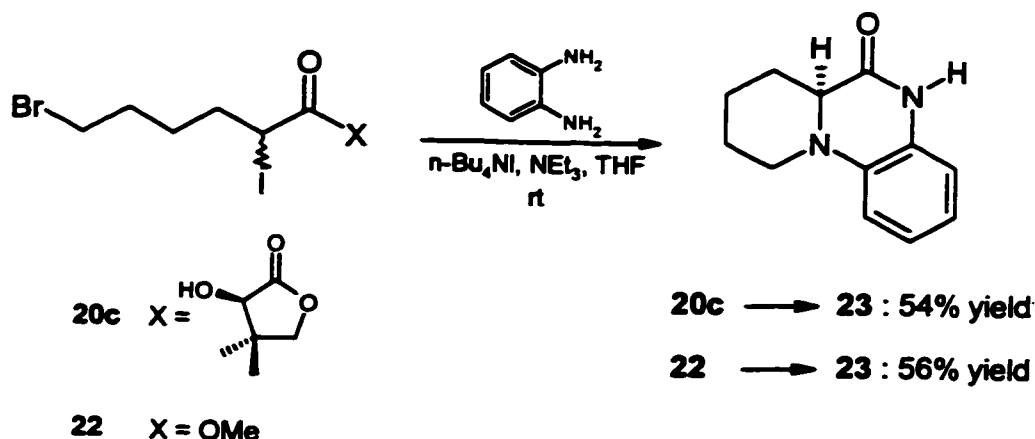


In this DKR reaction, there is initial attack at the alpha position to generate intermediate **A**, which is followed by a second attack by the nitrogen to displace the ω -bromine and form intermediate **B**. The second aniline group then displaces the [R]-pantolactone group to form the second heterocycle in the product. Steps **b** and **c** can be reversed depending on the ease of formation of the piperidine ring vs the acyl transfer reaction. The sequence **a>b>c** is illustrated by the formation of compound 31 while an **a>c>b** sequence would explain the formation of 28 that will be discussed later in this chapter. The stereochemistry assignment of the newly formed chiral center was based on precedent from results obtained in our laboratory. Therefore, all of the products formed were assigned the (S) configuration. This could not be verified via literature since none of the products obtained had previously been described in enantiomerically enriched form.

To determine the enantiomeric ratio of 23 prepared as above, by chiral HPLC, we required this compound in racemic form. Racemic 23 was obtained in 56% yield from

methyl 6-bromo-2-iodohexanoate **22** and 1,2-phenylenediamine using the same conditions as employed for obtaining enantiomerically enriched **23**. The spectroscopic properties of the two samples of **23** were identical. The yields in the two sequences were nearly identical, but the reaction time from **22** to **23** was significantly longer (90 h) than from **20c** to **23** (28 h) (scheme 2.3.2). However, this time difference can be attributed to the unclear TLC, as mentioned previously.

Scheme 2.3.2 : Preparation of 23 from 20c and 22



The enantiomer ratio obtained for **20c** to **23** was 4:1, determined by using a Chiralcel OB column eluting with a 96% to 4% ratio of hexanes to isopropanol (HPLC trace, see figure 2.3.3).

This ratio was disappointing and considerably lower than expected since previous DKR reactions of α -halo [*R*]-pantolactone esters with mono-substituted nucleophiles²⁷ such as, benzylamine, gave diastereomeric ratios ranging from 7:1 to 12:1.

In order to improve the enantiomeric excess in the synthesis of **23** from the C6 [*R*]-pantolactone ester **20c** and 1,2-phenylenediamine (**21**), the reaction was carried out in different solvents: acetonitrile, *N,N*-dimethylformamide, 1,4-dioxane and dichloromethane. The results are summarized in table 2.3.1.

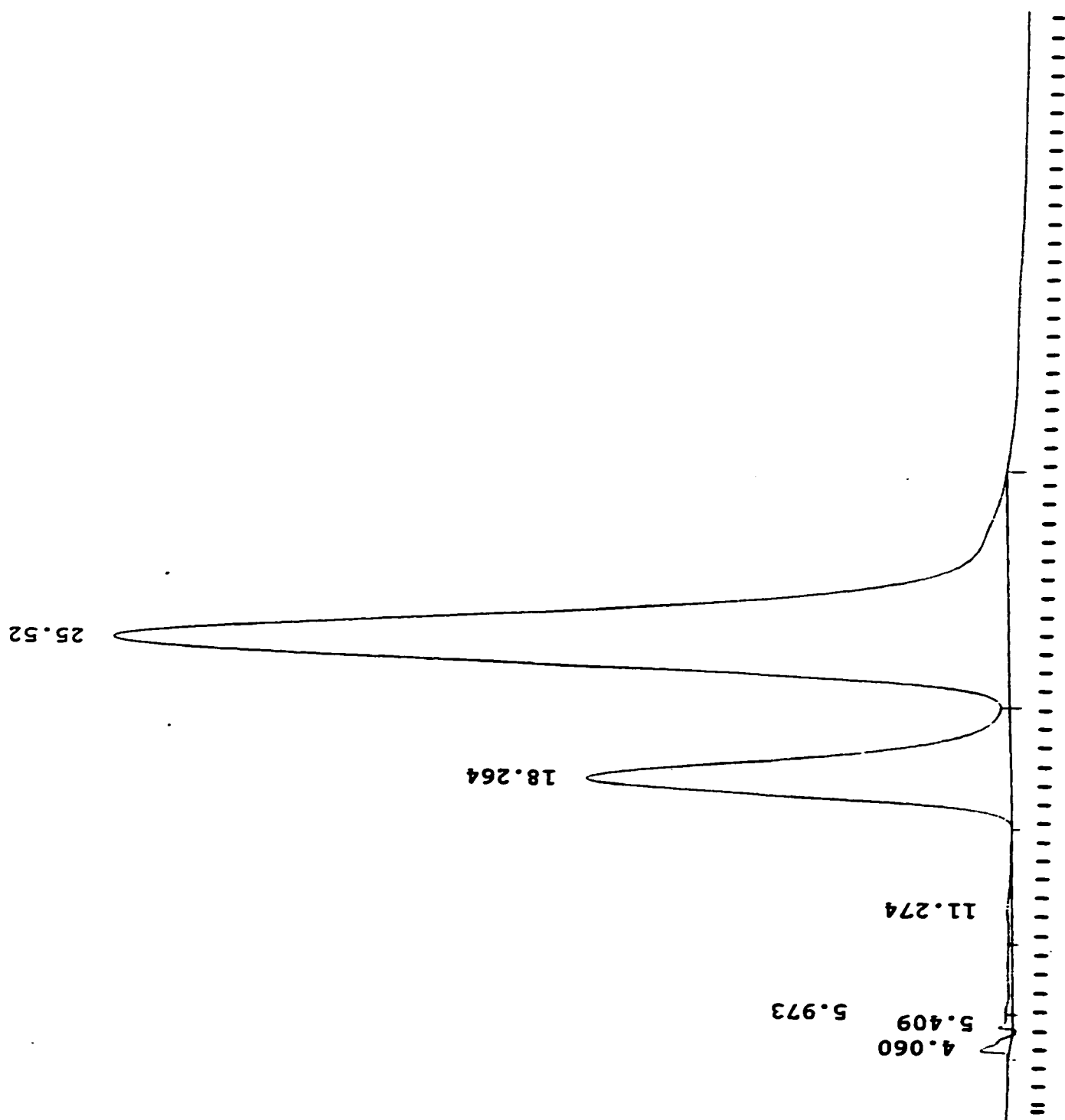
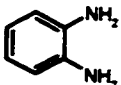


FIGURE 2.3.3: HPLC TRACE OF COMPOUND 23 WITH CHIRALCEL OB COLUMN

Table 2.3.1 : Solvent effect on the enantiomeric ratio of compound 23

<u>Run</u>	<u>Solvent</u>	<u>Equiv. of 21</u> 	<u>Equiv. of</u> <u>Et₃N</u>	<u>Equiv. of</u> <u>n-Bu₄NI</u>	<u>Result</u> <u>Yield / Ratio</u>
1	THF	1.0	3.1	0.5	54% / 4:1
2	THF	1.0	2.2	0.3	64% / ~ 4:1
3	CH ₃ CN	1.0	3.0	0.4	38% / ~ 3:1
4	DMF	1.0	3.0	0.4	60% / ~ 2:1
5	1,4-Dioxane	1.0	3.0	0.4	No rx. / All s.m.
6	CH ₂ Cl ₂	1.0	3.0	0.4	48% / 4.3:1

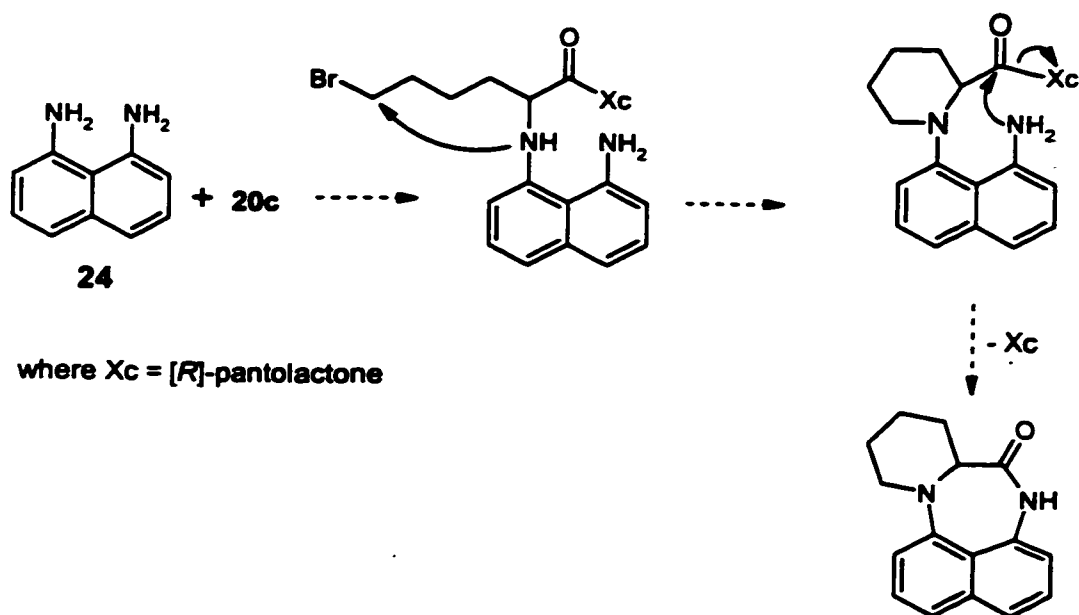
Prior to changing solvents, we wanted to determine if the amount of triethylamine present in the reaction mixture might effect the enantiomeric ratio by possible racemization of the product. The reaction was repeated in THF using 2.2 equivalents of base instead of 3.1. Under these conditions, we obtained a somewhat better yield of 64% versus 54% but the enantiomeric ratio remained approximately 4:1. In this case, it does not appear that the amount of base used was causing slow racemization of the product leading to the modest 4:1 ratio.

The ratios obtained using different solvents showed that solvent effect did not play a large role in modifying the amount of chiral induction for this reaction. The reaction performed in DMF gave a good yield but with a lower ratio of about 2:1, which probably results from epimerization of the final product. In dichloromethane, we obtained a slight increase of the diastereomeric ratio and a modest yield of 48%. Hence, all future reactions were done using THF as the solvent.

Following optimization, the 6-bromo-2-iodo [*R*]-pantolactone ester **20c** was reacted with a number of aliphatic and aromatic diamines and amino alcohols. The results are summarized in table 2.3.2.

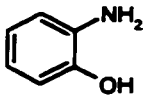
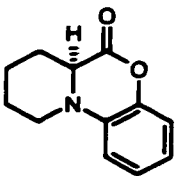
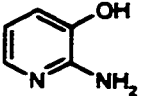
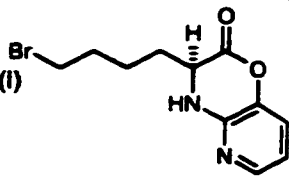
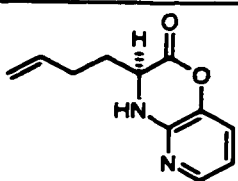
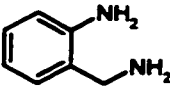
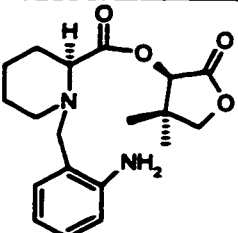
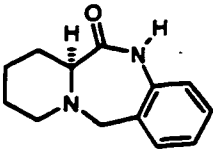
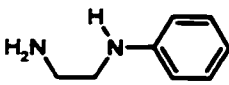
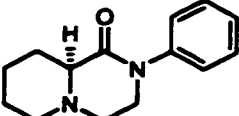
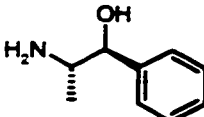
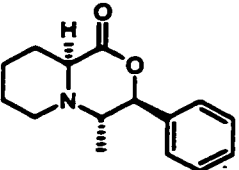
The addition of one equivalent of 1,8-diaminonaphthalene (**24**) to a solution of **20c** with 0.2 equiv. of $n\text{-Bu}_4\text{NI}$ and 3 equiv. of triethylamine with a reaction time of 10 days did not produce any isolable product. The TLC was very unclear but some diamine was still visible even after 10 days. The $^1\text{H-NMR}$ spectrum of the crude product indicated that the [*R*]-pantolactone moiety was still attached as an ester (scheme 2.3.3).

Scheme 2.3.3 : Proposed intermediates (products) for the reaction of **20c with **24****



This result is not totally surprising since amide formation (loss of [*R*]-pantolactone) involves formation of a seven-membered ring. As will be discussed later, more rigorous conditions than stirring at room temperature are required for this cyclization.

Table 2.3.2 : Heterocycles prepared via DKR of 6-bromo-2-iodo [*R*]-pantolactone ester **20c with bifunctional nucleophiles**

Entry	Nucleophile	Product	Yield (%)	Enantiomeric Ratio	Final Product (Extra step)
1	 25	 26	43	4 : 1	
2	 27	 28	38	—	 29
3	 30	 31	47	10 : 1	 32
4	 33	 34	61	—	
5	 35	 36	44	2 : 1	

Reaction of **20c** with one equivalent of 2-aminophenol (**25**) in THF gave, after purification by silica gel chromatography using 20:1 hexanes/ethyl acetate as the eluent, a 43% yield of the cyclized product **26** as a white solid (mp, 86.5 –89.5 °C, $[\alpha]_D = -12.4^\circ$ ($c=1.16$, CHCl_3)). The $^1\text{H-NMR}$ spectrum of **26** (see figure 2.3.4) is similar to that of

compound **23** but without the presence of the N-H peak. A carbonyl stretching frequency at 1763 cm^{-1} confirmed the presence of the δ -lactone function. The HRMS showed a strong M^+ ion (18.5%) at m/z 203.0925 which was in agreement with the calculated value of 203.0947. Preparation of compound **26** in racemic form allowed for the determination of the enantiomeric ratio via chiral HPLC. Using a Chiralcel OB column with 98% to 2% hexanes to isopropanol as the solvent system, we determined the ratio as being 4 to 1.

With this result in hand, the reaction with the pyridine derivative (**27**) was attempted. Reaction of 1.2 equivalents of 2-amino-3-hydroxy pyridine for approximately 4 days at room temperature gave, in a 38% yield after chromatography, the monocyclic product **28**. The structure assignment of **28** was based on a 3426 cm^{-1} peak in the IR spectrum and a broad singlet at 10.08 ppm in the ^1H -NMR spectrum due to the free N-H. The infrared also showed a peak at 1710 cm^{-1} , consistent with the lactone ring structure. The aliphatic portion of the proton spectrum was somewhat complex since exchange of the terminal bromide with iodide caused certain proton signals, especially the terminal CH_2 group, to split.

From the ratio of these peaks, it was determined that we had a 70 to 30% ratio of bromine versus iodine containing product. HRMS confirmed this mixture by showing a strong M^+ ion (10.4%) at 332.0022 which was in exact agreement with the calculated value for the iodine analog of 332.0022. The two ion peaks for the bromine-containing compound were visible at 286.0152 and 284.0202 compared to the calculated values of 286.0140 and 284.0160.

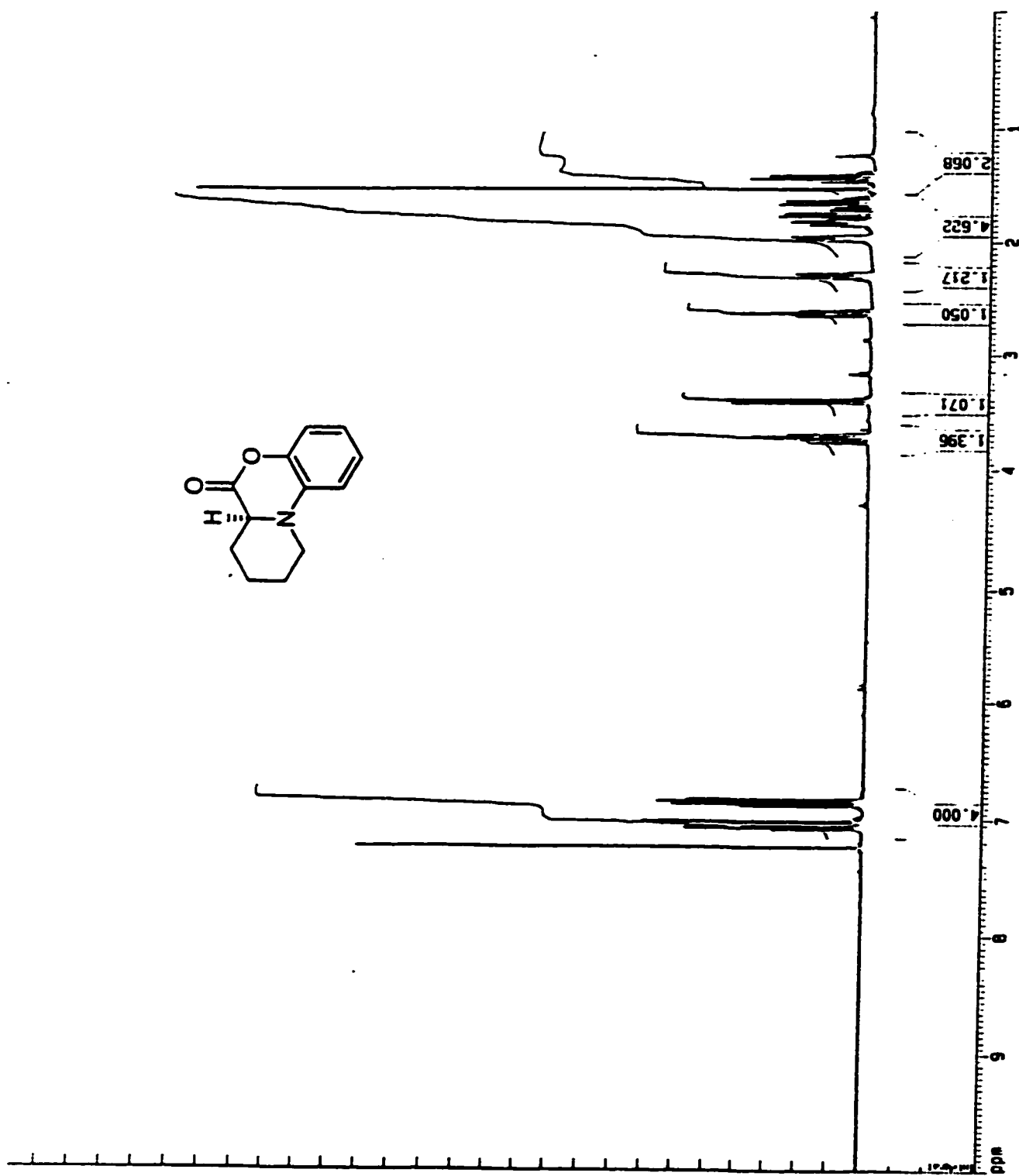
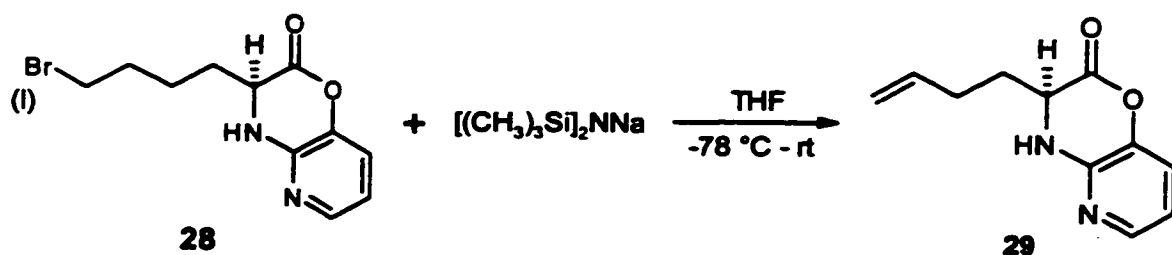


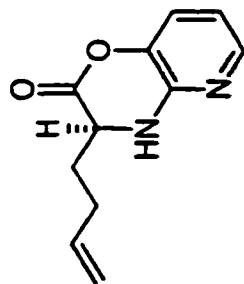
FIGURE 2.3.4: ¹H-NMR SPECTRUM OF 6,6A,7,8,9,10-HEXAHYDROBENZO[B]PYRIDO[1,2-D][1,4]OXAZIN-6-ONE 26

Two attempts were made to close the second ring in **28**. No reaction was observed when compound **28** was refluxed in THF with 1.5 equivalents of triethylamine for 3.5 h. In the second attempt, 1.0 equivalent of sodium bis(trimethylsilyl)amide was added to a solution of **28** in THF cooled to -78°C and then warmed to room temperature for about 3 h. Silica gel chromatography of the crude product gave 64% yield of a white solid, which was identified as the elimination product **29** (scheme 2.3.4). The failure of **28** to form the expected bicyclic product was surprising in view of the relative ease of formation of **23** and **26**.

Scheme 2.3.4 : Cyclization attempt of compound 28



The ^1H -NMR of **29** showed 3 olefinic protons as multiplets at 5.81, 5.04 and 4.62 ppm, consistent with a terminal double bond. This was confirmed by peaks at 124.1 and 116.0 ppm in the ^{13}C -NMR spectrum (see figure 2.3.5). The IR spectrum still showed N-H and lactone carbonyl stretch bands at 3380 cm^{-1} and 1709 cm^{-1} , respectively.



INDEX	FREQUENCY (PPM)	HEIGHT
1	167.540	9.5
2	141.450	9.3
3	140.694	28.2
4	138.840	6.6
5	136.766	22.4
6	124.071	28.4
7	119.458	31.0
8	115.987	24.9
9	85.812	11.1
10	77.444	97.5
11	77.230	10.0
12	77.021	101.0
13	76.598	104.4
14	30.133	25.7
15	29.708	13.3
16	28.667	24.7

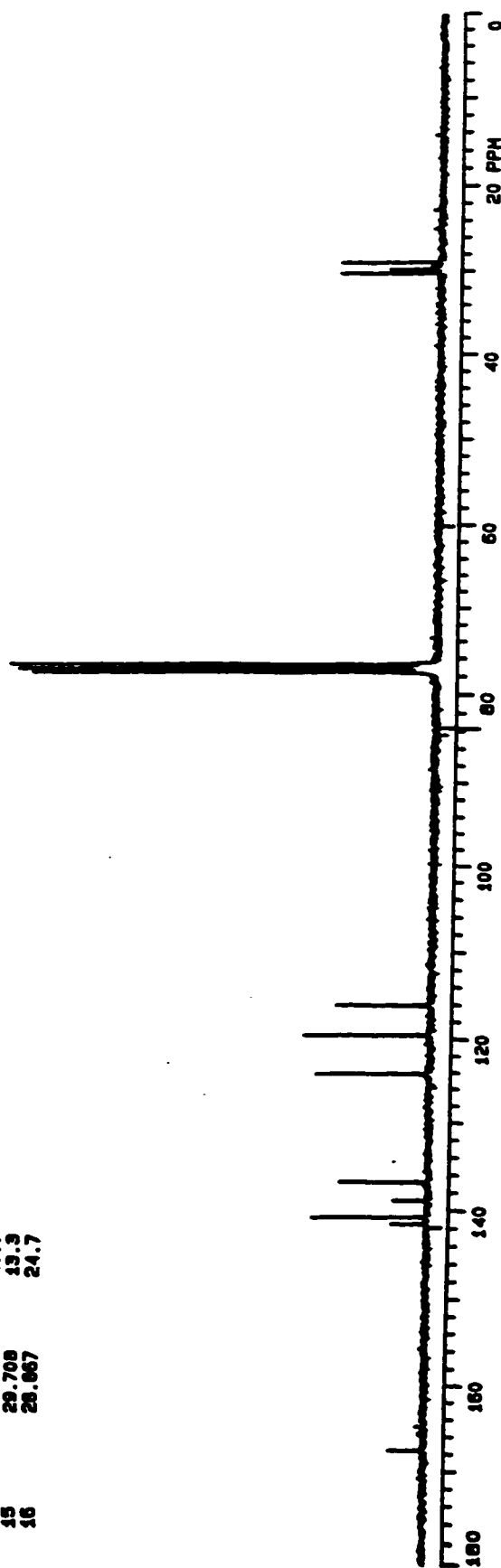
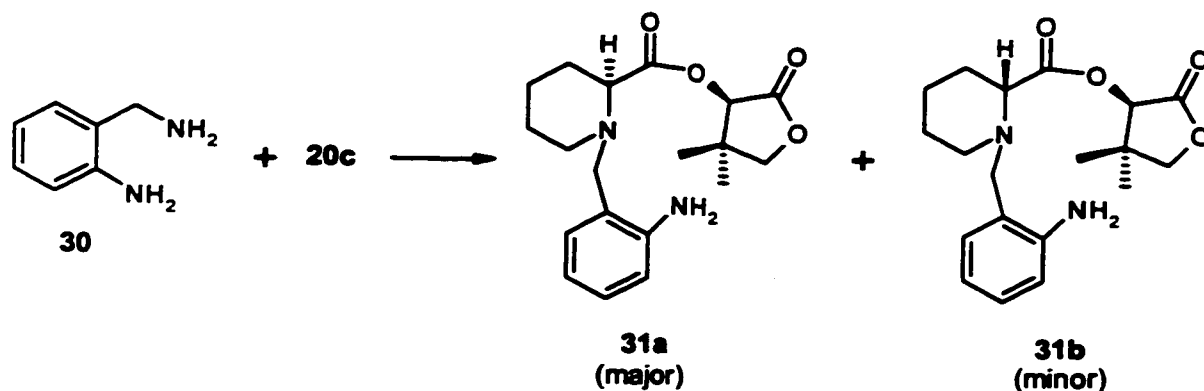


FIGURE 2.3.5: ^{13}C -NMR SPECTRUM OF 3-(3-BUTENYL)-3,4-DIHYDRO-2H-PYRIDO[3,2-B][1,4]OXAZIN-2-ONE 29

Since the formation of several [6,6] ring systems had been fruitful, we attempted to form [6,7] analogs using 2-aminobenzylamine (30) as the nucleophile. Reaction of ester 20c in THF with 169 mg of (30) under usual conditions, afforded 410 mg of product as a brown oil. The ^1H -NMR showed two peaks in the 5.4 δ range attributable to the methyne hydrogen of the lactone ring. One peak was considerably larger than the other indicating a successful DKR process. However, the exact ratio could not be determined. The fact that the [*R*]-pantolactone unit was still present in the form of an ester indicated that the second ring had not formed. This was confirmed by the presence of a broad singlet at 4.7 ppm assigned to the aromatic NH_2 group. The free NH_2 group signal was attributed to the aniline group since benzylamine is a much better nucleophile than aniline, hence it would undergo nucleophilic displacement of the iodide more readily. Chromatography afforded two pure products in a 10:1 ratio in a total yield of 47%. These compounds were assigned as the diastereomers 31a and 31b (scheme 2.3.5).

Scheme 2.3.5 : Preparation of isomers 31a and 31b

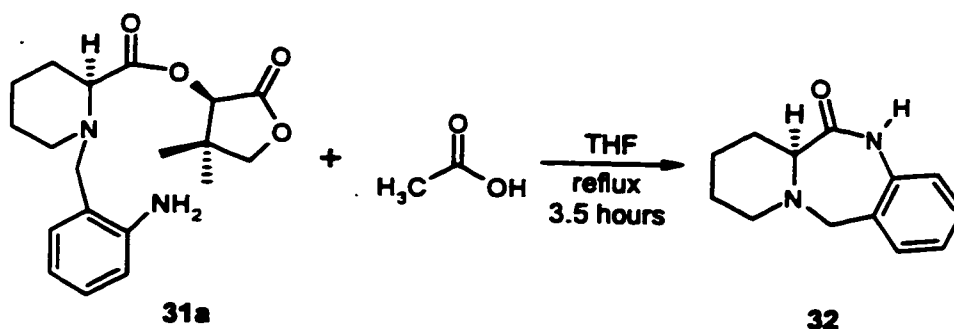


The ^1H -NMR of the major isomer (see figure 2.3.6) showed a singlet at 5.40 ppm for the alpha proton on the [*R*]-pantolactone ring, the two methyl singlets at 1.19 and 1.10 ppm, and the 2 benzylic protons appeared as sharp doublets at 3.95 and 3.36 ppm. The ^1H -NMR

spectrum of the minor isomer had the [*R*]-pantolactone singlet hydrogen at 5.39 ppm with the 2 methyls at 1.20 and 1.08 ppm, and the 2 benzylic hydrogens appeared as sharp doublets at 3.88 and 3.33 ppm. The IR spectrum showed the 2 carbonyl peaks at 1791 and 1749 cm^{-1} , as well as, the NH_2 stretches at 3447 and 3366 cm^{-1} . The ^{13}C -NMR spectrum (see figure 2.3.7) showed the 2 carbonyl group resonances at 172.5 and 171.9 ppm for the major isomer and at 172.7 and 172.0 ppm for the minor isomer. The HRMS showed a M^+ ion peak at m/z 346.1863 which corresponded with the calculated value of 346.1893.

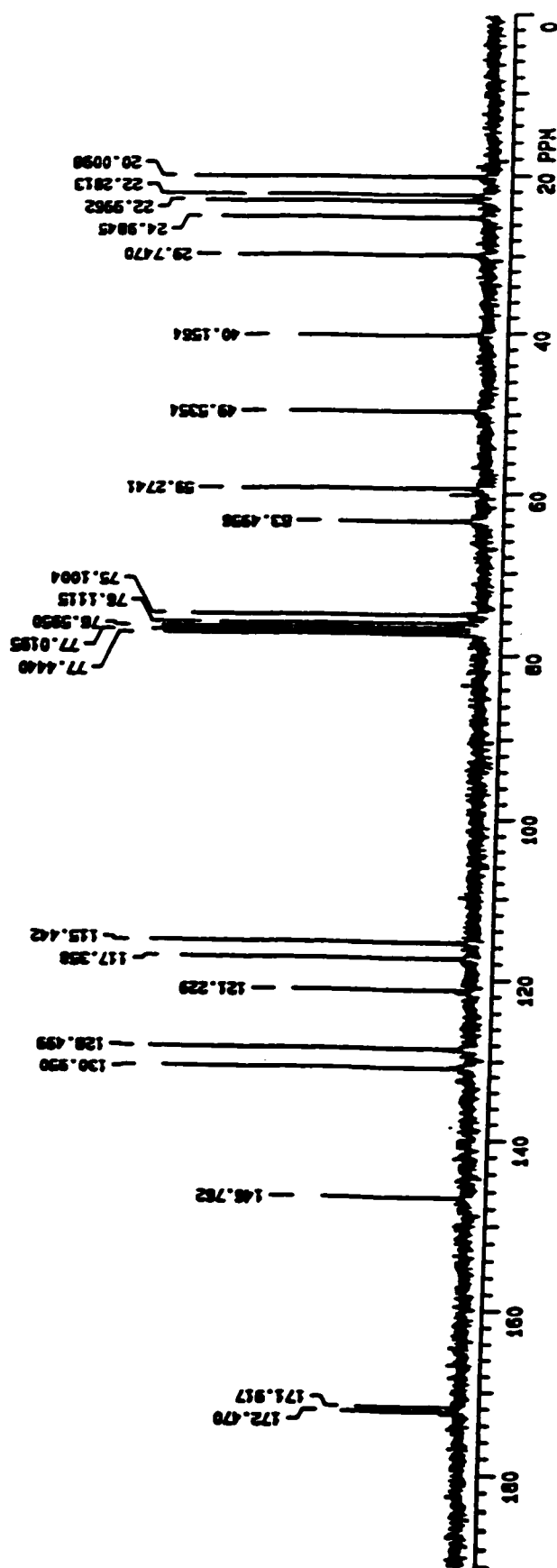
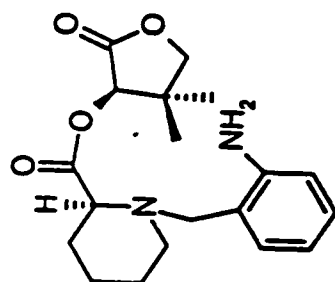
In order to form the seven-membered ring, compound **31a** was refluxed for 68 h in toluene. After workup, some [*R*]-pantolactone was recovered but none of the expected cyclized material was isolated. In a second attempt, compound **31a** was dissolved in THF, 3 drops of glacial acetic acid were added followed by refluxing for 3.5 h. After workup, the desired cyclized product **32** was obtained in 42% yield (scheme 2.3.6) as a white solid, (mp, 125.0–127.0 $^{\circ}\text{C}$, $[\alpha]_{\text{D}} = +282^{\circ}$ ($c=1.0$, CHCl_3)).

Scheme 2.3.6 : Formation of the 7-membered ring in **32 from compound **31a****



The ^1H -NMR spectrum of **32** (see figure 2.3.8) showed the N-H singlet at 7.88 ppm; the benzyl CH_2 appeared as an AB doublet at 4.04 and 3.55 ppm and the single hydrogen at the stereocenter appeared as a doublet of doublets at 2.85 ppm. The ^{13}C -NMR spectrum showed the carbonyl peak at 172.5 ppm (see figure 2.3.9). The IR spectrum showed the

FIGURE 2.3.6: ¹H-NMR SPECTRUM OF COMPOUND 31A

FIGURE 2.3.7: ¹³C-NMR SPECTRUM OF COMPOUND 31A

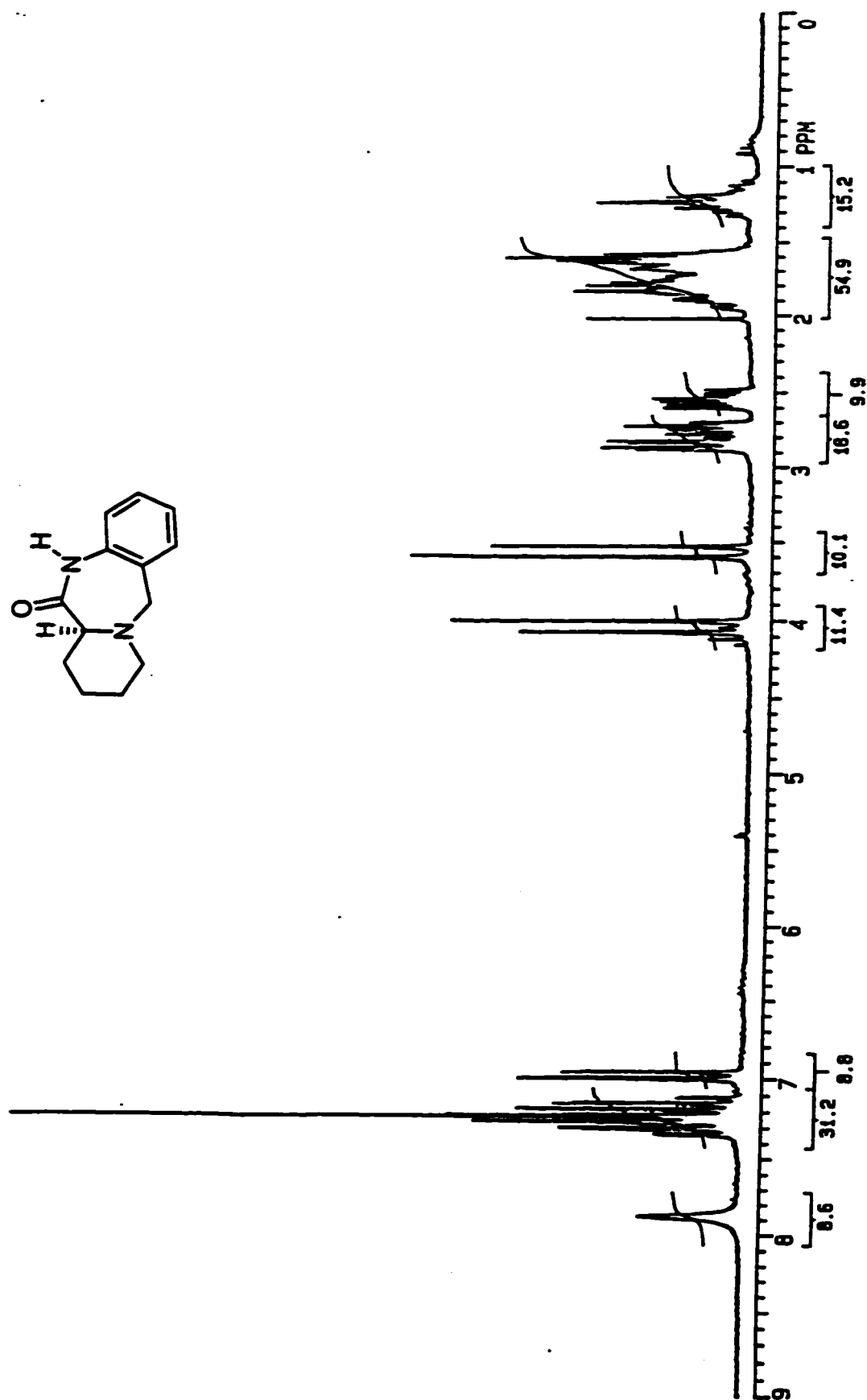
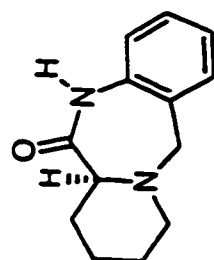


FIGURE 2.3.8: ¹H-NMR SPECTRUM OF 1,2,3,4,6,11,12,12A-OCTAHYDROBENZO[E]PYRIDO[1,2-A][1,4]DIAZEPIN-12-ONE 32



INDEX	FREQUENCY (PPM)	HEIGHT
1	172.493	11.9
2	137.924	10.4
3	130.321	37.1
4	128.763	33.6
5	128.436	13.4
6	125.348	34.8
7	120.491	35.5
8	77.432	108.0
9	77.244	43.4
10	77.008	108.8
11	76.595	105.3
12	60.635	21.2
13	58.228	27.2
14	53.891	26.7
15	27.035	31.2
16	25.846	28.7
17	22.308	27.6

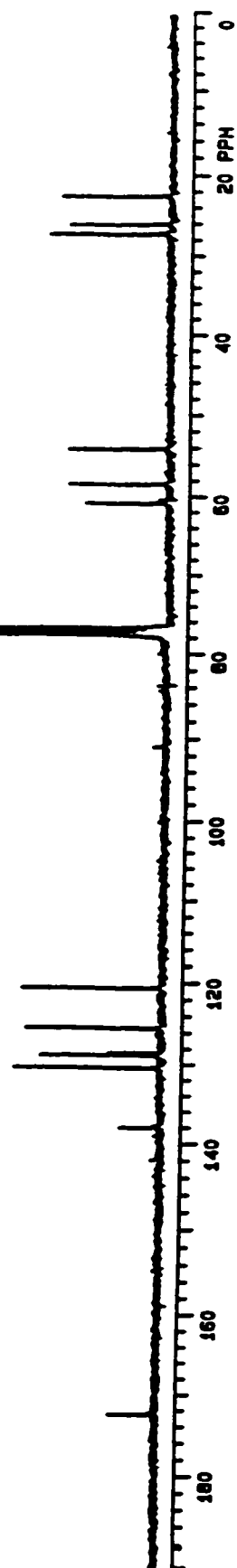
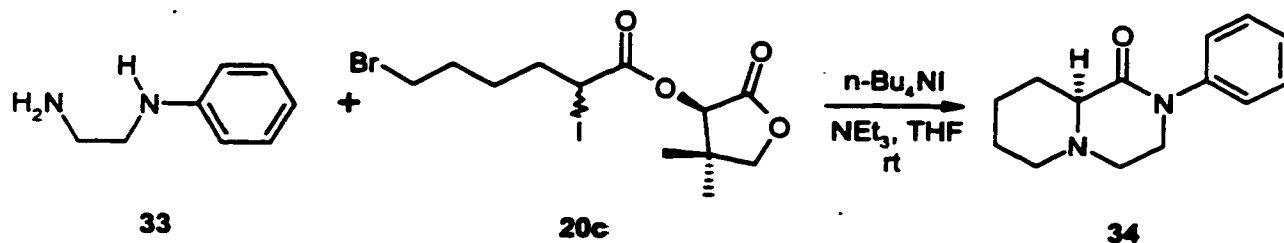


FIGURE 2.3.9: ^{13}C -NMR SPECTRUM OF 1,2,3,4,6,11,12,12A-OCTAHYDROBENZO[E]PYRIDO[1,2-A][1,4]DIAZEPIN-12-ONE 32

N-H stretch at 3387 cm^{-1} and the amide carbonyl stretch at 1687 cm^{-1} . The HRMS showed an M^+ ion peak (4.9%) at m/z 216.1280, in agreement with the calculated value of 216.1263.

An attempt to prepare the 2-oxo-piperazine **18** using ethylenediamine as the nucleophile was unfruitful and only led in the recovery of [*R*]-pantolactone after chromatography. This was attributed to the high water-solubility of the product or the diamine being too reactive and leading to undesirable side products. In order to reduce the nucleophilicity of the diamine and possibly get around this problem, we attempted the reaction with *N*-phenylethylenediamine (**33**) (scheme 2.3.7). To a solution of ester **20c** in THF with 0.5 equiv. of $n\text{-Bu}_4\text{NI}$ was added 1.2 equivalents of *N*-phenylethylenediamine (**33**) with 3.2 equiv. of triethylamine. The mixture was stirred for 19 h after which TLC showed the disappearance of the ester **20c**. Aqueous workup followed by two column chromatographies produced the desired cyclized product **34** in 61% yield as a yellow solid (mp, $78.0\text{--}83.5\text{ }^\circ\text{C}$, $[\alpha]_D = -58.5\text{ }^\circ$ ($c=1.0$, CHCl_3)).

Scheme 2.3.7 : Preparation of compound 34



The isolation of the product necessitated two columns because the second cyclization step to eliminate the chiral auxiliary does not occur during the reaction but rather under the acidic conditions of the silica. The two compounds having very different polarities, therefore required two very different solvent systems, with the non-cyclized product being surprisingly less polar than the cyclized compound **34**. Based on results obtained at a later date, the

cyclization could have been carried out by refluxing in THF with acetic acid, as in the case of compound 31a. The ^1H -NMR spectrum of 34 (see figure 2.3.10) showed the disappearance of the [*R*]-pantolactone peaks and the N-H peak that were present in the NMR spectrum of the crude reaction mixture. The IR spectrum showed the amide carbonyl stretch at 1663 cm^{-1} . The carbonyl group appeared in the ^{13}C -NMR spectrum at 168.6 ppm (see figure 2.3.11). The HRMS showed a strong M^+ ion peak (31.6%) at m/z 230.1421, in agreement with the calculated value of 230.1420.

Compound 34 was also prepared in racemic form with some difficulty in 16% yield from methyl 6-bromo-2-iodohexanoate 22. A number of attempts were then made to determine the enantiomeric ratio. Initial attempts were made to separate the enantiomers via chiral HPLC. Three different columns, which included the Chiralcel OB, [*R*]-3,5-dinitrobenzoyl phenylglycine propylsilyl and Supelcosil LC-(*R*)-Naphthyl Urea were used with varying solvent ratios of hexanes/isopropanol, hexanes/1,2-dichloroethane and hexanes/isopropanol/methanol. All attempts failed to separate the enantiomers. A second option was the chiral GC but this could not be used due to the high tendency of amines to stick to the column. In a final attempt to determine the enantiomeric ratio, proton NMR with a chiral shift reagent, Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], was explored. Unfortunately, due to the lack of simple peaks, such as a singlet or a doublet, and to the fact that almost every signal moved together, we could not determine any accurate ratio for compound 34.

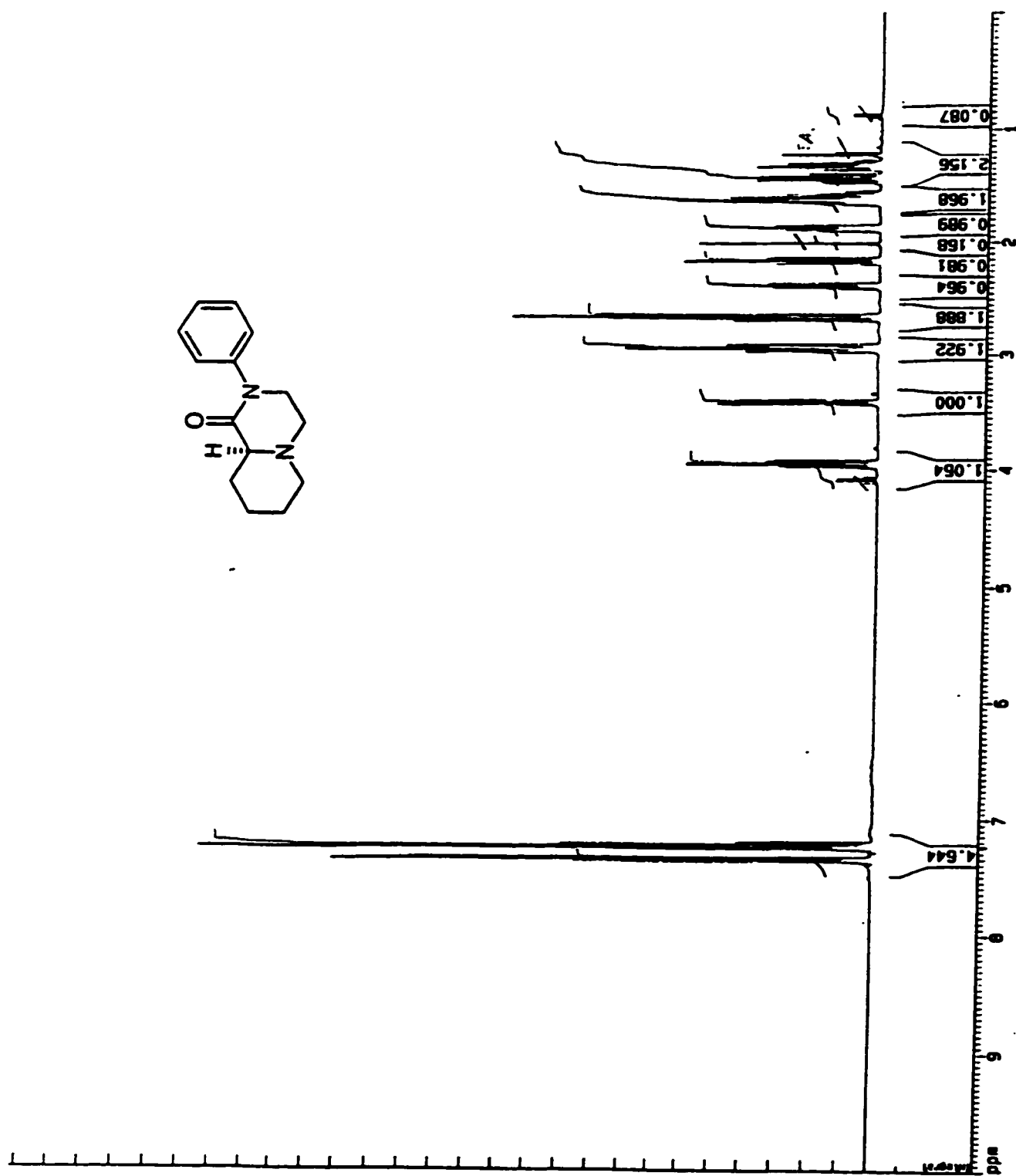


FIGURE 2.3.10: ¹H-NMR SPECTRUM OF 2-PHENYLPYRHYDOPYRIDO[1,2-A]PYRAZIN-1-ONE 34

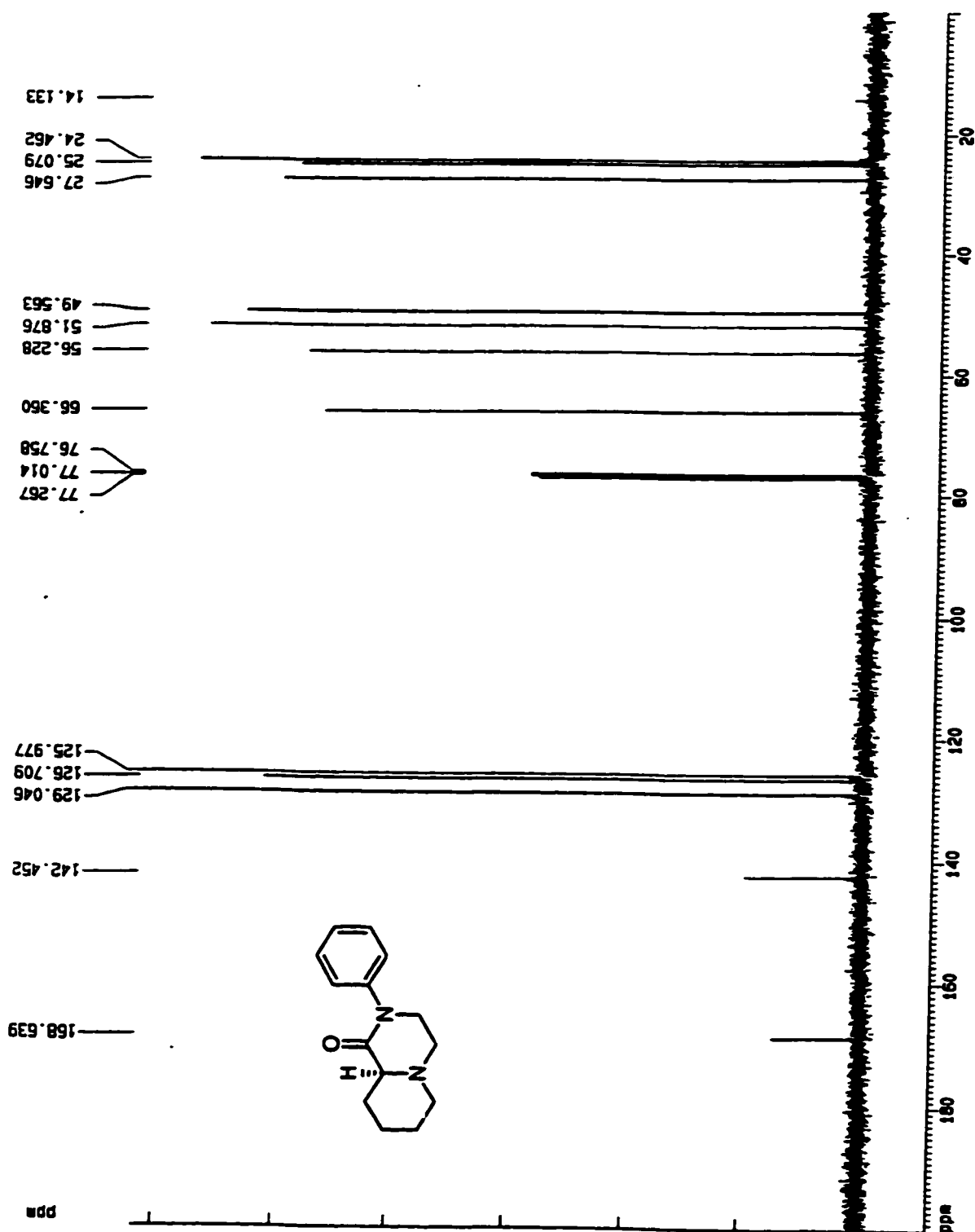
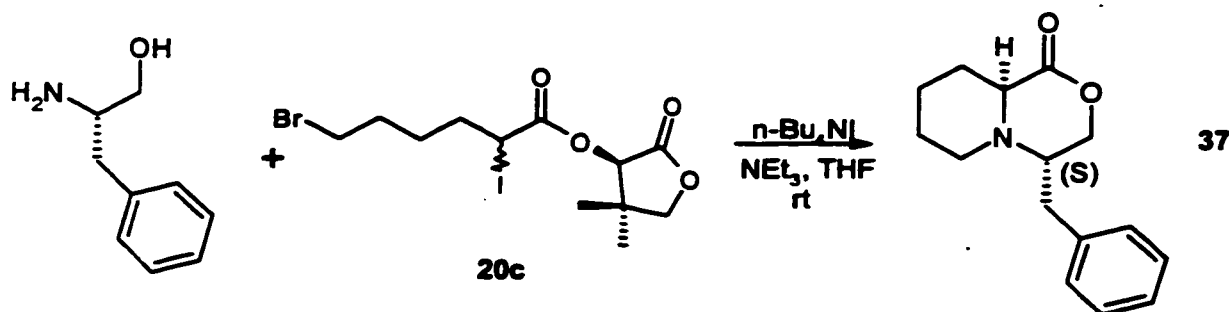


FIGURE 2.3.11: ^{13}C -NMR SPECTRUM OF 2-PHENYLPYRHYDOPYRIDO[1,2-A]PYRAZIN-1-ONE 34

Addition of 1.5 equivalents of norephedrine hydrochloride (**35**) to a solution of **20c** in THF was stirred for 28 h followed by aqueous workup. After column chromatography, the reaction afforded compound **36** in 44% yield as a clear oil. The ^1H -NMR spectrum of **36** showed the methyl doublet of each diastereomer at 0.77 and 0.72 ppm, which gave a diastereomeric ratio of $\sim 2:1$ based on the integration of each doublet. In the IR spectrum, only one carbonyl group was resolved at 1735 cm^{-1} . The ^{13}C -NMR spectrum showed the carbonyl group of each diastereomer at 170.3 and 170.1 ppm. The molecular ion was calculated to be 245.1416 and the HRMS showed a M^+ ion at m/z 245.1404.

Treatment of **20c** with a similar nucleophile, (*S*)-2-amino-3-phenyl propanol, for 67.5 hours followed by aqueous workup and then purification by column chromatography, led to the isolation of 40 to 44% of what appeared to be the desired compound **37** (based on comparison of its proton NMR with the one of compound **36**) (scheme 2.3.8). This could not be confirmed due to problems of purification.

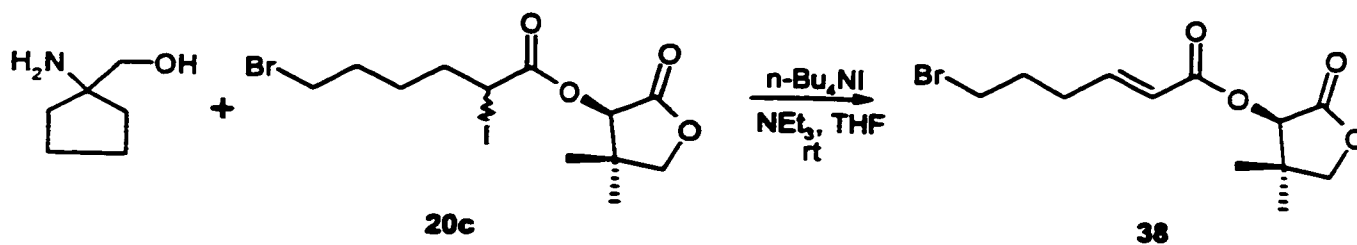
Scheme 2.3.8 : Possible preparation of compound 37



Reaction of ester **20c** with 1,2-diaminopropane for 48 h did not produce any product after column chromatography. This may have been the result of high water solubility of the product, which was therefore lost in the aqueous phase during workup or due to the high nucleophilicity of the diamine, which formed side products that could not be isolated.

Addition of 1.2 equiv. of 1-amino-1-cyclopentanemethanol to **20c** followed by stirring for 5 days at room temperature also did not produce any cyclized product after chromatography. The only products isolated were some [*R*]-pantolactone and the α,β -elimination product **38** in a 25% yield (scheme 2.3.9).

Scheme 2.3.9 : Formation of the major side product 38

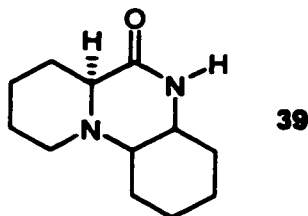


Formation of **38** was confirmed by the presence, in the ^1H -NMR spectrum, of a doublet of triplets at 7.01 ppm for the β -hydrogen and a second doublet of triplets at 5.95 ppm with a much-reduced coupling constant to the CH_2 group for the α -hydrogen. Presence of the [*R*]-pantolactone group peaks indicated that no substitution occurred at the carbonyl. This result may be explained by the hindered nature of the nucleophile since the amino group is on a quaternary carbon. Attack at the β -carbon causing elimination would therefore be favored since there is less steric hindrance at that position versus the α -position.

In order to prepare the cyclohexane analog of compound **23**, one equiv. of 1,2-diaminocyclohexane was added to a solution of **20c** in THF with 0.3 equiv. of $n\text{-Bu}_4\text{NI}$ followed by addition of 3.0 equiv. of triethylamine. The reaction was stirred for approximately 5 days at room temperature, followed by aqueous workup and column chromatography. As in the case of the 1-amino-1-cyclopentanemethanol, the only compound isolated was the α,β -elimination product **38**. Based on the results obtained, it appears that aliphatic amines which are somewhat hindered, act mainly as bases and lead to the formation

of the α,β -elimination product **38** rather than the desired displacement products. The lack of success with aliphatic amines may have also resulted from the greater polarity of the products formed. This was somewhat indicated by the large amount of lost product on the silica gel column during purification. This possibility is based on the fact that most times, the total weight of material recovered after purification was much less than the weight of the crude mixture.

In order to investigate if the higher nucleophilicity was the reason why no products were ever isolated, the reaction with 1,2-diaminocyclohexane was repeated a second time but at 4 °C. After stirring for 74 h followed by aqueous workup and column chromatography, we were still unable to obtain a pure product. Although no pure product was isolated after chromatography, the ^1H -NMR of the crude mixture appeared to indicate that some of the desired product had formed. This is based on the presence of a broad singlet at 6.40 ppm which would result from the resonance of the N-H group of the amide moiety (compound **39**).



In order to be able to prepare aliphatic compounds via this DKR approach it will be necessary to investigate further the reaction conditions and the purification steps since silica gel chromatography appears to be a problem area. Unfortunately, the reaction temperatures cannot be lowered significantly, otherwise the reaction times become much too long.

2.4 DKR of [*R*]-Pantolacto-5-Bromo-2-Iodopentanoate, 20b, with Bifunctional Nucleophiles

The reaction of [*R*]-pantolacto-5-bromo-2-iodopentanoate with the previously studied bifunctional nucleophiles was also examined. If successful, these reactions would generate the [5,6] ring system analogs of the [6,6] structures discussed above.

When 20b was stirred for 8 days with one equivalent of 1,2-phenylenediamine (21), compound 41 was obtained as a green solid (mp, 171.0 –172.0 °C, $[\alpha]_D = -54.8^\circ$ ($c=0.5$, CHCl_3)) in 61% yield after chromatography using the 3:1 hexanes/ethyl acetate solvent system. The $^1\text{H-NMR}$ of the solid (see figure 2.4.1) showed no evidence of the [*R*]-pantolactone, indicating that cyclization had occurred. IR peaks at 3214 and 1683 cm^{-1} and a broad singlet at 7.79 ppm in the $^1\text{H-NMR}$ confirmed the presence of a secondary amide unit. The doublet of doublets at 3.69 ppm was assigned to the hydrogen alpha to the carbonyl group. The $^{13}\text{C-NMR}$ spectrum (see figure 2.4.2) showed the 11 carbon signals required for 41 with the amide carbonyl peak at 168.8 ppm. The HRMS showed a strong M^+ ion peak (21.5%) at m/z 188.0955 which was in agreement with the calculated value of 188.0950. Racemic 41 was prepared from methyl 5-bromo-2-iodopentanoate 40 in 51% yield without the use of $n\text{-Bu}_4\text{NI}$ in the reaction (scheme 2.4.1). The spectroscopic properties of the two samples of 41 were identical.

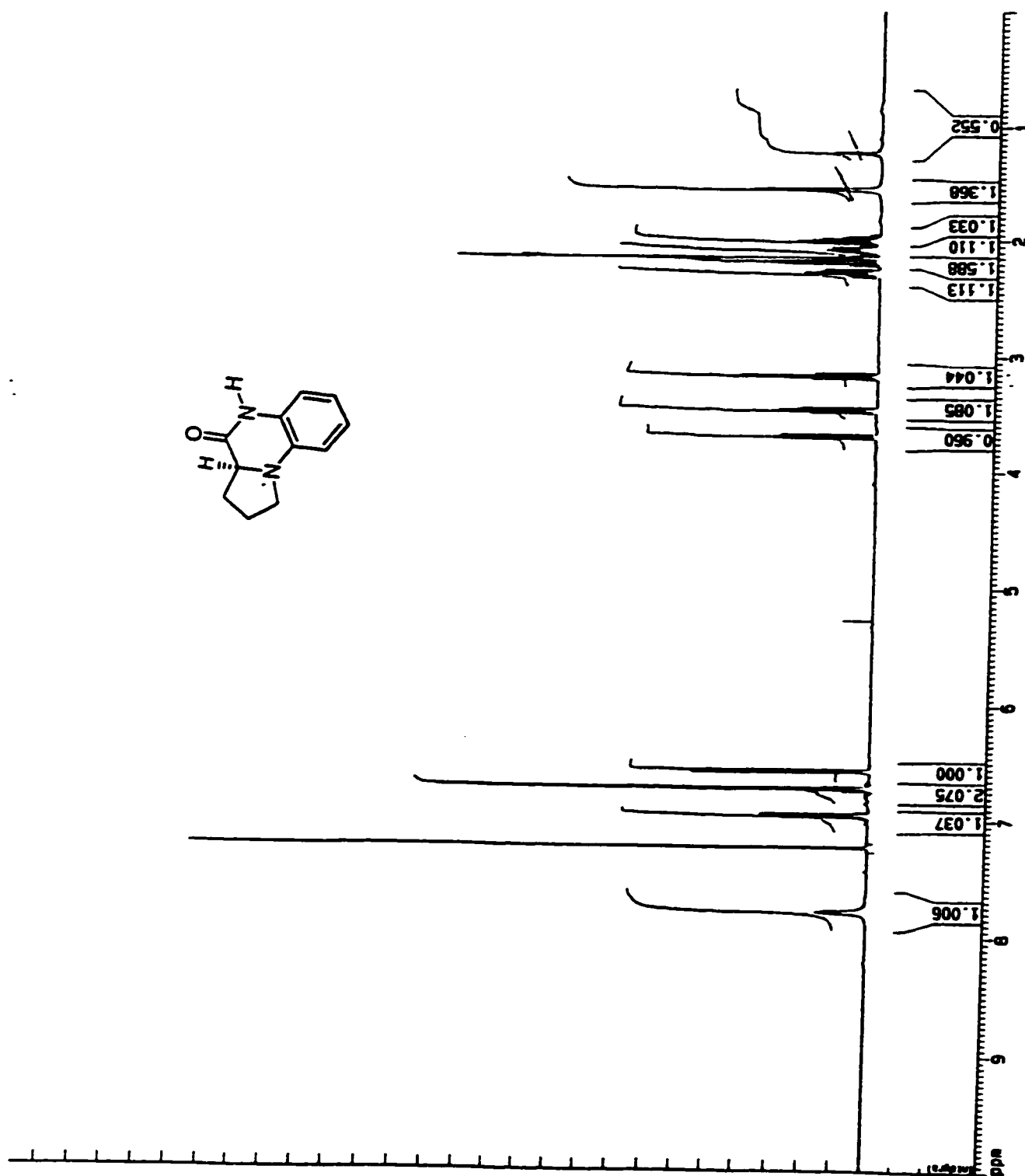
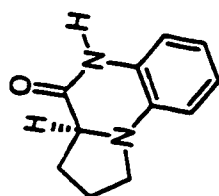


FIGURE 2.4.1: ¹H-NMR SPECTRUM OF 5,6,6A,7,8,9-HEXAHYDROPYRROLO[1,2-A]QUINOXALIN-6-ONE 41



INDEX	FREQUENCY (PPM)	HEIGHT
1	160.850	29.5
2	135.120	34.6
3	128.690	39.8
4	123.927	139.2
5	118.429	143.6
6	115.162	132.6
7	111.681	150.6
8	77.456	57.2
9	77.013	60.0
10	76.569	56.5
11	60.005	131.1
12	48.391	119.6
13	26.734	126.4
14	22.173	129.3

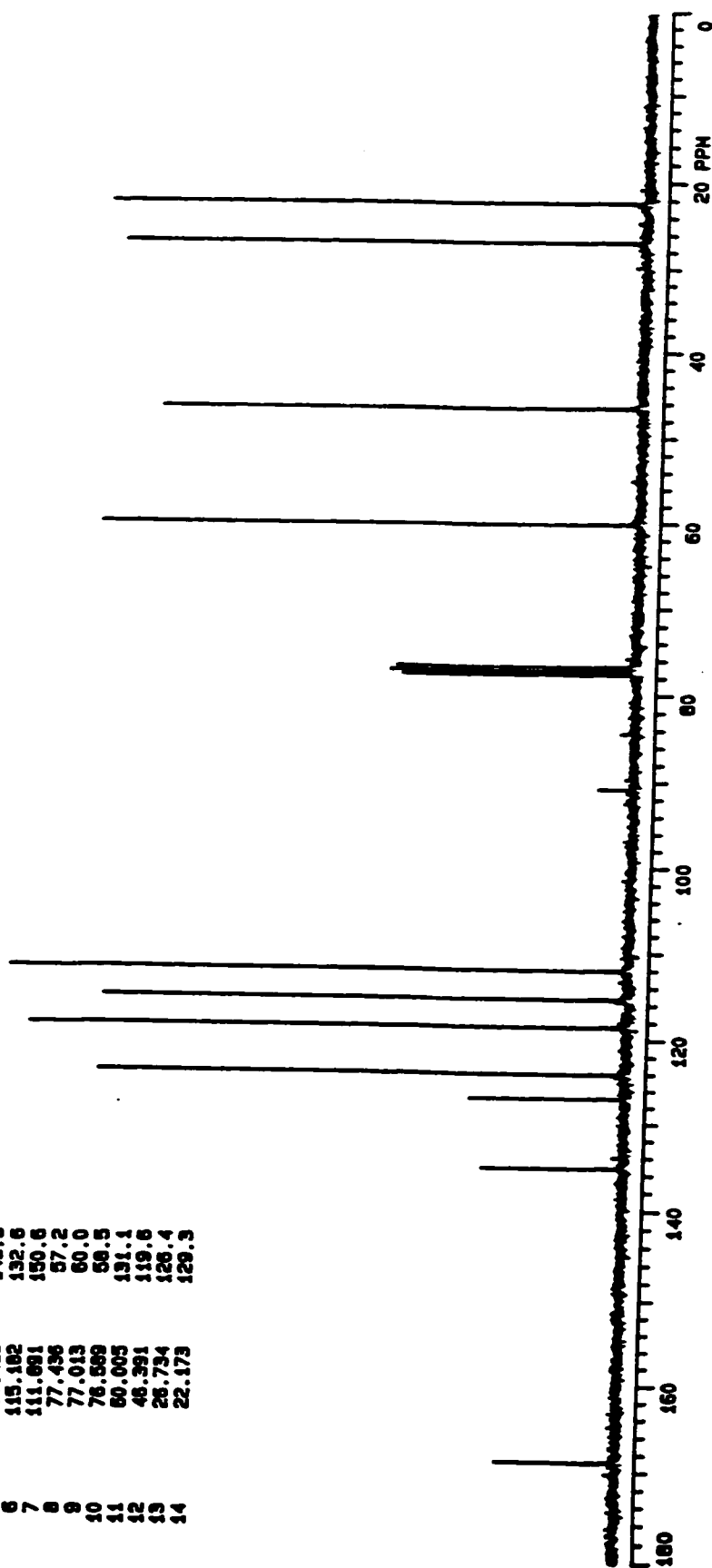


FIGURE 2.4.2: ^{13}C -NMR SPECTRUM OF 5,6,6a,7,8,9-HEXAHYDRO-1,2-a]QUINOXALIN-6-ONE 41

peaks at 5.43, 4.04, 1.20 and 1.11 ppm associated with the lactone ring. The key signals in the ^{13}C -NMR spectrum (see figure 2.4.5) included the two carbonyl peaks at 172.5 and 165.4 ppm, and the 4 alkenyl carbons at 146.8, 134.4, 127.0 and 120.3 ppm.

Similar results were obtained in the reaction of **20b** with 1,2-diaminocyclohexane and 1-amino-1-cyclopentanemethanol. In each case, the only identifiable product was the diene **42**. Other chromatographic fractions were often mixtures which could not be easily interpreted. The ^1H -NMR of the mixtures contained no peaks readily attributed to the desired bicyclic products.

Addition of 2-aminophenol (**25**) to a solution of **20b** in THF with 0.2 equiv. of $n\text{-Bu}_4\text{NI}$ followed by stirring for approximately 4 days, aqueous workup and column chromatography did not produce the desired displacement-cyclization product. The only compound isolated was the elimination product **42** in 25% yield. The reaction was repeated using dichloromethane and N,N -dimethylformamide as solvent. In each case, the major compound isolated was **42**, however, when the reaction was carried out in DMF, approximately 16% of a yellowish oil was obtained. Its ^1H -NMR spectrum was consistent with that expected of the desired product (based on the ^1H -NMR of compound **26**) but we were unable to purify it well enough for complete characterization.

Reaction of 2-amino-3-hydroxy pyridine (**27**) with **20b** in THF for ~ 6 days, resulted in formation of the monocyclic compound **43** in a 25% yield (scheme 2.4.3). This is analogous to the product obtained from the reaction of **20b** with (**27**).

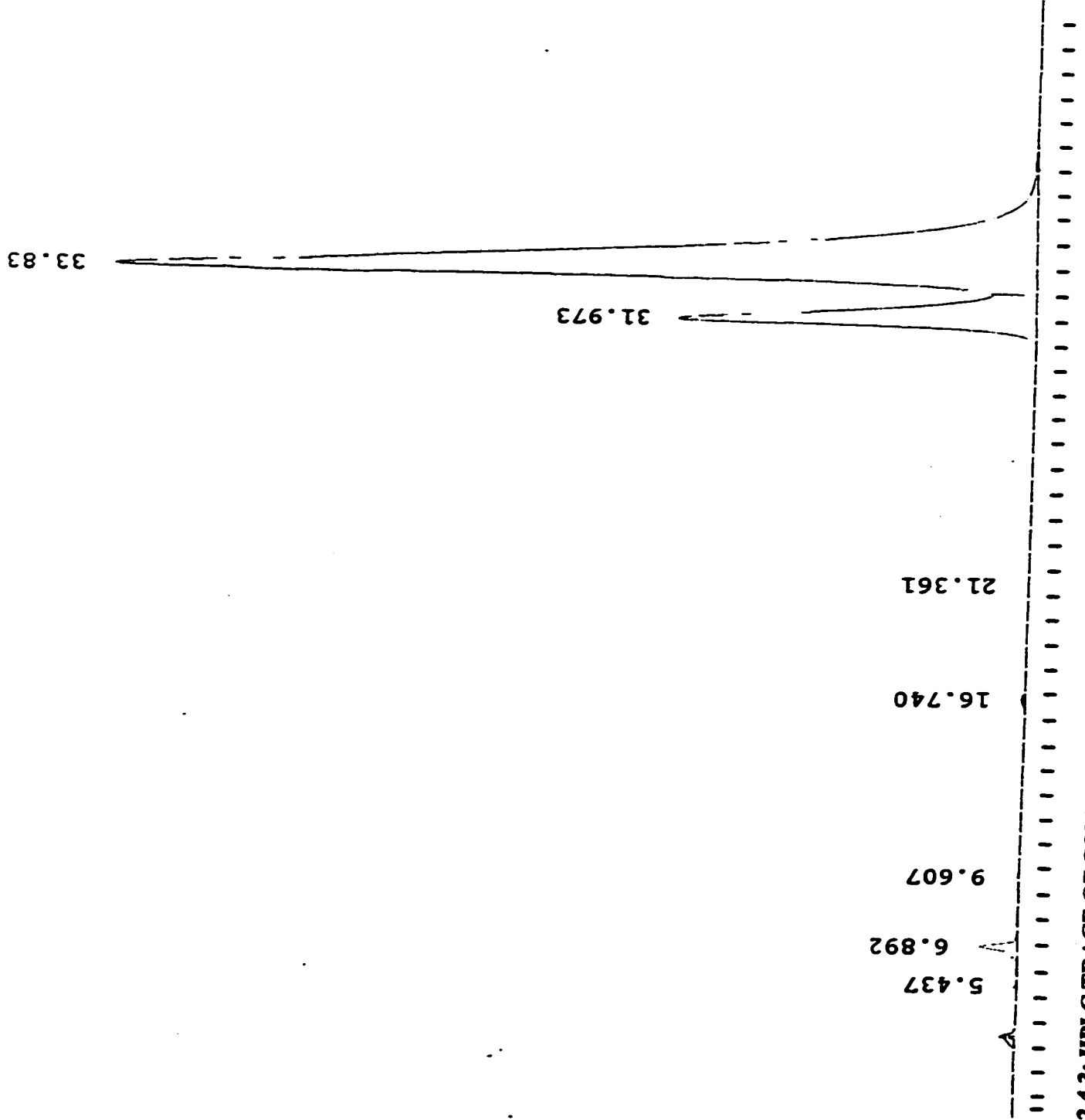
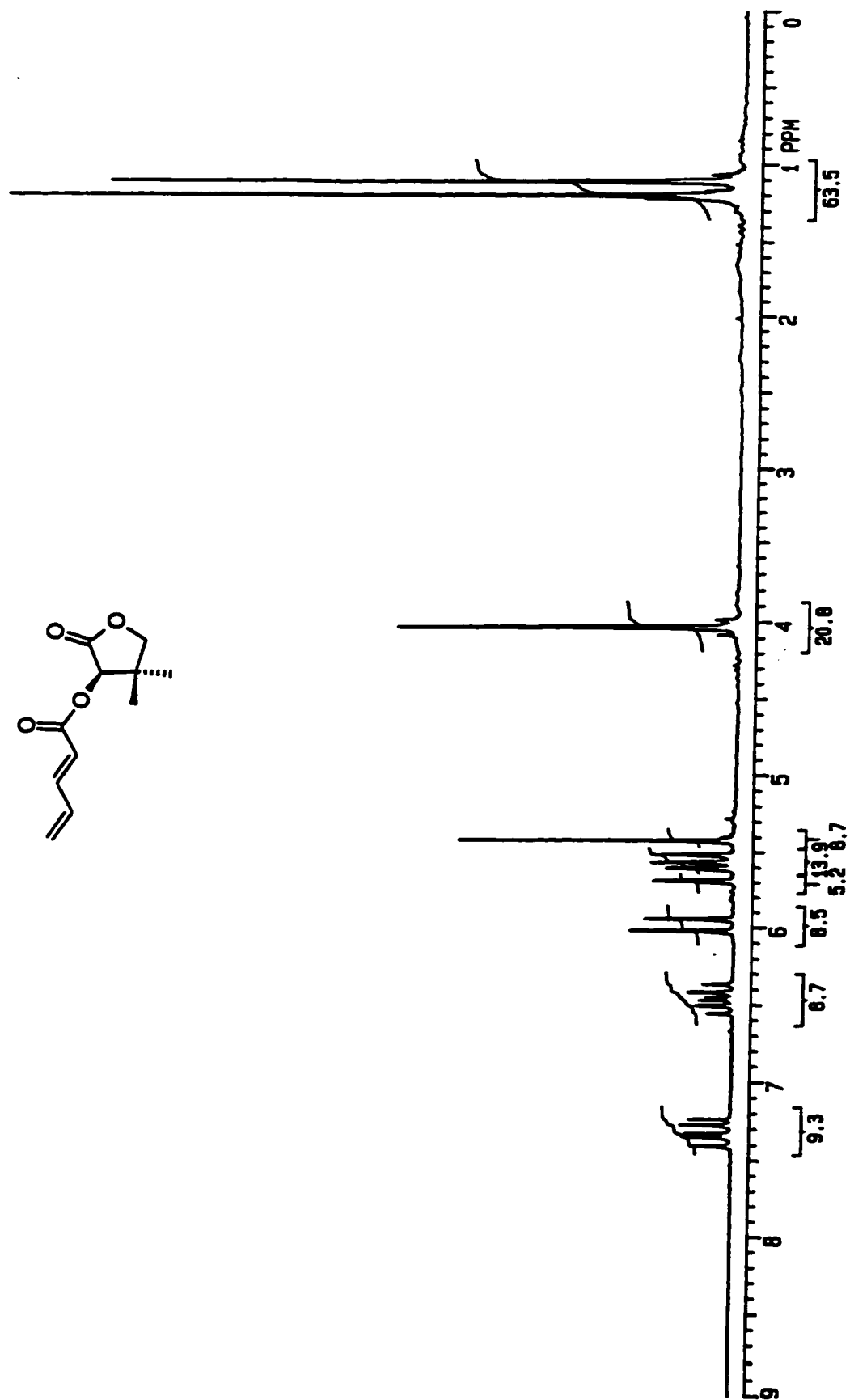


FIGURE 2.4.3: HPLC TRACE OF COMPOUND 41 WITH [R]-3,5-DINITROBENZOYL PHENYLGLYCINE PROPYLSILYL COLUMN

FIGURE 2.4.4: ^1H -NMR SPECTRUM OF COMPOUND 42

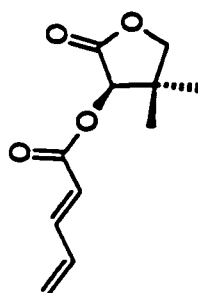
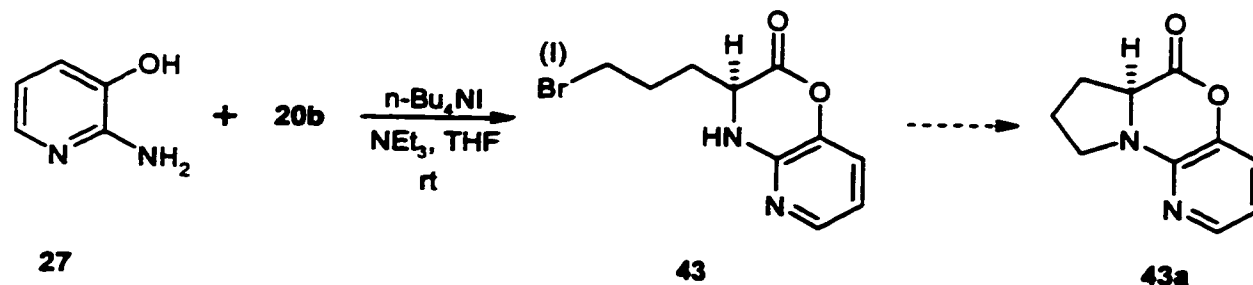


FIGURE 2.4.5: ^{13}C -NMR SPECTRUM OF COMPOUND 42

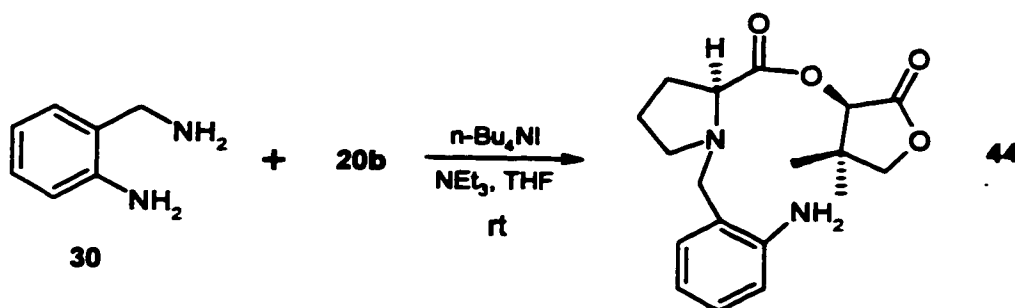
Scheme 2.4.3 : Formation of compound 43



Compound 42 was also isolated for this reaction in a small amount. No attempt was made to cyclize compound 43 to 43a.

Reaction of 2-aminobenzylamine (30) with 20b in THF under the usual reaction conditions gave, after column chromatography, the monocyclic proline derivative 44 in 42% yield (scheme 2.4.4).

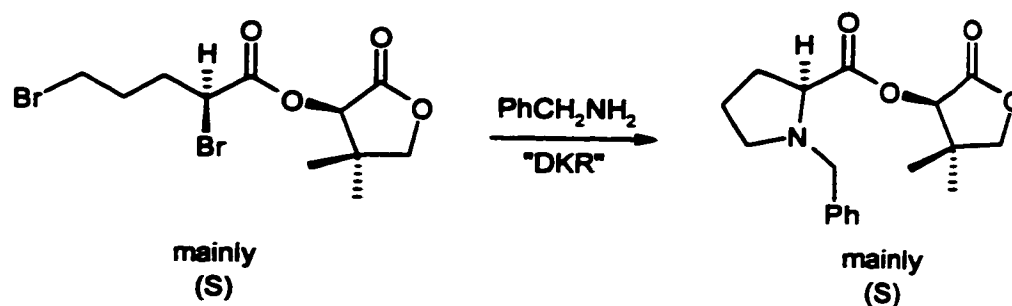
Scheme 2.4.4 : Formation of compound 44



The HRMS of 44 confirmed the elimination of the iodine and bromine. It showed an M^+ ion at m/z 332.1755 versus the calculated value of 332.1736. The ^{13}C -NMR spectrum showed the 4 carbonyl peaks for the two diastereomers at 173.50, 173.46 and 172.1, 172.0 ppm. The IR spectrum showed a very strong and broad peak for the NH_2 group at 3451 cm^{-1} along with the two carbonyl stretches at 1788 and 1754 cm^{-1} assigned to the lactone and ester carbonyl groups, respectively. The diastereomeric ratio was obtained from the proton spectrum and determined to be 4:1 based on the integration of the methyne proton of the

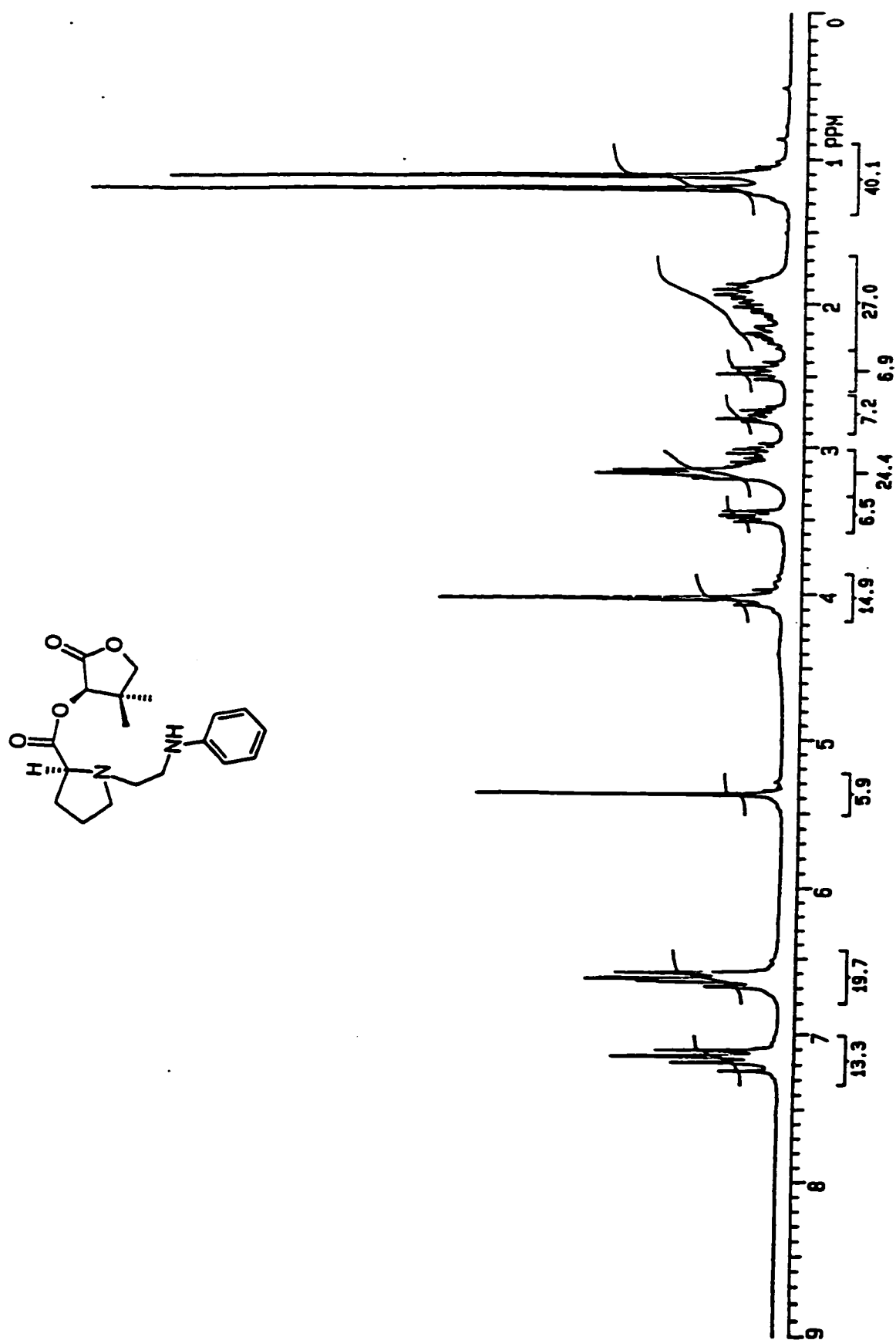
lactone ring. The formation of **44** in fair yield is not unexpected. Earlier reports from our laboratory had shown that N-benzyl proline derivatives have been obtained. In fact, the DKR discovery rested on the reaction shown in scheme 2.4.5.

Scheme 2.4.5 : Formation of N-benzyl proline derivatives via DKR process

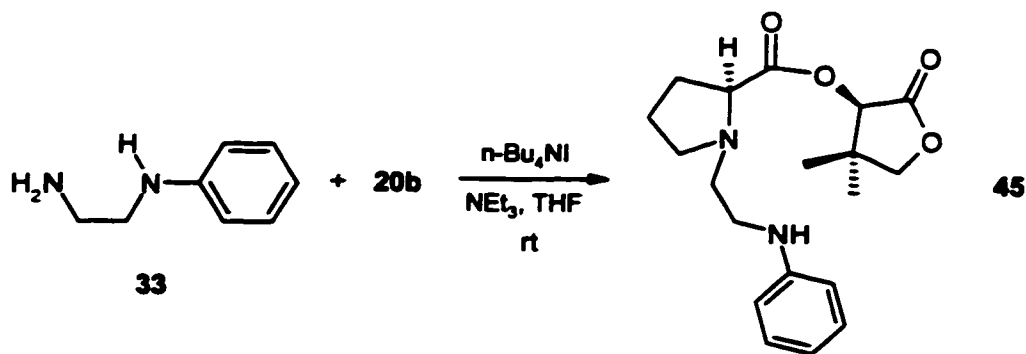


It is disappointing that changing benzylamine to 2-amino benzylamine reduces the diastereomer ratio from 7:1 to 4:1. No attempt was made to cyclize compound **44**.

When 1.2 equiv. of N-phenylethylenediamine (**33**) was added to a solution of **20b** with 0.5 equiv. of $n\text{-Bu}_4\text{NI}$ and 3.2 equiv. of triethylamine then stirred for 24 h, followed by aqueous workup, none of the desired product was isolated. Flashing of the column with methanol, also did not yield any product. We only recovered compound **45** in a 9% yield (scheme 2.4.6). The IR spectrum showed an N-H stretch at 3394 cm^{-1} and two carbonyl stretches at 1787 and 1757 cm^{-1} . The ^1H -NMR spectrum (see figure 2.4.6) displayed the [*R*]-pantolactone resonances and the mono-substituted phenyl ring pattern. The key resonances in the ^{13}C -NMR were the 4 carbonyl peaks of the two diastereomers at 177.7, 173.2, 172.2 and 171.3 ppm.

FIGURE 2.4.6: ¹H-NMR SPECTRUM OF COMPOUND 45

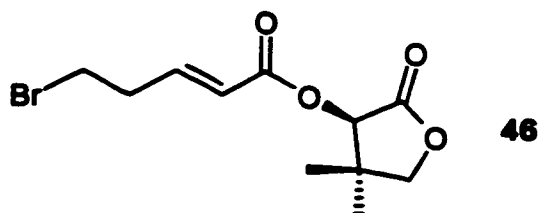
Scheme 2.4.6 : Formation of compound 45



Based on the quantity of 45 isolated and on the result obtained from reaction of (33) with 20c, it is possible that the compound did cyclize on the column as previously mentioned but we were unable to recover the desired cyclized product.

The reactions of 20b with norephedrine hydrochloride (35) and with 1,2-diaminopropane were attempted under the usual conditions but did not yield any isolable products. In the case of 1,2-diaminopropane, it is most probable that any desired product that may have formed went into the aqueous phase upon workup due to its high polarity.

Except for the formation of 41, the results obtained from the reaction of 20b with a variety of diamines and amino alcohols were quite disappointing. In some cases, low yields of monocyclic products were obtained. Often, the major isolated product is the diene ester 42 formed by a sequence of two elimination reactions. It is easy to appreciate that once the first elimination had taken place to give the allylic halide 46, a second elimination to 42 would be facile.

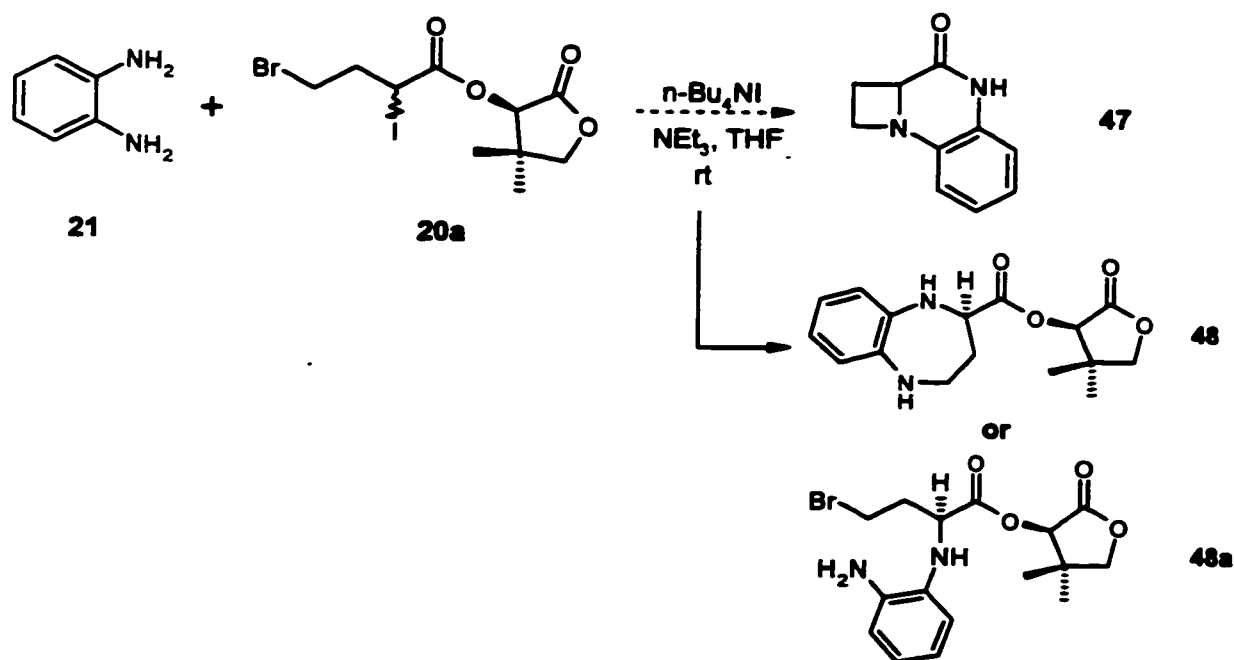


Considerable problems were always encountered during attempted chromatographic separation of the crude reaction mixtures. These problems were largely attributed to the high polarity of the products formed, which resulted in product loss on the column. Product loss in the water upon workup may have also contributed to the lack of success with **20b** for the reactions where small diamines were used. Further exploration is needed in the case of **20b** to possibly find better reaction conditions that would allow cyclization to take place with subsequent isolation of the product without loss during the workup or the purification step.

2.5 DKR of [*R*]-Pantolacto-4-Bromo-2-Iodobutanoate, **20a**, with Bifunctional

Nucleophiles

Based on the difficulties experienced in generating the various [6,6] and [5,6] ring systems as described earlier in this chapter, we were not surprised to discover that reaction of 1,2-phenylenediamine (**21**) and **20a** under the usual DKR conditions did not yield the tricyclic [4,6,6] product **47**.



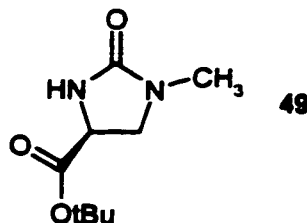
Proton NMR after silica gel chromatography of the main fraction isolated indicates the formation, in 27% yield, of compound **48** or **48a**.

The ^1H -NMR spectrum showed a multiplet at 6.51 ppm integrating for 4 aromatic hydrogens, as well as, the characteristic lactone resonances at 5.40, 4.02, 1.20 and 1.09 ppm. Nucleophilic displacement of the iodine by the amine has taken place based on the disappearance of the multiplet at 4.71 ppm representing the alpha proton in compound **20a**. In the case of the terminal CH_2 group, we do observe a change in the proton coupling pattern but cannot conclude with certainty that nucleophilic displacement of bromine has taken place. The formation of **48a** therefore involves initial displacement of the iodide by the amine, which, if followed by a second nucleophilic displacement of bromine by the free amino group, would generate compound **48**. In order to confirm the structure of the product, the reaction would need to be repeated for complete characterization.

Reaction of **20a** with 2-aminophenol gave no interpretable product. Based on these two results, no further DKR attempts were made with the C4 ester **20a** since it appeared that the four membered ring formation was not highly favored under these reaction conditions.

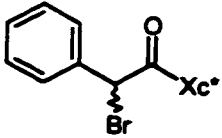
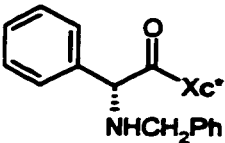
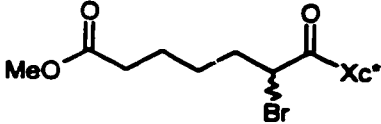
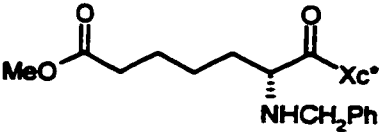
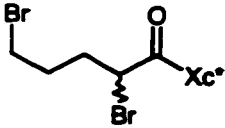
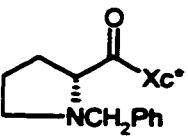
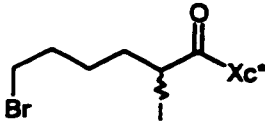
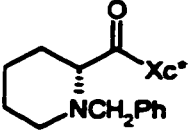
2.6 DKR of (4*S*)-1-methyl-3-(6-bromo-2-iodohexanoyl)-2-oxoimidazolidine-4-carboxylate with 1,2-phenylenediamine

Since the ketopiperazines and related heterocycles were obtained with only modest chiral induction when [*R*]-pantolactone was used as chiral auxiliary, it was decided to investigate the use of the chiral auxiliary, *t*-butyl-(4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate **49**.



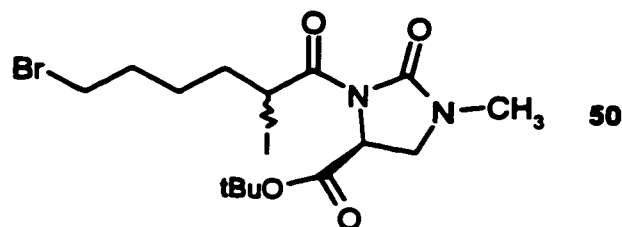
Nunami demonstrated the effectiveness of this auxiliary in the preparation of unnatural amino acids¹⁶ (see chapter 1). O'Meara also utilized this auxiliary in our group for the preparation of α -benzylamino derivatives.²⁸ Upon changing of the chiral auxiliary from [*R*]-pantolactone to the imidazolidinone **49**, the diastereoselectivity went from 7:1 to 20:1 for the [*R*]-pantolactone, to >98% in the case of the imidazolidinone. Interestingly, the absolute configuration at the α -carbon was (*R*) compared to (*S*) with the [*R*]-pantolactone derivatives. The results obtained by O'Meara are summarized in table 2.6.1.

Table 2.6.1 : Preparation of α -benzylamino derivatives

<u>Starting Material</u> ^a	<u>Product</u>	<u>Yield</u>	<u>de</u>
		83 %	>98 %
		83 %	>98 %
		87 %	>98 %
		66 %	>98 %

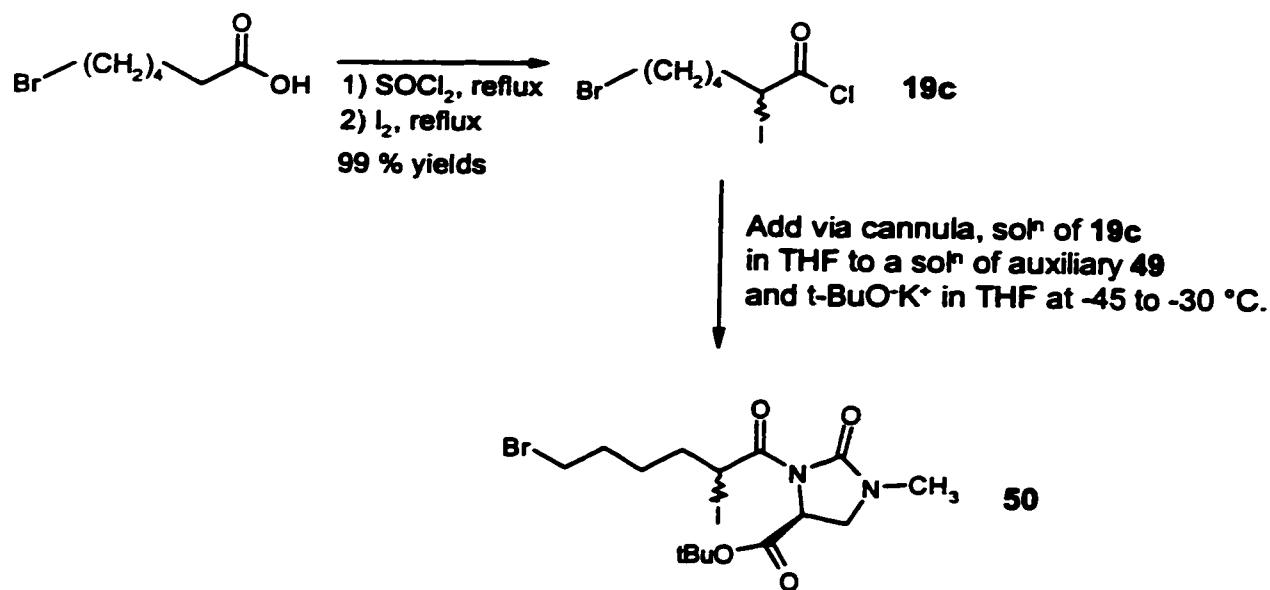
^a Xc* = 49

Based on these results, especially the last two entries which generated proline and pipercolic acid derivatives, we prepared the (4*S*)-1-methyl-3-(6-bromo-2-iodohexanoyl)-2-oxoimidazolidine-4-carboxylate **50**. We expected that reaction with 1,2-phenylenediamine would provide compound **23** with higher enantiomer ratio than the 4:1 observed previously.



The preparation of compound **50** from 6-bromohexanoic acid is shown below in scheme 2.6.1.

Scheme 2.6.1 : Preparation of starting material 50



Diastereomers separated by silica gel chromatography

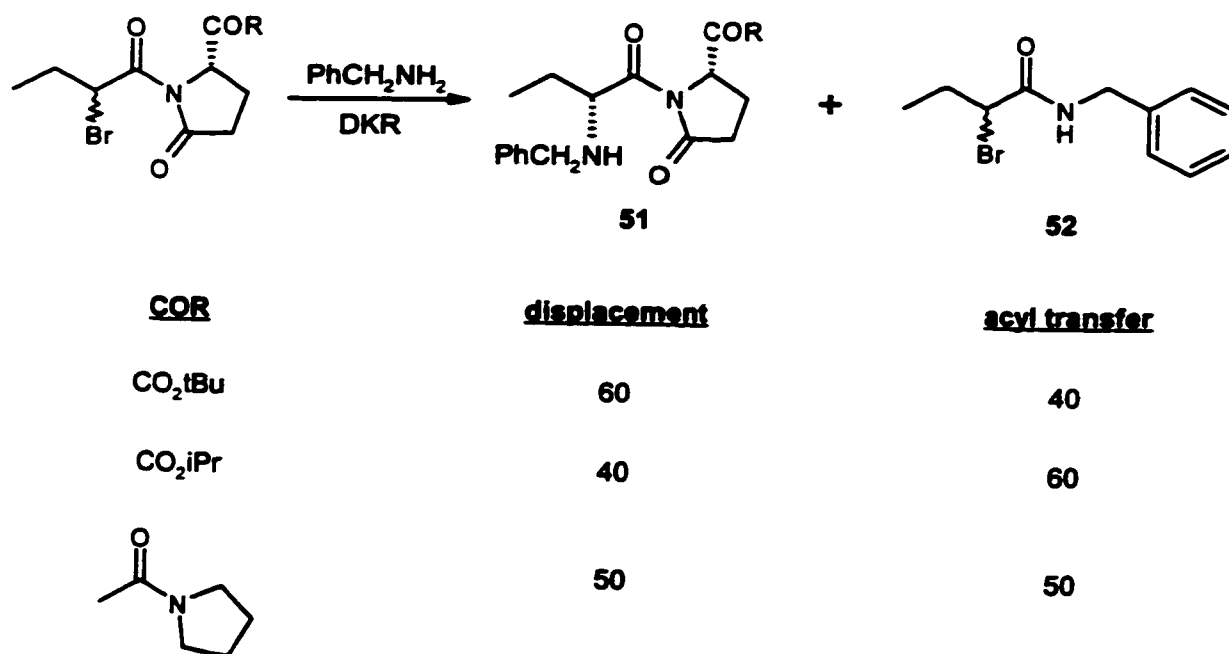
The acyl chloride 19c, prepared as described previously, was added via cannula to a solution of 0.97 equiv. of the auxiliary 49 and 1.1 equiv. of t-BuOK⁺ in dry THF at -45 °C. Purification by silica gel chromatography of the crude product, which was a 1:1 mixture of diastereomers as determined by ¹H-NMR, allowed for the separation of the two diastereomers. The ¹H-NMR clearly showed the nature of the product when compared to the spectrum of the previously prepared dibromide analog by O'Meara. The spectrum contained the two distinct triplets at 5.94 and 5.86 ppm, corresponding to the proton at the α-position of each diastereomer. Both of them also had distinct resonances for the three protons on the imidazolidinone ring at 4.6, 3.6 and 3.2 ppm. Each ¹³C-NMR spectrum showed the three carbonyl resonances and an intense peak corresponding to the CH₃'s of the t-butyl group. HRMS showed weak M⁺ ion (~ 2.0 %) peaks at 503.9904 and 501.9953 which corresponded with the calculated values of 503.9945 and 501.9965.

Since the two diastereomers were separated by chromatography, the DKR reactions with 1,2-phenylenediamine were carried out with each isomer. Isomer A was allowed to react for 41 h. Workup and purification afforded the desired compound **23** as a white solid in a 56% yield. The enantiomeric ratio was determined as previously via chiral HPLC with a Chiralcel OB column. Very much to our surprise, we obtained an almost 50:50 mixture of enantiomers. The formation of **23** was repeated with isomer B. It also gave racemic **23** in 56% yield.

2.7 Attempted Explanation of Observed Diastereoselectivity

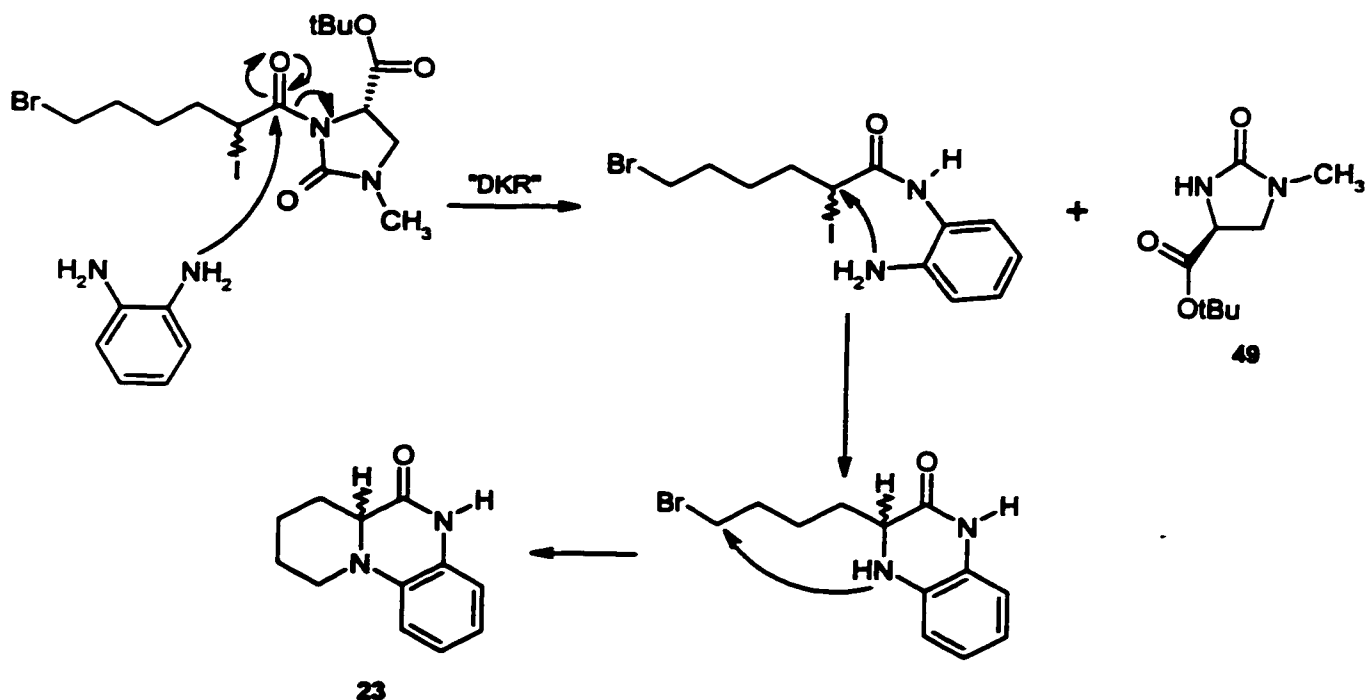
It was expected that the use of the chiral auxiliary **49** would produce a greater enantiomeric ratio than the [*R*]-pantolactone auxiliary. Also, it was expected that under the DKR conditions, the slower reacting isomer would epimerize to the faster reacting one and thus both would yield the same major diastereomer. This was not the case. Previous results by O'Meara give a possible explanation for the result mentioned above. O'Meara discovered that when performing DKR reactions using auxiliaries structurally similar to **49**, such as, pyroglutamate derivatives, the reaction not only afforded the displacement product **51** but also gave a fairly large amount of acyl transfer product **52**.²⁷ This is shown in scheme 2.7.1 with pyroglutamate as the auxiliary with specific ratios of the displacement versus acyl transfer summarized below.

Scheme 2.7.1 : DKR products from nucleophilic substitution of t-butyl pyroglutamate derivatives



In the case of the imidazolidinone auxiliary **49**, this ratio was determined to be 93:7. We propose that in the reaction of **50** with 1,2-phenylenediamine, the acyl transfer mechanism becomes by far the dominant pathway. It is proposed that the reason for this change in reaction pathway may result from the fact that we are using an aromatic ortho diamine that is not as nucleophilic as benzylamine, hence it may have more of a tendency to attack at the carbonyl prior to substitution at the α -position. Therefore, the chiral auxiliary is removed prior to the formation of the new chiral center resulting in complete loss of chiral induction in the crucial bond-forming step (scheme 2.7.2). The presence of Γ in the reaction mixture assures epimerization of the chiral center.

Scheme 2.7.2 : Proposed reaction pathway for the formation of 23 from 50



The proposed explanation could be confirmed by performing the reaction of optically pure **50** with 1,2-phenylenediamine without the epimerizing agent, tetrabutylammonium iodide. By doing this, the reaction would give enantiomerically pure product at the beginning of the reaction, which would lead to an enantiomerically enriched product. This is evident since without any epimerizing source in the reaction mixture, the initial substitution will produce an optically active product. As the reaction progresses one would then get accumulation of free iodine which would epimerize the remaining starting amide **50** that would from that point on, produce a racemic product.

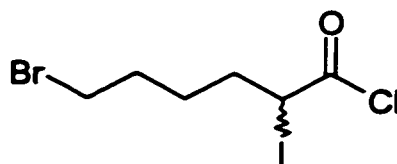
Such an explanation could also account for the lower than expected enantiomeric ratios obtained when using [*R*]-pantolactone as the chiral auxiliary.

2.8 Summary

The reaction of [*R*]-pantolactone esters **20a-c** with bifunctional nucleophiles via dynamic kinetic resolution conditions gave some interesting new compounds. The best results were obtained for the generation of the relatively unstrained [6,6] bicyclic ring system from ester **20c**. The enantiomer ratios were somewhat disappointing compared to previous results where mono-functional nucleophiles were reacted with α -halo [*R*]-pantolactone esters. As for reactions with ester **20b**, further study is needed to determine the optimal reaction conditions. Workup and purification are also two areas that would need to be optimized in order to be able to isolate the products formed without occurring great losses at those two steps of the procedure.

2.9 EXPERIMENTAL

General: All reactions, unless stated otherwise, were carried out in flame dried flasks under a nitrogen atmosphere using dry solvents. The THF used was dried over sodium benzophenone ketyl, and distilled prior to use. Methylene chloride was dried over CaH_2 , and distilled prior to use. Triethylamine was distilled from CaH_2 and stored under nitrogen over CaH_2 . All chemical reagents were obtained from commercial suppliers and used as is, unless stated otherwise. Solvents used for chromatographic purifications were routinely distilled prior to use. Reactions were monitored by thin-layer chromatography using Kieselgel 60 F_{254} precoated 0.25 mm thick glass plates. Column chromatography was performed using 230-400 mesh silica gel. Melting points were determined using a Thomas Hoover Capillary melting point apparatus and are uncorrected. ^1H and ^{13}C -NMR spectra were obtained from either a Varian Gemini-200 MHz, a Varian XL-300 MHz or a Bruker AMX-500 MHz spectrometer. Unless stated otherwise, all spectra were run in spectroscopic grade deuterated chloroform. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (brs), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), quartet (q), triplet (t), multiplet (m), quartet of triplets (qt). Infrared spectra were obtained on a Bomem-Michelson MB-100 FT/IR spectrophotometer either neat on NaCl plates or from a spectroscopic grade dichloromethane solution. Mass spectra were recorded on a VG 7070E or a Kratos 2H instrument. Optical rotation values were determined using a Perkin-Elmer polarimeter (model 241) set at the sodium D line (589 nm).

6-bromo-2-iodohexanoyl chloride 19c

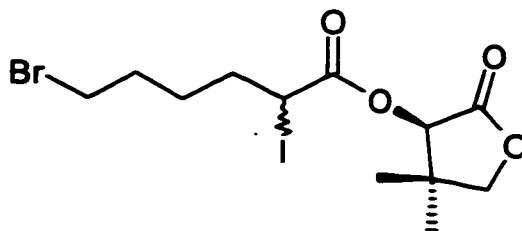
Thionyl chloride, 10.25 mL (140.98 mmol) was added via syringe to 5.0 g (25.63 mmol) of 6-bromo hexanoic acid kept under nitrogen. The mixture was protected from moisture with a drying tube and then refluxed for one hour. Once the solution cooled, 3.90 g (15.38 mmol) of iodine was added and the mixture refluxed for an additional 11 h until complete by proton NMR. The excess thionyl chloride was removed under reduced pressure and high vacuum. The reaction afforded 100% yield of clean material, which was used as is for the next step.

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz): $\delta(\text{ppm})$ 4.65 (t, 1H, $J=7.3$ Hz), 3.40 (t, 2H, $J=6.4$ Hz), 2.05 (m, 2H), 1.90 (m, 2H), 1.59 (m, 2H)

$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz): $\delta(\text{ppm})$ 171.0, 35.2, 32.8, 31.4, 30.0, 27.6

IR (neat): 2940, 1774, 1237 cm^{-1}

HRMS: Calcd. for $\text{C}_6\text{H}_9\text{OBrClI}$: 339.8550; found: 339.8545

[R]-Pantolacto-6-bromo-2-iodohexanoate 20c

Dry triethylamine, 8.93 mL (64.08 mmol) was added via syringe to a stirred solution of 3.17 g (24.35 mmol) of [*R*]-pantolactone in 80 mL of dry, freshly distilled CH₂Cl₂ cooled to 0 °C. The mixture was stirred for 10 minutes followed by addition via cannula of a solution of 8.70 g (25.63 mmol) of 6-bromo-2-iodohexanoyl chloride in 20 mL of CH₂Cl₂. Once the addition complete, the reaction was warmed to room temperature and stirred for 3 h after which TLC showed no [*R*]-pantolactone remained. The reaction mixture was washed 3 times with water, followed by washing of the combined aqueous layers with CH₂Cl₂ (2X). The organic layer was dried with MgSO₄, filtered and the solvent removed under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 5:1 hexanes/ethyl acetate produced 8.70 g (82% yield) of the desired product in a 55:45 mixture of diastereomers as a viscous brownish oil.

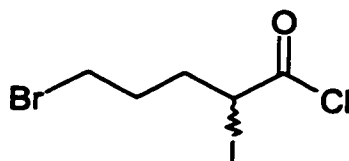
¹H-NMR (CDCl₃, 500 MHz): δ(ppm) Mixture of 2 *Diastereomers*: 5.34 and 5.31(d, total of 1H, J=1.8 Hz and J=2.9 Hz), 4.44 and 4.32 (broad td, total of 1H, J=1.9 Hz and J=2.4 Hz), 4.02 (m, 2H), 3.36 (m, 1H), 3.13 (m, 1H), 2.00 (m, 2H), 1.85 (m, 2H), 1.55 (m, 2H), 1.20 (d, 3H, J=8.8 Hz), 1.13 (d, 3H, J=9.0 Hz)

¹³C-NMR (CDCl₃, 125 MHz): Spectrum was too complicated to list all peaks (too many) due to iodide-bromine exchange. This is indicated by presence of eight carbonyl peaks.

IR (neat): 2964, 1794, 1746, 1131 cm⁻¹

HRMS: (- I^+ fragment) Calcd. for $C_{12}H_{18}O_4Br$: 305.0388 and 307.0368; found 305.0377 and 307.0388

5-bromo-2-iodopentanoyl chloride 19b



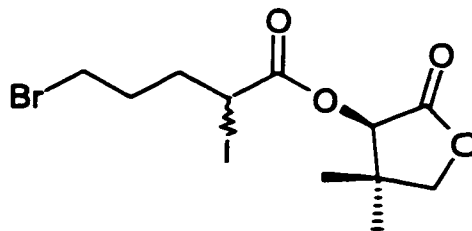
Thionyl chloride, 11.08 mL (151.90 mmol) was added via syringe to 5.0 g (27.61 mmol) of 5-bromovaleric acid kept under nitrogen. The mixture was protected from moisture with a drying tube and then refluxed for one hour. Once the solution cooled, 4.20 g (16.57 mmol) of iodine was added and the mixture refluxed for an additional 5 h until complete by proton NMR. The excess thionyl chloride was removed under reduced pressure and high vacuum. The reaction afforded 100% yield of clean material, which was used as is for the next step.

^1H -NMR ($CDCl_3$, 200 MHz): δ (ppm) 4.68 (t, 1H, $J=6.9$ Hz), 3.40 (t, 2H, $J=5.9$ Hz), 2.19 (m, 2H), 2.00 (m, 2H)

^{13}C -NMR ($CDCl_3$, 50 MHz): δ (ppm) 171.0, 34.7, 31.7, 31.3, 29.0

IR (neat): 2962, 1774 cm^{-1}

EIMS, m/z (rel. intensity, %): 291 (9.8), 289 (9.9), 263 (9.2), 261 (9.5), 199 (18.8), 197 (14.8), 135 (25.3), 133 (24.7)

[R]-Pantolacto-5-bromo-2-iodopentanoate 20b

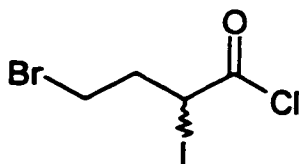
Dry triethylamine, 9.31 mL (66.84 mmol) was added via syringe to a stirred solution of 3.30 g (25.40 mmol) of [*R*]-pantolactone in 90 mL of dry, freshly distilled CH₂Cl₂ cooled to 0 °C. The mixture was stirred for 10 minutes and a solution of 8.70 g (26.74 mmol) of 5-bromo-2-iodopentanoyl chloride in 30 mL of CH₂Cl₂ was added via cannula. Once the addition complete, the reaction was warmed to room temperature and stirred for 2 h 15 min after which TLC showed no [*R*]-pantolactone remained. The reaction mixture was washed 3 times with water, followed by washing of the combined aqueous layers with CH₂Cl₂ (2X). The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 5:1 hexanes/ethyl acetate produced 8.17 g (77% yield) of the desired product in a 55:45 mixture of diastereomers as a viscous brown-yellow oil.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) *Mixture of 2 diastereomers*: 5.37 and 5.34 (s, total of 1H), 4.50 and 4.39 (m, total of 1H), 4.03 (m, 2H), 3.41 and 3.18 (m, total of 2H), 2.15 (m, 2H), 1.98 (m, 2H), 1.24 (d, 3H, J=8.2 Hz), 1.17 (d, 3H, J=7.4 Hz)

¹³C-NMR (CDCl₃, 125 MHz): Spectrum was too complicated to list all peaks (too many) due to iodide-bromine exchange. This is indicated by presence of eight carbonyl peaks.

IR (neat): 2965, 2940, 1795, 1745, 1250 cm⁻¹

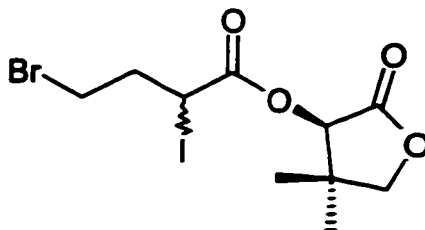
HRMS: (-I⁺ fragment) Calcd. for C₁₁H₁₆O₄Br: 291.0232 and 293.0211; found 291.0213 and 293.0222

4-bromo-2-iodobutanoyl chloride 19a

Thionyl chloride, 12.01 mL (164.66 mmol) was added via syringe to 5.0 g (29.94 mmol) of 4-bromobutyric acid kept under nitrogen. The mixture was protected from moisture with a drying tube and then refluxed for one hour. Once the solution cooled, 4.56 g (17.96 mmol) of iodine was added and the mixture refluxed for an additional 8.5 h until complete by proton NMR. The excess thionyl chloride was removed under reduced pressure and high vacuum over 6 h (monitor since product is volatile). The reaction afforded 100% yield of clean material which was used as is for the next step.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 4.98 (t, 1H, J=7.2 Hz), 3.49 (m, 2H), 2.50 (m, 2H)

HRMS: Calcd. for C₄H₅OBrClI: 311.8237 and 309.8257; found: 311.8207 and 309.8233

[R]-Pantolacto-4-bromo-2-iodobutanoate 20a

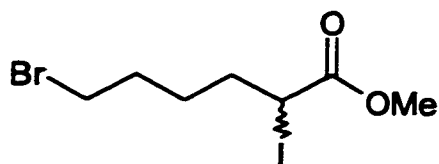
Dry triethylamine, 10.43 mL (74.84 mmol) was added via syringe to a stirred solution of 3.70 g (28.44 mmol) of [*R*]-pantolactone in 100 mL of dry, freshly distilled CH₂Cl₂ cooled to 0 °C. The mixture was stirred for 10 minutes after which a solution of 9.32 g (29.93 mmol) of 4-bromo-2-iodo butanoyl chloride in 20 mL of CH₂Cl₂ was added via cannula. Once the addition complete, the reaction was warmed to room temperature and stirred for 4 h after which TLC showed no [*R*]-pantolactone remained. The reaction mixture was washed 3 times with water, followed by a washing of the combined aqueous layers with CH₂Cl₂ (2X). The combined organic layers were dried with MgSO₄, filtered and the solvent evaporated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using 5:1 hexanes/ethyl acetate produced 5.75 g (50% yield) of the desired compound in a 55:45 mixture of diastereomers as a dark brown oil.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) *Mixture of 2 diastereomers*: 5.36 and 5.34 (d, total of 1H, J=2.2 Hz and 2.7 Hz), 4.65 (m, 1H), 4.03 (m, 2H), 3.54 (m, 1H), 3.30 (m, 1H), 2.47 (m, 2H), 1.24 (d, 3H, J=14.8 Hz), 1.18 (d, 3H, J=14.0 Hz)

¹³C-NMR (CDCl₃, 125 MHz): Spectrum was too complicated to list all peaks (too many) due to iodide-bromine exchange. This is indicated by presence of eight carbonyl peaks.

IR (neat): 2971, 1794, 1749 cm⁻¹

HRMS: Calcd. for C₁₀H₁₄O₄BrI: 403.9120 and 405.9100; found 403.9131 and 405.9112

Methyl 6-bromo-2-iodohexanoate 22

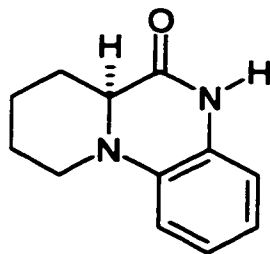
The 6-bromo-2-iodohexanoyl chloride was prepared as indicated previously. To 10.44 g (30.76 mmol) of the acyl chloride cooled to 0 °C was added dropwise a total of ~ 8 mL of methanol. Once the addition was complete, the reaction mixture was stirred for 30 minutes after which the MeOH was removed under reduced pressure and the remaining oil dissolved in ethyl acetate. The organic phase was washed twice with a saturated solution of sodium bicarbonate, dried with MgSO₄, filtered and the solvent evaporated under reduced pressure. The reaction yielded 9.63 g (93% yield) of the desired ester as a red oil without the need for further purification.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 4.29 (t, 1H, J=7.5 Hz), 3.74 (s, 3H), 3.39 (t, 2H, J=6.6 Hz), 1.95 (m, 4H), 1.15 (m, 2H),

¹³C-NMR (CDCl₃, 50 MHz): δ(ppm) 171.3, 52.6, 34.9, 32.8, 31.4, 27.7, 19.7

IR (CHCl₃): 2952, 1733, 1437 cm⁻¹

HRMS: Calcd. for C₇H₁₂O₂BrI: 335.9045 and 333.9065; found 335.9038 and 333.9010

6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxalin-6-one 23

To a solution of 400 mg (0.92 mmol) of [*R*]-pantolacto-6-bromo-2-iodohexanoate dissolved in 5 mL of dry distilled THF under N₂ was added 0.10 g (0.92 mmol) of 1,2-phenylenediamine, 0.28 mL (2.03 mmol) of dry triethylamine via syringe, and 0.1023 g (0.277 mmol) of *n*-tetrabutylammonium iodide. The mixture was stirred at room temperature for 28 h. The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 310 mg of crude material. Purification on silica gel chromatography using 3:1 hexanes/ethyl acetate afforded 100 mg (54% yield) of clean product as a white solid. The enantiomeric ratio of 4:1 was obtained by chiral HPLC using a Chiralcel OB column with 96% / 4% hexanes/isopropanol as the eluent. The retention times of 18.5 min and 26.3 min.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) 8.59 (brs, 1H), 6.97 (td, 1H, *J*=1.5; 7.8 Hz), 6.77 (m, 2H), 6.72 (m, 1H), 3.76 (td, 1H, *J*=1.9; 12.5 Hz), 3.53 (dd, 1H, *J*=3.1; 11.7), 2.71 (td, 1H, *J*=3.2; 12.5 Hz), 2.20 (m, 1H), 1.94 (broad d, 1H, *J*=13.1 Hz), 1.73 (m, 1H), 1.64 (m, 2H), 1.49 (qt, 1H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 169.7, 135.5, 126.3, 124.0, 119.3, 115.5, 112.1, 59.7, 46.6, 26.7, 23.7, 23.2

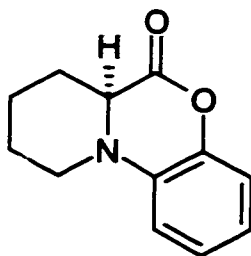
IR (KBr): 3466, 3197, 2940, 1679 cm^{-1}

HRMS: Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: 202.1106; found 202.1100

mp : 184.0-185.0 $^{\circ}\text{C}$

$[\alpha]_{\text{D}}^{23} = -15.5^{\circ}$ ($c=1.0$, CH_2Cl_2)

6,6a,7,8,9,10-hexahydrobenzo[*b*]pyrido[1,2-*d*][1,4]oxazin-6-one 26



To a solution of 500 mg (1.154 mmol) of [*R*]-pantolacto-6-bromo-2-iodohexanoate dissolved in 5 mL of dry distilled THF under N_2 was added 0.1260 g (1.154 mmol) of 2-aminophenol, 0.48 mL (3.46 mmol) of dry triethylamine via syringe, and 0.17 g (0.462 mmol) of *n*-tetrabutylammonium iodide. The mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 450 mg of crude material. Purification by silica gel chromatography using 20:1 hexanes/ethyl acetate afforded 100 mg (43% yield) of clean product as a yellow solid. The enantiomeric ratio of $\sim 4:1$ was obtained by chiral HPLC with a Chiralcel OB column using 98% / 2% hexanes/isopropanol as the eluent. The retention times were 14.6 and 20.0 minutes.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) 7.06 (td, 1H, J=1.5; 7.6 Hz), 7.01 (dd, 1H, J=1.5; 7.9 Hz), 6.86 (td, 1H, J=1.4; 7.7 Hz), 6.82 (dd, 1H, J=1.1; 8.1 Hz), 3.69 (m, 1H), 3.38 (dd, 1H, J=3.5; 11.6 Hz), 2.61 (td, 1H, J=3.1; 12.2 Hz), 2.27 (m, 1H), 1.94 (m, 1H), 1.81 (m, 1H), 1.73 (m, 1H), 1.63 (qt, 1H), 1.41 (qt, 1H)

¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) 167.3, 141.4, 135.7, 125.1, 120.3, 116.7, 112.9, 57.3, 46.7, 27.1, 23.5, 22.9

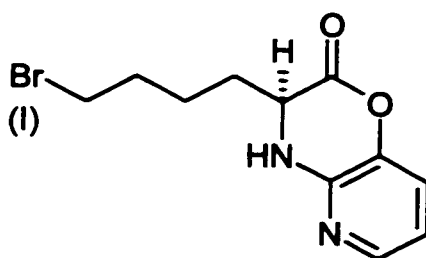
IR (KBr): 3072, 2940, 2865, 1763, 1206 cm⁻¹

HRMS: Calcd. for C₁₂H₁₃NO₂: 203.0946; found 203.0925

mp: 86.5 – 89.5 °C

[α]_D²³ = -12.4 ° (c=1.16, CHCl₃)

Compound **28**



mixture of the iodo and bromo

To a solution of 400 mg (0.923 mmol) of [*R*]-pantolacto-6-bromo-2-iodohexanoate dissolved in 5 mL of dry distilled THF under N₂ was added 0.1220 g (1.108 mmol) of 2-amino-3-hydroxypyridine, 0.41 mL (2.95 mmol) of dry triethylamine via syringe, and 0.17 g (0.461 mmol) of n-tetrabutylammonium iodide. The mixture was stirred at room temperature for 4 days, after which the reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl

acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 330 mg of crude material. Purification by silica gel chromatography using 2:1 hexanes/ethyl acetate afforded 100 mg (38% yield) of clean product as a white solid.

$^1\text{H-NMR}$ (CDCl_3 , 500 MHz): $\delta(\text{ppm})$ 10.08 (s, 1H), 8.01 (dd, 1H, $J=1.4$; 4.9 Hz), 7.26 (dd, 1H, $J=1.4$; 6.6 Hz), 6.95 (dd, 1H, $J=5.0$; 8.0 Hz), 4.60 (m, 1H), 3.40 (td, 0.6H, $J=1.9$; 6.7 Hz), 3.18 (td, 1.4 H, $J=3.2$; 6.9 Hz), 1.99 (m, 1H), 1.88 (m, 3H), 1.67 (m, 2H)

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ 167.6, 141.7, 140.9, 139.0, 124.3, 119.6, 77.4, 77.3, 77.1, 77.0, 76.7, 76.6, 33.3, 33.1, 32.4, 30.3, 30.0, 29.9, 26.1, 23.8, 6.2

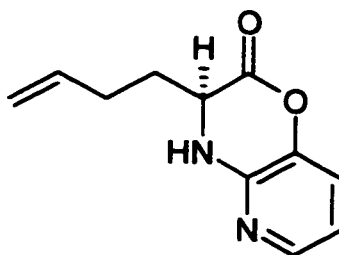
IR (neat): 3426, 3013, 2926, 1710 cm^{-1}

EIMS, m/z (rel. intensity, %): 332 (55.1), 286 (11.1), 284 (11.4), 205 (73.9), 163 (20.4), 161 (18.1), 150 (100)

HRMS: Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_2\text{Br}$: 284.0160 and 286.0140; found: 284.0202 and 286.0152

Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_2\text{I}$: 332.0022; found: 332.0022

3-(3-butenyl)-3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazin-2-one 29



To a solution of 30 mg (0.105 mmol) of compound **28** in 5 mL of dry distilled THF kept under nitrogen and cooled to $-78\text{ }^\circ\text{C}$, was added 0.11 mL (0.115 mmol) of sodium

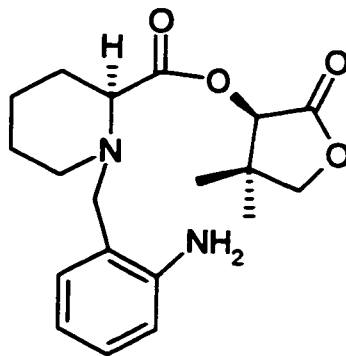
bis(trimethylsilyl)amide via syringe. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 minutes and then an additional 3 h at room temperature. The reaction mixture was quenched with water and diluted with ethyl acetate. The phases were separated and the organic layer washed (3X) with water. The combined aqueous layers were washed once with ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 15 mg of crude material. Purification by silica gel chromatography using 3:1 hexanes/ethyl acetate gave 12 mg (64% yield; 4 mg of SM recovered) of the elimination product **29** as a white solid.

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz): $\delta(\text{ppm})$ 8.01 (dd, 1H, $J=1.5$; 5.0 Hz), 7.28 (dd, 1H, $J=1.4$; 8.8 Hz), 6.94 (dd, 1H, $J=5.3$; 7.9 Hz), 5.81 (m, 1H), 5.04 (m, 2H), 4.62 (dd, 1H, $J=4.4$; 8.3 Hz), 2.31 (m, 2H), 2.01 (m, 2H), 1.61 (brs, 1H)

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ 167.5, 141.4, 140.7, 138.8, 136.8, 127.1, 119.5, 116.0, 30.1, 29.7, 28.9

IR (CH_2Cl_2): 3379, 3013, 2925, 2854, 1709, 1605 cm^{-1}

HRMS: Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$: 204.0899; found 204.0889

Compound 31

To a solution of 400 mg (0.923 mmol) of [*R*]-pantolacto-6-bromo-2-iodohexanoate dissolved in 5 mL of dry distilled THF under N₂ was added 0.1692 g (1.385 mmol) of 2-aminobenzylamine, 0.40 mL (2.86 mmol) of dry triethylamine via syringe, and 0.17 g (0.461 mmol) of *n*-tetrabutylammonium iodide. The mixture was stirred at room temperature for 21 h 30 min, after which the reaction mixture was diluted with ethyl acetate, water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 410 mg of crude material. Purification by silica gel chromatography using 3:1 hexanes/ethyl acetate afforded 150 mg (47% yield) of product as a yellow semi-solid in a 10:1 ratio of diastereomers (determined by weight). The 2 diastereomers were easily separated by chromatography.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) *Diastereomer A (minor)*: 7.05 (td, 1H, J=1.4; 7.6 Hz), 6.92 (d, 1H, J=6.9 Hz), 6.59 (m, 2H), 5.39 (s, 1H), 4.68 (brs, 2H), 4.02 (m, 2H), 3.88 (d, 1H, J=12.4 Hz), 3.33 (d, 1H, J=12.4 Hz), 3.23 (m, 1H), 2.97 (m, 1H), 2.17 (m, 1H), 1.90 (m, 2H), 1.63 (m, 1H), 1.53 (m, 2H), 1.43 (m, 1H), 1.20 (s, 3H), 1.08 (s, 3H)

Diastereomer B (major): 7.04 (td, 1H, $J=1.5$; 7.6 Hz), 6.95 (d, 1H, $J=6.7$ Hz), 6.60 (m, 2H), 5.40 (s, 1H), 4.64 (brs, 2H), 4.02 (m, 2H), 3.95 (d, 1H, $J=12.7$ Hz), 3.36 (d, 1H, $J=12.7$ Hz), 3.32 (m, 1H), 2.94 (m, 1H), 2.17 (m, 1H), 1.87 (m, 1H), 1.83 (m, 1H), 1.61 (m, 1H), 1.53 (m, 2H), 1.44 (m, 1H), 1.19 (s, 3H), 1.10 (s, 3H)

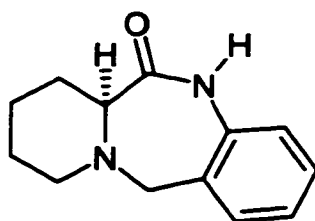
$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ *Diastereomer A*: 172.7, 172.0, 147.1, 130.8, 128.6, 121.4, 117.1, 115.4, 76.1, 74.8, 63.2, 59.4, 49.7, 40.1, 29.8, 25.3, 23.1, 22.3, 20.1

Diastereomer B: 172.5, 171.9, 146.8, 130.9, 128.5, 121.2, 117.4, 115.4, 76.1, 75.1, 63.5, 59.3, 49.5, 40.1, 29.7, 25.0, 23.0, 22.3, 20.0

IR (CH_2Cl_2): 3447, 3366, 3022, 2936, 2857, 1791, 1749 cm^{-1}

HRMS: Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$: 346.1893; found 346.1863

1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a][1,4]diazepin-12-one 32



A solution of 50 mg of compound **31a** in 5 mL of dry distilled THF kept under nitrogen with 3 drops of glacial acetic acid was refluxed for 6 h after which water and ethyl acetate were added. The two phases were separated and the organic layer washed (3X) with water. The combined aqueous layers were washed twice with ethyl acetate. The organic fractions were combined and dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 42 mg of crude material. Purification by silica gel chromatography

using 2:1 hexanes/ethyl acetate gave 13 mg (42% yield, obtained after flashing of column) of the desired cyclized product as a white solid.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.88 (brs, 1H), 7.22 (m, 3H), 6.98 (d, 1H, J=7.8 Hz), 4.04 (d, 1H, J=13.7 Hz), 3.55 (d, 1H, J=13.9 Hz), 2.85 (dd, 1H, J=3.1; 8.0 Hz), 2.75 (m, 1H), 2.55 (m, 1H), 1.75 (m, 5H), 1.23 (m, 1H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 172.5, 137.9, 130.3, 128.8, 128.4, 125.3, 120.5, 30.6, 58.2, 53.9, 27.0, 25.9, 22.3

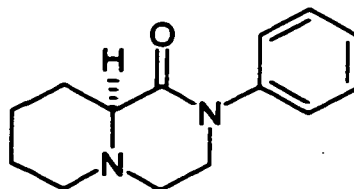
IR (CH₂Cl₂): 3387, 2940, 2854, 1687 cm⁻¹

HRMS: Calcd. for C₁₃H₁₆N₂O: 216.1263; found 216.1280

mp: 125.0 – 127.0 °C

[α]_D²³ = +282 ° (c=0.3, CHCl₃)

2-phenylperhydropyrido[1,2-a]pyrazin-1-one 34



To a solution of 400 mg (0.92 mmol) of [*R*]-pantolacto-6-bromo-2-iodohexanoate dissolved in 5 mL of dry distilled THF under N₂ was added 145 μL (1.108 mmol) of N-phenylethylenediamine, 0.41 mL (2.96 mmol) of dry triethylamine, and 0.17 g (0.46 mmol) of n-tetrabutylammonium iodide. The mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water.

The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 460 mg of crude material. The crude mixture was run through a silica gel column using 3:1 hexanes/ethyl acetate and the cyclized product flushed off the column with methanol to give 320 mg back. A second column using 2:1 ethyl acetate/hexanes afforded 130 mg (61% yield) of the desired product as a yellow solid.

$^1\text{H-NMR}$ (CDCl_3 , 500 MHz): $\delta(\text{ppm})$ 7.35 (m, 2H), 7.23 (m, 3H), 3.95 (td, 1H, $J=4.6$; 11.7 Hz), 3.41 (ddd, 1H, $J=1.3$; 4.0; 11.5 Hz), 2.94 (m, 2H), 2.65 (m, 2H), 2.37 (m, 1H), 2.16 (td, 1H, $J=3.4$; 11.4 Hz), 1.87 (m, 1H), 1.63 (m, 2H), 1.44 (m, 1H), 1.32 (m, 1H)

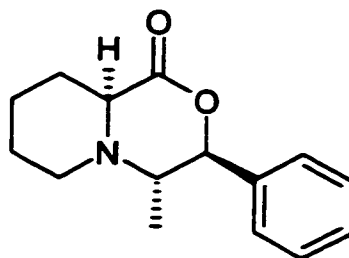
$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): $\delta(\text{ppm})$ 168.6, 142.4, 129.0, 126.7, 126.0, 66.4, 56.2, 51.9, 49.6, 27.6, 25.1, 24.5, 14.1

IR (KBr): 3071, 2933, 2846, 2746, 1663, 759, 695 cm^{-1}

HRMS: Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$: 230.1420; found: 230.1421

mp: 78.0 – 83.5 $^{\circ}\text{C}$

$[\alpha]_{\text{D}}^{23} = -58.5^{\circ}$ ($c=1.0$, CHCl_3)

(4S)-methyl-(3R)-phenylperhydropyrido[2,1-c][1,4]oxazin-1-one 36

To a solution of 400 mg (0.923 mmol) of [*R*]-pantolacto-6-bromo-2-iodohexanoate dissolved in 5 mL of dry distilled THF under N₂ was added 0.2095 g (1.385 mmol) of (1*R*, 2*S*)-norephedrine hydrochloride, 0.39 mL (2.77 mmol) of dry triethylamine via syringe, and 0.1279 g (0.346 mmol) of *n*-tetrabutylammonium iodide. The mixture was stirred at room temperature for 28 h, after which the reaction mixture was diluted with ethyl acetate, water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 500 mg of crude material. Purification by silica gel chromatography using 5:1 hexanes/ethyl acetate afforded 100 mg (44% yield) of the desired product as a clear oil in a 2:1 mixture of diastereomers (determined by ¹H-NMR).

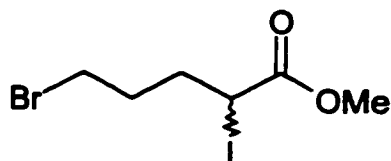
¹H-NMR (CDCl₃, 500 MHz): δ(ppm) (*mixture of 2 diastereomers*) 7.29 (m, 5H), 5.77 & 5.24 (d, total of 1H, *J*=3.1; 4.1 Hz), 3.13 (m, 1H), 2.96 (m, 1H), 2.78 (broad d, total of 1H, *J*=11.1 Hz) & 2.45 (td, total of 1H, *J*=3.3; 11.3 Hz), 2.32 (m, 1H), 1.98 & 1.88 (m, total of 2H), 1.61 (m, 2H), 1.33 (, 1H), 0.77 & 0.72 (d, total of 3H, *J*=6.7 Hz)

¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) (*mixture of 2 diastereomers*) 170.3, 170.1, 137.0, 136.0, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 125.6, 125.2, 112.5, 83.4, 82.7, 63.5, 57.7, 57.4, 57.4, 52.0, 51.0, 28.8, 28.5, 25.3, 24.8, 24.1, 22.9, 15.2, 3.1

IR (CH₂Cl₂): 3016, 2941, 2858, 1735 cm⁻¹

HRMS: Calcd. for C₁₅H₁₉NO₂: 245.1416; found 245.1404

Methyl 5-bromo-2-iodopentanoate 40



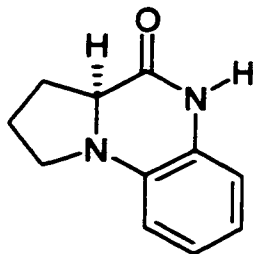
The 5-bromo-2-iodopentanoyl chloride was prepared as indicated previously. To 10.78 g (33.14 mmol) of the acyl chloride cooled to 0 °C was added dropwise a total of ~ 8 mL of methanol. Once the addition was complete, the reaction mixture was stirred for 30 minutes after which the MeOH was evaporated and the remaining oil dissolved in ethyl acetate. The organic layer was washed twice with a saturated solution of sodium bicarbonate, dried with MgSO₄, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography using pure hexanes afforded 7.11 g (67% yield) of the desired ester as a dark red oil.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 4.31 (t, 1H, J=7.3 Hz), 3.74 (s, 3H), 3.39 (t, 2H, J=6.4 Hz), 2.10 (m, 2H), 1.94 (m, 2H)

¹³C-NMR (CDCl₃, 50 MHz): δ(ppm) 171.4, 52.9, 34.3, 32.1, 31.8, 18.9

IR (neat): 2951, 1734, 1435, 1144 cm⁻¹

HRMS: Calcd. for C₆H₁₀O₂BrI: 319.8909 and 321.8889; found 319.8901 and 321.8875

5,6,6a,7,8,9-hexahydropyrrolo[1,2-a]quinoxalin-6-one 41

To a solution of 400 mg (0.95 mmol) of [*R*]-pantolacto-5-bromo-2-iodopentanoate dissolved in 5 mL of dry distilled THF under N₂ was added 0.1032 g (0.95 mmol) of 1,2-phenylenediamine, 0.29 mL (2.10 mmol) of dry triethylamine via syringe, and 0.1058 g (0.286 mmol) of n-tetrabutylammonium iodide. The mixture was stirred at room temperature for 8 days. The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent evaporated under reduced pressure to afford 290 mg of crude material. Purification on silica gel chromatography using 3:1 hexanes/ethyl acetate afforded 110 mg (61% yield) of clean product as a dark green solid. The enantiomeric ratio of 4:1 was obtained by chiral HPLC using a (*R*)-3,5-dinitrobenzoyl phenylglycine propylsilyl column (# 256127AA) with 98% / 2% hexanes/isopropanol as the eluent. The retention times were 31.9 and 33.8 minutes.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) 7.79 (brs, 1H), 6.96 (m, 1H), 6.73 (m, 2H), 6.58 (d, 1H, J=7.8 Hz), 3.69 (dd, 1H, J=9.2; 6.8 Hz), 3.46 (td, 1H, J=8.6; 5.0 Hz), 3.17 (td, 1H, J=9.2; 6.1 Hz), 2.28 (m, 1H), 2.17 (m, 1H), 2.08 (m, 1H), 2.02 (m, 1H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 168.8, 135.1, 126.9, 123.9, 118.4, 115.2, 111.9, 60.0, 46.4, 29.7, 22.2

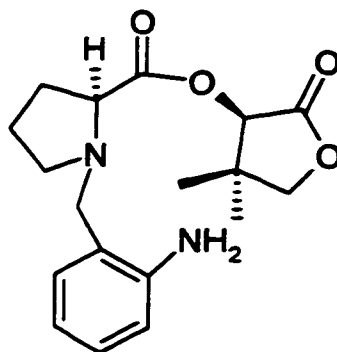
IR (KBr): 3214, 3080, 2976, 2928, 1683 cm^{-1}

HRMS: Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: 188.0950; found 188.0955

mp: 171.0 – 172.0 $^{\circ}\text{C}$

$[\alpha]_{\text{D}}^{23} = -54.8^{\circ}$ ($c=0.5$, CHCl_3)

Compound 44



To a solution of 500 mg (1.193 mmol) of [*R*]-pantolacto-5-bromo-2-iodopentanoate dissolved in 6 mL of dry distilled THF under N_2 was added 0.1457 g (1.193 mmol) of 2-aminobenzylamine, 0.50 mL (3.58 mmol) of dry triethylamine via syringe, and 0.0881 g (0.239 mmol) of *n*-tetrabutylammonium iodide. The mixture was stirred at room temperature for 2 days, after which the reaction mixture was diluted with ethyl acetate, water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 440 mg of crude material. Purification by silica gel chromatography using 3:1 hexanes/ethyl acetate afforded 170 mg (42% yield) of 44 as a solid in a 4:1 ratio of diastereomers (determined by ^1H -NMR).

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) (*mixture of 2 diastereomers*) 7.05 (td, 1H, J=1.5; 7.6 Hz), 6.97 (dd, 1H, J=1.5; 7.7 Hz), 6.60 (m, 2H), 5.39 & 5.32 (s, total of 1H), 4.65 (brs, 2H), 4.03 & 3.93 (m, total of 4H), 3.46 & 3.28 (d, total of 1H, J=12.2 Hz), 3.39 & 3.34 (AB d, total of 1H), 2.97 & 2.89 (m, total of 1H), 2.28 (m, 2H), 1.99 (m, total of 1H), 1.80 (m, 2H), 1.20 & 1.10 + 1.13 & 1.03 (s, total of 6H)

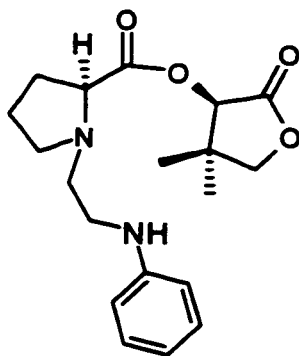
¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) (*mixture of 2 diastereomers*) 173.50, 173.46, 172.1, 172.0, 147.1, 146.8, 130.0, 129.9, 128.5, 128.5, 122.6, 122.5, 117.2, 117.0, 115.4, 115.2, 76.1, 75.7, 75.0, 65.2, 64.8, 57.8, 57.7, 53.8, 53.3, 52.9, 40.2, 10.0, 30.1, 29.9, 23.4, 23.1, 23.1, 22.9, 20.0, 19.8

IR (CH₂Cl₂): 3451 (broad), 3019, 2923, 2878, 1789, 1754 cm⁻¹

HRMS: Calcd. for C₁₈H₂₄N₂O₄: 332.1736; found 332.17549

mp: 120.0 – 123.0 °C

Compound 45



To a solution of 400 mg (0.95 mmol) of [*R*]-pantolacto-5-bromo-2-iodopentanoate dissolved in 5 mL of dry distilled THF under N₂ was added 150 μL (1.145 mmol) of N-phenylethylenediamine, 0.43 mL (3.05 mmol) of dry triethylamine via syringe, and 0.18 g (0.477 mmol) of n-tetrabutylammonium iodide. The mixture was stirred at room temperature

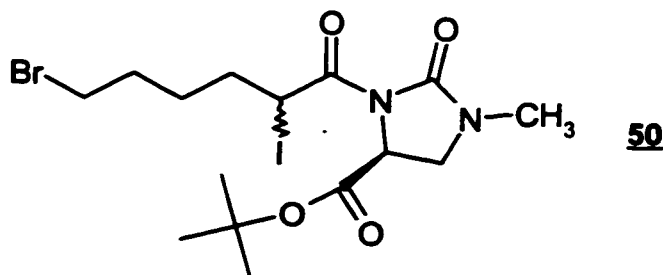
for 24 h. The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 460 mg of crude material. The crude mixture was purified by silica gel chromatography using 2:1 hexanes/ethyl acetate as the eluent to afford 30 mg (9% yield) of compound **45** as a brown oil.

^1H -NMR (CDCl_3 , 200 MHz): δ (ppm) 7.25 (t, 2H, $J=7.1$ Hz), 6.65 (m, 3H), 5.39 (s, 1H), 4.39 (brs, 1H) 4.01 (s, 2H), 3.49 (m, 1H), 3.19 (m, 2H), 3.05 (m, 2H), 2.77 (m, 1H), 2.46 (m, 1H), 2.20 (m, 1H), 1.94 (m, 3H), 1.20 (s, 3H), 1.11 (s, 3H)

^{13}C -NMR (CDCl_3 , 75 MHz): δ (ppm) 177.7, 173.1, 172.2, 171.3, 148.6, 147.1, 129.4, 129.2, 129.1, 129.1, 126.9, 125.7, 117.7, 116.9, 112.9, 112.8, 112.7, 76.3, 76.1, 75.5, 75.1, 70.4, 65.3, 55.3, 54.8, 53.4, 52.9, 42.3, 40.7, 40.2, 40.0, 29.6, 29.0, 23.5, 23.4, 23.0, 22.8, 20.0, 18.9

IR (CH_2Cl_2): 3394, 3017, 2905, 1787, 1757, 1604 cm^{-1}

HRMS: Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$: 346.1893; found: 346.1888

(4S)-tert-butyl 3-(6-bromo-2-iodohexanoyl)-1-methyl-2-oxo-4-imidazolidinecarboxylate

The 6-bromo-2-iodohexanoyl chloride was prepared as indicated previously.

**General procedure taken from Jeff A. O'Meara M.Sc. Thesis, 1995. To a solution of 1.28 g (6.43 mmol) of t-butyl-(4S)-1-methyl-2-oxoimidazolidine carboxylate in 40 mL of dry distilled THF cooled to $-45\text{ }^{\circ}\text{C}$ was added, over a period of 2 minutes, 7.29 mL (7.29 mmol) of a 1.0 M solution of potassium t-butoxide. The solution was stirred for 30 minutes after which a solution of 2.25 g (6.629 mmol) of 6-bromo-2-iodohexanoyl chloride in 10 mL of THF was added via cannula over 5 min. The reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 75 min. and then poured into a mixture of ether (50 mL), acetic acid (2.0 mL) and brine (50 mL). The organic phase was separated and washed successively with brine, 2% NaOH and water. The aqueous layer was washed once with ether. The combined organic layers were dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 3.16 g of crude material in a 1:1 mixture of diastereomers. Purification on silica gel using 2:1 hexanes/ethyl acetate as the eluent gave 560 mg and 800 mg of the 2 separated diastereomers as yellow oils.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) *Diastereomer A*: 5.94 (t, 1H, J=7.5 Hz), 4.59 (dd, 1H, J=3.9; 10.2 Hz), 3.69 (t, 1H, J=9.9 Hz), 3.37 (t, 2H, J=6.7 Hz), 3.27 (dd, 1H, J=3.9; 9.7 Hz), 2.89 (s, 3H), 2.05 (m 3H), 1.88 (m, 3H), 1.45 (s, 9H)

Diastereomer B: 5.86 (t, 1H, J=7.6 Hz), 4.63 (dd, 1H, J=4.7; 10.4 Hz), 3.66 (t, 1H, J=9.7 Hz), 3.36 (m, 3H), 2.89 (s, 3H), 2.05 (m, 3H), 1.85 (m, 3H), 1.48 (s, 9H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) *Diastereomer A*: 170.5, 168.1, 152.9, 82.7, 53.1, 46.1, 34.6, 32.9, 31.6, 30.5, 27.6, 27.5, 20.5

Diastereomer B: 170.3, 167.9, 153.0, 83.1, 53.0, 46.2, 34.4, 33.1, 31.7, 30.5, 27.8, 27.7, 20.0

IR (neat): 3457, 3193, 2942, 2614, 1731, 1680 cm⁻¹

HRMS: Calcd. for C₁₅H₂₄BrIN₂O₄: 501.9965 and 503.9945; found 501.9953 and 503.9904

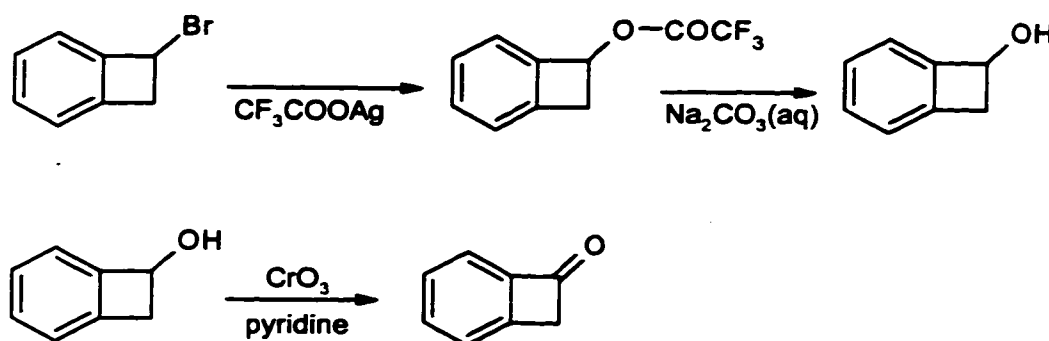
Chapter 3

Applications and Preparation of Benzocyclobutenols and Benzocyclobutenones

3.0 Evolution and Use of Benzocyclobutenones and Benzocyclobutenols in Synthetic Chemistry

The precursor to benzocyclobutenone, benzocyclobutene, made its first appearance back in 1909 when a student by the name of H. Finkelstein prepared 1,2-dibromobenzocyclobutene as part of his doctoral thesis.²⁹ After this first synthesis, 47 years would pass until M.P. Cava repeated the synthesis of benzocyclobutene, and then in 1960, published the first paper on the preparation of benzocyclobutenol and benzocyclobutenone via the 1-bromobenzocyclobutene (scheme 3.0.1).³⁰

Scheme 3.0.1 : Original preparation of benzocyclobutenol and benzocyclobutenone

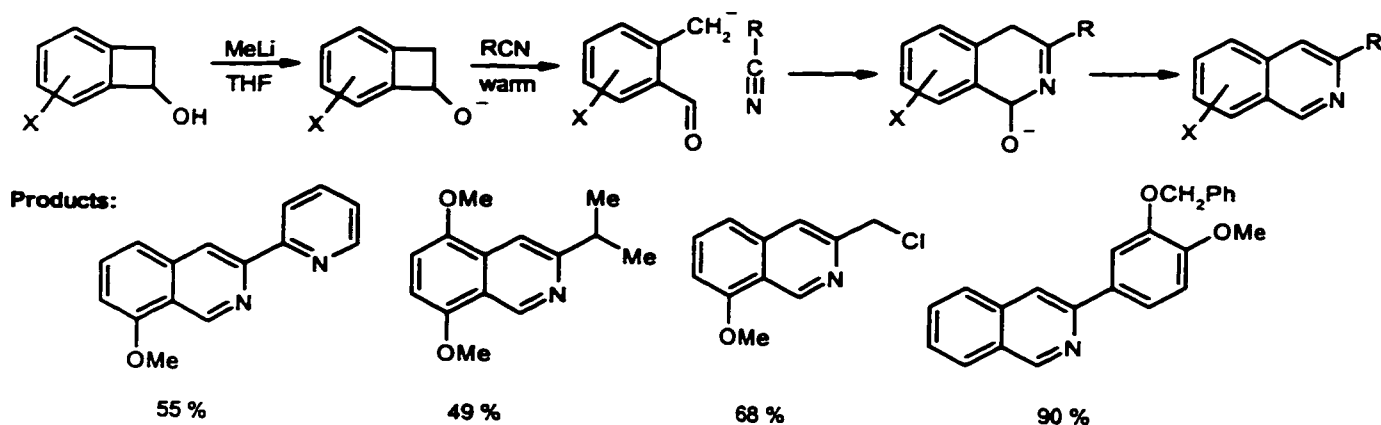


The current day level of interest for these compounds stems from their great versatility in organic synthesis. Their significance is due to the fact that under mild thermal conditions (80 – 140 °C) they stereoselectively ring open to generate α -oxy-o-quinodimethanes, which are very useful intermediates for the preparation of polycyclic

compounds, heterocycles and other useful compounds.³¹ These can now function as electron-rich dienes in $[4\pi + 2\pi]$ cycloadditions.³²

In current day chemistry, there are a number of examples where benzocyclobutenones and benzocyclobutenols are used as precursors. These include the synthesis of isoquinolines³³, naphthalene derivatives³⁴, quinones³⁵, substituted 5-membered rings³⁶ and 2-substituted indoles.³⁷ Shown below are some examples of the preparation of these important compounds.

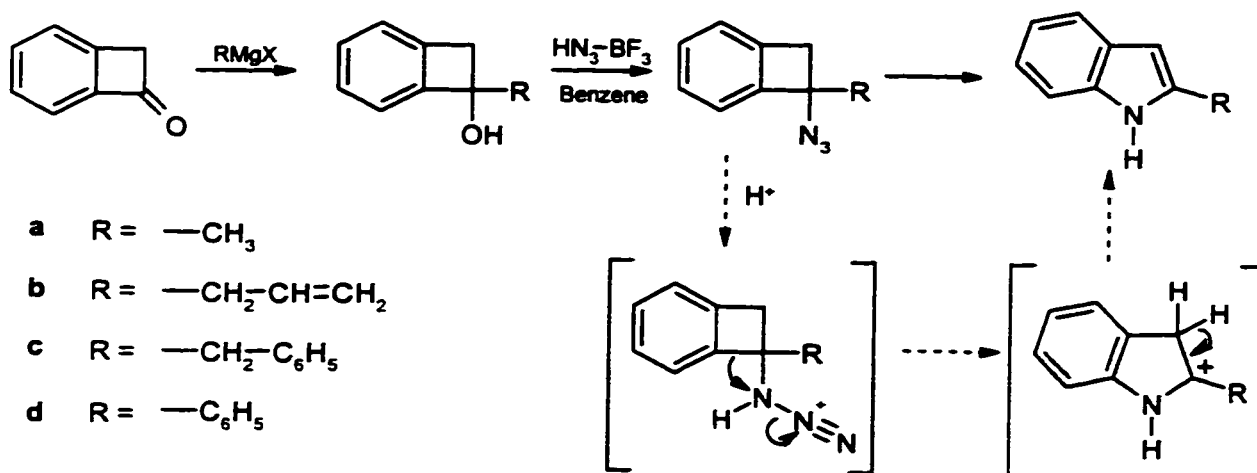
Scheme 3.0.2 : Preparation of substituted isoquinolines



This preparation of isoquinolines (scheme 3.0.2) is achieved by deprotonation of the benzocyclobutenol to form the alkoxy adduct, which upon heating, undergoes a bond cleavage to open up the ring. The intermediate species is reacted with various nitriles to afford isoquinolines in reasonable to good yields. This procedure was also applied to the synthesis of the alkaloid, Hypecumine, using it as the final step.

Scheme 3.0.3 shows a method developed by Plat for the preparation of heterocyclic rings, e.g., indoles.

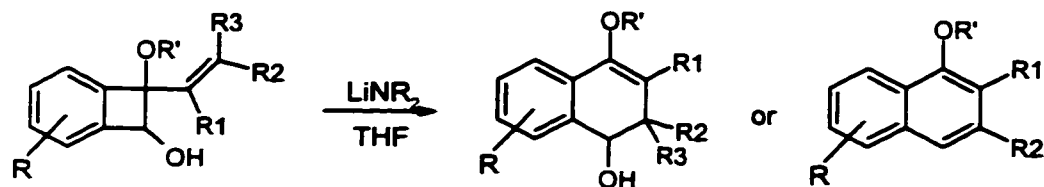
Scheme 3.0.3 : Preparation of 2-substituted indoles



With this procedure, one can envision many possibilities for substitution since a number of diverse benzocyclobutenones can be prepared via current synthetic methods, some of which will be described later in this chapter. Once the starting benzocyclobutenone is prepared, it is reacted with different Grignards to generate the benzocyclobutenol, which is then converted to the azide. Final acid catalyzed ring expansion gives the desired indole in competitive yields, according to the authors of this paper.

Other classes of compounds attainable using benzocyclobutenones are naphthalene derivatives. One example of this involves the reaction of the mono protected benzocyclobutenedione with various substituted vinyl lithiums (scheme 3.0.4) to first generate the starting benzocyclobutenol. Upon treatment with lithium dialkyl amides, ring opening occurs leading to the stereoselective cyclization that generates the new six-membered ring. As expected and seen from compounds **f** and **g**, the product composition is based on the geometry of the olefins used.

Scheme 3.0.4 : Preparation of substituted naphthalene derivatives



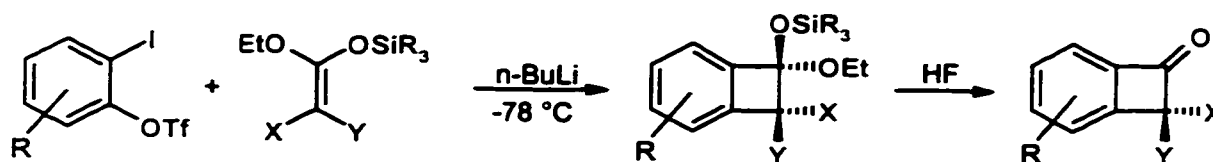
Benzocyclobutenol	Product	Yield %
a	e	91
b	f	89 (f:g = 14:1)
c	g	78 (single diast.)
d	h	93

Preceding the current usage of benzocyclobutenols and benzocyclobutenones, much effort was expended to develop effective and regiospecific routes to these compounds. What follows is a brief look at some of the methods of preparation of these useful intermediates.

3.1 Synthetic Methods for Generating Benzocyclobutenones and Benzocyclobutenols

In order to meet the ever-growing need for substituted benzocyclobutenones in organic synthesis, many different types of syntheses have been developed in recent years. Synthetic routes described prior to 1990 were reviewed by Breau and Durst.³⁸ Thus, only a few of the recently developed methods are described in this section. In general, these methods can involve 2+2 cycloaddition of benzyne with alkenes,^{39,40,41} intramolecular cyclization of ortho-haloaryl compounds⁴² or metal catalyzed cyclization of acylsilanes.⁴³ Use of the 2+2 cycloaddition was made recently by Suzuki⁴⁴ where ortho-iodo triflates were used to generate a benzyne species, which was then reacted with a series of ketene silyl acetals (scheme 3.1.1).

Scheme 3.1.1 : 2+2 Cycloaddition

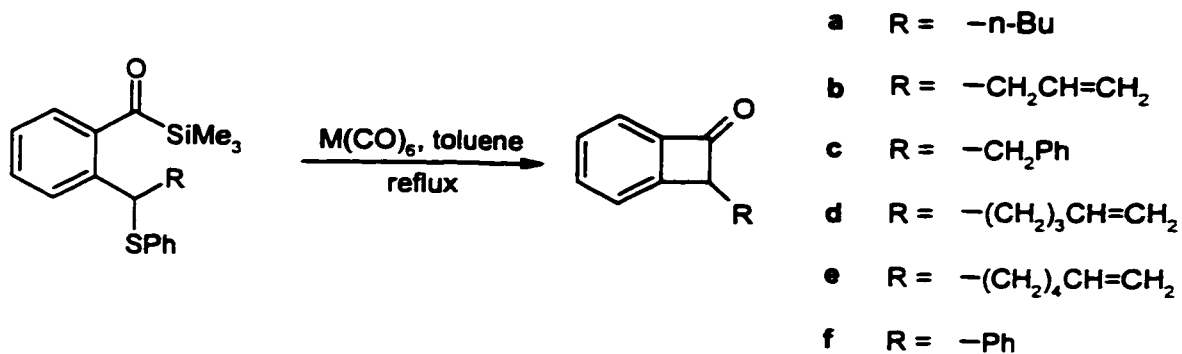


For this paper, X and Y were either H, OR, or alkyl groups. The yields for this procedure ranged from 54 to 88% for the silylated product and 64 to 99% for the final hydrolysis step. The lowest yield of 37% was obtained for the non-activated alkene, which gave the basic benzocyclobutenone ring system.

Acylsilanes have also been recently combined with group 6 metal carbonyls to generate the four-membered ring¹⁵ (scheme 3.1.2). Different metals were used including chromium and molybdenum. This method functioned best when the acylsilane contained a

thiophenyl moiety on the ortho substituted carbon. The compounds shown below were obtained in yields of 43 to 76%.

Scheme 3.1.2 : Benzocyclobutenones from acylsilanes



For this project, two different methods of preparation of benzocyclobutenones and benzocyclobutenols were attempted, the results of which will be discussed in the following chapter.

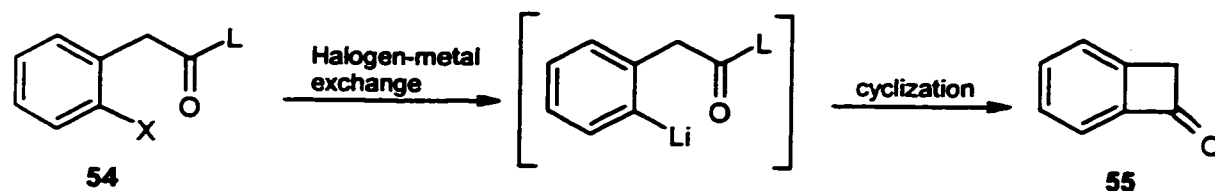
CHAPTER 4

Exploration of New Paths to Benzocyclobutenones and Benzocyclobutenols

4.0 Benzocyclobutenone Preparation via Halogen-Metal Exchange (Background)

The use of aryl halogen-metal exchange in the preparation of benzocyclobutenones has been shown to be a very useful method. The procedure involves treating a substrate which has a halogen ortho to a “functionalized arm”, such as an ester, with an alkyllithium such as *t*-BuLi (scheme 4.0.1).⁴⁵ Intramolecular attack on the carbonyl group, followed by subsequent elimination of the leaving group yields the cyclobutenone ring.

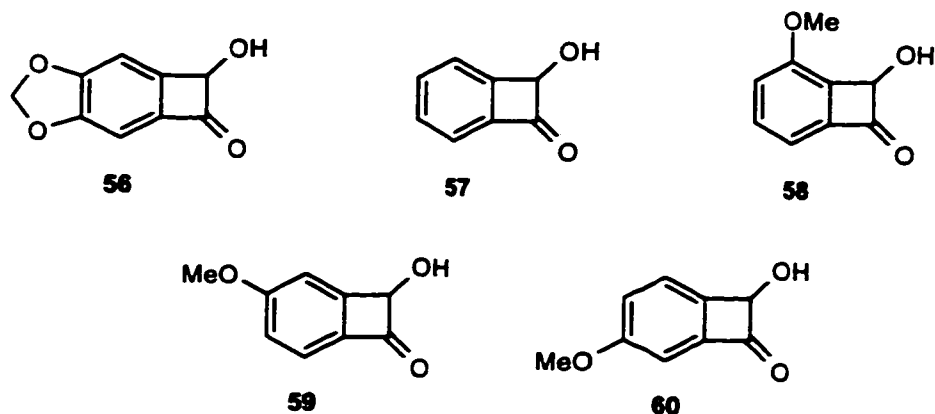
Scheme 4.0.1 : Halogen-metal exchange approach



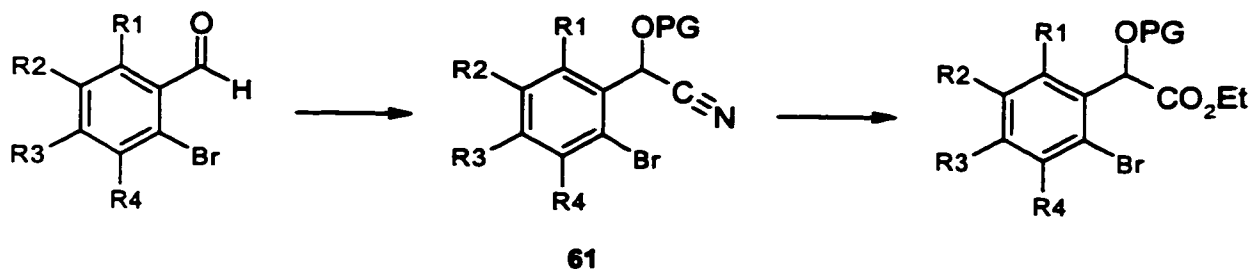
X = halogen, L = leaving group

Halogen-metal exchange was used by Lear⁴⁵ for the preparation of 2-hydroxybenzocyclobutenones such as compounds 56 to 60 (figure 4.0.1).

Figure 4.0.1 : 2-Hydroxybenzocyclobutenones

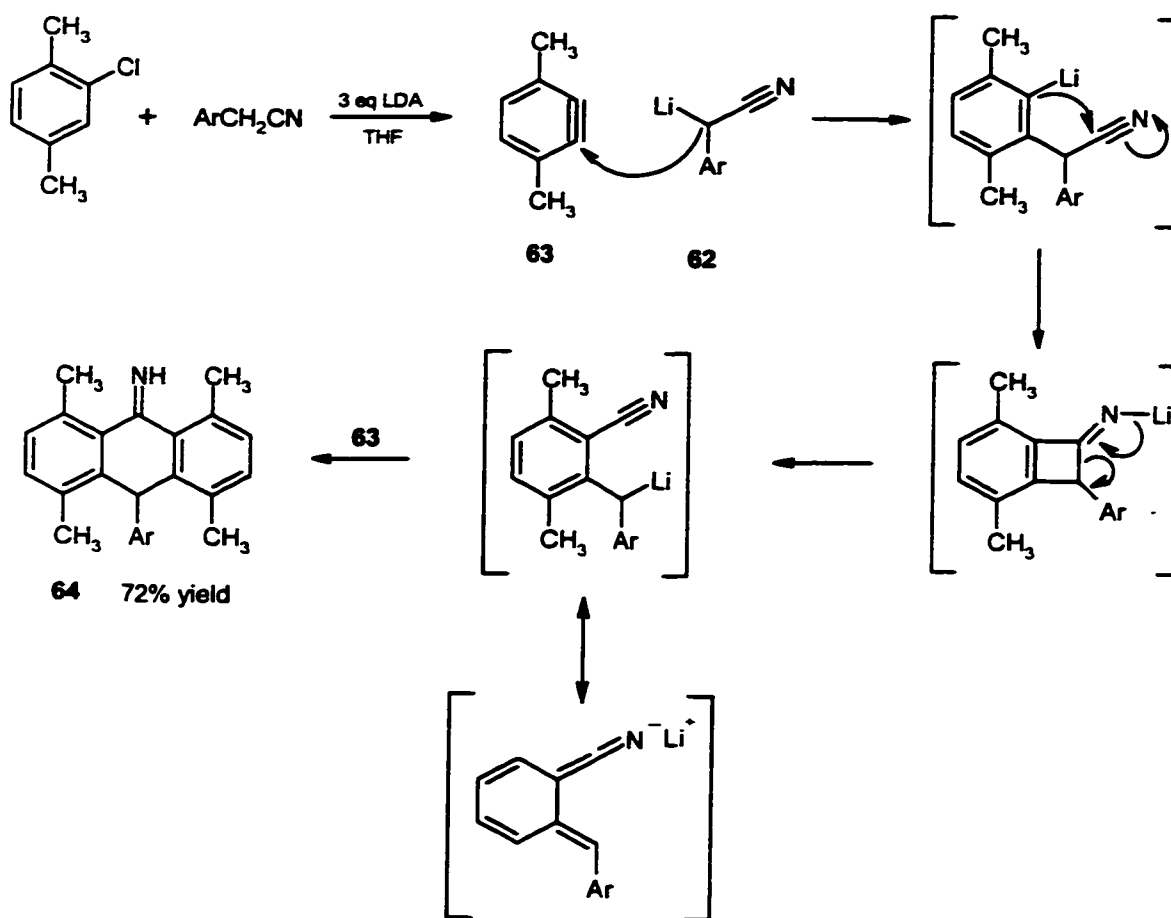


The general procedure for preparing these compounds involved at least five steps, starting from the ortho-halo aromatic aldehyde and going through a protected cyanohydrin intermediate **61**.



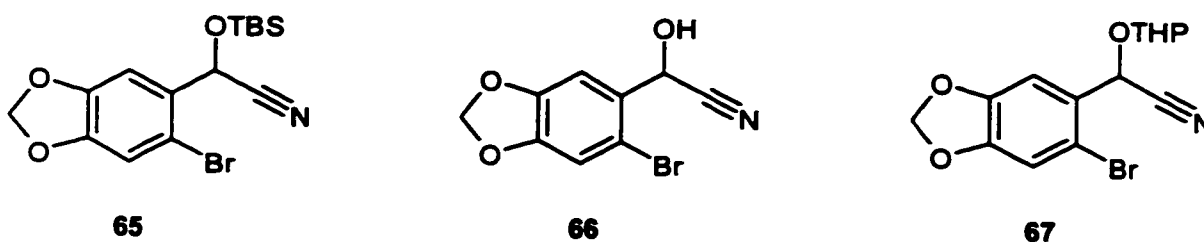
Since preparation of the cyanohydrin intermediate was the first step in the synthesis, it was envisioned that the benzocyclobutenones might be prepared in only two steps by direct cyclization of this intermediate. A literature precedent for this cyclization did exist. Biehl⁴⁶ showed that the reaction of benzylic nitriles with *o*-chloro-*p*-xylene in the presence of 3 equivalents of LDA generated the anthrone imine **64**. The proposed pathway involved reaction of the α -lithionitrile **62** with *in situ* generated benzyne **63**, formation of a lithiated benzocyclobutene imine, ring opening to form an ortho-quinodimethane equivalent and finally, reaction of this intermediate with another benzyne moiety (scheme 4.0.2).

Scheme 4.0.2 : Biehl's Anthrone imine synthesis

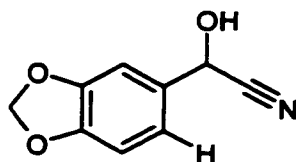


Lear attempted benzocyclobutenone formation directly from the cyanohydrins. This reaction was investigated using t-butyldimethylsilyl protected cyanohydrin **65** of 6-bromopiperonal, the unprotected cyanohydrin **66**, and the THP protected cyanohydrin **67**.

Figure 4.0.2

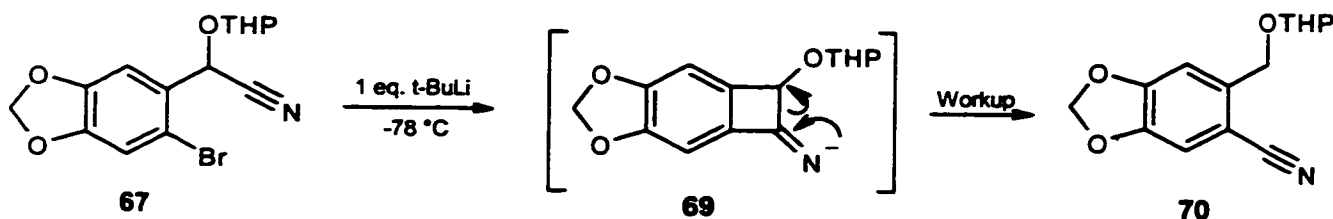


When treated with >2 equivalents of *t*-BuLi, compound **65** gave a complex mixture of products, and compound **66** gave compound **68** resulting from halogen-metal exchange and subsequent quenching with H₂O.

**68**

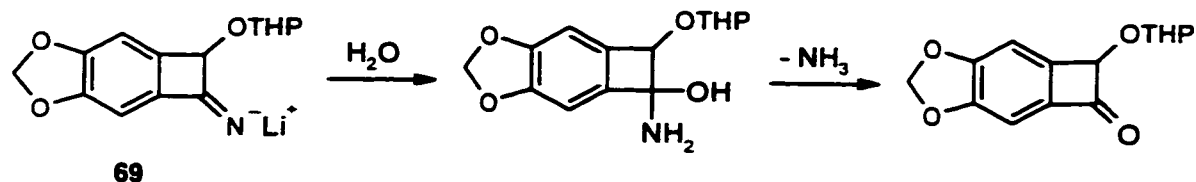
When the THP protected cyanohydrin **67** was treated with *t*-BuLi, the reaction product was **70**. Analogous to the Biehl proposal, it was suggested that this product, in which the nitrile group was transposed from the benzylic to the ortho position, was formed via the unstable cyclic intermediate **69**, as shown below.

Scheme 4.0.3 : Proposed mechanism for conversion of **67** to **70**



Since it appeared that cyclobutene formation was taking place with some *o*-lithiated benzylic nitriles, we wanted to explore the possibility of avoiding the ring opening by modifying the reaction conditions. If the intermediates such as **69** could be trapped by protonation via addition of water, then benzocyclobutenones should be isolated (scheme 4.0.4).

Scheme 4.0.4 : Proposed formation of cyclobutenone ring via intermediate 69



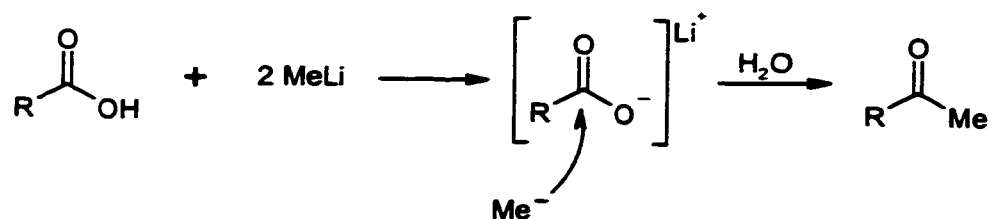
Since having lithium coordinated to the nitrogen anion did not keep the ring from opening up, we envisaged that replacing the lithium by more electronegative magnesium might allow the intermediate **69** to be stabilized enough to avoid the formation **70** because magnesium would form a more covalent bond than lithium with the nitrogen.

Prior to attempting the cyclobutene formation from the nitrile **71**, we performed halogen-metal exchange reactions on 2-(2-bromophenyl) acetic acid **72**, methyl 2-(2-bromophenyl) acetate **73** and the corresponding Weinreb amide **74** of the ester.

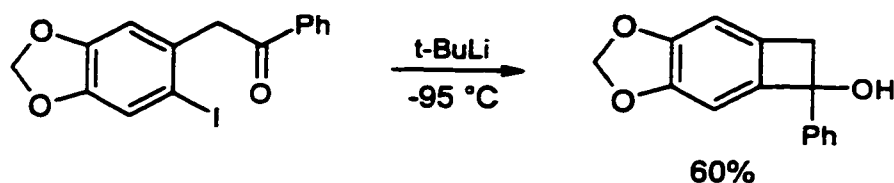
4.1 Results of Halogen-Metal Exchange in **72**, **73**, and **74**

Even though these reactions might be considered somewhat speculative, there nevertheless is literature precedent to indicate that they might have a reasonable chance of success. It would particularly be useful if the readily available acid **72** could be transformed directly into benzocyclobutenone. Included in this background are the following observations.

- Halogen-metal exchange of an acid such as **72** will initially form the deprotonated carboxylate which should reduce the acidity of the benzylic hydrogens, allowing for halogen-lithium exchange to take place.
- Reaction of an acid with methyllithium gives the methyl ketone as shown below.

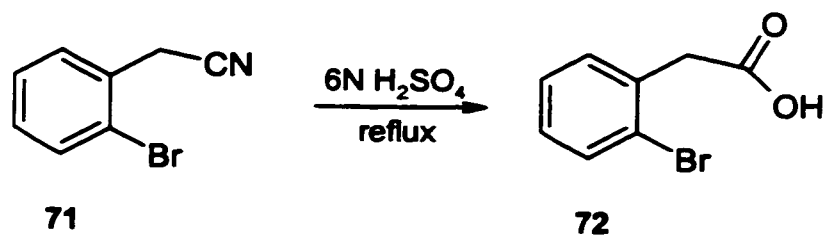


- Cyclobutenol formation via halogen-metal exchange of similar substrates have been shown in the literature⁴⁷ (shown below).



The 2-(2-bromophenyl)acetic acid **72** was prepared in quantitative yield from 2-bromophenyl acetonitrile **71** by refluxing in 6N H₂SO₄ for 17 h (scheme 4.1.1). The structure was confirmed by ¹H-NMR, ¹³C-NMR, infrared and HRMS.

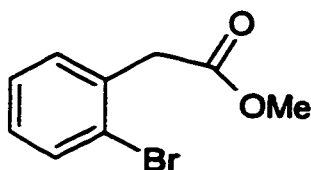
Scheme 4.1.1 : Preparation of 2-(2-bromophenyl)acetic acid



Compound **72** was subsequently treated with 2.0 equivalents of n-BuLi at $-78\text{ }^\circ\text{C}$ with gradual warming to room temperature, followed by aqueous workup. None of the desired benzocyclobutenone was isolated. This reaction produced a complex mixture of compounds which was not investigated further. Much of the crude material was also lost in the aqueous phase based on the mass of crude material obtained compared to the amount of

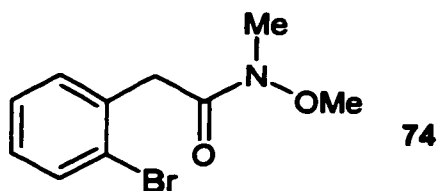
acid used. The reaction was repeated with 3.0 equiv. of t-BuLi at $-78\text{ }^{\circ}\text{C}$ with gradual warming to room temperature but afforded the same result.

Acid **72** was converted to the methyl ester **73** in 94% yield by reflux in methanol with a catalytic amount of H_2SO_4 . The structure was confirmed by ^1H -NMR, ^{13}C -NMR, infrared and HRMS.

**73**

When compound **73** was treated with 3.0 equiv. of t-BuLi at $-78\text{ }^{\circ}\text{C}$, the reaction again gave a complex mixture of compounds. Based on the aromatic portion of the ^1H -NMR spectrum of the crude reaction mixture, it did appear that most of the starting material underwent halogen-metal exchange. The reaction was repeated with 1.5 equiv. of t-BuLi at $-78\text{ }^{\circ}\text{C}$ but gave only starting material. A third attempt with 2.0 equiv. of t-BuLi did not yield any of the desired benzocyclobutenone. It appears that deprotonation of the relatively acidic benzylic hydrogens is a facile process.

Based on results obtained by Lear⁴⁵, compound **73** was converted to the Weinreb amide **74**.

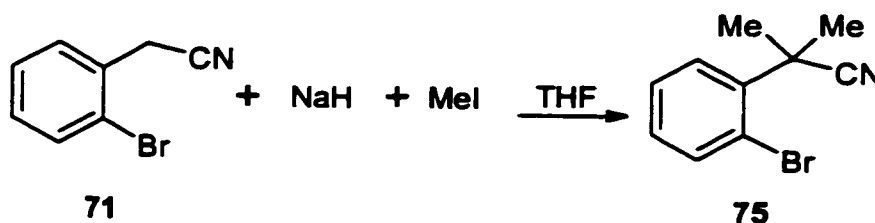
**74**

The amide **74** was prepared in 42% yield using trimethylaluminum and N,O-dimethylhydroxylamine hydrochloride.⁴⁵ The ^1H -NMR spectrum of **74** showed both methyl

groups as a broad singlet at 3.00 ppm and the benzylic hydrogens at 3.80 ppm. The ^{13}C -NMR spectrum showed the carbonyl resonance of the amide group at 170.1 ppm and the two methyls at 37.5 and 35.8 ppm. The carbonyl stretch of the amide was also visible in the IR spectrum at 1644 cm^{-1} .

Compound **74** was reacted with 2.0 equiv. of $t\text{-BuLi}$ at $-78\text{ }^{\circ}\text{C}$ but did not produce any benzocyclobutenone product. The crude reaction product consisted mostly of starting material. Based on these results, we concluded that halogen-metal exchange was not taking place because the benzylic hydrogens were too acidic. Deprotonation at the benzylic position was therefore occurring faster than the halogen-metal exchange could take place. In an attempt to avoid this problem, 2-(2-bromophenyl)-2-methylpropanenitrile **75** was prepared by methylation of the benzylic position of 2-bromobenzyl cyanide **71** (scheme 4.1.2).

Scheme 4.1.2 : Preparation of 2-(2-bromophenyl)-2-methylpropanenitrile **75**

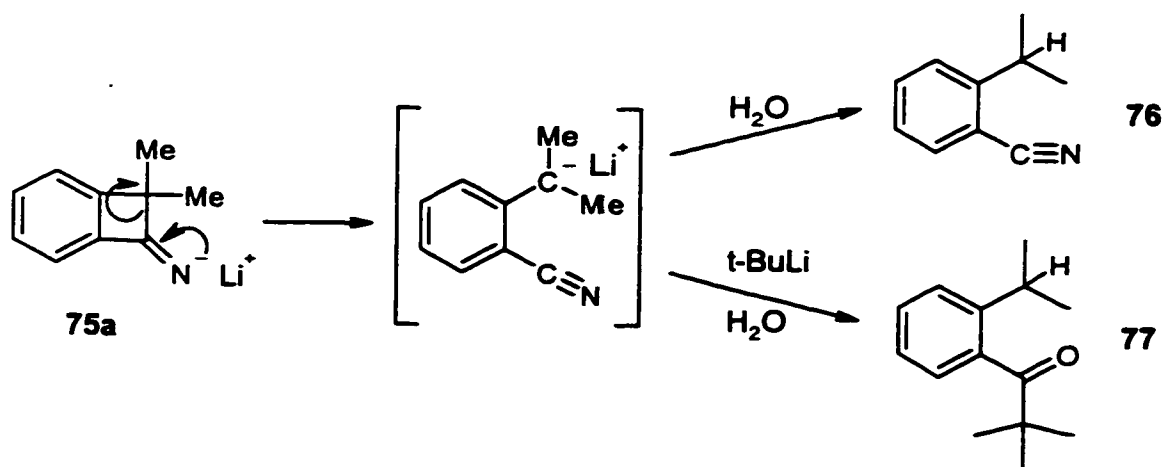


Compound **71** was added to a solution of NaH in THF and stirred at room temperature until hydrogen gas evolution had ceased. After cooling to $0\text{ }^{\circ}\text{C}$, methyl iodide was added to the reaction followed by gradual warming to room temperature with stirring until complete (confirmed by ^1H -NMR). Purification by chromatography afforded the desired product **75** in 85% yield as a clear oil. The ^1H -NMR spectrum showed the disappearance of the benzylic hydrogens at 3.80 ppm and the appearance of a singlet at 1.88 ppm integrating for the 6 hydrogens of the two methyl groups. The IR spectrum showed the nitrile stretch at 2234 cm^{-1} and aliphatic C-H stretches at 2984 and 2939 cm^{-1} . The HRMS

showed two very strong M^+ ion peaks (50.7%; 48.1%) at m/z 223.0000 and 224.9991 which corresponded with the calculated values of 222.9997 and 224.9977 for the ^{79}Br and ^{81}Br containing molecules.

Compound **75** was treated with 2.0 equiv. of $t\text{-BuLi}$ at -78°C with gradual warming to room temperature followed by aqueous ammonium chloride workup. Infrared spectroscopy of the crude reaction mixture did not show any evidence of the formation of the desired benzocyclobutenone. The $^1\text{H-NMR}$ spectrum of the crude product showed that all starting material had been consumed. Based on the presence of two heptets at 3.35 and 1.61 ppm, and of 2 doublets at 1.28 and 1.19 ppm, it appeared that the mixture consisted of at least two different products, each containing an isopropyl group, probably compound **76** and **77**. These compounds could arise via *o*-metallation, cyclization to **75a** and subsequent ring fragmentation (scheme 4.1.3).

Scheme 4.1.3 : Ring opening products from the reaction of compound **75 with $t\text{-BuLi}$**

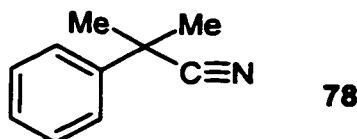


The reaction of **75** with $t\text{-BuLi}$ was repeated several times with the results summarized in table 4.1.1. All reactions were carried out with 2 equivalents of $t\text{-BuLi}$ and stirred for 1 to 1.5 h.

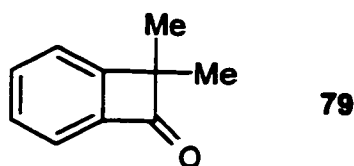
Table 4.1.1 : Reaction of compound 75 with t-BuLi

Entry	temperature	additive	Product
1	-78 °C	--	Compound 78
2	-78 to -50 °C	--	Mixture of 76, 78 and some of 79
3	-78 to -6 °C	--	Mixture of 76, 77 and some of 79
4	-78 to -65 °C	--	Mixture of 76 and 78
5	-78 to rt	MgBr ₂	Complex mixture

Reaction of **75** with t-BuLi at -78 °C resulted in halogen-metal exchange without subsequent cyclization since quenching with saturated NH₄Cl solution gave the mono-substituted product **78**.



The reaction was repeated with addition of t-BuLi taking place at -78 °C and then gradual warming to -50 °C. After workup, the ¹H-NMR spectrum of the crude product indicated the presence of the nitrile transfer product **76** and the mono-substituted product **78**. The IR spectrum of the crude mixture did indicate the formation of some benzocyclobutenone **79** by the presence of a carbonyl stretch at 1757 cm⁻¹. This assumption is made based on the fact that the carbonyl stretch of the benzocyclobutenone **55** appears at 1775 cm⁻¹. None of the benzocyclobutenone could be isolated.

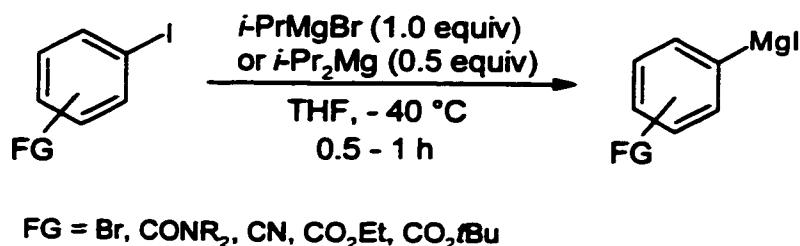


When carried out at temperatures of $-78\text{ }^{\circ}\text{C}$ to $-6\text{ }^{\circ}\text{C}$, the reaction afforded compound **76** in a greater amount, along with some of the *t*-butyl addition product **77**. Again, the IR spectrum showed a medium carbonyl stretch peak at 1756 cm^{-1} indicating the formation of some of product **79**. A final temperature variation was made, attempting the reaction at a temperature of $-78\text{ }^{\circ}\text{C}$ to $-65\text{ }^{\circ}\text{C}$. Compound **76** and the reduction product **78** were again the only isolated products.

The reaction was then attempted with MgBr_2 added to the reaction mixture in order to verify if having magnesium coordinated to nitrogen versus lithium might keep the expected intermediate **75a** from opening. The reaction was carried out with addition of 1 equivalent of MgBr_2 at $-78\text{ }^{\circ}\text{C}$ following the *t*-BuLi treatment. The mixture was then warmed to room temperature. Aqueous workup afforded a complex mixture of products that included all of the previously identified products. The IR spectrum did not contain any carbonyl peak.

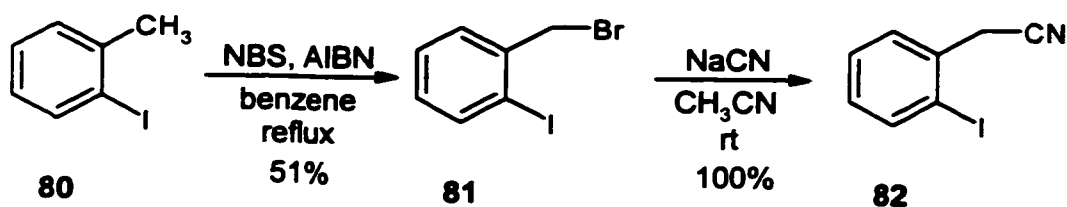
With these results in hand, attempts to prepare benzocyclobutenones via this method were put aside, until a communication by Knochel appeared describing the “preparation of highly functionalized Grignard reagents by an iodine-magnesium exchange reaction”.⁴⁸ In this communication, he details a general route to highly functionalized arylmagnesium iodides via the procedure shown in scheme 4.1.4.

Scheme 4.1.4 : Functionalized arylmagnesium iodide preparation

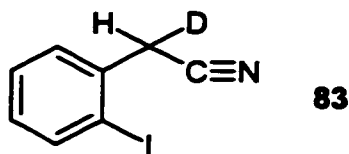


Based on the results presented in this communication, we attempted to generate the benzocyclobutenone via the reaction of 2-iodophenyl acetonitrile **82** with isopropyl magnesium bromide. Compound **82** was prepared from 2-iodotoluene as shown in scheme 4.1.5. All products were confirmed by ^1H -NMR, ^{13}C -NMR, infrared and HRMS.

Scheme 4.1.5 : Preparation of 2-iodobenzyl cyanide

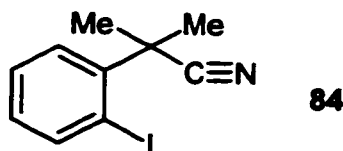


To a solution of **82** in dry THF kept at $-40\text{ }^\circ\text{C}$ was added 1.05 equiv. of a freshly prepared solution of isopropyl magnesium bromide. After stirring at $-40\text{ }^\circ\text{C}$ for 1 h, the solution was warmed to $0\text{ }^\circ\text{C}$ and stirred for another 3 h. The reaction was quenched with D_2O prior to aqueous workup. Removal of the solvent under reduced pressure afforded clean product **83** in quantitative yield.



The ^1H -NMR spectrum clearly showed the singlet at 3.80 ppm integrating for 1 proton versus 2 for compound **82**. No halogen metal-exchange had taken place, instead the

basic Grignard reagent had reacted with an acidic benzylic proton. To remove this possibility, we methylated the benzylic position in the same way as described previously to afford compound **84** in 94% yield.

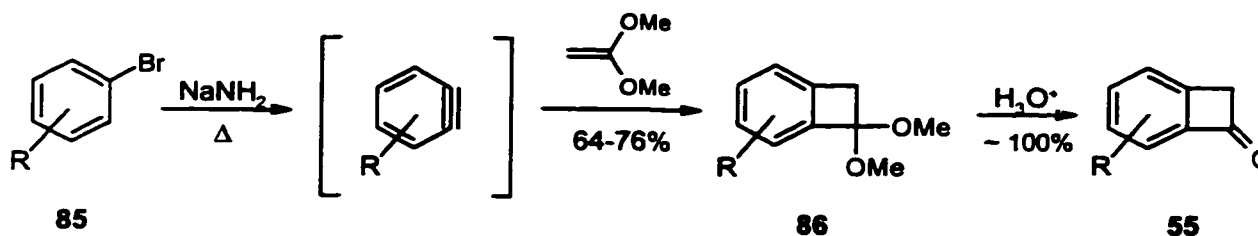


Compound **84** was submitted to the same reaction conditions as **82**; no iodine-magnesium exchange was observed, probably for steric reasons, and mainly the starting material **84** was recovered.

4.2 Exploration of Benzocyclobutenol and Benzocyclobutenone Preparation via a Benzyne Route

The use of benzyne in the preparation of benzocyclobutenones has been demonstrated in the literature. Stevens and Bisacchi have shown that 1,1-dimethoxyethylene reacted in a [2+2] fashion with benzyne generated by the NaNH_2 -induced dehydrobromination of bromobenzenes **85** to yield the intermediate benzocyclobutenone ketals **86**. Subsequent acid hydrolysis gave the substituted benzocyclobutenones **55** in good yields (scheme 4.2.1).⁴⁰

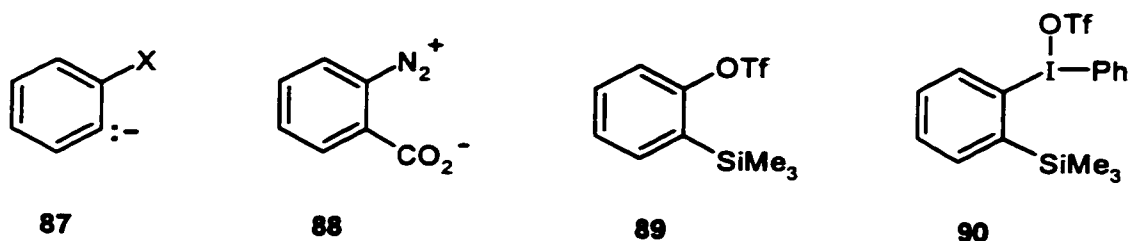
Scheme 4.2.1 : Synthesis of benzocyclobutenones from benzyne and 1,1-dimethoxyethylene



A more recent publication by Suzuki⁴⁹, discussed in chapter 3, involved the use of ortho-iodo triflates as the benzyne precursors. These were trapped with ketene silyl acetals to generate the benzocyclobutenone silanes, which upon hydrolysis gave the benzocyclobutenones.

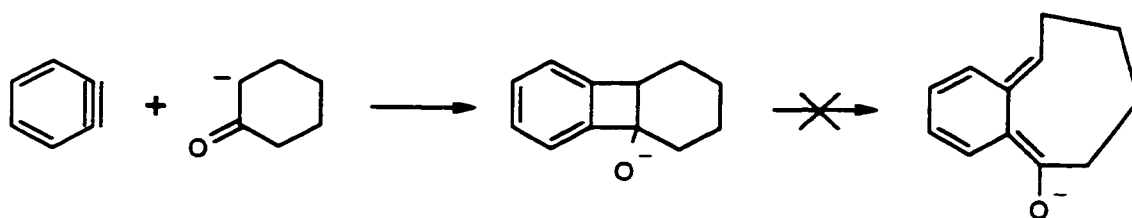
Over the last decades, many methods for benzyne generation have been reported, utilizing different precursors. These included *o*-halogenophenyl anions **87**, benzenediazonium-2-carboxylate **88**, *o*-trimethylsilylphenyl triflates **89** and (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate **90** (figure 4.2.1).⁵⁰

Figure 4.2.1 : Benzyne precursors



4.3 Benzocyclobutenol and Benzocyclobutenone Formation via Reaction of Benzyne with Amide, Ketone and Ester Enolates

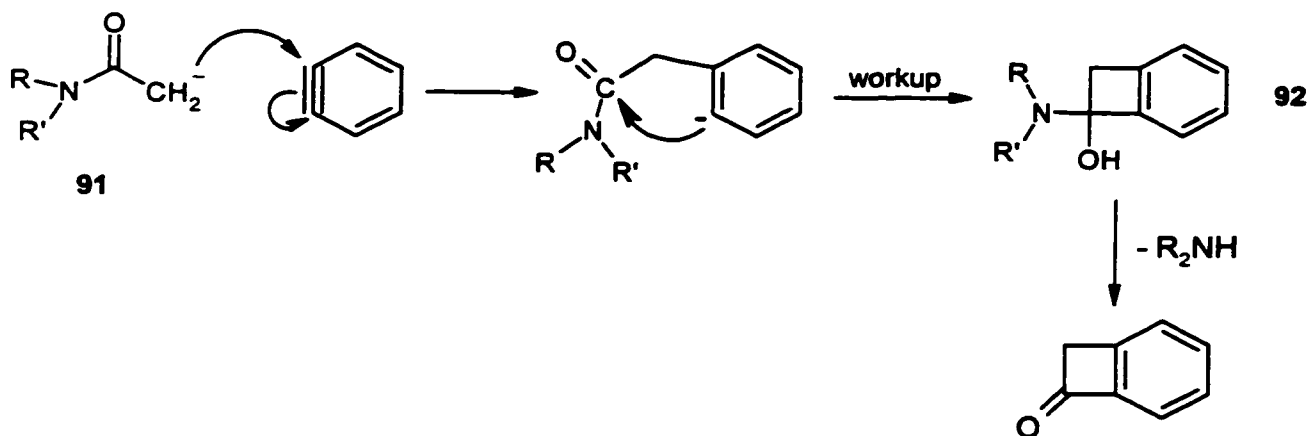
In the literature, there are examples of cyclic ketone enolates reacting with benzyne. Benzocyclobutenols were isolated when 5 or 6-membered ring ketone enolates were used since subsequent ring opening of the intermediate alkoxide is sterically very difficult; it involves forming a trans cyclooctene.



With other ketone enolates, products derived from further reaction of the cyclobutene intermediate were observed.⁵¹

There appear to be no examples of the reaction of benzyne involving amide or ester enolates. Amide enolates would appear to be useful nucleophiles since we envisioned that the anion generated alpha to the carbonyl group **91** would attack the benzyne, formed *in situ*, followed by anionic attack onto the carbonyl group to form the product **92** (scheme 4.3.1). Product **92** is an α -aminoalcohol and should fragment to benzocyclobutenone and the secondary amine.

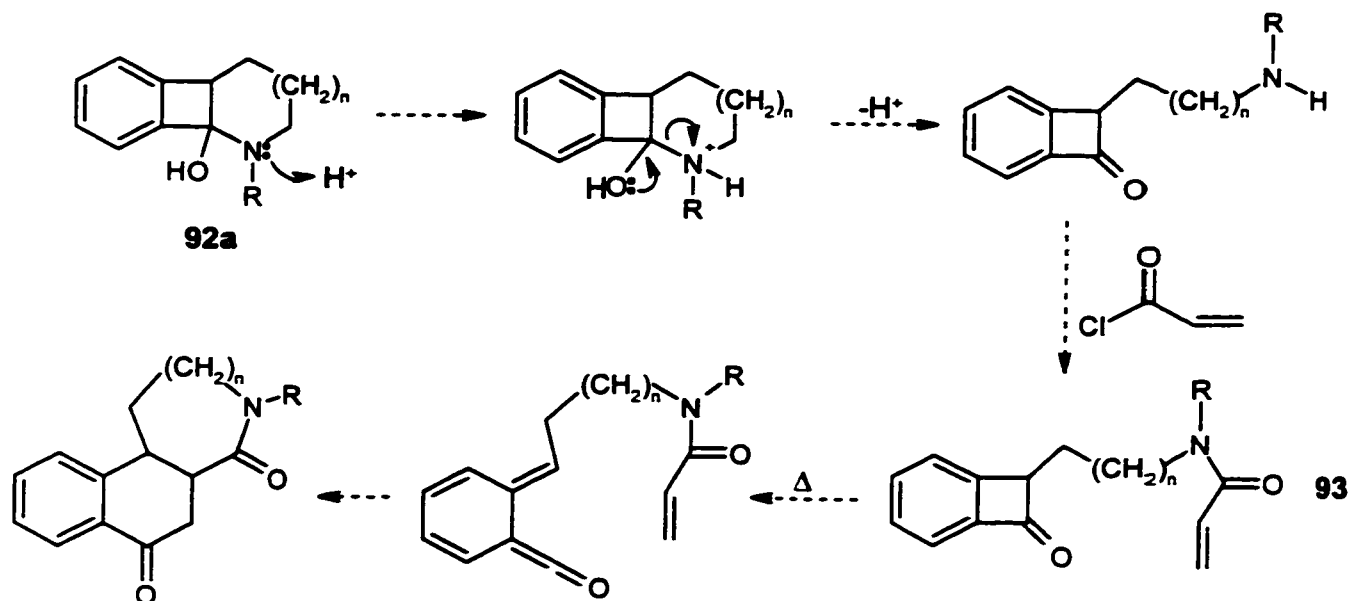
Scheme 4.3.1 : Proposed benzocyclobutenone synthesis



In the case of a cyclic amide enolate, the intermediate **92a** should have considerable stability. Subsequent treatment with acid would generate a benzocyclobutenone carrying a side chain ending as a secondary amine. It was envisaged that acylation of this or of **92a** directly would generate **93**. When heated, compound **93** should open to form the *o*-

quinodimethane, which could undergo an intramolecular Diels-Alder reaction to generate a tricyclic ring system (scheme 4.3.2).

Scheme 4.3.2 : Proposed application of products formed from the reaction of cyclic amides with benzyne

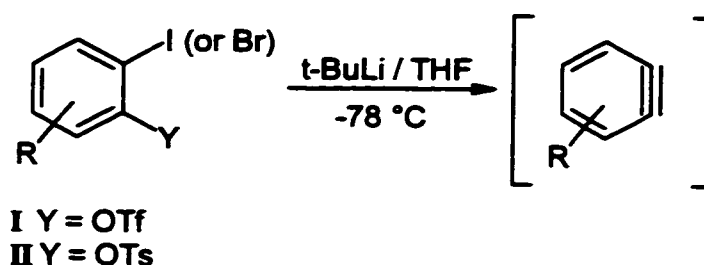


In the following section, the results from the reaction of amide, ester and ketone enolates with *in situ* generated benzyne will be discussed.

4.4 Attempted Benzyne Generation From *o*-Iodophenyl Tosylate

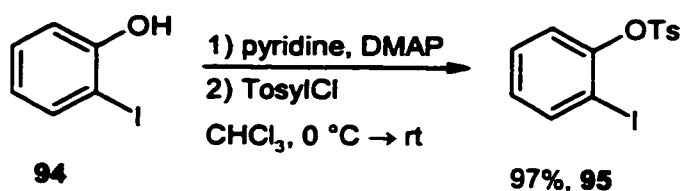
With the types of substrates that would be used for the preparation of these benzocyclobutenols, we desired a method that could generate the benzyne species under cold conditions in order to keep the cyclobutene ring from opening up following its formation. Suzuki developed one such method where *ortho*-haloaryl triflates (I) or *ortho*-haloaryl tosylates (II) are treated with *t*-BuLi at -78°C to generate the benzyne intermediate (figure 4.4.1).⁵²

Figure 4.4.1 : Suzuki protocol for benzyne generation



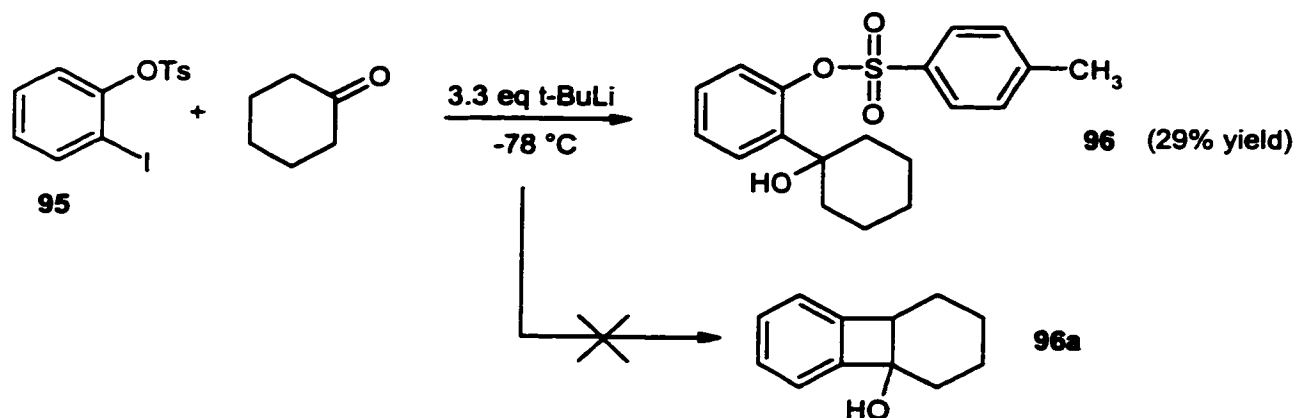
We therefore prepared the *o*-iodophenyl tosylate **95** in 97% yield from 2-iodophenol **94** for use in our reactions (scheme 4.4.1). The structure was confirmed by ^1H -NMR, ^{13}C -NMR, infrared and HRMS.

Scheme 4.4.1 : Preparation of 2-iodophenyl tosylate **95**



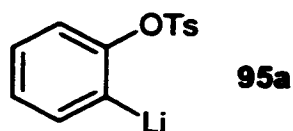
With compound **95** in hand, we attempted to form the benzocyclobutenol **96a** via the reaction of the benzyne with cyclohexanone. To a solution of **95** with 1.05 equiv. of cyclohexanone in dry THF cooled to $-78\text{ }^\circ\text{C}$ was added 3.3 equiv. of *t*-BuLi. After 20 minutes, the reaction was quenched with wet THF followed by addition of NH_4Cl solution and ethyl acetate. Extraction followed by removal of the solvent *in vacuo* afforded compound **96** in a 29% yield as a white solid (scheme 4.4.2).

Scheme 4.4.2 : Reaction of *o*-iodophenyl tosylate and cyclohexanone with *t*-BuLi



The structure of compound **96** was elucidated from key signals in the ^1H -NMR spectrum, which included the methyl singlet at 2.45 ppm and the presence of 10 aliphatic protons between 1.0 and 2.0 ppm, thus showing the incorporation of the cyclohexanone moiety (see figure 4.4.2). The IR spectrum showed the asymmetric and symmetric stretches of the sulfonyl group at 1350 and 1187 cm^{-1} along with two peaks at 3535 and 3447 cm^{-1} representative of the OH. The HRMS showed an M^+ ion peak at m/z 346.1249 which corresponded with the calculated value of 346.1239.

The formation of **96** in somewhat reasonable yield under non-optimized conditions is quite surprising. It indicates that iodine-lithium exchange in **95** with *t*-BuLi is somewhat faster than deprotonation of cyclohexanone. Additionally, the lithio derivative **95a** is stable enough to react with cyclohexanone.

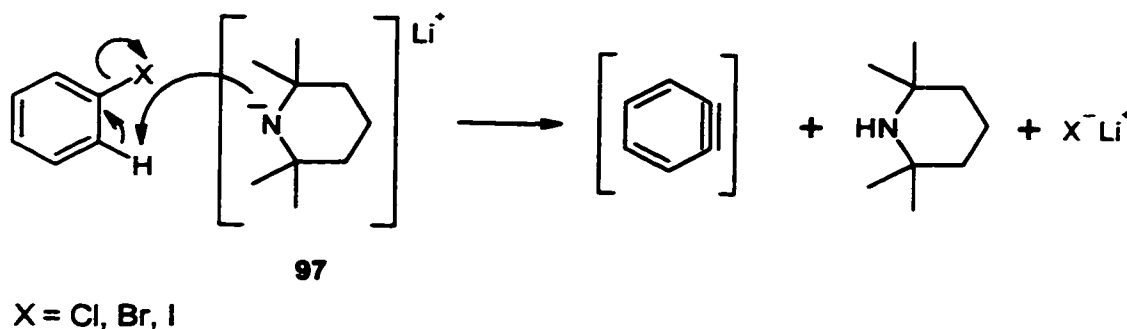


This result indicates that 2-iodophenol could be converted into a variety of 2-substituted phenols via **95a**. Furthermore, it suggests the possibility of generating **95a** via

deprotonation of phenoxy *p*-toluene sulfonate and that the tosyloxy group could be a stable directed ortho metallation group. Currently phenols are *o*-metallated by first converting them to their THP or MOM ethers.⁵³ Despite these possibilities, we opted to continue searching for low temperature approaches to benzyne generation.

Olofson reported a new method for aryne generation in a communication⁵⁴ in 1973 which resulted from attempts to find a base that would selectively abstract protons from substrates which contained sites that were more reactive towards nucleophilic attack. It was found that lithium 2,2,6,6-tetramethylpiperidide (LTMP) **97** was a very effective base for deprotonating haloaryls, resulting in elimination of the halogen to form the benzyne species (scheme 4.4.3). The key feature of this base was that it did not compete with other nucleophiles for the benzyne. This communication did not discuss reaction conditions but we hoped to be able to generate benzyne via this route at low temperatures.

Scheme 4.4.3 : Benzyne generation by deprotonation of phenyl halides with LTMP



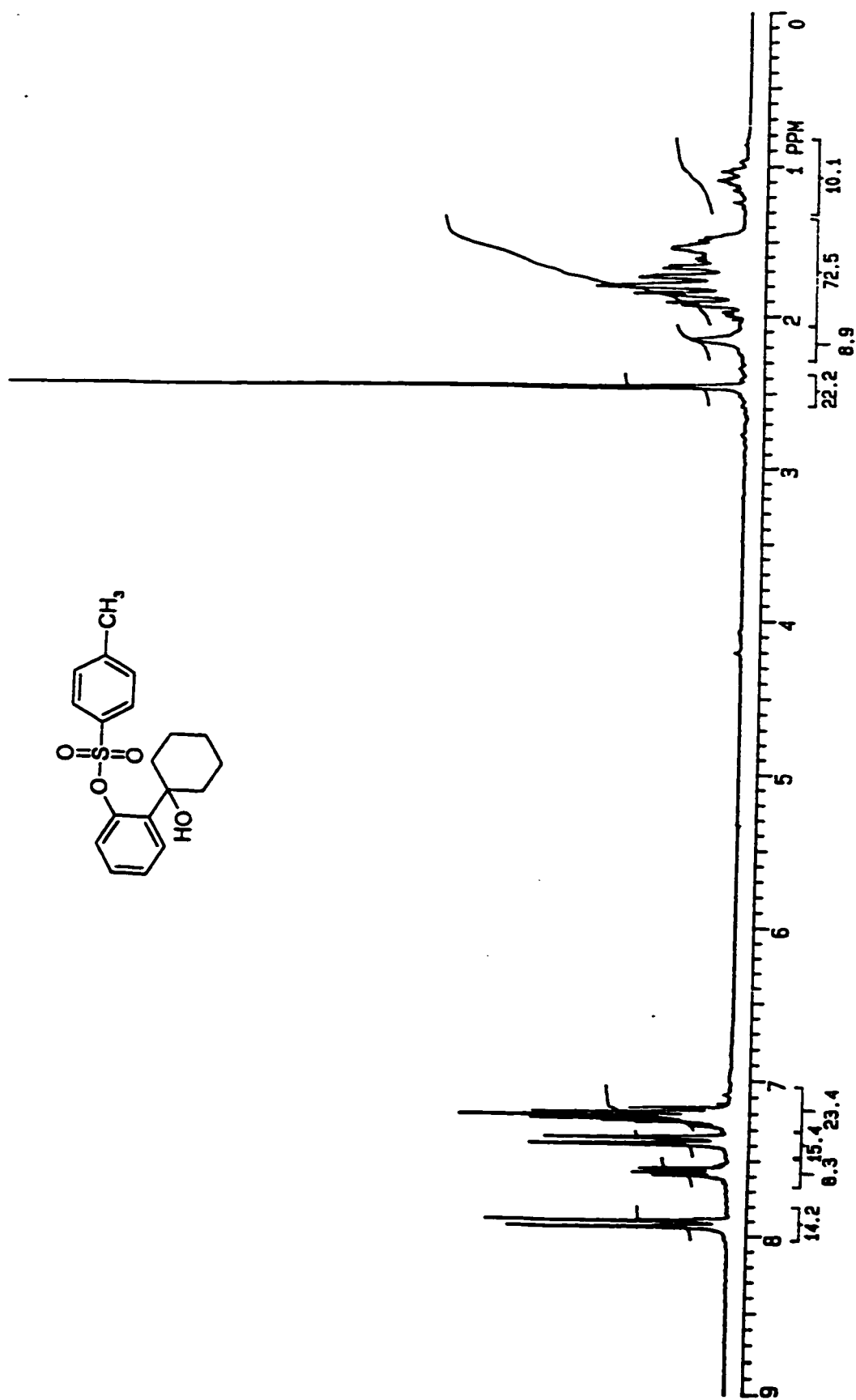
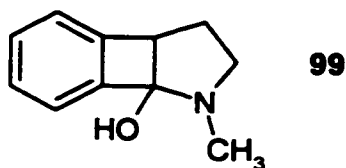


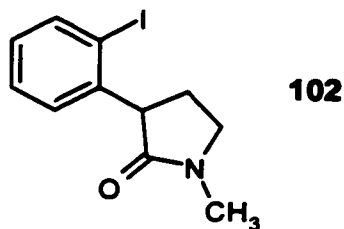
FIGURE 4.4.2: ¹H-NMR SPECTRUM OF 2-(1-HYDROXYCYCLOHEXYL)-1-[(4-METHYLPHENYL)SULFONYLOXY] BENZENE 26

4.5 Benzyne Generation by Deprotonation of Aryl Halides with Lithium 2,2,6,6-Tetramethylpiperidide

The generation of benzyne from iodobenzene and LTMP was carried out at 0 °C in the presence of 1.05 equiv. of the enolate of N-methyl-2-pyrrolidinone. The reaction was warmed and stirred for 2 h at room temperature. Purification of the crude reaction mixture gave one product in pure form in 8% yield, which appeared to be the desired cyclized compound **99** based on the ^1H -NMR spectrum only. From the ^1H -NMR spectrum, it was clear that we had an unsymmetrically ortho substituted benzene ring. The methyne proton appeared as a triplet at 4.00 ppm, with the methyl singlet at 2.94 ppm (see figure 4.5.1). The HRMS of this compound was taken and showed what appeared to be the M^+ ion peak at the calculated mass of **99**.



However, based on the ^{13}C -NMR spectrum, it was evident the product contained an amide carbonyl group which appeared at 174.2 ppm (see figure 4.5.2). Infrared spectroscopy confirmed this by the presence of a strong band at 1678 cm^{-1} . The data was consistent with **102**. X-ray analysis finally confirmed that the product obtained was in fact compound **102**.



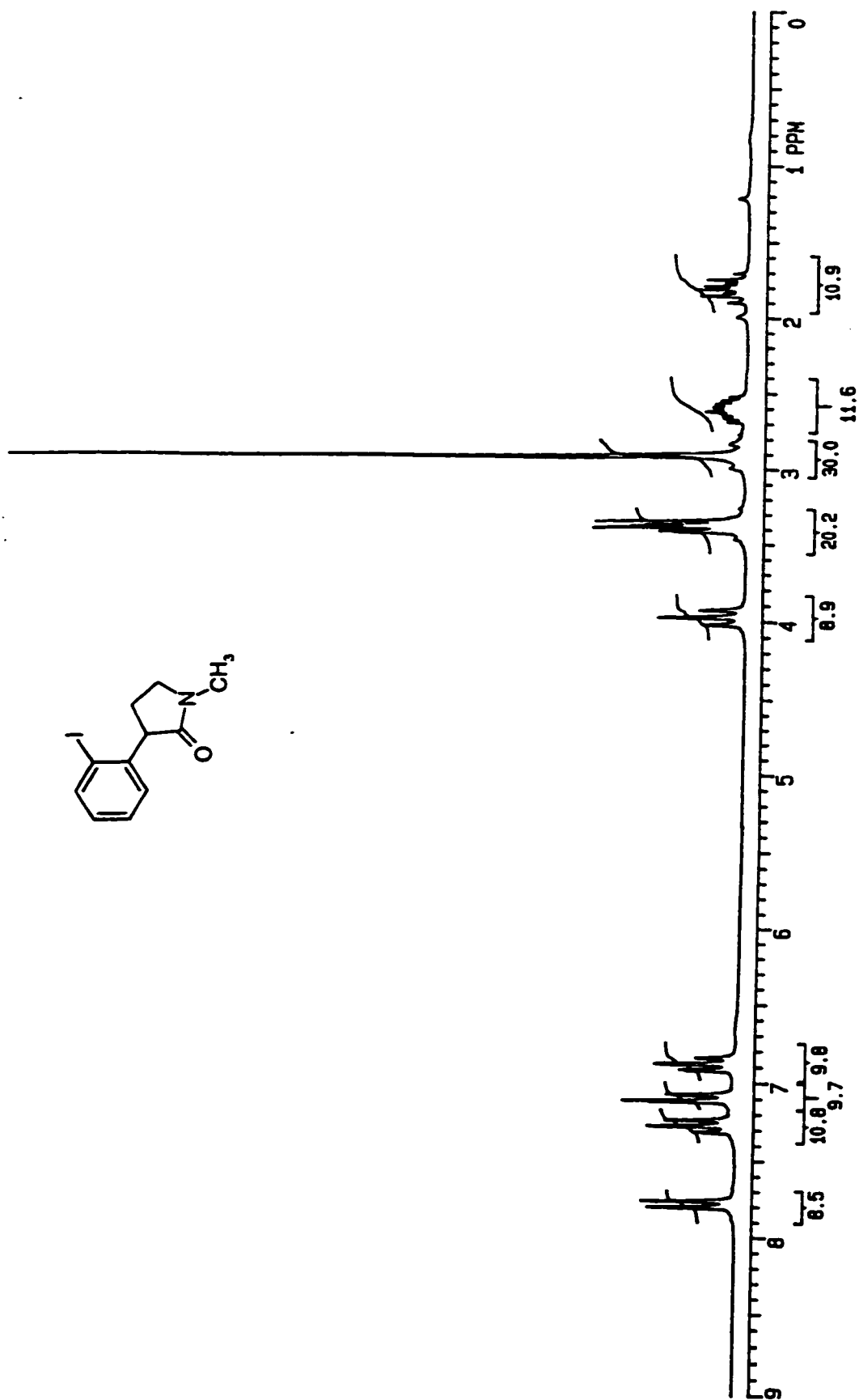


FIGURE 4.5.1: ^1H -NMR SPECTRUM OF 3-(2-IODOPHENYL)-N-METHYL-2-PYRROLIDINONE 102

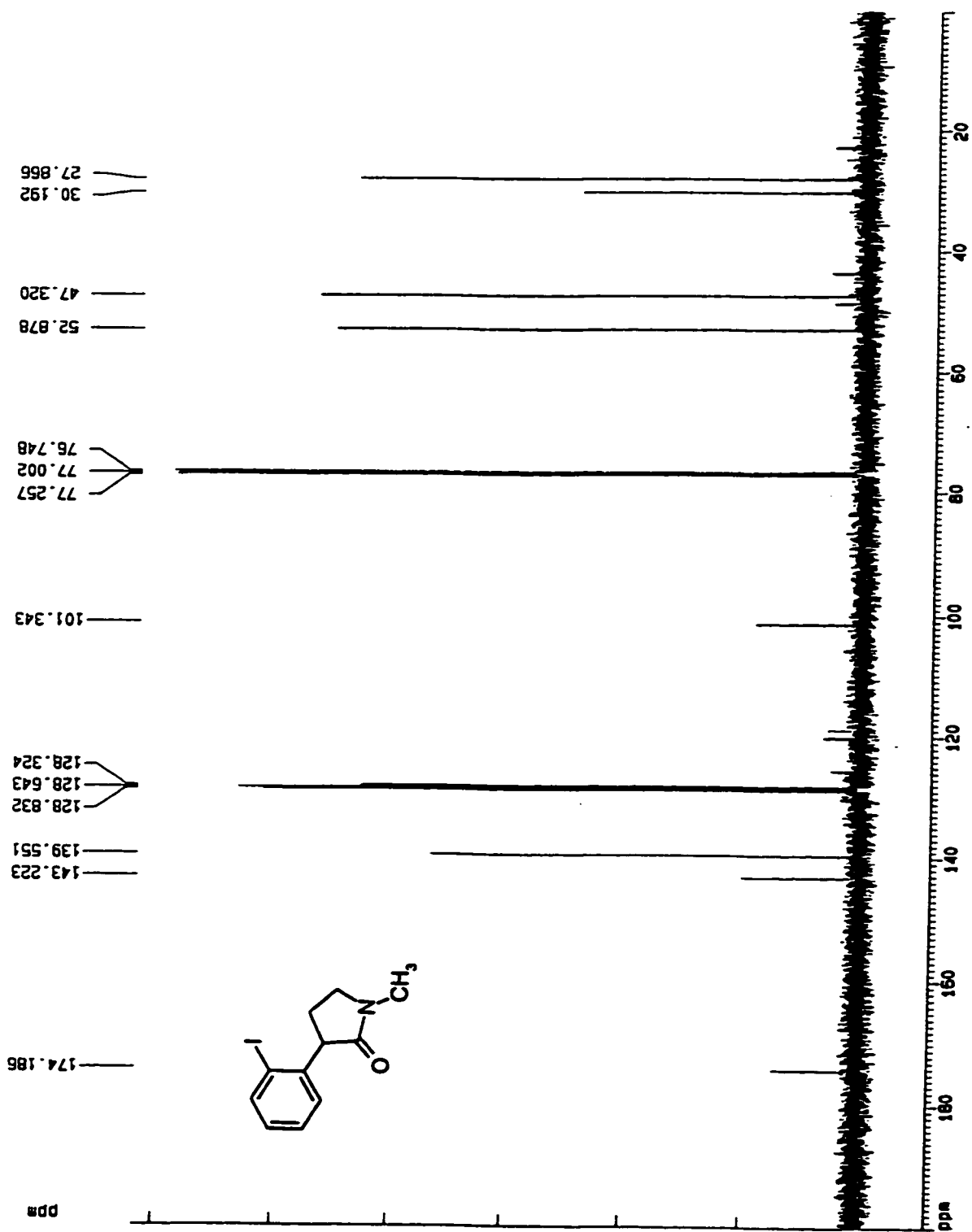
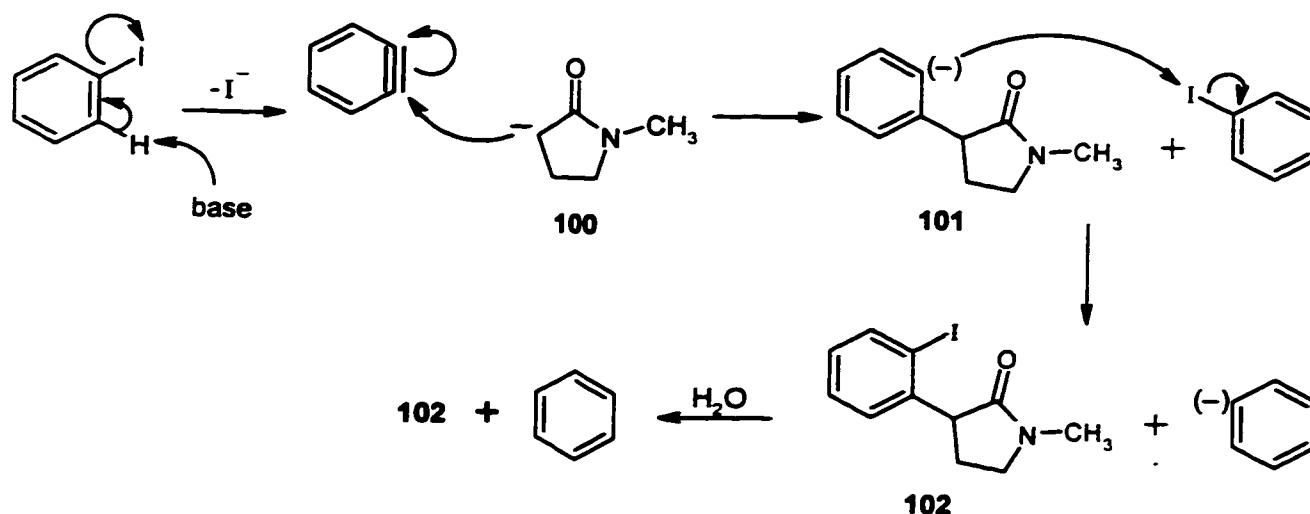


FIGURE 4.5.2: ^{13}C -NMR SPECTRUM OF 3-(2-IODOPHENYL)-N-METHYL-2-PYRROLIDINONE 102

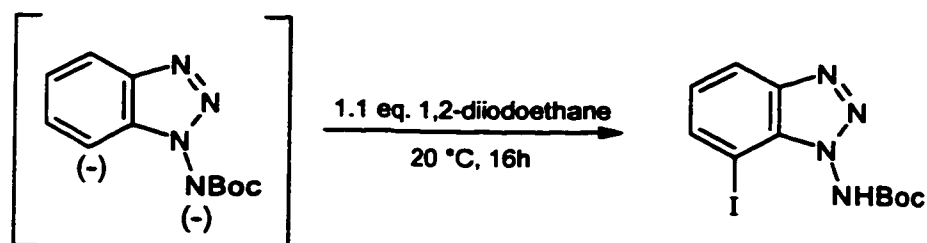
The formation of **102** is rationalized as shown in scheme 4.5.1.

Scheme 4.5.1 : Proposed mechanism for the formation of **102**



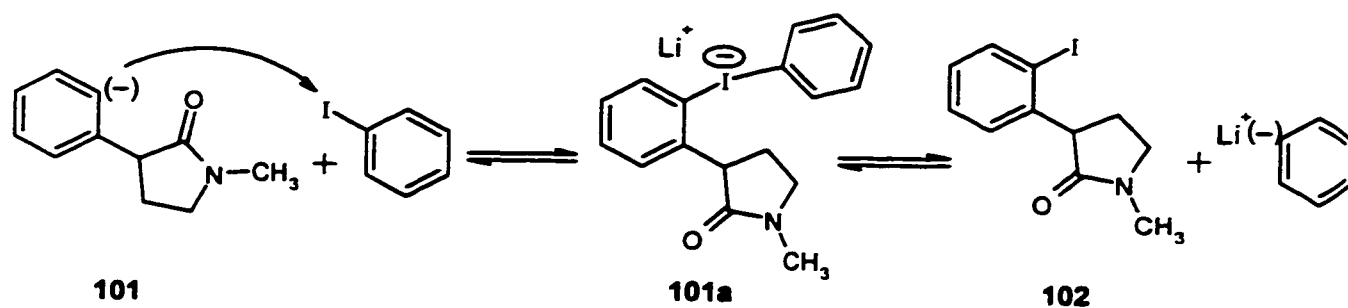
It has one disappointing and one very surprising feature. We were disappointed that the lithio species **101** did not cyclize to **99**. We were surprised that iodobenzene acted as a source of electrophilic iodine (I^+). Traditionally, 1,1-diiodoethane has served as a positive iodine source⁵⁵ (figure 4.5.3). We were not aware of the use of iodobenzene as a positive halogen species.

Figure 4.5.3 : Iodination of anion with 1,2-diiodoethane

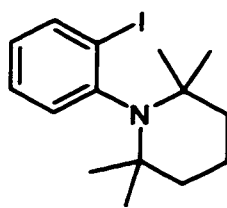


The reaction of **101** with iodobenzene to give **102** requires the intermediacy of the hypervalent iodine intermediate **101a**. Apparently **101a** fragments preferentially towards **102** and phenyllithium rather than **101** and iodobenzene (scheme 4.5.2).

Scheme 4.5.2 : Hypervalent iodine intermediate



Prior to the structure of **102** being elucidated, we reacted iodobenzene with LTMP at $-30\text{ }^{\circ}\text{C}$ in the absence of other nucleophiles. After workup and silica gel chromatography, the major product isolated was compound **103** in 36% yield.



103

The ^1H -NMR showed that iodine was in fact on the phenyl ring by the presence of a doublet of doublets at 7.92 ppm (see figure 4.5.4). Two methyl peaks at 1.28 and 0.91 ppm, each integrating for 6H and multiplets from 1.56 to 1.89 ppm representing the 6 other alkane hydrogens, confirmed addition of LTMP to the benzyne. The HRMS showed a weak M^+ ion peak (0.7%) at m/z 343.0788 which was in agreement with the calculated value of 343.0798.

The formation of **103** shows that contrary to the Olofson suggestion, LTMP does add to benzyne, especially if no other nucleophiles are added. Again, the reacquisition of the iodine by transfer from iodobenzene is somewhat surprising since one might have imagined

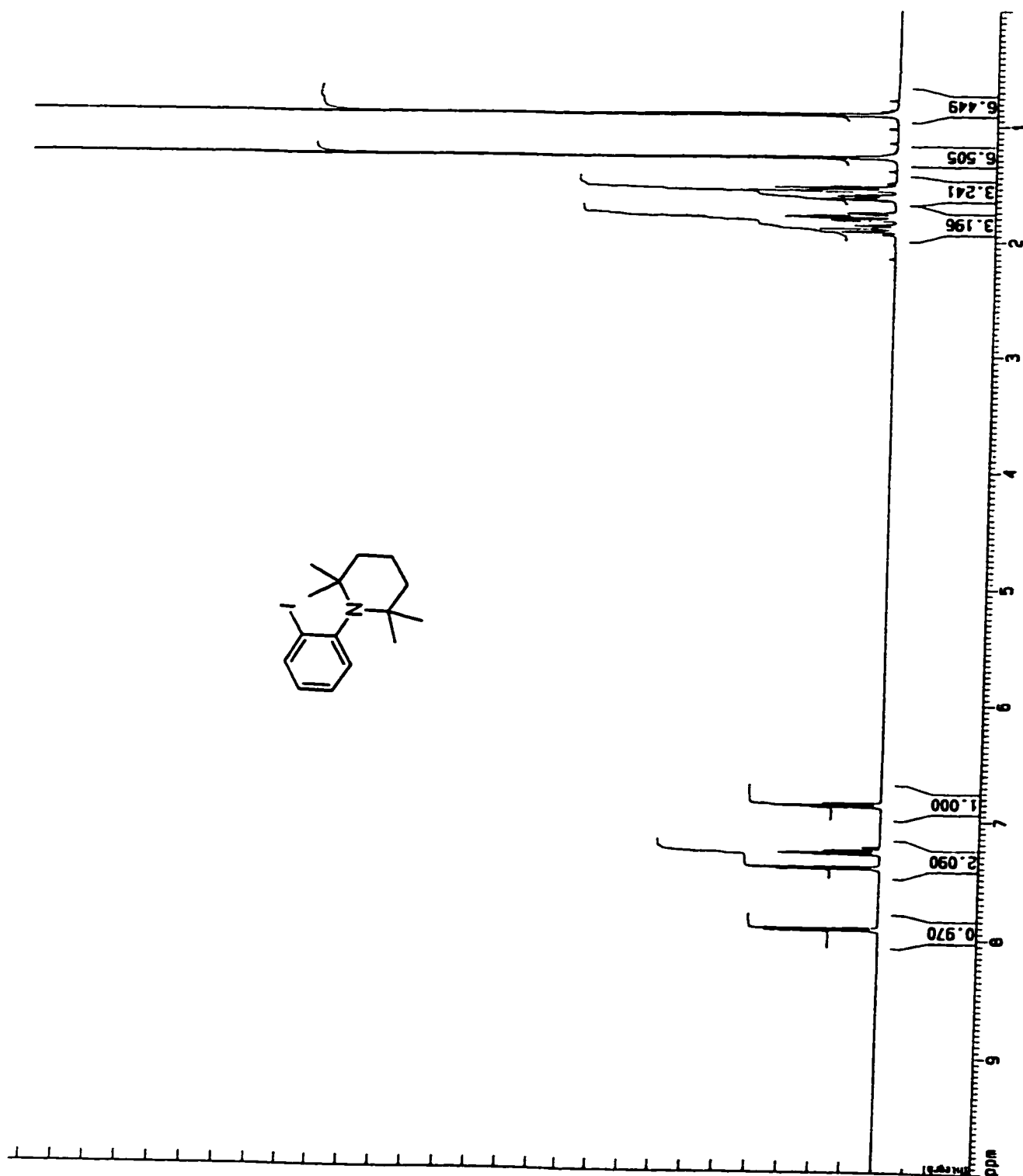
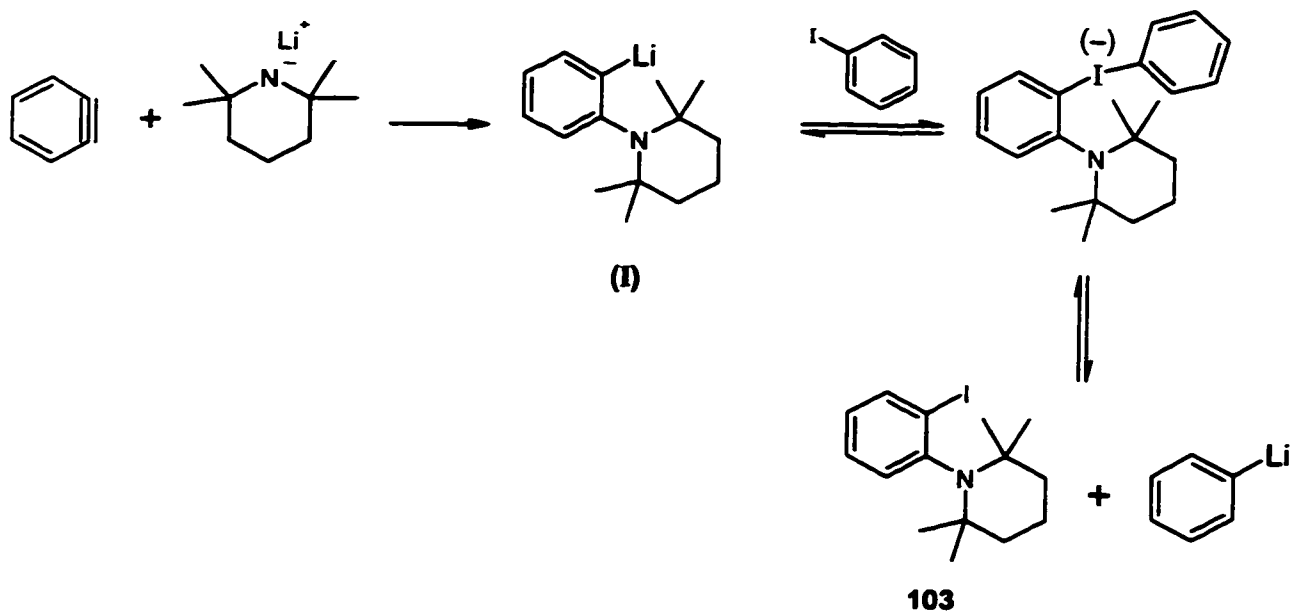


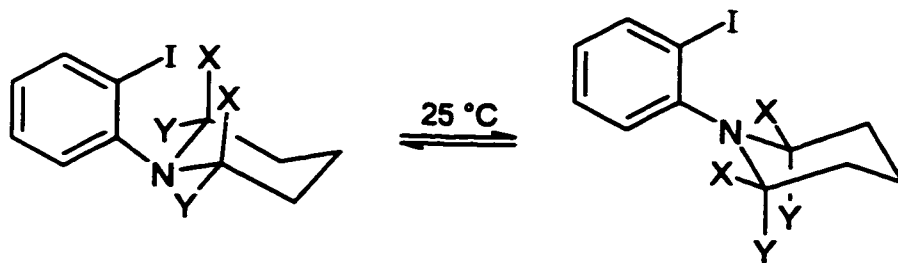
FIGURE 4.5.4: ^1H -NMR SPECTRUM OF N-(2-IODOPHENYL)-2,2,6,6-TETRAMETHYLPYPERIDINE 103

possible stabilization of the intermediate (I) by complexation of the lithium to the nitrogen (scheme 4.5.3).

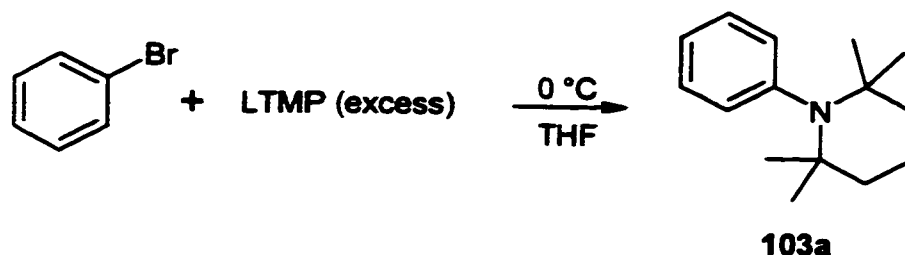
Scheme 4.5.3 : Proposed formation of compound 103



The ^1H -NMR spectrum of **103** is quite interesting. The fact that the four methyl groups show as two singlets (CH_3 's X and Y) indicates that the conformation of **103** is quite rigid. The combination of chair-chair interconversion and nitrogen inversion are not the reason for the different methyl groups. The differentiation is due to a very high (42.2 Kcal) barrier to rotation about the C-N bond (Molecular modeling carried out by Dr. S. Brownstein; personal communication).



In contrast, the ^1H -NMR spectrum of **103a**, prepared from LTMP and bromobenzene shows only one set of methyl signals indicating that the methyl groups are equilibrating rapidly by a combination of chair-chair interconversion and nitrogen inversion. Because of the symmetry of the aromatic ring, rotation around the C-N bond is not required for “equilibrating” the methyl groups.



The generation of benzyne from bromobenzene and LTMP was carried out at $-20\text{ }^\circ\text{C}$ in the presence of 1.5 equiv. of the enolate of N-methyl-2-pyrrolidinone. The reaction was stirred for 3.5 h at $-20\text{ }^\circ\text{C}$ followed by aqueous workup. Purification of the crude reaction mixture by silica gel chromatography afforded one major compound in 26% yield. The reaction was repeated twice at $0\text{ }^\circ\text{C}$ and at room temperature giving the same product with similar yields. Mass spectral analysis of this compound gave a weight of 274. This weight indicated that the product contained two units of N-methyl pyrrolidinone and a phenyl ring. From the ^1H -NMR spectrum, we could see that the benzene ring was mono-substituted based on the 5 protons in the aromatic region (see figure 4.5.5). The ^{13}C -NMR spectrum showed two carbonyl peaks at 205.4 and 169.8 ppm, which indicated that the product contained a ketone and an amide carbonyl (see figure 4.5.6). This was later confirmed by the infrared spectrum, which showed the two carbonyl stretches at 1716 and 1684 cm^{-1} . Taking into account the mechanistical aspects of this reaction, one possible structure appeared to be compound **104**.

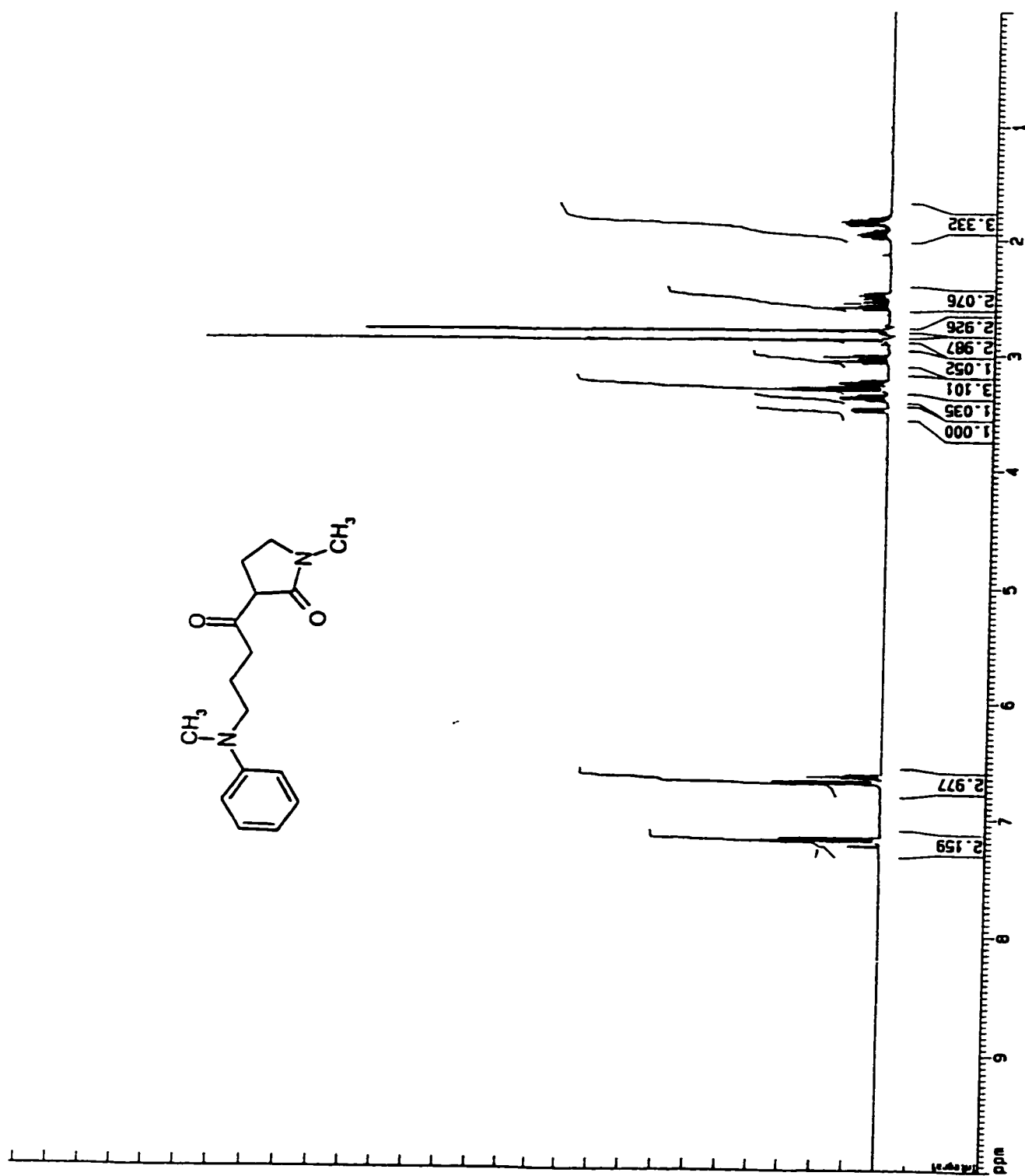
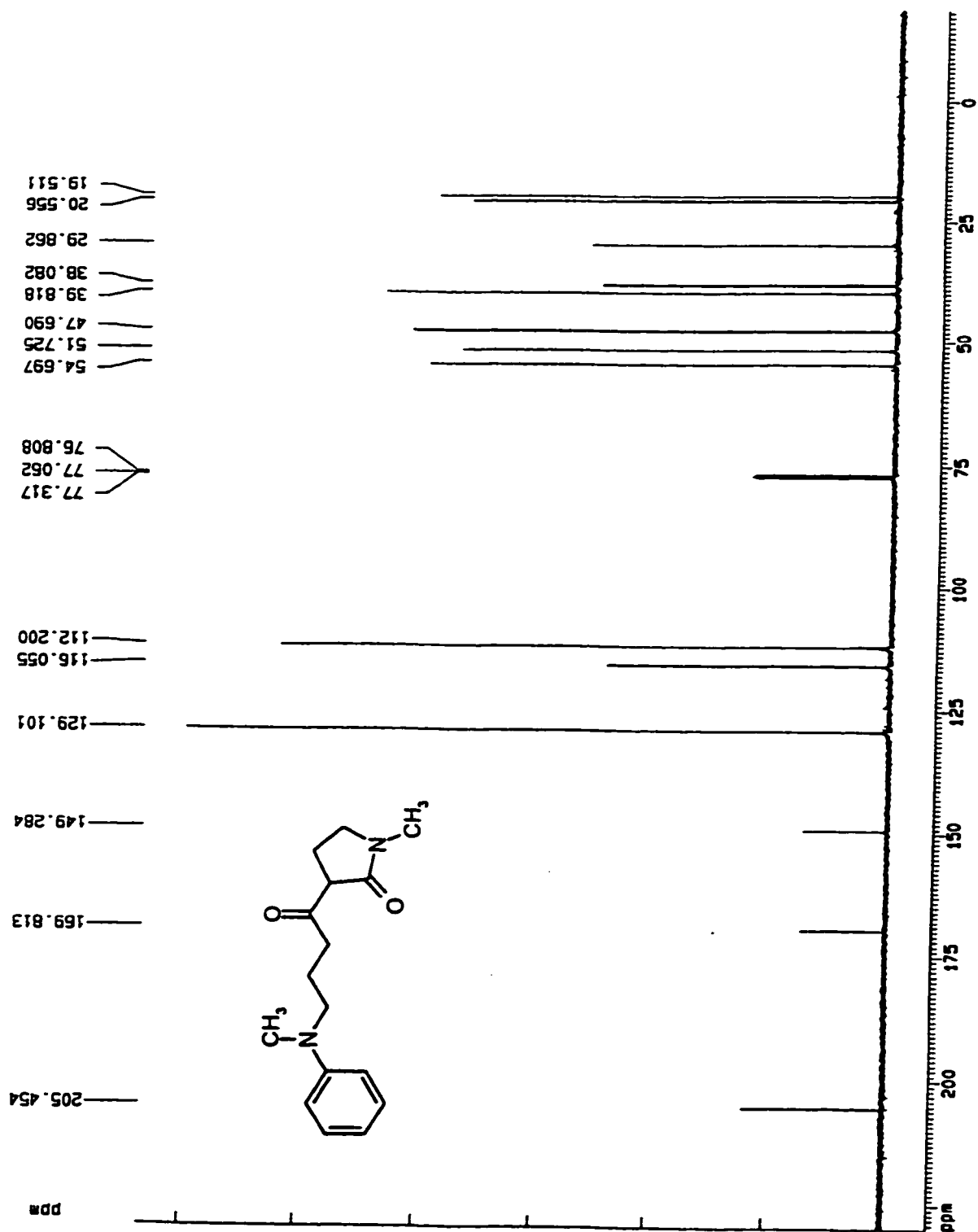
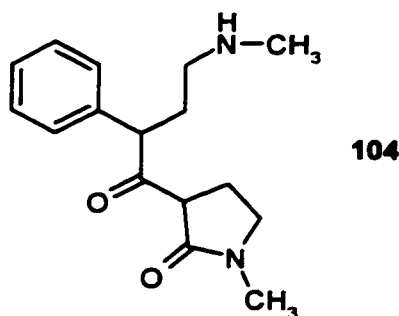


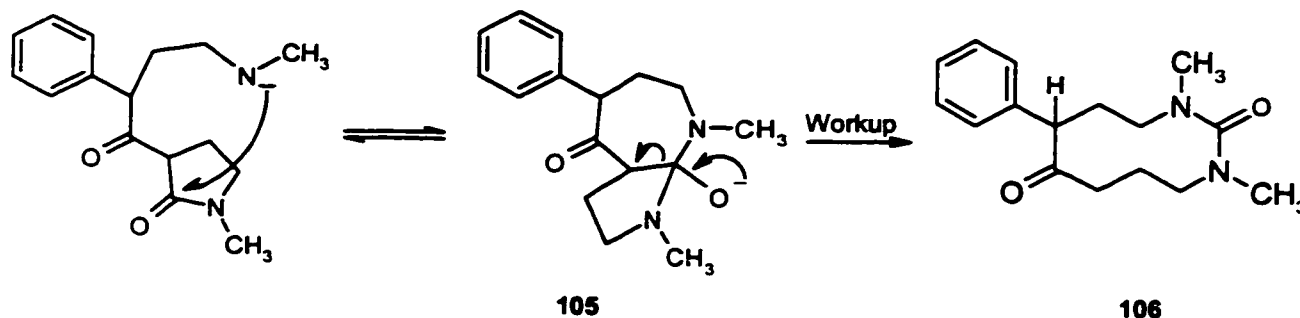
FIGURE 4.5.5: ^1H -NMR SPECTRUM OF COMPOUND 108





Unfortunately, we could not see any N-H peak in the infrared spectrum. From the DEPT spectrum obtained later, we could see that the product contained 5 CH₂ groups, which eliminated compound **104**. Since the compound did not contain any free N-H group, we proposed that compound **104** may initially form and is followed by attack of the nitrogen onto the amide carbonyl. Following formation of the tetrahedral intermediate **105**, opening of the pyrrolidine ring upon regeneration of the carbonyl group leads to compound **106** after workup, in the manner shown in scheme 4.5.4.

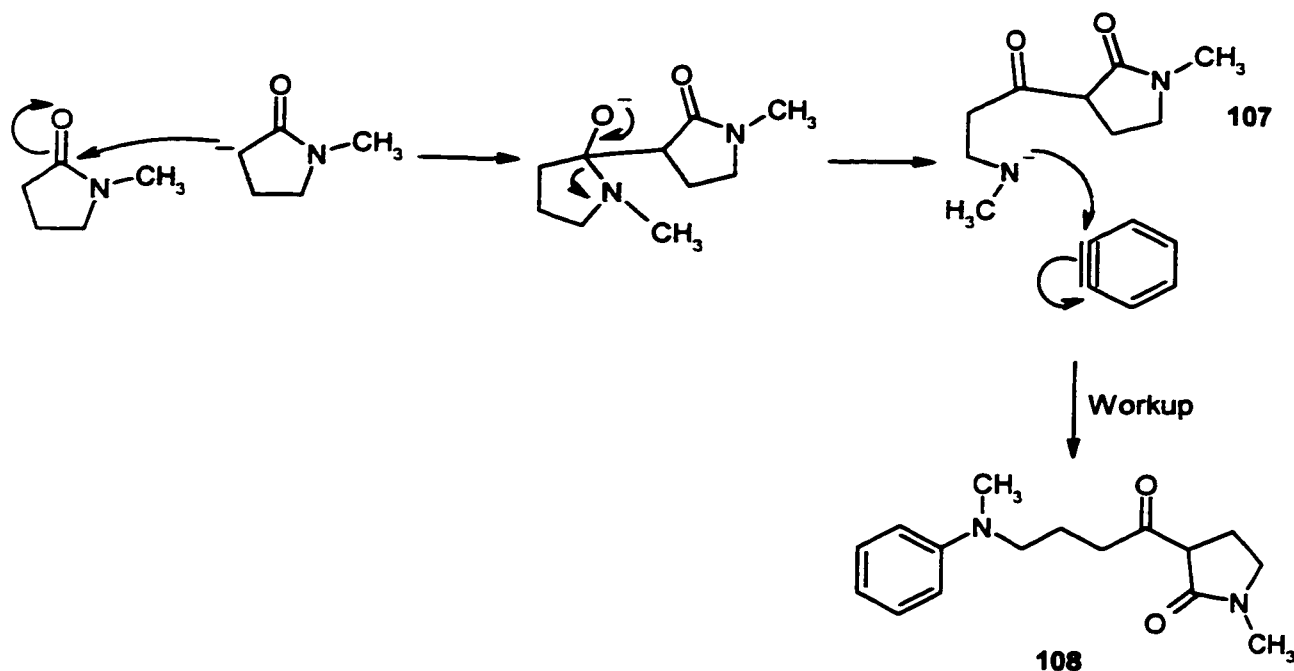
Scheme 4.5.4 : Formation of the proposed structure 106



Compound **106** agreed with the 5 CH₂ groups present in the DEPT spectrum and also contained the molecular fragments determined from the COSY spectrum. The ¹H-NMR spectrum corresponded well with compound **106**, except for one area. That one key feature in the ¹H-NMR spectrum was that it showed aromatic peaks around 6.65 ppm which was an indication that the nitrogen may be attached directly to the phenyl ring and would therefore

eliminate 106 as a possibility. To account for this feature, we proposed the mechanism shown in scheme 4.5.5 which eventually leads to what appears to be the actual structure of the compound obtained.

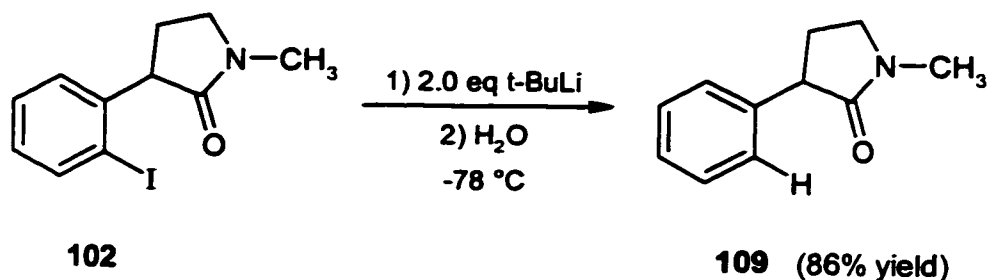
Scheme 4.5.5 : Proposed mechanism to final product 108



As shown above, compound 108 would form by initially having one pyrrolidinone enolate molecule attacking the carbonyl of a non-deprotonated molecule of N-methyl-2-pyrrolidinone to generate the open chained intermediate 107. The nitrogen would then add to the benzyne, and following aqueous workup would yield compound 108. Although this type of mechanism appears somewhat difficult to foresee, the compound formed appears to correspond with all of the spectral data. One other piece of spectral data that appeared to confirm the structure of compound 108 is the fragmentation pattern of the mass spectrum, which shows a peak (100%) at 120. This mass would represent the ion generated from breaking of the carbon-carbon bond α to the nitrogen attached to the benzene ring.

The reaction with N-methyl-2-pyrrolidinone enolate was repeated a final time using chlorobenzene. The reaction was carried out under the same conditions as mentioned previously with no pure products being isolated after chromatography.

With compound **102** identified, we attempted to cyclize it to the benzocyclobutenol by halogen-metal exchange. To a solution of **102** in THF cooled to $-78\text{ }^{\circ}\text{C}$ was added 2.0 equiv. of t-BuLi. The reaction was quenched at $-78\text{ }^{\circ}\text{C}$ after $\sim 1\text{ h}$ followed by aqueous workup. Unfortunately, the anion generated did not cyclize and was quenched upon workup to afford the protonated compound **109** in 86% yield.



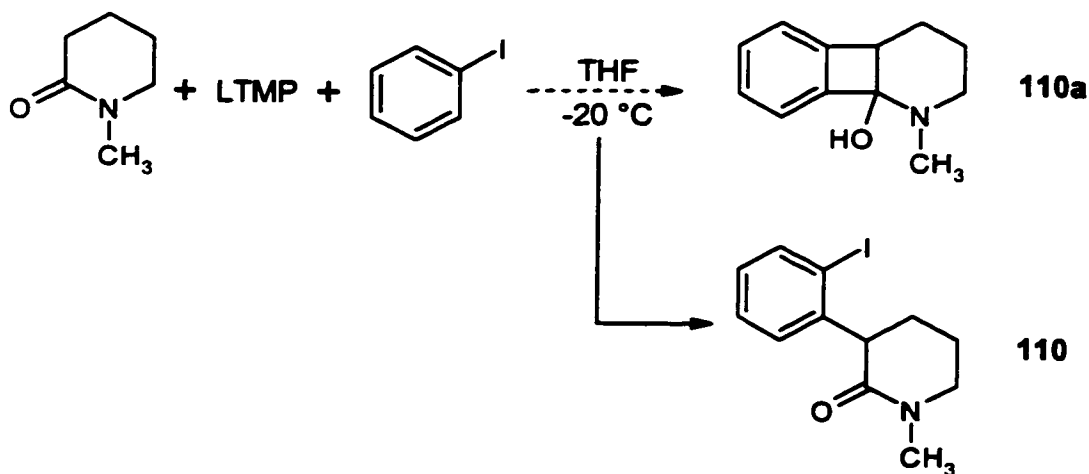
This compound was easily identified by the multiplet in the aromatic region of the ^1H -NMR spectrum integrating for 5 protons, and by the carbonyl peak in the IR spectrum at 1681 cm^{-1} .

Below is a summary of the reactions carried out with the enolate of N-methyl-2-pyrrolidinone and benzyne under various conditions, using different halobenzenes as the benzyne source (table 4.5.1)

Table 4.5.1 : Reaction of N-methyl-2-pyrrolidinone enolate with benzyne generated from different phenyl halides

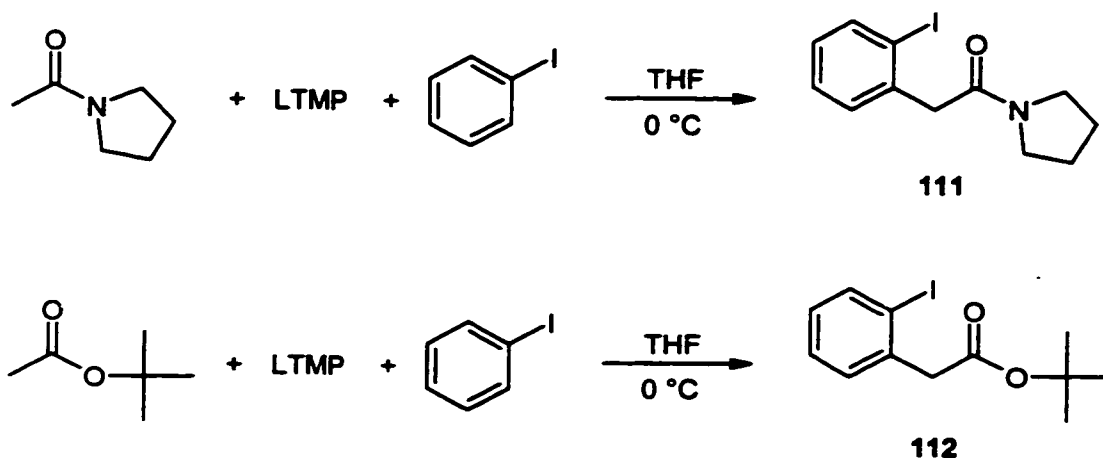
<u>Entry</u>	<u>Aryl halide</u>	<u>LTMP (equiv.)</u>	<u>Amide (equiv.)</u>	<u>Reaction Conditions</u>	<u>Product</u>
1	Iodobenzene	2.0	1.05	0 °C → rt ~ 2 h	102 (8%), 108 and 109 in small amount
2	Iodobenzene	2.2	1.05	0 °C → rt 17 h	102 (14%), 108 (5%)
3	Iodobenzene	3.0	1.5	0 °C 1 h	102 (37%), 108 (9%), 109
4	Iodobenzene	3.5	1.5	0 °C 4 h	102 (44%), 108 (10%), trace of 109
5	Bromobenzene	3.0	1.5	-20 °C 3.5 h	108 (26%), 109 (16%)
6	Chlorobenzene	2.5	1.3	0 °C 3 h	No isolated products

An attempt to prepare benzocyclobutenol was subsequently made using N-methyl-2-piperidinone enolate as the nucleophile since we expected the desired **110a** to be less strained and thus possibly formed more easily than **99**. To a solution of 3.2 equiv. of LTMP in THF cooled to -20 °C was added 1.5 equiv. of the amide followed by iodobenzene and stirred for 3 h. Aqueous workup followed by chromatography on silica gel afforded compound **110** in 20% yield.



The ^1H -NMR spectrum of **110** contained all of the same features as for compound **102**. The IR spectrum showed the amide carbonyl at 1638 cm^{-1} and the HRMS showed an M^+ ion peak at m/z 315.0132 which corresponded with the calculated value of 315.0121. The reaction was repeated at $0\text{ }^\circ\text{C}$ for 3.5 h with compound **110** being isolated in 21% yield.

Following the results obtained with cyclic nucleophiles, we attempted the reaction with an acyclic amide and ester enolate. We opted to use *N*-acetyl pyrrolidine and *t*-butyl acetate. Both reactions were done at $0\text{ }^\circ\text{C}$ over a period of 3 h using iodobenzene as the benzyne precursor with 1.5 equiv. of substrate and 3.2 equiv. of LTMP. The reaction with the amide enolate as the nucleophile afforded compound **111** in 88% yield while the reaction with the ester enolate gave a 69% yield of compound **112**.



Both compounds were confirmed by ^1H -NMR, ^{13}C -NMR, infrared and HRMS.

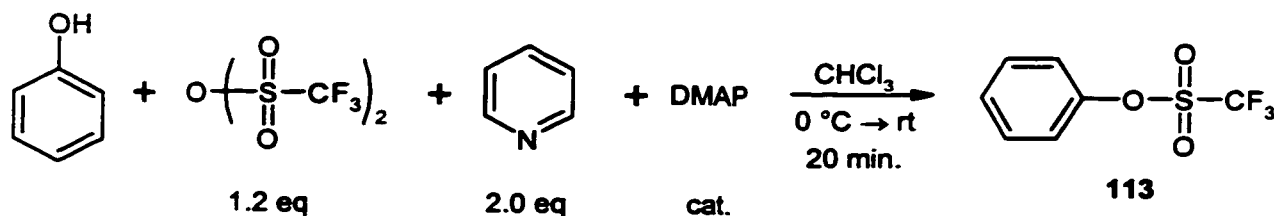
4.6 Benzyne Generation by Deprotonation of Phenyl Triflate with Lithium 2,2,6,6-Tetramethylpiperidide

With the results of the aryl halides in hand, we attempted to form the benzocyclobutenols via benzyne route but using phenyl triflate as the benzyne precursor.

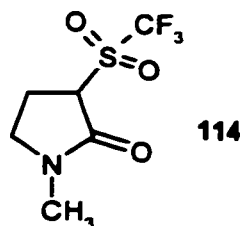
The reason behind this was that the triflate group could not be transferred to the anion generated after attack of the benzyne by the nucleophile, as was the case when iodobenzene was used. Hence, the anion would remain free to react with the ketone to hopefully cyclize to the cyclobutenol.

The triflate **113** was thus prepared from phenol using common reaction conditions in 68% yield after chromatography (scheme 4.6.1).

Scheme 4.6.1 : Preparation of phenyl triflate



To a solution 3.0 equiv. of LTMP in THF cooled to 0 °C, was added 1.5 equiv. of N-methyl-2-pyrrolidinone and stirred for 5 minutes prior to the addition of the triflate **113**. The reaction mixture was stirred for 3 h and then quenched with wet THF followed by an aqueous workup. Purification by chromatography did not afford any of the desired product but instead gave compound **114** in 51% yield as a white solid.



The ^1H -NMR spectrum (see figure 4.6.1) showed the methyl peak at 2.88 ppm and the ^{13}C -NMR spectrum (see figure 4.6.2) showed the carbonyl at 162.3 ppm with the CF_3 group being clearly identified as a quartet centered at 119 ppm. The IR spectrum showed the

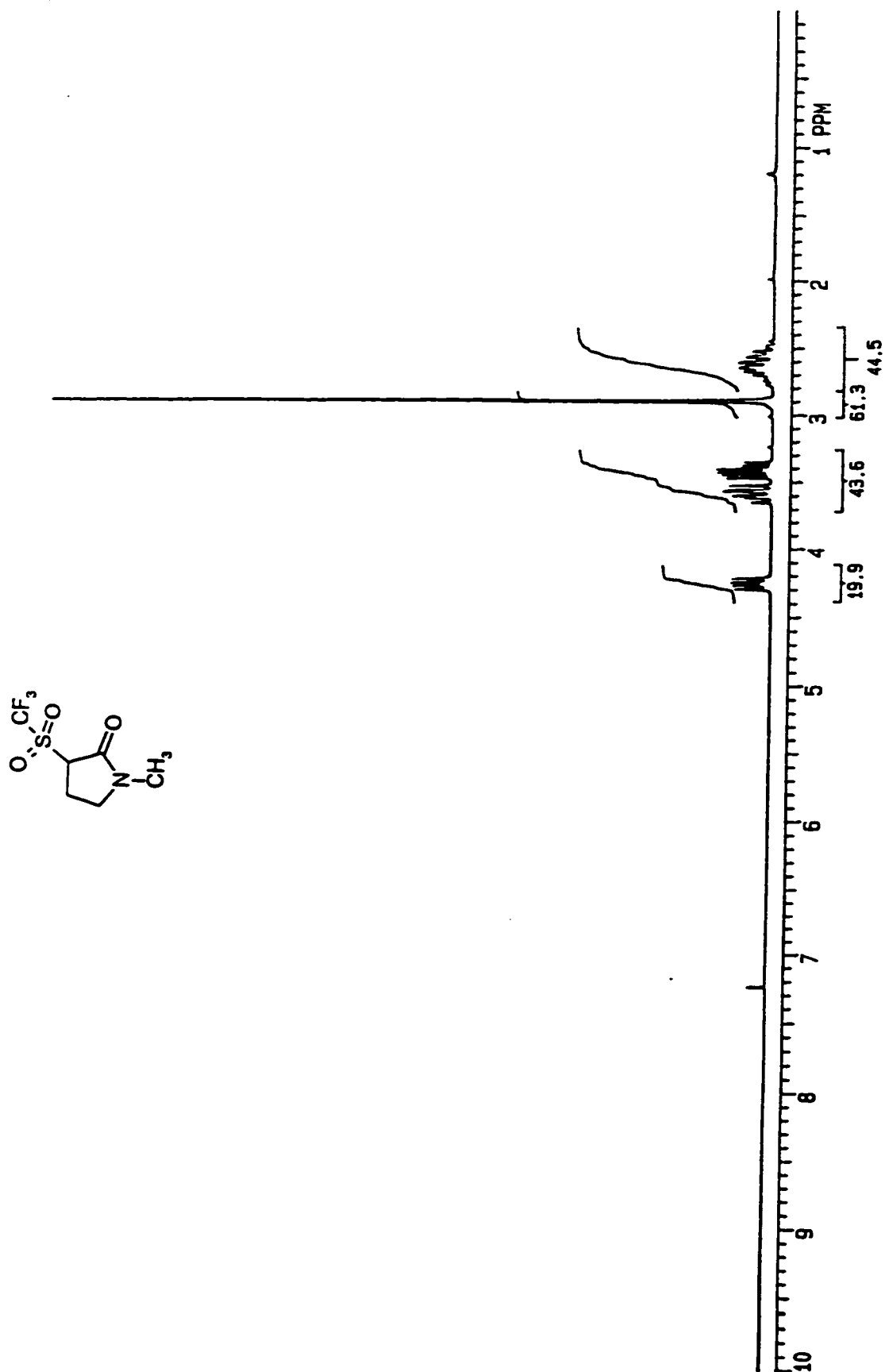


FIGURE 4.6.1: ^1H -NMR SPECTRUM OF N-METHYL-5-((TRIFLUOROMETHYL)SULFONYL)-2-PYRROLIDINONE 114

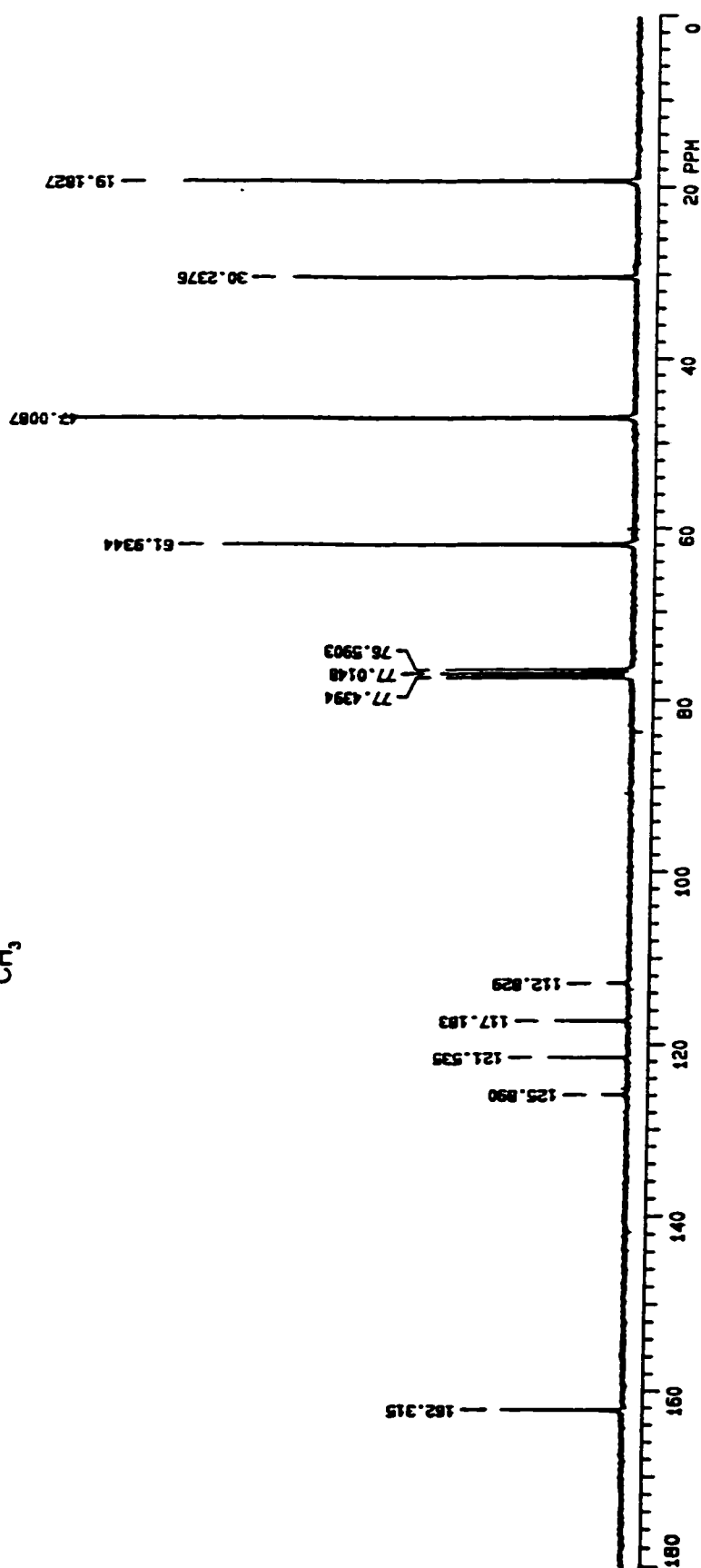
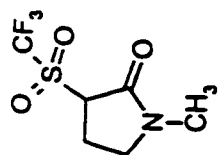


FIGURE 4.6.2: ^{13}C -NMR SPECTRUM OF N-METHYL-5-[(TRIFLUOROMETHYL)SULFONYL]-2-PYRROLIDINONE 114

SO₂ stretches at 1366 and 1197 cm⁻¹. The HRMS showed a strong M⁺ ion peak (12.6%) at *m/z* 231.0174 which was in agreement with the calculated value of 231.0177.

From this result, it was clear that, under these reaction conditions, the attack of the pyrrolidine enolate onto the triflate group was much faster than the formation of the benzyne species. Based on this result, this route was not pursued any further.

4.7 Summary

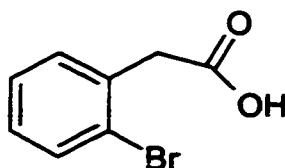
A number of different approaches have been attempted to generate benzocyclobutenols and benzocyclobutenones but without success. Although the desired products could not be obtained, we did get an interesting result when reacting *o*-iodophenyl tosylate with cyclohexanone and *t*-BuLi. The result obtained should actually be investigated further to study the possibility of applying this procedure to the preparation of ortho-substituted phenols. If successful, this would therefore provide a new route for the preparation of these compounds. In the case of the benzyne route using LTMP as the base, future work should involve attempting the reaction of the amide and ester enolate substrates with substituted phenyl rings as opposed to iodobenzene. Having an ortho substituent like a methoxy group for example, should modify the reactivity of the benzyne intermediate generated, since the lithium derivative would show significant complexation to the triple bond due to the polarization effect of the ortho methoxy group. It is envisaged that this may give positive results based on the fact that literature has shown that the yields obtained when preparing the simple benzocyclobutenone adduct **55** are usually somewhat lower than when the benzene ring is substituted, especially with methoxy groups. Although this reaction pathway did not yield the desired benzocyclobutenols, it did provide an interesting result. It

showed that under the reaction conditions used, iodobenzene could serve as a positive iodine source.

4.8 EXPERIMENTAL

General: See experimental section 2.9 for general procedures

2-(2-bromophenyl) acetic acid 72



To 2.0 g (10.20 mmol) of 2-bromo benzyl cyanide was added 10 mL of 6N H₂SO₄. The solution was refluxed for 17 h and allowed to cool down. Added 30 mL of water and obtained a hard white solid. The solid was filtered to yield 2.19 g (100% yield) of clean product as a white solid.

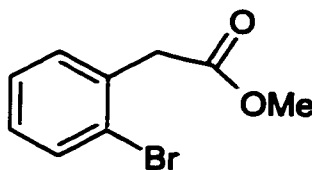
¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 9.10 (brs, 1H), 7.56 (d, 1H, J=8.0 Hz), 7.28 (d, 2H, J=3.6 Hz), 7.15 (m, 1H), 3.83 (s, 2H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 176.8, 133.5, 132.9, 131.6, 129.2, 127.6, 125.1, 41.4

IR (KBr): 3015, 2909, 1707 cm⁻¹

HRMS: Calcd. for C₈H₇O₂Br: 213.9629 and 215.9609; found: 213.9642 and 215.9609

mp: 100.0 – 102.0 °C

Methyl 2-(2-bromophenyl) acetate 73

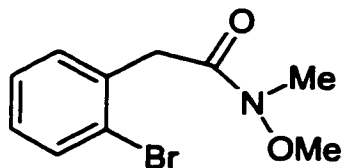
To a solution of 800 mg (3.72 mmol) of 2-(2-bromophenyl)acetic acid dissolved in 5 mL of MeOH was added 0.5 mL of concentrated H₂SO₄. The mixture was refluxed lightly for one hour (complete by TLC). The solution was neutralized with the addition of 1M NaOH and then extracted with CH₂Cl₂. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 800 mg (94% yield) of clean product.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.54 (d, 1H, J=7.8 Hz), 7.26 (d, 2H, J=4.3 Hz), 7.13 (m, 1H), 3.78 (s, 2H), 3.69 (s, 3H)

¹³C-NMR (CDCl₃, 50 MHz): δ(ppm) 171.0, 134.1, 132.8, 131.4, 128.9, 127.5, 125.0, 52.2, 41.5

IR (neat): 3016, 2948, 1741 cm⁻¹

HRMS: Calcd. for C₉H₉BrO₂: 227.9786 and 229.9766; found: 227.9781 and 229.9754

Compound 74

****General procedure taken from Yvonne Lear Ph.D. Thesis, 1997, p.59**

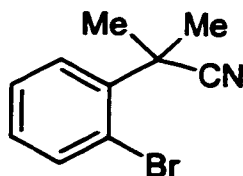
To a solution of 0.26 g (2.64 mmol) of N,O-dimethylhydroxylamine hydrochloride in 9 mL of dry distilled CH_2Cl_2 kept under nitrogen, was added 3.00 mL (6.00 mmol) of trimethylaluminum. The solution was stirred for 15 minutes at room temperature, followed by addition, via cannula, of a solution of 550 mg (2.40 mmol) of methyl 2-(2-bromophenyl) acetate in 2 mL of CH_2Cl_2 . The reaction was refluxed for 26 h and then carefully quenched by dropwise addition through the condenser of 10% HCl until gas evolution ceased. The organic and aqueous layers were separated and the aqueous phase was washed with CH_2Cl_2 (2X). The combined organic layers were washed with water (2X) and brine. The organic layer was dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 570 mg of crude material. Purification with silica gel chromatography using 2:1 hexanes/ethyl acetate afforded 260 mg (42% yield) of the desired amide.

$^1\text{H-NMR}$ (CDCl_3 , 500 MHz): $\delta(\text{ppm})$ 7.54 (dd, 1H, $J=1.1$ Hz), 7.25 (m, 2H), 7.10 (m, 1H), 3.80 (s, 2H), 3.00 (brs, 6H)

$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): $\delta(\text{ppm})$ 170.1, 135.3, 132.7, 130.7, 128.5, 127.6, 124.7, 40.8, 37.5, 35.7

IR (neat): 3046, 2946, 1644, 1140 cm^{-1}

FAB MS, m/z (rel. intensity, %): 244 (97.8), 242 (100.0), 163 (1.3)

2-(2-bromophenyl)-2-methylpropanenitrile 75

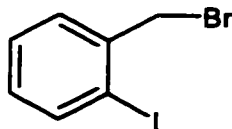
To a solution of 1.11 g (45.90 mmol) of sodium hydride in 50 mL of dry distilled THF under nitrogen was added via syringe, 1.99 mL (15.30 mmol) of 2-bromophenyl acetonitrile. The reaction mixture was stirred until H₂ gas evolution had ceased. The solution was cooled to 0 °C and 3.80 mL (61.21 mmol) of methyl iodide was added slowly via syringe. The reaction was stirred at room temperature for 20 h after which a thick white precipitate was obtained. Completion was confirmed by ¹H-NMR. The reaction was quenched slowly with ammonium chloride solution and extracted with ether. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography using 15:1 hexanes/ethyl acetate afforded 2.94 g (85% yield) of clean product as a clear oil.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.64 (dd, 1H, J=1.5; 7.8 Hz), 7.47 (dd, 1H, J=1.8; 8.0 Hz), 7.33 (td, 1H, J=1.5; 7.3 Hz), 7.17 (td, 1H, J=1.8; 7.8 Hz), 1.88 (s, 6H)

¹³C-NMR (CDCl₃, 50 MHz): δ(ppm) 138.1, 135.5, 129.5, 127.8, 127.1, 123.3, 122.5, 37.3, 27.4

IR (neat): 3065, 2984, 2237 cm⁻¹

HRMS: Calcd. for C₁₀H₁₀BrN: 222.9997 and 224.9977; found: 223.0000 and 224.9991

2-iodobenzyl bromide 81

To a solution of 8.00 g (36.69 mmol) of 2-iodo toluene in 60 mL of dry distilled benzene under N₂ atmosphere was added 7.18 g (40.36 mmol) of N-bromosuccinimide and 0.60 g (3.67 mmol) of AIBN. The mixture was refluxed for 90 minutes (complete by TLC). The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed 3 times with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent evaporated under reduced pressure to afford 9.88 g of crude material. After purification by silica gel chromatography using pure heptane, 5.57 g (51% yield) of clean product was obtained as a white solid.

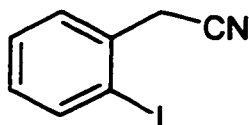
¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 4.58 (s, 2H), 6.96 (td, 1H, J=1.8; 7.5 Hz), 7.32 (td, 1H, J=1.1; 7.4 Hz), 7.46 (dd, 1H, J=1.8; 7.6 Hz), 7.84 (dd, 1H, J=1.3; 7.9 Hz)

¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) 140.1, 140.0, 130.4, 130.0, 128.8, 100.0, 38.7

IR (neat): 3054, 2987, 1422 cm⁻¹

HRMS: Calcd. for C₇H₆BrI: 295.8698 and 297.8678; found: 295.8689 and 297.8663

mp: 55.0 - 55.5 °C

2-iodophenyl acetonitrile 82

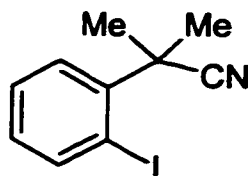
To a solution of 3.45 g (11.63 mmol) of 2-iodobenzyl bromide dissolved in 30 mL of acetonitrile under N₂ was added sodium cyanide (freshly grounded into a fine powder). The mixture was stirred vigorously at room temperature for 30 h (complete by ¹H-NMR). The reaction mixture was diluted with ethyl acetate and water and washed 3 times with water. The combined aqueous layers were washed 3 times with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 2.82 g (100% yield) of clean product as a yellowish liquid.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 3.80 (s, 2H), 7.03 (td, 1H, J=1.1; 7.3 Hz), 7.38 (t, 1H, J=7.3 Hz), 7.49 (d, 1H, J=7.7 Hz), 7.86 (d, 1H, J=7.9 Hz)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 139.7, 133.2, 129.8, 129.0, 129.0, 117.1, 99.0, 29.9

IR (neat): 3058, 2902, 2250 cm⁻¹

HRMS: Calcd. for C₈H₆IN: 242.9545; found: 242.9545

2-(2-iodophenyl)-2-methylpropanenitrile 84

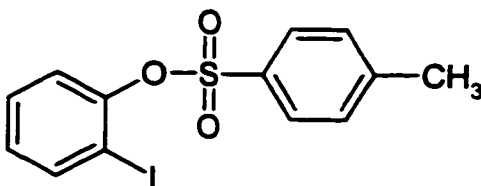
To a solution of 0.28 g (11.52 mmol) of sodium hydride in 10 mL of dry distilled THF under nitrogen was added, via cannula, a solution of 800 mg (3.29 mmol) of 2-iodophenyl acetonitrile dissolved in 5 mL of THF. The reaction mixture was stirred at room temperature until H_2 gas evolution had ceased. The solution was cooled to 0 °C and 0.92 mL (14.81 mmol) of methyl iodide was added slowly via syringe. The reaction was warmed to room temperature and stirred for 16 h. Completion was confirmed by ^1H -NMR. The reaction was quenched by slow addition of a saturated ammonium chloride solution, followed by dilution with ethyl acetate. The organic layer was washed 3 times with water and the combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 840 mg (94% yield) of clean product as a yellow oil.

^1H -NMR (CDCl_3 , 200 MHz): $\delta(\text{ppm})$ 8.02 (dd, 1H, $J=1.3$; 7.9 Hz), 7.40 (m, 2H), 6.97 (m, 1H), 1.89 (s, 6H)

^{13}C -NMR (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ 143.1, 140.4, 129.5, 128.5, 126.7, 123.1, 95.8, 38.9, 27.8

IR (neat): 3062, 2982, 2936, 2229, 1462, 1009 cm^{-1}

HRMS: Calcd. for $\text{C}_{10}\text{H}_{10}\text{NI}$: 270.9859; found: 270.9869

2-iodo-1-[(4-methylphenyl)sulfonyloxy]benzene 95

To a solution of 800 mg (3.63 mmol) of 2-iodophenol in 15 mL of CHCl_3 cooled to 0 °C was added 0.59 mL (7.27 mmol) of pyridine and 0.04 g (0.36 mmol) of 4-dimethylamino pyridine followed by the addition of 1.04 g (5.45 mmol) of p-toluenesulfonyl chloride in small portions with constant stirring. The solution was stirred for 18 h at room temperature after which TLC showed no starting material. Ethyl acetate and water were added and the organic layer was washed once with 10 % HCl, once with a saturated solution of sodium bicarbonate and then twice with water. The organic layer was dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 1.60 g of crude product. The excess p-toluenesulfonyl chloride was removed by dissolving the crude product in ~ 15 mL of THF and ~ 15 mL of water with ~ 2 mL of triethylamine. The solution was stirred at room temperature for 2 days after which TLC showed no chloride left. After water/ethyl acetate workup, 1.32 g (97% yield) of the tosylated product was obtained as a yellow solid.

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz): $\delta(\text{ppm})$ 7.76 (m, 3H), 7.30 (m, 4H), 6.96 (m, 1H), 2.44 (s, 3H)

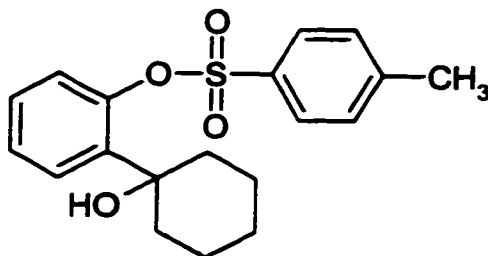
$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ 149.9, 145.6, 140.0, 132.7, 129.7, 129.4, 128.7, 128.2, 122.9, 90.1, 21.7

IR (KBr): 3101, 3058, 2915, 1380, 1156 cm^{-1}

HRMS: Calcd. for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{SI}$; 373.9474; found: 373.9462

mp: 78.0 – 80.0 °C

2-(1-hydroxycyclohexyl)-1-[(4-methylphenyl)sulfonyloxy] benzene 96



To a solution of 300 mg (0.8017 mmol) of **95** and 87.2 μ L (0.8418 mmol) of cyclohexanone dissolved in 15 mL of dry distilled THF under nitrogen, cooled to -78°C , was added 1.56 mL (2.645 mmol) of t-butyllithium via syringe. The reaction was stirred for 20 minutes and quenched at -78°C with wet THF. The reaction mixture was diluted with ethyl acetate and some saturated NH_4Cl solution and then washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 190 mg of crude material. Purification by silica gel chromatography using 5:1 hexanes\ethyl acetate did not afford the desired product but gave 80 mg (29% yield) of compound **96** as the major product.

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz): $\delta(\text{ppm})$ 7.92 (m, 2H), 7.57 (m, 1H), 7.37 (m, 2H), 7.21 (m, 3H), 2.45 (s, 3H), 2.15 (brs, 1H), 1.74 (m, 9H), 1.80 (m, 1H)

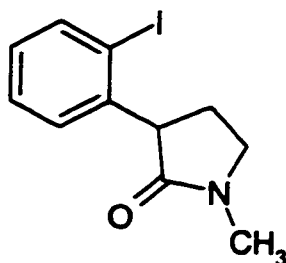
$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ 147.8, 145.5, 140.1, 133.9, 129.9, 128.2, 128.1, 127.6, 126.4, 121.5, 72.9, 36.8, 25.2, 21.8, 21.7

IR (KBr): 3535, 3447, 3071, 2978, 2927, 2859, 1450, 1350, 1187, 1087, 861 cm^{-1}

HRMS: Calcd. for $C_{19}H_{22}O_4S$: 346.1239; found: 346.1249

mp: 97.5 – 99.0 °C

3-(2-iodophenyl)-N-methyl-2-pyrrolidinone 102



To a solution of 0.99 mL (5.88 mmol) of 2,2,6,6-tetramethylpiperidine in 8.0 mL of dry distilled THF kept under nitrogen at 0 °C, was added 3.47 mL (5.88 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.28 mL (2.94 mmol) of N-methyl-2-pyrrolidinone was slowly added dropwise via syringe and stirred for 5 minutes followed by the slow addition of 0.22 mL (1.96 mmol) of iodobenzene. The solution was stirred at 0 °C for 3 h, then quenched with water at 0 °C. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to afford 520 mg of crude material. Purification by silica gel chromatography using 2:1 ethyl acetate/hexanes as the eluent afforded 129 mg (44% yield, based on proposed mechanism) of product **102** as a yellow solid.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) 7.81 (dd, 1H, J=7.9; 1.2 Hz), 7.29 (td, 1H, J=7.5; 1.3 Hz), 7.12 (dd, 1H, J=7.7; 1.7 Hz), 6.90 (td, 1H, J=7.4; 1.7 Hz), 4.00 (t, 1H, J=9.2 Hz), 3.40 (m, 2H), 2.94 (s, 3H), 2.64 (m, 1H), 1.84 (m, 1H)

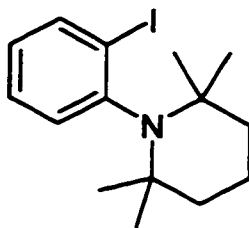
¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) 174.2, 143.2, 139.5, 128.8, 128.6, 128.3, 101.3, 52.9, 47.3, 30.2, 27.9

IR (KBr): 3051, 2955, 2923, 1678 cm⁻¹

HRMS: Calcd. for C₁₁H₁₂INO: 300.99643; found 300.99726

mp: 119.0 - 121.0 °C

N-(2-iodophenyl)-2,2,6,6-tetramethylpiperidine 103



To a solution of 0.49 mL (2.94 mmol) of 2,2,6,6-tetramethylpiperidine in 8.0 mL of dry distilled THF kept under nitrogen at -30 °C was added 1.73 mL (2.94 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.22 mL (1.96 mmol) of iodobenzene was added via syringe. The reaction was stirred at -30 °C for 40 minutes and quenched with wet THF. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 210 mg of crude material. Purification on silica gel using pure hexanes as the eluent afforded 120 mg (36%) of compound **103** as the major product as a white semi-solid.

¹H-NMR (CDCl₃, 500 MHz): δ(ppm) 7.92 (dd, 1H, J=7.9; 1.5 Hz), 7.41 (dd, 1H, J=7.9; 1.6 Hz), 7.27 (td, 1H, J=7.8; 1.5 Hz), 6.87 (td, 1H, J=7.9; 1.6 Hz), 1.89 (m, 1H), 1.80 (broad td, 2H, J=12.1; 2.5 Hz), 1.63 (m, 1H), 1.56 (m, 2H), 1.28 (s, 6H), 0.91 (s, 6H)

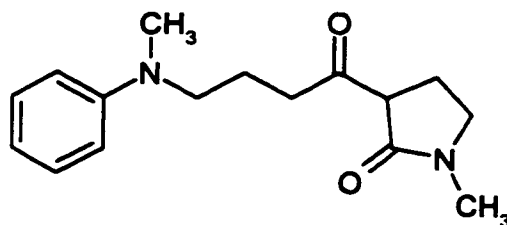
¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) 148.9, 139.7, 131.6, 128.0, 127.2, 114.3, 56.1, 41.3, 31.6, 25.6, 18.6

IR (CH₂Cl₂): 3010, 2928, 2870, 1014 cm⁻¹

HRMS: Calcd. for C₁₅H₂₂Nl: 343.0798; found 343.0788

mp: 47.0 – 49.0 °C

Compound 108



To a solution of 1.60 mL (9.55 mmol) of 2,2,6,6-tetramethylpiperidine in 8 mL of dry distilled THF kept under nitrogen at -20 °C was added 5.62 mL (9.55 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.46 mL (4.78 mmol) of N-methyl-2-pyrrolidinone was slowly added and stirred for 10 minutes followed by the slow addition of 0.34 mL (3.18 mmol) of bromobenzene. The solution was stirred at -20 °C for 3.5 h and quenched at -20 °C with water. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure.

Purification by silica gel chromatography using 3:7 hexanes\ethyl acetate afforded 170 mg (26%) of compound **108** as a semi-solid.

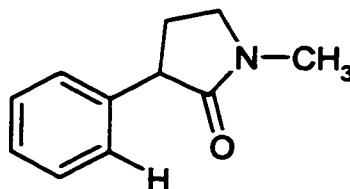
¹H-NMR (CDCl₃, 500 MHz): δ(ppm) 7.18 (m, 2H), 6.69 (dd, 2H, J=0.8; 8.8 Hz), 6.64 (td, 1H, J=0.9; 7.3 Hz), 3.48 (dd, 1H, J=6.0; 9.3 Hz), 3.38 (td, 1H, J=5.1; 9.3 Hz), 3.30 (broad t, 2H, J=8.1 Hz), 3.25 (td, 1H, J=5.4; 8.9 Hz), 3.04 (dt, 1H, J=7.0; 18.3 Hz), 2.88 (s, 3H), 2.79 (s, 3H), 2.57 (dt, 1H, J=6.9; 18.3 Hz), 2.48 (m, 1H), 1.96 (m, 1H), 1.87 (m, 2H)

¹³C-NMR (CDCl₃, 125 MHz): δ(ppm) 205.4, 169.8, 149.3, 129.1, 116.0, 112.2, 54.7, 51.7, 47.7, 39.8, 38.1, 29.9, 20.6, 19.5

IR (CH₂Cl₂): 3015, 2921, 2885, 1716, 1684 cm⁻¹

HRMS: Calcd. for C₁₆H₂₂N₂O₂: 274.1682; found 274.1670

N-methyl-3-phenyl-2-pyrrolidinone **109**



To a solution of 80 mg (2.647 mmol) of 3-(2-iodophenyl)-N-methyl-2-pyrrolidinone in 4 mL of dry distilled THF kept under nitrogen and cooled to -78 °C was added 3.11 mL (5.295 mmol) of t-BuLi via syringe. The solution was stirred for 75 minutes and quenched with water and ethyl acetate at -78 °C. The organic layer was washed (3X) with water. The combined aqueous layers were washed (2X) with ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 40 mg of compound **109** as a liquid that needed no further purification.

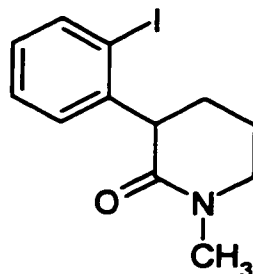
¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.25 (m, 5H), 3.63 (t, 1H J=8.7 Hz), 3.42 (m, 2H), 2.91 (s, 3H), 2.50 (m, 1H), 2.10 (m, 1H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 174.8, 139.9, 128.6, 127.8, 126.9, 47.9, 47.6, 30.0, 27.9

IR (neat): 3029, 2922, 2876, 1681 cm⁻¹

HRMS: Calcd. for C₁₁H₁₃NO: 175.0998; found 175.0974

3-(2-iodophenyl)-N-methyl-2-piperidinone 110



To a solution of 1.06 mL (6.27 mmol) of 2,2,6,6-tetramethylpiperidine in 8.0 mL of dry distilled THF kept under nitrogen at 0 °C was added 3.69 mL (6.27 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.33 mL (2.94 mmol) of N-methyl-2-piperidone was slowly added dropwise via syringe and stirred for 5 minutes followed by the slow addition of 0.22 mL (1.96 mmol) of iodobenzene. The solution was stirred at 0 °C for 3 h and quenched at 0 °C with water. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 510 mg of crude material. Purification by silica gel chromatography using 2:1 ethyl acetate/hexanes afforded 60 mg (21% yield, based on proposed mechanism) of the solid product.

¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.80 (dd, 1H, J=1.3; 7.9 Hz), 7.25 (td, 1H, J=1.2; 7.6 Hz), 7.07 (dd, 1H, J=1.7; 7.7 Hz), 6.87 (td, 1H, J=1.7; 7.5 Hz), 3.92 (t, 1H, J=5.8 Hz), 3.39 (m, 2H), 3.01 (s, 3H), 2.11 (m, 1H), 1.86 (m, 3H)

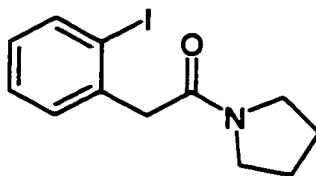
¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 169.9, 144.4, 139.7, 129.2, 128.3, 128.2, 100.8, 53.0, 50.3, 35.1, 29.4, 21.2

IR (CH₂Cl₂): 2936, 2867, 1638, 1011 cm⁻¹

HRMS: Calcd. for C₁₂H₁₄INO: 315.01209; found 315.01316

mp: 88.0 – 90.5 °

2-(2-iodophenyl)-1-tetrahydro-1*H*-1-pyrrolyl-1-ethanone 111



To a solution of 1.32 mL (7.84 mmol) of 2,2,6,6-tetramethylpiperidine in 10.0 mL of dry distilled THF kept under nitrogen at 0 °C was added 4.60 mL (7.84 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.415 g (3.67 mmol) of N-acetylpyrrolidine was slowly added and stirred for 5 minutes followed by the slow addition of 0.27 mL (2.45 mmol) of iodobenzene. The solution was stirred at 0 °C for 3 h and quenched at 0 °C with a saturated solution of NH₄Cl. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography using 2:1 ethyl acetate/hexanes afforded 338 mg (88% yield, based on proposed mechanism) of **111** as a clear liquid.

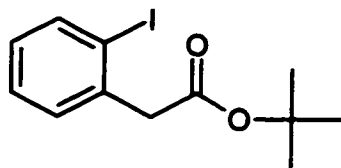
¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.79 (d, 1H, J=8.0 Hz), 7.28 (m, 2H), 6.91 (m, 1H), 3.73 (s, 2H), 3.49 (m, 4H), 1.89 (m, 4H)

¹³C-NMR (CDCl₃, 50 MHz): δ(ppm) 168.4, 139.1, 138.6, 130.0, 128.4, 128.3, 101.1, 46.8 (2C's), 45.8, 26.0, 24.3

IR (CH₂Cl₂): 3015, 2951, 2877, 1650, 1015 cm⁻¹

HRMS: Calcd. for C₁₂H₁₄INO: 315.0120; found 188.1076 (-I⁺) : Calc. for -I⁺: 188.1076

***tert*-butyl 2-(2-iodophenyl)acetate 112**



To a solution of 1.32 mL (7.84 mmol) of 2,2,6,6-tetramethylpiperidine in 10.0 mL of dry distilled THF kept under nitrogen at 0 °C was added 4.60 mL (7.84 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.5 mL (3.67 mmol) of t-butyl acetate was slowly added and stirred for 5 minutes followed by the slow addition of 0.27 mL (2.45 mmol) of iodobenzene. The solution was stirred at 0 °C for 3 h and quenched at 0 °C with a solution of saturated NH₄Cl. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography using 9:1 hexanes\ethyl acetate afforded 220 mg (69% yield, based on proposed mechanism) of **112** as a clear liquid.

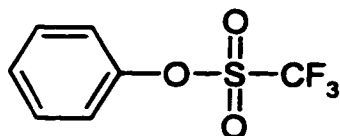
¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.82 (d, 1H, J=8.1 Hz), 7.25 (m, 2H), 6.91 (m, 1H), 3.69 (s, 2H), 1.47 (s, 9H)

¹³C-NMR (CDCl₃, 50 MHz): δ(ppm) 169.7, 139.4, 138.5, 130.6, 128.6, 128.3, 101.0, 81.2, 47.4, 28.1

IR (CH₂Cl₂): 3007, 2930, 1728, 1015 cm⁻¹

HRMS: Calcd. for C₁₂H₁₅IO₂: 318.0117; found 318.0138

Phenyl trifluoromethanesulfonate 113



To a solution of 1.70 g (18.06 mmol) of phenol in chloroform cooled to 0 °C under nitrogen atmosphere, was added 2.92 mL (36.12 mmol) of pyridine and ~ 40 mg (cat.) of 4-dimethylamino pyridine. The solution was stirred for ~ 5 minutes followed by the addition of 3.65 mL (21.67) of triflic anhydride over 3 minutes. The reaction was done after 20 minutes and quenched with water. The organic layer was washed 3X with water and the combined aqueous layers were washed once with chloroform. The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford 2.77 g (68% yield) of clean product as a clear liquid.

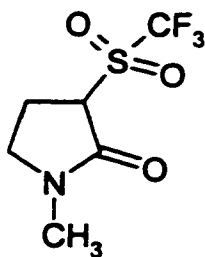
¹H-NMR (CDCl₃, 200 MHz): δ(ppm) 7.41 (m, 3H), 7.27 (m, 2H)

¹³C-NMR (CDCl₃, 75 MHz): δ(ppm) 149.7, 130.2, 128.4, CF₃ quartet (125.2, 121.0, 116.7, 112.5), 121.2

IR (neat): 3071, 1583, 1487, 1416, 1223, 1139, 907 cm^{-1}

HRMS: Calcd. for $\text{C}_7\text{H}_5\text{F}_3\text{O}_3\text{S}$: 228.9911; found 225.9920

N-methyl-5-[(trifluoromethyl)sulfonyl]-2-pyrrolidinone 114



To a solution of 0.895 mL (5.30 mmol) of 2,2,6,6-tetramethylpiperidine in 8.0 mL of dry distilled THF kept under nitrogen at 0 °C was added 3.12 mL (5.30 mmol) of t-BuLi via syringe. After ~ 1 minute, 0.25 mL (2.65 mmol) of N-methyl-2-pyrrolidinone was slowly added dropwise via syringe and stirred for 5 minutes followed by the slow addition of 0.40 g (1.77 mmol) of phenyl trifluoromethanesulfonate. The solution was stirred at 0 °C for 3 h and quenched at 0 °C. The reaction mixture was diluted with ethyl acetate and washed 3 times with water. The combined aqueous layers were washed twice with ethyl acetate. The combined organic layers were dried with MgSO_4 , filtered and the solvent removed under reduced pressure to afford 530 mg of crude material. Purification by silica gel chromatography using 2:1 ethyl acetate/hexanes (product was flashed off the column) afforded 160 mg (51% yield) of **114** as a white solid.

^1H -NMR (CDCl_3 , 200 MHz): δ (ppm) 4.25 (dd, 1H, $J=5.3$; 9.7 Hz), 3.57 (m, 1H), 3.42 (m, 1H), 2.89 (s, 3H), 2.62 (m, 2H)

^{13}C -NMR (CDCl_3 , 75 MHz): $\delta(\text{ppm})$ 162.3, CF_3 quartet (125.9, 121.5, 117.2, 112.8), 61.9, 47.0, 30.2, 19.2

IR (CH_2Cl_2): 2931, 2893, 1709, 1366, 1197, 1115 cm^{-1}

HRMS: Calcd. for $\text{C}_6\text{H}_8\text{F}_3\text{NO}_3\text{S}$: 231.0177; found 231.0174

mp: 76.0 – 78.0 $^\circ\text{C}$

REFERENCES

1. Prelog, V.; Driza, G. J. *Coll. Czech. Chem. Commun.* **1933**, *5*, 497.
2. Rossen, K.; Weissman, Steven A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 6419.
3. Rawls, Rebecca L. *Chem. & Eng.* **1998**, *April 20th*, 67.
4. Broekkamp, C.L.E.; Leysen, D.; Peeters, B.W.M.M.; Pinder, R.M. *J. Med. Chem.* **1995**, *38*, 4615.
5. Mahmood, Iftexhar; Sahajwalla, Chandra *Clinical pharmacokinetics* **1999**, *36*, 277.
6. Bhatt, Ulhas; Mohamed, Nazim; Just, George *Tetrahedron Lett.* **1997**, *38*, 3679.
7. Hagiwara, Teruhiko; Yasuno, Tetsuko; Suzuki, Sukeji; Saito, Kazuo *Shokuhin Eiseigaku Zasshi* **1999**, *40*, 62.
8. Bell, Leonard N. *ACS Symposium Series* **1997**, *675*, 67.
9. Gaines, Susan M.; Bada, Jeffrey L. *J. Org. Chem.* **1988**, *53*, 2757.
10. Williams, Theresa M.; Ciccarone, Terrence M.; MacTough, Suzanne C.; Bock, Rhonda L.; Conner, Micheal W.; Davide, Joseph P.; Hamilton, Kelly *J. Med. Chem.* **1996**, *39*, 1345.
11. Corbet, Jeffrey W. *Org. Prep. Proced. Int.* **1998**, *30*, 489.
12. Camps, Pelayo; Pérez, Francesc; Soldevilla, Nuria; Borrego, Miguel A. *Tetrahedron: Asymmetry* **1999**, *10*, 493.
13. Roos, Gregory H.P. *S. Afr. J. Chem.* **1998**, *51*, 7.
14. Kubota, Hitoshi; Kubo, Akira; Takahashi, Masami; Shimizu, Ryo; Da-te, Tadamasa; Okamura, Kimio; Nunami, Ken-ichi *J. Org. Chem.* **1995**, *60*, 6776.

15. Ward, Robert S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.
16. Kubo, Akira; Kubota, Hitoshi; Takahashi, Masami; Nunami, Ken-ichi *J. Org. Chem.* **1997**, *62*, 5830.
17. Koh, Kevin; Ben, Robert N.; Durst, Tony *Tetrahedron Lett.* **1993**, *34*, 4473.
18. Camps, Pelayo; Pérez, Francesc; Soldevilla, Nuria *Tetrahedron: Asymmetry* **1998**, *9*, 2065.
19. O'Meara, Jeff A.; Gardee, Nizar; Jung, Manfred; Ben, Robert N.; Durst, Tony *J. Org. Chem.* **1998**, *63*, 3117.
20. Jacquith, James Ph.D. Thesis, University of Ottawa, May **1999**, 82.
21. Freed, Meier E.; Day, Allan R. *J. Org. Chem.* **1960**, *25*, 2108.
22. Lai, John T. *Synthesis, BRD* **1982**, *Jan.*, 71.
23. Adegoke, E.A.; Alo, Babajide *J. Heterocyclic Chem.* **1983**, *20*, 1509.
24. Rees, David C. *J. Heterocyclic Chem.* **1987**, *24*, 1297.
25. Baiocchi, Leandro; Picconi, Giuseppe *Tetrahedron: Asymmetry* **1991**, *2*, 231.
26. Harp, D.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.*, **1975**, *40*, 3420.
27. O'Meara, Jeff A. M.Sc. Thesis, University of Ottawa, **1995**, 24.
28. O'Meara, Jeff A.; Jung, Manfred; Durst, Tony *Tetrahedron Lett.* **1995**, *36*, 2559.
29. Klundt, Irwin L. *Chemical Reviews* **1970**, *70*, 471.
30. Cava, M.P.; Muth, K. *J. Am. Chem. Soc.* **1960**, *82*, 652.

31. Kobayashi, Kazuhiro; Kawakita, Masataka; Uchida, Masaharu; Nishimura, Koichi; Mannami, Tohru; Irisawa, Susumu; Morikawa, Osamu; Konishi, Hisatoshi *J. Org. Chem.* **1999**, *64*, 3557.
32. Azadi-Ardakani, Manouchehr; Wallace, Timothy W. *Tetrahedron* **1988**, *44*, 5939.
33. Fitzgerald, John J.; Michael, Forrest E.; Olofson, R.A. *Tetrahedron Lett.* **1994**, *35*, 9191.
34. Matsumoto, Takashi; Hamura, Toshiyuki; Miyamoto, Makoto; Suzuki, Keisuke *Tetrahedron Lett.* **1998**, *39*, 4853.
35. Liebeskind, Lanny S.; Iyer, Suresh; Jewell, Jr., Charles F. *J. Org. Chem.* **1986**, *51*, 3065.
36. Liebeskind, Lanny S.; Chidambaram, Ramakrishnan; Mitchell, David; Foster, Bruce S. *Pure & appl. Chem.* **1988**, *60*, 27.
37. Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1985**, *41*, 399.
38. Trost, Barry M.; Fleming, Ian *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Pergamon Press: New York, Vol. 5, **1991**, p 675.
39. Wassermann, H.; Solodar, J. *J. Am. Chem. Soc.* **1965** *87*, 4002.
40. Stevens, R.; Bisacchi, G.S. *J. Org. Chem.* **1982**, *47*, 2393.
41. Durr, H.; Nickels, H. *J. Org. Chem.* **1981**, *45*, 973
42. Aidhen, Indrapal S.; Narasimhan, N.S. *Tetrahedron Lett.* **1991**, *32*, 2171.
43. Kang, Jahyo; Ro Choi, Young; Ju Kim, Byoung; Jeong, Jae; Lee, Seongsu; Hyoung Lee, Jae; Pyun, Chongsuh *Tetrahedron Lett.* **1990**, *31*, 2713.
44. Hosoya, Takamitsu; Hasegawa, Takayuki; Kuriyama, Yokusu; Matsumoto, Takashi; Suzuki, Keisuke *Synlett* **1995**, 177.

45. Lear, Yvonne Ph.D Thesis, University of Ottawa, 1997.
46. Dutt, Mahesh; Fravel, Brad; Ford, George P.; Biehl, Edward R. *J. Org. Chem.* **1994**, *59*, 497.
47. Aidhen, Indrapal S.; Narasimhan, N. S. *Tetrahedron Lett.* **1991**, *32*, 2171.
48. Boymond, Laure; Rottländer, Mario; Cahiez, Gérard; Knochel, Paul *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.
49. Hosoya, Takamitsu; Hasegawa, Takayuki; Kuriyama, Yokusu; Suzuki, Keisuke *Tetrahedron Lett.* **1995**, *36*, 3377.
50. Kitamura, Tsugio; Yamane, Masakatsu *J. Chem. Soc., Chem. Commun.* **1995**, 983.
51. Jamart-Gregoire, Brigitte; Leger, Christian; Caubere, Paul *Tetrahedron Lett.* **1990**, *31*, 7599.
52. Matsumoto, Takashi; Hosoya, Takamitsu; Katsuki, Miyoko; Suzuki, Keisuke *Tetrahedron Lett.* **1991**, *32*, 6735.
53. Snieckus, V. *Chemical Reviews* **1990**, *90*, 880.
54. Olofson, R.A.; Dougherty *J. Am. Chem. Soc.* **1973**, *95*, 582.
55. Knight, David W.; Little, Paul B. *Synlett* **1998**, *Oct*, 1141.

CLAIMS TO ORIGINAL RESEARCH

- 1) Preparation of bicyclic piperazines and other heterocycles in an enantiomerically enriched form. These compounds include the following:
 - 6,6a,7,8,9,10-hexahydro-5*H*-pyrido[1,2-*a*]quinoxalin-6-one **23**
 - 6,6a,7,8,9,10-hexahydrobenzo[*b*]pyrido[1,2-*d*][1,4]oxazin-6-one **26**
 - 1,2,3,4,6,11,12,12a-octahydrobenzo[*e*]pyrido[1,2-*a*][1,4]diazepin-12-one **32**
 - 2-phenylperhydropyrido[1,2-*a*]pyrazin-1-one **34**
 - (4*S*)-methyl-(3*R*)-phenylperhydropyrido[2,1-*c*][1,4]oxazin-1-one **36**
 - 5,6,6a,7,8,9-hexahydropyrrolo[1,2-*a*]quinoxalin-6-one **41**
- 2) Generation of benzyne via reaction of lithium 2,2,6,6-tetramethylpiperidide with halobenzenes at low temperatures.
- 3) Preparation of the following compounds via reaction of benzyne generated from iodobenzene as detailed in 2), with amide and ester enolates:
 - 3-(2-iodophenyl)-*N*-methyl-2-pyrrolidinone **102**
 - 3-(2-iodophenyl)-*N*-methyl-2-piperidinone **110**
 - 2-(2-iodophenyl)-1-tetrahydro-1*H*-1-pyrrolyl-1-ethanone **111**
 - *tert*-butyl 2-(2-iodophenyl)acetate **112**
- 4) Use of iodobenzene as a positive iodine source in the preparation of **102**, **110**, **111**, **112**.

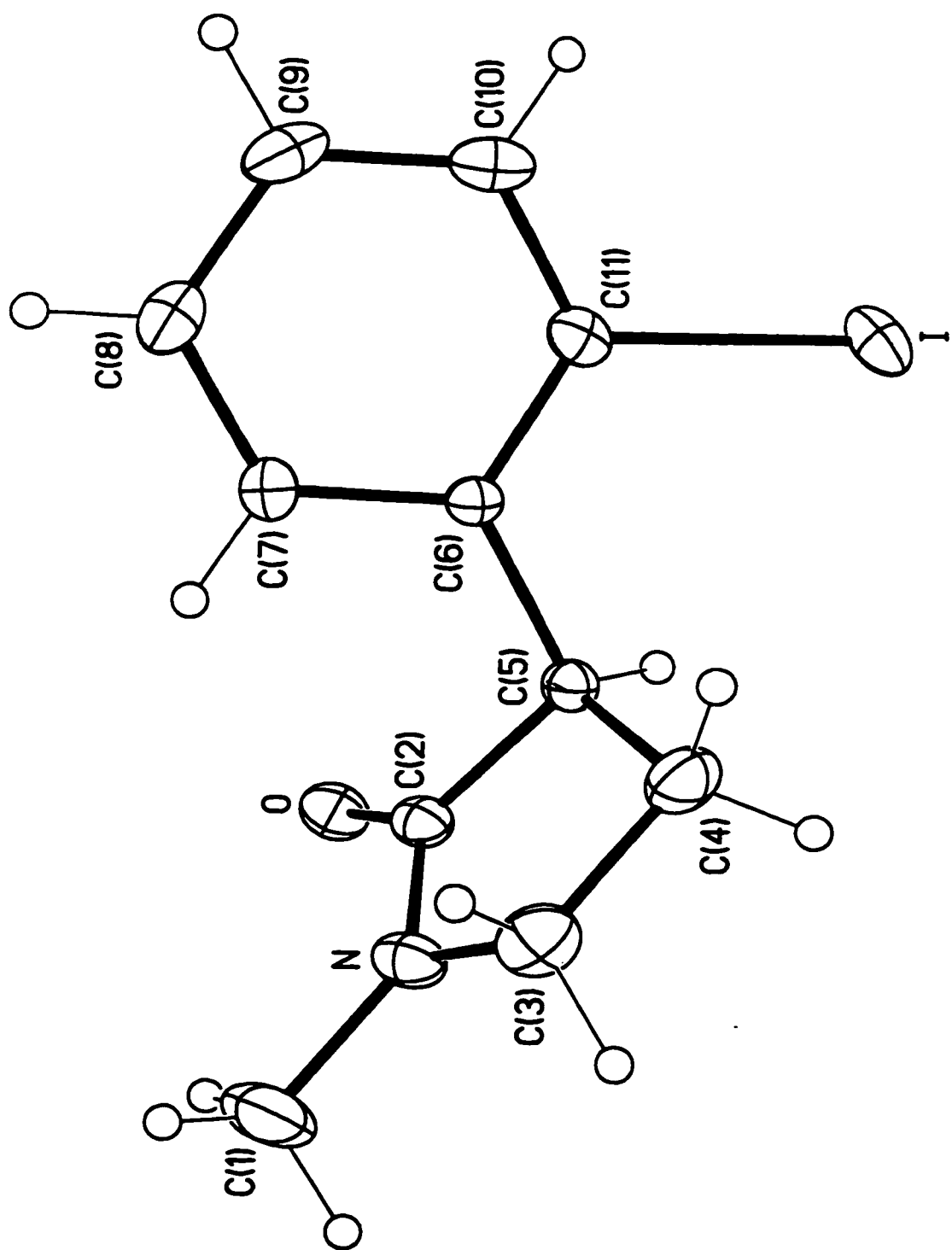


Table 1. Crystal data and structure refinement for td001.

Identification code	td001
Empirical formula	C11 H12 I N O
Formula weight	301.12
Temperature	203(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 7.6683(6) Å alpha = 90 deg. b = 8.7539(6) Å beta = 90 deg. c = 16.334(1) Å gamma = 90 deg.
Volume	1096.4(1) Å ³
Z, Calculated density	4, 1.824 Mg/m ³
Absorption coefficient	2.888 mm ⁻¹
F(000)	584
Crystal size	0.1 x 0.1 x 0.1 mm
Theta range for data collection	2.49 to 28.70 deg.
Limiting indices	-9<=h<=9, -11<=k<=8, -20<=l<=21
Reflections collected / unique	8470 / 2610 [R(int) = 0.0783]
Completeness to theta = 28.70	94.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.981276 and 0.584381
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2610 / 0 / 128
Goodness-of-fit on F ²	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.0562
R indices (all data)	R1 = 0.0489, wR2 = 0.0580
Absolute structure parameter	-0.05(3)
Extinction coefficient	0.0046(5)
Largest diff. peak and hole	0.661 and -0.851 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for td001. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
I	9764 (1)	9428 (1)	8668 (1)	41 (1)
O	3159 (3)	8291 (4)	9556 (2)	37 (1)
N	3766 (4)	9983 (4)	10584 (2)	37 (1)
C (1)	2085 (6)	9926 (6)	10997 (3)	59 (1)
C (2)	4140 (5)	9183 (4)	9907 (2)	29 (1)
C (3)	5128 (6)	10999 (5)	10843 (2)	45 (1)
C (4)	6724 (5)	10474 (6)	10368 (2)	44 (1)
C (5)	5978 (4)	9583 (5)	9636 (2)	28 (1)
C (6)	5979 (4)	10482 (4)	8838 (2)	25 (1)
C (7)	4501 (4)	11301 (4)	8584 (2)	31 (1)
C (8)	4494 (5)	12140 (5)	7872 (2)	39 (1)
C (9)	5947 (6)	12177 (5)	7377 (3)	43 (1)
C (10)	7427 (6)	11394 (5)	7614 (3)	40 (1)
C (11)	7438 (4)	10547 (5)	8332 (2)	30 (1)

Table 3. Bond lengths [Å] and angles [deg] for td001.

I-C(11)	2.108(4)
O-C(2)	1.227(5)
N-C(2)	1.339(5)
N-C(3)	1.436(5)
N-C(1)	1.455(5)
C(2)-C(5)	1.518(5)
C(3)-C(4)	1.520(6)
C(4)-C(5)	1.538(5)
C(5)-C(6)	1.522(5)
C(6)-C(7)	1.404(5)
C(6)-C(11)	1.393(5)
C(7)-C(8)	1.375(5)
C(8)-C(9)	1.377(6)
C(9)-C(10)	1.381(7)
C(10)-C(11)	1.388(6)
C(2)-N-C(3)	114.3(3)
C(2)-N-C(1)	123.6(4)
C(3)-N-C(1)	121.9(4)
O-C(2)-N	126.0(4)
O-C(2)-C(5)	125.4(3)
N-C(2)-C(5)	108.6(3)
N-C(3)-C(4)	104.4(3)
C(3)-C(4)-C(5)	104.5(3)
C(2)-C(5)-C(6)	111.7(3)
C(2)-C(5)-C(4)	103.6(3)
C(6)-C(5)-C(4)	113.8(4)
C(7)-C(6)-C(11)	116.8(3)
C(7)-C(6)-C(5)	121.1(3)
C(11)-C(6)-C(5)	122.0(3)
C(8)-C(7)-C(6)	121.8(3)
C(9)-C(8)-C(7)	120.4(4)
C(8)-C(9)-C(10)	119.3(4)
C(11)-C(10)-C(9)	120.4(4)
C(10)-C(11)-C(6)	121.3(4)
C(10)-C(11)-I	118.3(3)
C(6)-C(11)-I	120.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for td001.
The anisotropic displacement factor exponent takes the form:
 $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
I	26 (1)	38 (1)	58 (1)	-2 (1)	9 (1)	2 (1)
O	35 (1)	36 (2)	40 (2)	-1 (1)	6 (1)	-7 (1)
N	42 (2)	33 (2)	35 (2)	-2 (1)	10 (1)	4 (1)
C (1)	55 (3)	67 (3)	55 (3)	1 (3)	28 (2)	10 (2)
C (2)	33 (2)	27 (2)	28 (2)	6 (2)	6 (1)	4 (2)
C (3)	60 (3)	40 (2)	37 (2)	-7 (2)	-1 (2)	3 (2)
C (4)	47 (2)	57 (3)	30 (2)	-1 (2)	-6 (2)	-9 (2)
C (5)	28 (2)	30 (2)	27 (2)	0 (2)	1 (1)	0 (2)
C (6)	27 (1)	24 (2)	24 (2)	-1 (2)	1 (1)	-4 (2)
C (7)	26 (2)	32 (2)	34 (2)	-1 (2)	-3 (2)	-2 (1)
C (8)	40 (2)	36 (2)	41 (2)	4 (2)	-13 (2)	0 (2)
C (9)	59 (3)	40 (3)	31 (2)	9 (2)	-7 (2)	-12 (2)
C (10)	45 (2)	39 (2)	36 (2)	0 (2)	10 (2)	-11 (2)
C (11)	29 (2)	28 (2)	33 (2)	-5 (2)	0 (1)	-5 (2)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for td001.

	x	y	z	U(eq)
H(1A)	1341	9185	10727	88
H(1B)	1541	10925	10974	88
H(1C)	2253	9631	11563	88
H(3A)	5324	10917	11434	54
H(3B)	4837	12060	10709	54
H(4A)	7464	9815	10707	53
H(4B)	7414	11350	10181	53
H(5A)	6655	8630	9561	34
H(7A)	3489	11275	8908	37
H(8A)	3492	12693	7723	47
H(9A)	5931	12728	6883	52
H(10A)	8434	11436	7286	48

Table 6. Observed and calculated structure factors for td001

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	0	0	1585	1601	32	1	11	0	158	147	12	9	4	1	251	246	9	1	10	1	235	227	10	-1	4	2	247	237	6
4	0	0	1015	1030	21	2	11	0	139	104	21	-9	5	1	253	251	13	2	10	1	131	129	10	0	4	2	31	13	30
6	0	0	431	425	20	3	11	0	112	90	34	-8	5	1	147	140	11	3	10	1	217	212	18	1	4	2	259	248	6
8	0	0	226	221	12	1	0	1	861	841	17	-7	5	1	366	377	9	4	10	1	137	104	33	2	4	2	410	409	7
1	1	0	376	391	10	2	0	1	409	409	7	-6	5	1	212	211	7	5	10	1	169	154	19	3	4	2	243	238	7
3	1	0	396	419	43	3	0	1	1164	1147	19	-5	5	1	328	333	8	-3	11	1	0	125	1	4	4	2	642	643	11
4	1	0	471	459	8	4	0	1	552	547	9	-4	5	1	472	477	8	-2	11	1	133	145	65	5	4	2	137	136	8
5	1	0	102	88	9	5	0	1	683	669	13	-3	5	1	219	226	6	-1	11	1	135	127	13	6	4	2	539	546	10
6	1	0	779	774	14	6	0	1	498	492	10	-2	5	1	832	834	17	0	11	1	201	165	22	7	4	2	72	58	24
7	1	0	226	226	8	7	0	1	424	420	10	-1	5	1	187	193	7	1	11	1	134	123	13	8	4	2	404	407	10
8	1	0	492	496	12	8	0	1	427	426	10	0	5	1	670	671	16	2	11	1	162	148	12	9	4	2	73	56	29
9	1	0	146	139	10	9	0	1	103	83	19	1	5	1	184	190	7	3	11	1	143	125	21	-9	4	2	134	118	16
0	0	0	476	464	11	-9	1	1	149	149	11	2	5	1	852	838	15	0	0	2	229	312	201	-8	5	2	25	30	24
0	0	0	1988	2029	65	-8	1	1	454	460	10	3	5	1	211	211	6	1	0	2	612	601	9	-7	5	2	264	264	8
2	2	0	1487	1494	23	-7	1	1	379	381	9	4	5	1	479	483	8	2	0	0	205	209	13	-6	5	2	71	64	24
2	2	0	881	933	27	-6	1	1	629	633	12	5	5	1	319	330	8	5	0	0	525	520	9	-5	5	2	459	536	60
3	2	0	1143	1123	16	-5	1	1	719	701	12	6	5	1	212	207	7	4	0	0	404	377	7	-4	5	2	135	133	7
4	2	0	679	682	10	-4	1	1	491	484	8	7	5	1	379	381	11	5	0	0	716	712	12	-3	5	2	797	798	13
5	2	0	562	549	10	-3	1	1	1125	1082	18	8	5	1	149	140	11	6	0	2	118	92	11	-2	5	2	164	166	6
6	2	0	338	336	7	-2	1	1	345	390	36	9	5	1	255	251	20	7	0	0	429	435	10	-1	5	2	1049	1047	21
7	2	0	239	239	8	-1	1	1	347	350	6	-8	6	1	133	130	14	8	0	0	49	43	49	0	0	2	297	310	9
8	2	0	252	255	8	0	1	1	501	451	28	-7	6	1	204	202	9	9	0	0	458	466	12	-1	1	5	1065	1040	21
9	2	0	59	56	43	1	1	1	280	291	4	-6	6	1	266	314	34	-9	1	2	97	68	19	-8	1	5	151	157	7
1	2	0	171	169	5	2	1	1	352	374	22	-5	6	1	351	356	9	-8	1	2	211	210	9	-7	1	5	794	798	13
2	2	0	480	479	7	3	1	1	1105	1091	16	-4	6	1	467	469	9	-7	1	2	109	88	16	-6	1	5	120	131	14
3	2	0	348	378	23	4	1	1	475	473	8	-3	6	1	353	364	9	-6	1	2	406	399	9	-5	1	5	548	547	11
4	2	0	592	586	9	5	1	1	721	699	14	-2	6	1	397	481	64	-4	1	2	238	233	6	6	6	2	79	60	21
5	2	0	332	338	7	6	1	1	632	632	13	0	6	1	361	368	10	-3	1	2	985	964	16	-2	1	5	259	262	9
6	2	0	590	600	10	7	1	1	383	389	9	1	6	1	476	495	12	-1	1	2	476	552	69	8	5	2	41	33	41
7	2	0	356	357	9	8	1	1	449	455	10	2	6	1	357	358	10	-2	1	2	673	1581	672	-9	5	2	146	117	34
8	2	0	379	443	43	9	1	1	151	153	10	3	6	1	495	491	11	-1	1	2	764	741	12	-8	6	2	279	279	12
9	2	0	151	156	10	-9	2	1	239	238	10	4	6	1	366	366	9	-7	1	2	1848	1814	50	-6	6	2	236	239	9
0	2	0	262	263	12	-8	2	1	309	306	9	5	6	1	469	463	11	-5	1	2	713	721	9	-4	6	2	372	375	12
1	2	0	1259	1277	25	-7	2	1	339	342	9	6	6	1	320	351	13	-6	1	2	1501	1569	29	-5	6	2	226	270	36
2	2	0	138	131	5	-6	2	1	477	476	10	7	6	1	312	315	9	-4	1	2	573	559	8	-3	6	2	360	363	8
3	2	0	842	844	12	-5	2	1	511	535	13	-2	6	1	203	200	12	-2	1	2	990	970	13	-1	6	2	189	188	8
4	2	0	90	68	12	-4	2	1	595	606	10	8	6	1	125	132	15	-1	1	2	233	227	6	0	6	2	258	262	8
5	2	0	821	822	13	-3	2	1	831	829	13	-8	7	1	214	215	18	-2	1	2	393	387	9	-1	6	2	219	216	9
6	2	0	56	39	32	-2	2	1	645	872	164	-7	7	1	178	200	27	0	0	2	107	95	16	0	6	2	130	126	12
7	2	0	354	357	9	-1	2	1	1258	1271	18	-6	7	1	275	284	9	-9	1	2	208	203	8	-8	6	2	224	221	9
8	2	0	89	71	20	-5	2	1	417	427	7	-4	7	1	249	257	9	-9	1	2	97	64	19	-7	6	2	274	269	8
9	2	0	109	83	18	-4	2	1	1276	1295	18	-3	7	1	305	309	9	-8	2	2	320	322	9	-6	6	2	197	194	8
0	2	0	208	197	7	-3	2	1	842	850	12	-2	7	1	323	331	8	-7	2	2	292	293	9	-5	6	2	371	366	10
1	2	0	397	388	8	-2	2	1	842	825	12	-1	7	1	302	318	16	-6	2	2	365	376	9	-4	6	2	248	261	9
2	2	0	26	9	25	-1	2	1	623	619	9	-6	7	1	375	378	11	-5	2	2	412	408	9	-3	6	2	369	370	10
3	2	0	575	578	10	0	2	1	540	531	9	-2	7	1	390	387	11	0	0	2	544	553	9	-1	6	2	233	236	12
4	2	0	125	121	10	6	2	1	470	459	9	1	7	1	390	383	11	-4	2	2	404	407	7	-8	6	2	283	281	13
5	2	0	465	469	10	7	2	1	339	344	9	-3	7	1	315	313	8	-2	2	2	538	539	9	-7	6	2	132	114	30
6	2	0	161	163	8	8	2	1	309	309	9	-2	7	1	332	331	9	-1	2	2	296	294	6	-6	6	2	140	149	16
7	2	0	387	400	11	-9	2	1	235	232	9	5	7	1	310	306	11	0	0	2	814	813	13	-5	7	2	153	170	36
8	2	0	152	119	34	-8	2	1	256	254	9	-7	8	1	255	261	9	-6	2	2	689	673	12	-4	7	2	212	214	8
9	2	0	481	478	18	-6	2	1	181	184	13	-5	8	1	254	279	50	-3	2	2	823	814	12	-2	7	2	393	394	10
0	2	0	792	802	19	-2	2	1	441	444	11	-1	8	1	209	203	9	3	2	2	283	276	5	0	7	2	403	415	9
1	2	0	680	665	14	-5	2	1	305	311	7	6	8	1	120	108	16	-4	2	2	556	548	8	-3	7	2	494	500	11
2	2	0	561	554	12	-2	2	1	596	601	9	-2	8	1	237	239	11	-1	2	2	421	431	16	-2	7	2	443	453	12
3	2	0	354	352	8	-1	2	1	445	453	7	0	8	1	260	261	11	0	0	2	565	558	10	0	7	2	656	685	16
4	2	0	385	394	10	-4	2	1	670	646	10	-3	8	1	147	145	11	-1	1	2	420	419	9	-1	7	2	431	447	12
5	2	0	105	115	11	-2	2	1	635	844	122	0	8	1	375	391	12	0	0	2	388	389	11	2	7	2	539	500	

Table 6. Observed and calculated structure factors for td001

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
3	9	2	36	38	35	-7	4	3	402	452	30	-1	9	3	382	397	11	9	3	4	216	209	9	-4	9	4	112	90	40
4	9	2	330	311	12	-6	4	3	286	315	11	0	9	3	15	35	15	-9	4	4	125	146	34	-3	9	4	172	176	10
5	9	2	99	76	28	-5	4	3	390	396	7	0	9	3	400	404	14	-8	4	4	136	137	8	-2	9	4	50	30	50
-6	9	2	169	157	12	-4	4	3	501	504	8	2	9	3	110	70	22	-7	4	4	233	227	7	-1	9	4	116	119	12
-4	10	2	126	116	49	-3	4	3	406	407	7	3	9	3	309	303	12	-6	4	4	179	183	7	0	9	4	39	10	39
-3	10	2	138	138	9	-2	4	3	735	741	11	4	9	3	88	58	32	-5	4	4	435	436	7	1	9	4	118	118	12
-2	10	2	113	95	13	-1	4	3	245	243	6	5	9	3	226	220	11	-4	4	4	192	186	6	2	9	4	42	38	41
-1	10	2	116	70	30	0	4	3	531	549	9	6	9	3	149	139	17	-3	4	4	964	970	14	3	9	4	174	174	11
0	10	2	90	50	44	1	4	3	232	227	6	-4	10	3	136	137	18	-2	4	4	307	306	5	4	9	4	132	94	21
1	10	2	135	71	27	2	4	3	746	739	12	-3	10	3	163	160	11	-1	4	4	1384	1412	24	5	9	4	232	234	11
2	10	2	148	91	16	3	4	3	421	416	7	-2	10	3	129	124	10	0	4	4	137	137	6	6	9	4	57	86	57
3	10	2	153	142	12	4	4	3	505	506	9	-1	10	3	111	103	13	1	4	4	1469	1427	24	-4	10	4	209	182	15
4	10	2	118	118	15	5	4	3	399	405	8	0	10	3	158	92	23	-3	10	4	326	322	6	-3	10	4	123	105	37
-3	11	2	177	167	15	6	4	3	317	316	8	1	10	3	124	111	12	5	4	4	992	981	14	-2	10	4	314	309	11
-2	11	2	210	204	11	7	4	3	440	452	10	2	10	3	153	120	16	-1	10	4	182	179	6	-1	10	4	194	186	11
-1	11	2	203	197	9	8	4	3	149	153	9	3	10	3	169	162	12	5	4	4	436	433	8	0	10	4	331	329	11
0	11	2	301	293	11	-9	4	3	305	298	9	4	10	3	160	136	13	6	4	4	187	189	8	1	10	4	200	180	11
1	11	2	211	202	11	-8	5	3	156	154	14	-3	11	3	139	132	19	7	4	4	225	221	8	2	10	4	322	307	12
2	11	2	218	201	18	-7	5	3	108	109	20	-2	11	3	177	171	16	8	4	4	128	133	10	3	10	4	124	111	15
3	11	2	1313	1284	18	-6	5	3	253	282	26	0	11	3	128	105	45	9	4	4	150	146	12	4	10	4	209	187	12
4	11	2	379	371	6	-5	5	3	413	427	9	1	11	3	161	134	12	-9	5	4	52	38	52	-2	11	4	75	51	75
5	11	2	936	1048	68	-4	5	3	175	174	6	1	11	3	160	108	14	-8	5	4	336	334	9	-1	11	4	0	23	1
6	11	2	757	727	11	-3	5	3	590	596	10	2	0	4	170	157	4	-7	5	4	53	56	52	0	11	4	77	45	76
7	11	2	481	467	9	-2	5	3	309	303	6	3	0	4	1609	1586	23	-6	5	4	433	454	9	1	11	4	61	18	60
8	11	2	616	618	11	-1	5	3	740	738	13	4	0	4	390	358	6	-5	5	4	130	129	7	2	0	5	1338	1311	19
9	11	2	331	337	9	0	5	3	176	182	7	5	0	4	1165	1138	17	-4	5	4	467	476	8	3	0	5	900	895	13
-9	0	0	512	521	11	1	5	3	790	807	19	6	0	4	185	187	6	-3	5	4	219	218	6	4	0	5	150	150	7
-8	0	0	116	91	16	2	5	3	186	184	6	7	0	4	560	562	10	-2	5	4	349	351	7	5	0	5	588	596	10
-7	1	1	148	142	10	3	5	3	749	733	12	8	0	4	238	240	8	-1	5	4	241	236	6	6	0	5	212	229	21
-6	1	1	345	348	8	4	5	3	301	298	6	9	1	4	119	113	13	1	5	4	253	234	9	7	0	5	212	209	7
-5	1	1	267	264	9	5	5	3	592	584	11	0	1	4	380	382	10	2	5	4	360	352	7	8	0	5	279	278	8
-4	1	1	562	556	10	6	5	3	178	177	7	-9	1	4	196	199	9	3	5	4	211	215	6	9	0	5	101	75	19
-3	1	1	586	583	10	7	5	3	426	432	9	0	1	4	494	492	11	4	5	4	469	470	9	-9	1	5	140	134	10
-2	1	1	307	307	24	8	5	3	280	284	10	-8	1	4	196	199	9	5	5	4	127	124	8	-8	1	5	402	401	10
-1	1	1	719	717	12	9	5	3	106	99	19	-5	1	4	211	219	11	6	5	4	436	449	11	-7	1	5	256	245	10
0	1	1	420	425	7	0	5	3	176	155	21	-4	1	4	637	633	11	7	5	4	62	58	35	-6	1	5	475	468	9
1	1	1	918	1524	477	-7	6	3	167	192	24	-3	1	4	703	685	11	8	5	4	338	334	11	-5	1	5	477	473	9
2	1	1	75	58	16	-6	6	3	289	333	34	-2	1	4	151	150	5	-8	6	4	83	39	82	-4	1	5	757	748	12
3	1	1	771	1516	692	-5	6	3	267	273	9	1	1	4	483	483	8	-7	6	4	126	96	25	-3	1	5	425	432	7
4	1	1	387	424	32	-4	6	3	318	327	7	0	1	4	804	839	20	-6	6	4	202	192	9	-2	1	5	449	447	8
5	1	1	710	710	10	-3	6	3	263	262	7	-6	6	4	480	467	8	-5	6	4	217	217	9	-1	1	5	748	762	11
6	1	1	280	292	5	-2	6	3	300	316	8	2	1	4	166	167	5	-4	6	4	334	330	8	0	1	5	137	139	6
7	1	1	580	576	9	-1	6	3	510	503	11	3	1	4	577	690	76	-3	6	4	338	347	8	1	1	5	792	781	12
8	1	1	555	557	11	0	6	3	340	341	10	4	1	4	381	372	6	-2	6	4	505	509	11	2	1	5	442	435	7
9	1	1	272	273	8	1	6	3	483	484	12	5	1	4	624	622	11	-1	6	4	361	379	9	3	1	5	435	439	7
-9	0	0	346	345	9	2	6	3	337	348	10	6	1	4	231	223	7	0	6	4	629	631	15	4	1	5	765	750	11
-8	0	0	152	142	10	3	6	3	507	502	11	7	1	4	488	496	11	1	6	4	477	475	17	5	1	5	413	474	45
-7	0	0	206	209	9	4	6	3	327	319	8	8	1	4	204	205	9	2	6	4	679	634	53	6	1	5	468	469	9
-6	0	0	373	367	11	5	6	3	250	255	10	9	1	4	379	387	10	3	6	4	387	376	9	7	1	5	254	253	8
-5	0	0	470	475	9	6	6	3	329	341	9	0	2	4	125	124	12	4	6	4	536	516	15	8	1	5	396	401	10
-4	0	0	486	574	68	7	6	3	323	329	12	-8	2	4	187	191	9	5	6	4	270	350	165	9	2	5	132	134	11
-3	0	0	518	546	17	8	6	3	200	200	12	-7	2	4	201	228	20	6	6	4	328	331	9	-9	2	5	133	142	11
-2	0	0	690	671	11	-7	7	3	145	154	25	-5	2	4	346	346	7	0	6	4	227	221	9	-8	2	5	246	251	8
-1	0	0	489	489	8	-6	7	3	129	128	11	-4	2	4	496	495	9	-7	7	4	189	185	12	-6	2	5	237	243	8
0	0	0	556	556	9	-5	7	3	189	185	9	-3	2	4	767	770	14	-2	7	4	128	100	21	-5	2	5	285	286	7
1	0	0	1221	1245	25	-4	7	3	215	212	8	-2	2	4	770	765	12	-8	7	4	176	112	35	-4	2	5	445	449	8
2	0	0	423	573	92	-3	7	3	289	290	8	-1	2	4	945	939	15	-6	7	4	237	244	11	-3	2	5	473	558	65
3	0	0	500	496	7	-2	7	3	399	405	9	0	2	4	1349	1352	19	-5	7	4	148	151	9	-2	2	5	911	910	15
4	0	0	701	686	10																								

Table 6. Observed and calculated structure factors for td001

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
7	3	5	464	467	12	-2	9	5	70	36	69	-9	4	6	68	53	68	2	9	6	394	372	13	-1	4	7	99	93	7
8	3	5	230	229	9	-1	0	9	219	215	10	-8	4	6	331	332	9	3	9	6	67	43	67	0	4	7	437	439	8
-9	3	5	317	316	9	0	1	9	0	0	1	-7	4	6	104	87	16	4	9	6	307	288	12	-1	4	7	106	107	9
-9	4	4	176	178	11	1	2	9	222	216	10	-6	4	6	424	422	8	5	9	6	122	118	14	2	4	7	319	306	6
-8	4	4	86	67	18	2	1	9	60	46	59	-5	4	6	221	215	6	4	10	6	119	113	19	3	4	7	409	398	9
-7	4	4	214	225	15	3	3	9	196	186	11	-4	4	6	342	340	7	-3	10	6	157	92	23	4	4	7	447	446	8
-6	4	4	445	452	8	4	3	9	211	197	12	-3	4	6	197	203	6	-2	10	6	125	81	28	5	4	7	405	406	9
-5	4	4	288	287	7	5	5	9	156	142	12	-2	4	6	462	459	8	-1	10	6	80	49	56	6	4	7	232	233	8
-4	4	4	613	622	10	6	6	9	193	193	15	0	4	6	231	238	5	0	10	6	140	146	12	7	4	7	420	428	10
-3	4	4	333	329	7	-4	10	5	161	91	34	1	4	6	70	39	25	1	10	6	65	51	65	8	4	7	132	130	10
-2	4	4	827	842	13	-3	10	5	221	219	10	2	4	6	241	243	7	2	10	6	110	88	28	9	4	7	301	309	20
-1	4	4	227	227	6	-2	10	5	157	156	11	3	4	6	413	452	31	3	10	6	142	94	26	-8	5	7	96	74	26
0	4	4	710	735	13	-1	10	5	270	267	24	4	4	6	200	202	7	-1	11	6	171	172	17	-7	5	7	124	115	12
1	4	4	239	227	7	0	10	5	147	84	24	5	4	6	363	357	7	0	11	6	192	182	16	-6	5	7	292	299	8
2	4	4	771	838	44	1	10	5	278	262	11	6	4	6	228	222	6	1	0	7	490	493	8	-5	5	7	235	236	8
3	4	4	346	339	7	2	10	5	165	156	12	7	4	6	431	426	10	2	0	7	240	239	5	-4	5	7	465	467	11
4	4	4	621	623	10	3	10	5	220	212	11	8	4	6	111	88	15	3	0	7	539	535	8	-3	5	7	181	177	7
5	4	4	288	284	7	4	10	5	146	91	37	9	4	6	342	337	9	4	0	7	572	563	10	-2	5	7	741	763	13
6	4	4	435	448	10	-1	11	5	136	77	43	0	5	6	50	52	50	5	0	7	344	343	7	-1	5	7	91	66	18
7	4	4	223	221	8	0	11	5	175	87	35	-8	5	6	128	134	15	6	0	7	576	580	10	0	5	7	766	799	13
8	4	4	91	69	19	1	11	5	116	113	7	-7	5	6	232	231	9	7	0	7	184	182	7	-1	5	7	84	52	30
9	4	4	174	173	15	2	11	5	531	504	10	-6	5	6	226	229	7	8	0	7	435	439	10	2	5	7	780	762	12
-8	5	5	147	148	11	3	11	5	381	376	6	-5	5	6	324	325	7	9	0	7	113	84	17	3	5	7	165	161	9
-7	5	5	357	366	9	4	11	5	413	413	6	-4	5	6	226	233	6	-9	0	7	114	88	17	4	5	7	467	469	9
-6	5	5	328	333	8	5	11	5	255	246	6	-3	5	6	622	636	10	-8	1	7	151	145	9	5	5	7	235	236	9
-5	5	5	342	351	7	6	11	5	534	534	9	-2	5	6	218	217	6	-7	1	7	332	337	7	6	5	7	291	297	10
-4	5	5	405	406	7	7	11	5	36	24	35	-1	5	6	877	882	15	-6	1	7	200	200	7	7	5	7	115	109	15
-3	5	5	348	352	7	8	11	5	589	587	10	0	5	6	295	255	6	-5	1	7	545	544	9	8	5	7	86	66	24
-2	5	5	367	372	7	9	11	5	28	33	27	-4	5	6	895	874	15	-3	1	7	358	354	7	-8	6	7	165	170	12
-1	5	5	184	176	6	0	11	5	324	319	9	3	5	6	227	216	15	-2	1	7	796	807	13	-7	6	7	252	251	11
0	5	5	443	450	10	-9	11	5	139	150	16	4	5	6	633	632	12	-1	1	7	456	461	7	-6	6	7	188	189	8
1	5	5	204	192	6	-8	11	5	201	210	8	5	5	6	242	240	7	0	1	7	1029	1051	16	-5	6	7	173	175	8
2	5	5	383	363	7	-7	11	5	208	196	7	6	5	6	332	320	8	-4	0	7	421	425	10	-4	6	7	355	369	9
3	5	5	348	345	9	-6	11	5	477	483	9	7	5	6	219	228	9	-3	1	7	1059	1053	16	-3	6	7	212	221	9
4	5	5	406	399	8	-5	11	5	275	279	7	8	5	6	233	230	9	-2	1	7	461	457	7	-2	6	7	206	215	9
5	5	5	335	338	8	-4	11	5	647	664	11	-3	5	6	129	126	12	-1	1	7	810	814	12	-1	6	7	189	187	10
6	5	5	323	338	10	-3	11	5	168	170	6	0	5	6	200	201	12	0	1	7	355	354	7	0	6	7	121	118	12
7	5	5	365	367	11	-2	11	5	1210	1203	17	-7	6	6	146	145	12	5	1	7	545	549	10	1	6	7	200	197	9
8	5	5	146	154	11	-1	11	5	682	683	10	-6	6	6	284	280	11	6	1	7	200	200	7	2	6	7	242	229	10
-8	6	6	129	120	20	0	11	5	1174	1356	101	-5	6	6	252	250	8	7	1	7	328	332	7	3	6	7	207	230	65
-7	6	6	178	176	12	1	11	5	689	677	11	-4	6	6	353	353	9	8	1	7	127	143	19	4	6	7	361	361	12
-6	6	6	282	289	11	2	11	5	1220	1198	17	-3	6	6	289	311	10	9	1	7	117	89	17	5	6	7	193	182	10
-5	6	6	126	122	8	3	11	5	178	181	5	-2	6	6	327	342	8	-9	2	7	268	265	11	6	6	7	195	187	12
-4	6	6	373	383	8	4	11	5	658	661	11	-1	6	6	142	139	11	-8	2	7	327	330	9	7	6	7	261	250	12
-3	6	6	341	341	9	5	11	5	282	285	7	0	6	6	230	232	9	-6	2	7	384	385	8	-7	7	7	109	117	22
-2	6	6	676	694	14	6	11	5	482	480	10	1	6	6	362	353	9	-5	2	7	471	479	9	-6	7	7	181	181	16
-1	6	6	403	409	11	7	11	5	201	195	7	2	6	6	335	305	23	-4	2	7	527	527	9	-5	7	7	277	276	14
0	6	6	502	517	13	8	11	5	208	210	9	3	6	6	368	357	12	-3	2	7	449	543	68	-4	7	7	221	215	10
1	6	6	399	403	11	-9	11	5	157	149	10	4	6	6	262	256	10	-2	2	7	457	519	32	-3	7	7	409	427	12
2	6	6	793	702	56	-8	11	5	262	263	9	-7	6	6	283	287	12	-1	2	7	334	342	8	-2	7	7	291	304	10
3	6	6	326	328	15	7	11	5	252	251	8	0	6	6	151	150	13	0	2	7	92	57	10	-1	7	7	396	411	11
4	6	6	407	395	16	-6	11	5	357	355	9	-7	6	6	140	143	13	1	2	7	336	343	6	0	7	7	232	236	10
5	6	6	140	130	9	-5	11	5	283	282	7	-6	6	6	227	225	11	2	2	7	496	522	20	1	7	7	403	411	11
6	6	6	291	289	12	-4	11	5	433	432	8	-5	6	6	230	228	8	3	2	7	526	529	8	2	7	7	332	315	11
7	6	6	185	176	12	-3	11	5	191	208	11	-4	6	6	335	349	11	4	2	7	543	533	8	3	7	7	417	415	13
-7	7	7	224	222	11	-2	11	5	346	340	6	-3	6	6	211	208	10	5	2	7	378	382	7	4	7	7	219	219	11
-6	7	7	252	254	11	-1	11	5	90	90	6	-2	6	6	341	348	10	6	2	7	471	479	12	5	7	7	284	276	11
-5	7	7	174	165	8	0	11	5	402	403	9	-1	6	6	401	418	11	-6	2	7	394	389	9	6	7	7	169	178	18

Table 6. Observed and calculated structure factors for td001

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	10	7	139	102	23	8	4	8	160	157	10	-5	1	9	322	321	8	-6	6	9	189	189	17	-3	2	10	398	401	10
3	10	7	180	84	35	-8	5	8	227	228	10	-4	1	9	396	393	8	-5	6	9	173	177	14	-2	2	10	341	333	9
0	11	7	148	145	18	-7	5	8	123	99	19	-3	1	9	176	174	6	-4	6	9	335	342	25	-1	2	10	288	286	7
0	0	8	1116	1120	23	-6	5	8	301	305	9	-2	1	9	308	313	5	-3	6	9	199	200	9	0	2	10	311	315	7
1	0	8	79	53	15	-5	5	8	216	222	8	-1	1	9	343	346	6	-2	6	9	459	477	12	1	2	10	291	284	6
2	0	8	1071	1058	15	-4	5	8	374	383	12	0	1	9	57	6	34	-1	6	9	274	277	10	2	2	10	335	335	6
3	0	8	349	349	6	-3	5	8	191	206	10	1	1	9	337	335	6	0	6	9	608	624	15	3	2	10	415	405	7
4	0	8	715	705	12	-2	5	8	359	360	8	2	1	9	317	317	5	1	6	9	282	285	9	4	2	10	250	245	7
5	0	8	329	330	7	-1	5	8	194	200	6	3	1	9	188	185	5	2	6	9	459	463	13	5	2	10	269	272	7
6	0	8	264	262	7	0	5	8	119	83	17	4	1	9	391	390	8	3	6	9	203	191	10	6	2	10	211	212	7
7	0	8	139	139	8	1	5	8	214	216	8	5	1	9	314	315	7	4	6	9	351	346	11	7	2	10	209	214	8
8	0	8	171	167	9	2	5	8	329	355	28	6	1	9	445	447	8	5	6	9	185	182	17	8	2	10	184	176	11
9	0	8	216	203	11	3	5	8	222	223	7	7	1	9	230	229	7	6	6	9	187	187	18	-8	3	10	217	206	13
-9	1	8	294	290	11	4	5	8	397	380	9	8	1	9	391	393	10	7	6	9	111	87	37	-7	3	10	192	176	24
-8	1	8	103	79	21	5	5	8	222	225	11	9	1	9	152	155	21	-6	7	9	203	198	10	-6	3	10	288	352	49
-7	1	8	352	348	8	6	5	8	308	305	10	-9	2	9	95	82	50	-5	7	9	185	182	10	-5	3	10	125	96	16
-6	1	8	128	126	8	7	5	8	108	100	14	-8	2	9	103	85	21	-4	7	9	178	177	10	-4	3	10	530	543	14
-5	1	8	331	328	7	8	5	8	231	228	13	-7	2	9	213	212	8	-3	7	9	175	181	13	-3	3	10	347	363	8
-4	1	8	402	396	8	-7	6	8	187	190	16	-6	2	9	241	247	7	-2	7	9	109	78	28	-2	3	10	648	634	14
-3	1	8	470	464	8	-6	6	8	218	217	20	-5	2	9	424	443	9	-1	7	9	134	74	22	-1	3	10	284	283	8
-2	1	8	433	430	6	-5	6	8	251	249	10	-4	2	9	259	262	7	0	7	9	6	15	5	0	3	10	593	627	22
-1	1	8	221	217	5	-4	6	8	218	217	10	-3	2	9	421	432	9	1	7	9	119	65	42	1	3	10	321	348	12
0	1	8	730	724	15	-3	6	8	377	381	11	-2	2	9	449	453	8	2	7	9	122	81	21	2	3	10	559	552	12
1	1	8	230	226	5	-2	6	8	312	335	10	-1	2	9	641	659	12	3	7	9	179	179	11	3	3	10	94	88	20
2	1	8	431	426	7	-1	6	8	512	532	13	0	2	9	580	577	11	4	7	9	168	164	11	4	3	10	343	350	8
3	1	8	471	456	7	0	6	8	426	441	12	1	2	9	657	653	11	5	7	9	180	184	18	5	3	10	222	220	8
4	1	8	404	392	8	1	6	8	522	540	13	2	2	9	445	440	7	6	7	9	203	196	18	6	3	10	264	262	8
5	1	8	328	329	7	2	6	8	339	339	11	3	2	9	441	443	7	-6	8	9	141	90	40	7	3	10	216	206	9
6	1	8	125	121	8	3	6	8	344	373	24	4	3	9	250	253	6	-5	8	9	195	201	10	8	4	10	207	222	20
7	1	8	349	346	8	4	6	8	212	203	10	5	3	9	449	448	8	-4	8	9	115	80	28	-7	4	10	49	33	48
8	1	8	109	81	16	5	6	8	272	256	17	6	3	9	246	249	7	-3	8	9	317	331	11	-6	4	10	263	261	9
9	1	8	288	287	9	6	6	8	214	212	17	7	2	9	208	206	8	-2	8	9	114	123	12	-5	4	10	195	197	9
-9	2	8	166	150	14	7	6	8	196	193	12	8	2	9	111	89	14	-1	8	9	361	372	11	-4	4	10	372	370	10
-8	2	8	150	142	11	-6	7	8	161	106	22	9	3	9	102	77	39	0	8	9	150	152	10	-3	4	10	198	201	8
-7	2	8	186	180	8	-5	7	8	209	214	10	-9	3	9	256	244	19	1	8	9	361	373	16	-2	4	10	211	210	8
-6	2	8	333	331	8	-4	7	8	169	179	10	-8	3	9	177	172	11	2	8	9	111	120	14	-1	4	10	339	351	7
-5	2	8	394	397	8	-3	7	8	230	240	10	-7	3	9	362	366	9	3	8	9	336	325	12	0	4	10	47	44	47
-4	2	8	547	544	9	-2	7	8	125	130	11	-6	3	9	195	219	25	4	8	9	101	77	27	1	4	10	311	347	26
-3	2	8	452	454	8	-1	7	8	47	33	47	-5	3	9	370	373	8	5	8	9	209	198	19	2	4	10	222	214	7
-2	2	8	626	718	47	0	7	8	164	164	10	-4	3	9	315	318	8	-5	9	9	151	125	17	3	4	10	208	207	7
-1	2	8	524	699	119	1	7	8	24	41	24	-3	3	9	380	384	8	-4	9	9	120	120	12	4	4	10	372	360	10
0	2	8	626	684	25	2	7	8	135	133	12	-2	3	9	223	224	8	-3	9	9	110	109	13	5	4	10	194	195	9
1	2	8	714	702	11	3	7	8	235	239	11	-1	3	9	227	227	8	-2	9	9	125	103	38	6	4	10	273	262	8
2	2	8	725	718	11	4	7	8	192	182	11	0	3	9	325	317	7	-1	9	9	131	73	24	7	4	10	40	33	40
3	2	8	459	460	7	5	7	8	222	212	17	1	3	9	237	229	7	0	9	9	123	68	27	8	4	10	209	229	27
4	2	8	541	539	9	6	7	8	123	111	29	2	3	9	236	229	7	1	9	9	136	71	37	-7	5	10	194	186	12
5	2	8	403	398	8	-5	8	8	171	184	10	3	3	9	388	387	8	2	9	9	111	103	15	-6	5	10	200	208	11
6	2	8	334	334	8	-4	8	8	198	187	10	4	3	9	307	322	12	3	9	9	137	101	24	-5	5	10	294	303	13
7	2	8	185	184	8	-3	8	8	112	95	28	5	3	9	336	375	45	4	9	9	115	115	15	-4	5	10	210	215	11
8	2	8	131	147	18	-2	8	8	405	413	12	6	3	9	222	221	9	-2	10	9	163	91	32	-3	5	10	443	446	15
9	2	8	146	148	12	-1	8	8	166	168	10	7	3	9	369	365	8	1	10	9	210	211	11	-2	5	10	167	165	8
-9	3	8	150	147	14	0	8	8	379	390	11	8	3	9	157	170	19	0	10	9	152	145	17	-1	5	10	479	488	9
-8	3	8	248	247	10	1	8	8	169	168	10	-8	4	9	112	105	15	1	10	9	221	209	11	0	5	10	156	157	8
-7	3	8	155	164	12	2	8	8	439	423	13	-7	4	9	99	77	18	0	0	10	747	723	19	1	5	10	501	492	11
-6	3	8	294	317	18	3	8	8	101	94	15	-6	4	9	222	218	7	2	0	10	83	50	15	2	5	10	183	171	7
-5	3	8	275	276	7	4	8	8	185	198	44	-5	4	9	176	173	9	3	0	10	252	251	6	3	5	10	439	445	9
-4	3	8	402	406	9	5	8	8	204	188	16	-4	4	9	421	421	10	4	0	10	246	240	7	4	5	10	217	217	9
-3	3	8	507	498	10	-5	9	8	164	149	16	-3	4	9	171	177	9	5	0	10	220	219	7	5	5	10	294	294	12
-2	3	8	296	294	7																								

Table 6. Observed and calculated structure factors for td001

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
-5	8	10	139	142	12	0	4	11	200	194	9	1	1	12	175	175	7	-3	7	12	137	141	11	-1	4	13	140	141	8
-4	8	10	126	119	12	1	4	11	162	180	33	2	1	12	260	259	7	-2	7	12	154	165	10	0	4	13	448	449	11
-3	8	10	205	206	16	2	4	11	114	106	9	3	1	12	355	351	9	-1	7	12	111	123	12	1	4	13	132	138	9
-2	8	10	135	90	23	3	4	11	223	217	7	4	1	12	383	383	9	0	7	12	89	84	20	2	4	13	422	415	9
-1	8	10	51	33	51	4	4	11	166	156	10	5	1	12	172	167	8	1	7	12	118	118	12	3	4	13	24	32	24
0	8	10	137	134	11	5	4	11	332	328	10	6	1	12	161	156	8	2	7	12	181	170	11	4	4	13	367	359	11
1	8	10	50	35	50	6	4	11	120	92	14	7	1	12	197	196	8	3	7	12	140	138	12	5	4	13	42	42	42
2	8	10	131	93	21	7	4	11	265	258	9	8	1	12	142	95	19	4	7	12	98	78	37	6	4	13	174	167	11
3	8	10	211	207	11	8	4	11	110	80	48	-8	2	12	177	169	13	5	7	12	138	123	22	7	4	13	22	34	22
4	8	10	119	119	14	-7	5	11	86	48	44	-7	2	12	196	194	10	-4	8	12	143	145	11	-7	5	13	171	180	21
5	8	10	163	149	20	-6	5	11	119	121	14	-6	2	12	218	212	9	-3	8	12	130	98	26	-6	5	13	104	71	31
-4	9	10	130	126	18	-5	5	11	111	97	16	-5	2	12	199	193	9	-2	8	12	220	223	17	-5	5	13	217	213	11
-3	9	10	99	81	35	-4	5	11	369	390	12	-4	2	12	181	181	9	-1	8	12	61	44	61	-4	5	13	103	78	27
-2	9	10	239	237	10	-3	5	11	90	53	31	-3	2	12	376	385	10	0	8	12	267	262	15	-3	5	13	152	153	11
-1	9	10	58	32	58	-2	5	11	498	507	11	-2	2	12	398	405	9	1	8	12	70	40	45	-2	5	13	86	67	24
0	9	10	234	228	15	-1	5	11	203	198	7	-1	2	12	361	357	8	2	8	12	231	219	11	-1	5	13	143	149	8
1	9	10	44	31	44	0	5	11	525	534	10	0	2	12	351	406	45	3	8	12	90	95	34	0	5	13	106	83	18
2	9	10	247	238	11	1	5	11	199	200	8	1	2	12	363	354	9	4	8	12	159	142	20	1	5	13	156	153	9
3	9	10	99	82	31	2	5	11	525	514	10	2	2	12	399	398	7	-2	9	12	164	107	33	2	5	13	91	66	17
4	9	10	115	130	20	3	5	11	79	51	22	3	2	12	394	380	8	-1	9	12	65	29	65	3	5	13	157	151	10
-1	10	10	91	53	90	4	5	11	411	392	11	4	2	12	176	174	8	0	9	12	132	140	17	4	5	13	98	72	21
2	0	11	58	15	45	5	5	11	107	98	15	5	2	12	189	188	8	1	0	12	54	29	54	5	5	13	224	211	12
3	0	11	300	310	7	6	5	11	123	123	14	6	2	12	213	212	8	2	9	12	151	109	21	6	5	13	102	70	27
4	0	11	162	164	8	7	5	11	62	50	61	7	2	12	194	191	10	3	9	12	158	154	16	-6	6	13	129	118	18
5	0	11	317	320	8	-7	6	11	122	130	19	8	2	12	173	167	14	1	0	13	583	596	11	-5	6	13	141	82	39
6	0	11	252	256	8	-5	6	11	160	159	11	-8	3	12	201	192	12	2	0	13	181	184	9	-4	6	13	218	220	14
7	0	11	467	466	10	-4	6	11	218	229	10	-7	3	12	130	120	12	3	0	13	372	372	9	-3	6	13	162	162	15
8	0	11	129	124	10	-3	6	11	172	170	10	-6	3	12	208	203	9	4	0	13	158	157	9	-2	6	13	270	278	14
-8	1	11	363	360	9	-2	6	11	148	153	10	-5	3	12	143	139	10	5	0	13	248	246	9	-1	6	13	189	194	10
-7	1	11	77	54	29	1	6	11	89	45	35	-4	3	12	169	203	35	6	0	13	24	26	23	0	6	13	332	328	15
-6	1	11	183	184	9	0	6	11	104	112	12	-3	3	12	216	258	48	7	0	13	153	151	11	1	6	13	197	188	11
-5	1	11	145	145	9	1	6	11	134	76	22	-2	3	12	160	177	16	8	0	13	114	63	63	2	6	13	288	285	11
-4	1	11	350	354	8	2	6	11	111	108	12	-1	3	12	335	398	76	-8	1	13	259	248	16	3	6	13	171	161	11
-3	1	11	157	155	10	3	6	11	46	32	46	0	3	12	76	73	27	-7	1	13	126	112	14	4	6	13	226	218	17
-2	1	11	728	728	15	4	6	11	157	148	11	1	3	12	423	410	9	-6	1	13	315	317	10	5	6	13	123	85	32
-1	1	11	194	193	6	5	6	11	181	171	17	2	3	12	175	173	6	-5	1	13	224	223	9	6	6	13	122	118	23
0	1	11	626	625	11	6	6	11	232	228	17	3	3	12	261	265	7	-4	1	13	293	296	13	-4	7	13	132	116	21
1	1	11	307	315	7	7	6	11	156	156	19	4	3	12	213	206	9	-3	1	13	255	257	8	-3	7	13	93	59	36
2	1	11	618	616	10	8	6	11	146	87	41	5	3	12	152	142	10	-2	1	13	104	98	13	-2	7	13	115	101	20
3	1	11	203	198	6	-5	7	11	152	147	13	6	3	12	212	208	10	-1	1	13	100	82	13	-1	7	13	20	10	20
4	1	11	744	731	13	-4	7	11	142	148	11	7	3	12	128	123	13	0	1	13	109	99	10	0	7	13	0	3	1
5	1	11	144	145	8	-3	7	11	215	226	12	8	3	12	199	189	14	1	1	13	98	89	13	1	7	13	61	11	60
6	1	11	338	348	8	-2	7	11	192	188	10	-7	4	12	159	159	10	2	1	13	107	93	12	2	7	13	112	105	15
7	1	11	150	146	9	-1	7	11	359	376	12	-6	4	12	190	190	9	3	1	13	253	254	8	3	7	13	97	64	28
8	1	11	186	185	8	0	7	11	273	282	10	-5	4	12	260	259	9	4	1	13	306	305	9	4	7	13	116	116	23
-8	2	11	72	53	33	1	7	11	374	379	16	-4	4	12	193	194	9	5	1	13	230	224	9	5	7	13	122	115	23
-7	2	11	255	243	10	2	7	11	188	187	11	-3	4	12	274	281	9	6	1	13	321	320	10	-3	8	13	225	229	10
-6	2	11	230	230	9	3	7	11	229	222	11	-2	4	12	141	145	9	7	1	13	123	111	14	-2	8	13	109	78	30
-5	2	11	267	268	9	4	7	11	148	143	19	-1	4	12	472	471	9	8	1	13	249	247	16	-1	8	13	230	230	14
-4	2	11	380	390	10	5	7	11	164	150	19	0	4	12	118	134	10	-8	2	13	161	88	41	0	8	13	120	120	17
-3	2	11	233	233	9	-5	8	11	106	94	20	1	4	12	434	476	36	-7	2	13	119	110	15	1	8	13	239	229	11
-2	2	11	378	387	10	-4	8	11	131	123	12	2	4	12	140	140	8	-6	2	13	140	139	11	2	8	13	110	82	26
-1	2	11	73	54	30	-3	8	11	120	54	27	3	4	12	274	272	7	-5	2	13	225	229	9	3	8	13	229	228	19
0	2	11	54	38	53	-2	8	11	39	38	39	4	4	12	199	193	9	-4	2	13	266	274	9	-2	9	13	86	72	86
1	2	11	208	225	21	-1	8	11	106	59	28	5	4	12	268	262	10	-3	2	13	283	290	8	0	9	13	52	25	52
2	2	11	70	49	23	0	8	11	45	25	44	6	4	12	197	193	10	-2	1	13	245	250	8	1	0	14	231	237	11
3	2	11	71	48	21	1	8	11	104	66	24	7	4	12	160	153	11	-1	2	13	496	503	10	1	0	14	23	10	23
4	2																												

Table 6. Observed and calculated structure factors for td001

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	2	14	242	245	8	-1	1	15	375	389	10	-6	1	16	115	108	13	3	1	17	36	33	35	-2	4	18	95	107	14
3	2	14	253	254	8	0	1	15	119	116	8	-5	1	16	127	104	16	4	1	17	208	203	10	-1	4	18	162	167	8
4	2	14	159	160	10	1	1	15	347	397	32	-4	1	16	147	145	10	5	1	17	71	69	45	0	4	18	52	38	51
5	2	14	138	136	11	2	1	15	156	154	9	-3	1	16	61	46	36	-5	2	17	135	134	12	1	4	18	159	163	20
6	2	14	158	148	11	3	1	15	294	301	9	-2	1	16	265	268	8	-4	2	17	162	158	10	2	4	18	117	103	21
7	2	14	142	98	19	4	1	15	202	195	9	-1	1	16	145	143	9	-3	2	17	195	197	9	3	4	18	164	157	13
-7	3	14	166	159	13	5	1	15	243	249	10	0	1	16	221	219	7	-2	2	17	199	204	8	-4	4	18	61	41	60
-6	3	14	168	165	10	6	1	15	95	62	27	1	1	16	139	138	8	-1	2	17	212	215	9	-4	5	18	75	71	74
-5	3	14	250	250	9	-6	2	15	154	154	10	2	1	16	270	265	9	0	2	17	189	180	9	-2	5	18	107	57	50
-4	3	14	254	260	9	-5	2	15	171	180	9	3	1	16	56	42	56	1	2	17	216	222	9	-1	5	18	121	124	18
-3	3	14	271	280	9	-4	2	15	130	131	11	4	1	16	134	136	11	2	2	17	213	210	9	0	5	18	123	109	13
-2	3	14	187	189	8	-3	2	15	83	58	22	5	1	16	113	104	14	3	2	17	192	199	9	1	5	18	120	121	14
-1	3	14	355	356	10	-2	2	15	218	228	8	6	1	16	119	108	13	4	2	17	160	156	10	2	5	18	83	61	37
0	3	14	109	81	19	-1	2	15	112	111	10	-6	2	16	115	104	15	5	2	17	145	143	11	3	5	18	126	90	35
1	3	14	372	362	8	0	2	15	39	14	38	-5	2	16	134	134	11	-5	3	17	167	165	10	0	6	18	160	84	35
2	3	14	188	192	7	1	2	15	116	111	8	-4	2	16	144	143	10	-4	3	17	69	58	38	1	6	18	68	62	68
3	3	14	284	285	9	2	2	15	227	225	8	-3	2	16	127	126	10	-3	3	17	97	70	22	2	0	19	62	42	47
4	3	14	252	261	9	3	2	15	93	72	21	-2	2	16	215	222	11	-2	3	17	67	60	30	3	0	19	0	24	1
5	3	14	247	242	13	4	2	15	131	131	11	-1	2	16	144	143	9	-1	3	17	117	93	15	4	0	19	52	36	51
6	3	14	164	166	14	5	2	15	182	179	10	0	2	16	162	166	7	0	3	17	78	54	27	4	0	19	141	97	20
7	3	14	155	157	26	6	2	15	154	160	11	1	2	16	160	156	7	1	3	17	114	97	12	-4	1	19	0	25	1
-6	4	14	130	128	11	-6	3	15	107	108	13	2	2	16	221	219	8	2	3	17	87	62	24	-3	1	19	147	144	10
-5	4	14	124	96	18	-5	3	15	111	77	20	3	2	16	127	129	11	3	3	17	92	71	22	-2	1	19	121	123	10
-4	4	14	141	141	10	-4	3	15	245	246	9	4	2	16	143	147	11	4	3	17	60	62	59	-1	1	19	156	198	47
-3	4	14	245	245	9	-3	3	15	184	184	9	5	2	16	135	132	12	5	3	17	153	161	15	0	1	19	80	70	36
-2	4	14	48	32	47	-2	3	15	277	279	8	6	2	16	129	97	22	-5	4	17	57	48	57	1	1	19	200	200	9
-1	4	14	210	205	7	-1	3	15	212	217	9	-6	3	16	126	104	19	-4	4	17	197	193	10	2	1	19	123	121	11
0	4	14	32	21	31	0	3	15	440	443	14	-5	3	16	131	131	11	-3	4	17	116	102	13	3	1	19	155	150	10
1	4	14	232	213	10	1	3	15	212	216	7	-4	3	16	138	146	10	-2	4	17	183	192	8	4	1	19	20	24	19
2	4	14	34	26	34	2	3	15	270	272	8	-3	3	16	149	154	10	-1	4	17	76	71	20	-4	2	19	57	51	57
3	4	14	244	246	11	3	3	15	181	181	9	-2	3	16	96	73	20	0	4	17	249	289	51	-3	2	19	110	82	18
4	4	14	138	141	14	4	3	15	254	251	9	-1	3	16	158	155	9	1	4	17	89	72	34	-2	2	19	24	11	23
5	4	14	111	95	18	5	3	15	103	81	32	0	3	16	137	132	12	2	4	17	205	201	12	-1	2	19	63	54	45
6	4	14	124	132	32	6	3	15	129	115	26	1	3	16	153	144	8	3	4	17	119	104	17	0	1	19	99	68	21
7	4	14	59	56	59	-6	4	15	81	59	34	2	3	16	75	61	28	4	4	17	203	193	14	-2	2	19	83	55	29
-6	5	14	163	171	13	-5	4	15	184	183	10	3	3	16	154	150	9	5	4	17	79	51	51	-2	2	19	4	17	4
-5	5	14	150	150	12	-4	4	15	50	41	49	4	3	16	144	146	10	-4	5	17	64	50	64	-3	2	19	111	80	19
-4	5	14	162	166	12	-3	4	15	112	80	20	5	3	16	143	129	17	-3	5	17	35	26	34	3	3	19	127	121	12
-3	5	14	209	208	11	-2	4	15	59	48	36	6	3	16	144	111	41	-2	5	17	144	73	33	-2	3	19	120	122	11
-2	5	14	139	141	10	-1	4	15	91	68	16	-6	4	16	169	153	20	-1	5	17	9	15	9	-1	3	19	118	117	10
-1	5	14	308	316	7	0	4	15	105	102	12	-5	4	16	116	109	13	0	5	17	44	37	43	0	3	19	112	103	12
0	5	14	74	43	31	1	4	15	109	67	33	-4	4	16	107	101	13	1	5	17	0	19	1	1	3	19	135	125	22
1	5	14	307	313	17	2	4	15	48	46	47	-3	4	16	200	202	9	2	5	17	99	73	26	2	3	19	128	120	15
2	5	14	151	143	8	3	4	15	64	85	64	-2	4	16	120	119	10	3	5	17	38	30	37	3	3	19	132	126	15
3	5	14	224	214	10	4	4	15	24	45	24	-1	4	16	207	206	7	4	5	17	84	48	70	-3	4	19	61	71	60
4	5	14	166	168	11	5	4	15	147	175	78	0	4	16	7	13	7	-2	5	17	139	137	17	-2	4	19	0	21	1
5	5	14	162	149	13	6	4	15	58	61	57	1	4	16	215	205	11	4	6	17	146	79	36	-1	4	19	50	35	50
6	5	14	181	175	13	-6	5	15	139	154	23	2	4	16	119	117	14	-1	6	17	171	168	15	0	4	19	113	89	20
-5	6	14	118	112	19	-5	5	15	51	36	50	3	4	16	186	199	15	1	6	17	64	78	63	0	4	19	0	33	1
-4	6	14	116	118	18	-4	5	15	231	231	11	4	4	16	127	106	23	0	7	17	142	77	36	3	4	19	0	20	1
-3	6	14	149	156	15	-3	5	15	113	77	24	5	4	16	108	101	22	1	7	17	79	36	79	2	4	19	73	72	46
-2	6	14	106	106	18	-2	5	15	250	257	14	6	4	16	157	152	25	-1	8	17	200	178	11	-1	5	19	140	89	38
-1	6	14	158	157	10	-1	5	15	105	81	14	-5	5	16	100	85	50	0	9	17	72	49	32	0	5	19	222	207	11
0	6	14	139	134	15	0	5	15	341	342	10	-4	5	16	116	112	16	2	0	18	235	237	9	1	5	19	117	83	27
1	6	14	162	153	11	1	5	15	102	84	24	-3	5	16	153	151	12	3	0	18	0	11	1	2	5	19	139	126	17
2	6	14	121	111	12	2	5	15	263	256	8	-2	5	16	98	89	15	4	0	18	149	150	11	3	0	20	60	63	59
3	6	14	163	155	18	3	5	15	104	72	27	-1	5	16	173	165	9	5	0	18	97	54	83	1	0	20	0	23	1
4	6	14	130	118	20	4	5	15	235																				