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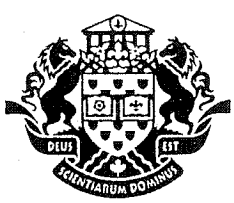

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FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

Joseph Shiban JEBREEN

AUTEUR DE LA THÈSE - AUTHOR OF THESIS

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W. Ogilvie

DIRECTEUR DE LA THÈSE - THESIS SUPERVISOR

CO-DIRECTEUR DE LA THÈSE - THESIS CO-SUPERVISOR

EXAMINATEURS DE LA THÈSE - THESIS EXAMINERS

R. Ben

T. Durst

J.-M. De Koninck, Ph.D.

LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

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The Attempted Formation of Quaternary Centers Via a Novel Intramolecular Para-C-Alkylation and the Use of the Aza-Ireland-Claisen Rearrangement in the Attempted Formation of Adjacent Stereocenters

A thesis submitted to the School of Graduate Studies and Research

In partial fulfillment of the requirements for
the degree of Master of Science

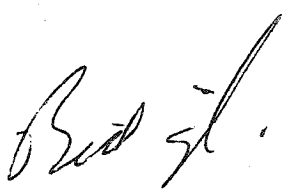
Ottawa-Carleton Chemistry Institute
Department of Chemistry
University of Ottawa
Ottawa, Ontario
Canada

January 2004

Candidate

Joseph S. Jebreen

Supervisor



Dr. William W. Ogilvie

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'To my brother Peter, the "rock" upon which my achievements are founded; the icon of inner strength and inspiration in my life... for instilling in me the personal desire to continue seeking success and the utmost confidence in reaching new heights.'

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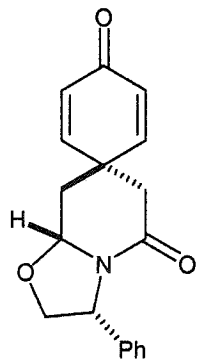
List of Abbreviations

AcOH	acetic acid
9-BBN	9-borabicyclononane
BHT	2,6-ditertbutyl-4-methylphenol
BTMA ICl2	benzyl trimethyl ammonium dichloroiodate
BuLi	butyl lithium
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CI	chemical ionization
COSY	proton correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0.]undec-7-ene
DMF	N,N-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
EI	Electron impact ionization
EtOAc	ethyl acetate
IR	infrared spectroscopy
KHMDS	potassium hexamethyldislylazide
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
M+	molecular ion peak
Mmol	millimoles

MS	mass spectrometry
NEt_3	triethylamine
NOESY	nuclear overhauser enhancement spectroscopy
NMR	nuclear magnetic resonance
$Pd_2(dba)_3$	palladium dibenzylideneacetone
Pd(II)dppf	paladium diphenylphosphinoferrocene
$Pd(PPh_3)_4$	paladium tetrakistriphenylphosphine
Pg	protecting group
PhMe	toluene
PIFA	phenyl iodonium bis(trifluoroacetate)
p-TsOH	para toluenesulfonicacid
Pyr	pyridine
Rf	retardation factor
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBS	tert-butyl dimethylsilyl
t-BuOK	tert-butoxide
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-n-propylammonium perruthenate

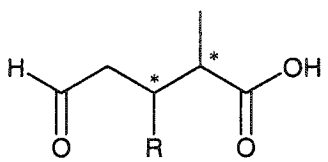
Abstract

The formation of quaternary centers is a formidable challenge. Once these quaternary centers become part of a spirocyclic system, the project becomes even more challenging. The intramolecular para-C-alkylation has been previously used with success. However, no literature precedence is available for an asymmentric version of this reaction. The attempts in synthesizing molecules similar to **123** by using such methodologies are described herein.



123

Also described is a second project which involved the effective use of the aza-Ireland-Claisen rearrangement in constructing medium-sized rings. These rings can be easily hydrolyzed to produce useful, functionalized synthetic fragments **157** containing two adjacent stereocenters as shown below.



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Chapter 1: Introduction

Following, are particulars delineating attempts to construct quaternary centers using chiral auxiliaries derived from amino alcohols. The first major project of this thesis involved a novel diastereoselective alkylation reaction of para- and ortho- substituted phenols. Later efforts concentrated on building quaternary centers using a [3,3] sigmatropic aza-Ireland-Claisen rearrangement. Before delving into the background of these projects however, a brief introduction to quaternary centers, along with a literature review on common chiral auxiliaries and their applications to asymmetric reactions will be detailed.

1.1 Formation of Quaternary Centers

A Hot Topic for Research in Organic Chemistry

The formation of quaternary carbons in an asymmetric manner has been a longstanding, formidable challenge in modern synthetic chemistry.[1] Quaternary centers have indeed become a hot topic for the organic chemist.[2] The significance of this research is embedded in the structures of several enantiomerically pure natural products and pharmaceuticals. Natural products are regularly being isolated from organisms around the world. Often by mimicking nature, pharmaceutical companies are continuously synthesizing and optimizing newer drugs. The benefits of several of these natural products and pharmaceuticals are numerous including several anti-HIV agents.[3]

---

[1] Fuji, K. *Chem. Rev.* **1993**, 2037.
[2] Barriault, L.; Denissova, I. *Tetrahedron* **2003**, 59, 10105.
[3] (a)Devita, V.T.; Hellman, S.; Rosenberg, S.A. *AIDS: Etiology, Diagnosis, Treatment and Prevention,4th Ed.* Philadelphia: Lippincott-Raven, **1997**. (b) Klunder, J.M.; Hoermann, M.; Cywin, C.L.; David, E.; Schwartz, R.; Barringer, K.J.; Pauletti, D.; Shih, C.; Erickson, D.A.; Sorge, C.L.; Joseph, D.P.; Hattox, S.E. *J. Med. Chem.* **1999**, 41, 2960.

There are several reliable methods for the generation of tertiary stereocenters using chiral auxiliaries and catalytic reagents. However, the search for efficient and novel enantioselective methods for the construction of quaternary carbons remains a top priority.[4] Every enantioselective process that forms a quaternary center is another valuable tool for the synthetic community.

Different strategies have been developed over the last few years for the asymmetric formation of quaternary centers. The practical use of chiral auxiliaries has made a huge impact on the construction of quaternary centers. Although chiral auxiliaries are utilized stoichiometrically, the paramount importance of these auxiliaries is evidenced through their broad range of pertinent applications in several total syntheses.[5] An alternative strategy makes use of chiral catalysts.[4] However, the use of these chiral catalysts in building quaternary centers is relatively new. These catalysts can be strategically employed in small quantities, while still allowing the creation of large amounts of optically active product. Another feature is that there is no need to be concerned with their removal and recovery. Catalysts can also be synthesized with inexpensive and readily available ligands and their utility is often generalized to an extensive array of substrates.[6]

Both strategies involving the use of chiral auxiliaries or chiral catalysts have their advantages and disadvantages. As the present projects involved the use of chiral auxiliaries, examples of recent applications of enantioselective quaternary carbon formation using stoichiometric processes follow.

---

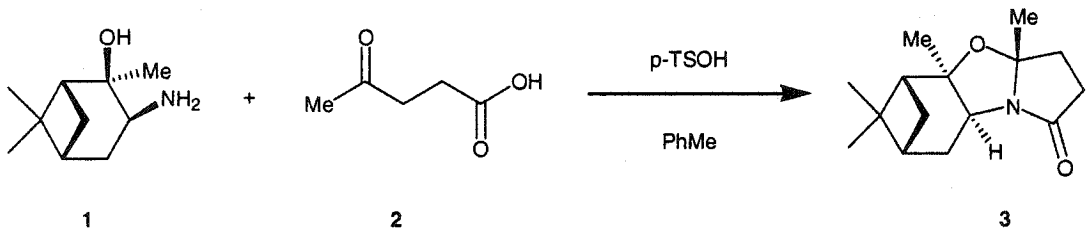
[4] (a) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, 59 10105. (b) Christoffers, J.; Mann, A. *Ang. Chem. Int. Ed.* **2001**, 40, 4591. (c) Corey, E.J.; Guzmann-Perez, A. *Ang. Chem. Int. Ed.* **1998**, 37, 388.

[5] Groaning, M.D.; Meyers, A.I. *Tetrahedron* **2000**, 56, 9843.

[6] Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.

Chiral Bicyclic Lactams

Diastereoselective alkylations are one of the more studied methods in asymmetric quaternary center formation.[4] One method entails the use of chiral bicyclic lactams in asymmetric reactions. Using these auxiliaries, one could transform a prochiral substrate into an optically pure compound.[7] These bicyclic lactams are easily synthesized via a condensation reaction between dicarbonyl compounds and chiral amino alcohols in the presence of p-toluene sulfonic acid (p-TSOH). As an example, pinene derivative **1** reacts with levulinic acid **2** to yield the bicyclic lactam **3** (Scheme 1.1).[8] Upon treatment with a strong base and a suitable electrophile, compound **3** can be alkylated diastereoselectively.



1 2 3

Scheme 1.1: Formation of chiral bicyclic lactams.

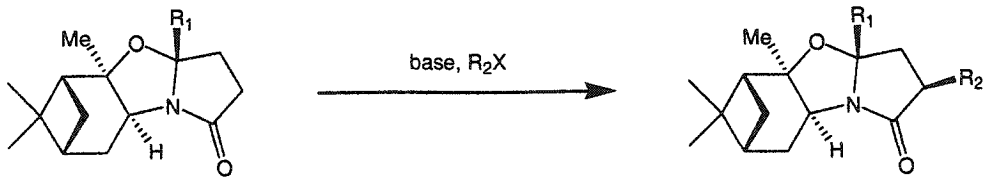
This reaction proceeds with high exo facial selectivity yielding product **5** (Table1.1). Accounting for this facial selectivity are steric interactions. The bridging gem-dimethyl groups or the axial methyl group effect a facial blocking of the α-face of the enolate generated from **4**. Concurrent studies[8] demonstrate that the alkylation of bicyclic lactams of different structure than the pinene derivative, selectively yield the endo product. Hence, by simply altering the structure of the chiral auxiliary, facial selectivity can be controlled.

---

[7] Romo, D.; Meyers, A.I. *Tetrahedron* **1991**, 47, 9503.

[8] (a) Roth, G.P.; Leonard, S.F.; Tong, L.J. *J. Org. Chem.* **1996**, 61, 571. (b) Meyers, A.I.; Seefeld, M.A.; Lefker, B.A. *J. Org. Chem.* **1996**, 61, 5712.

Table 1.1: Alkylation of a pinene-derived bicyclic lactam.



4 5

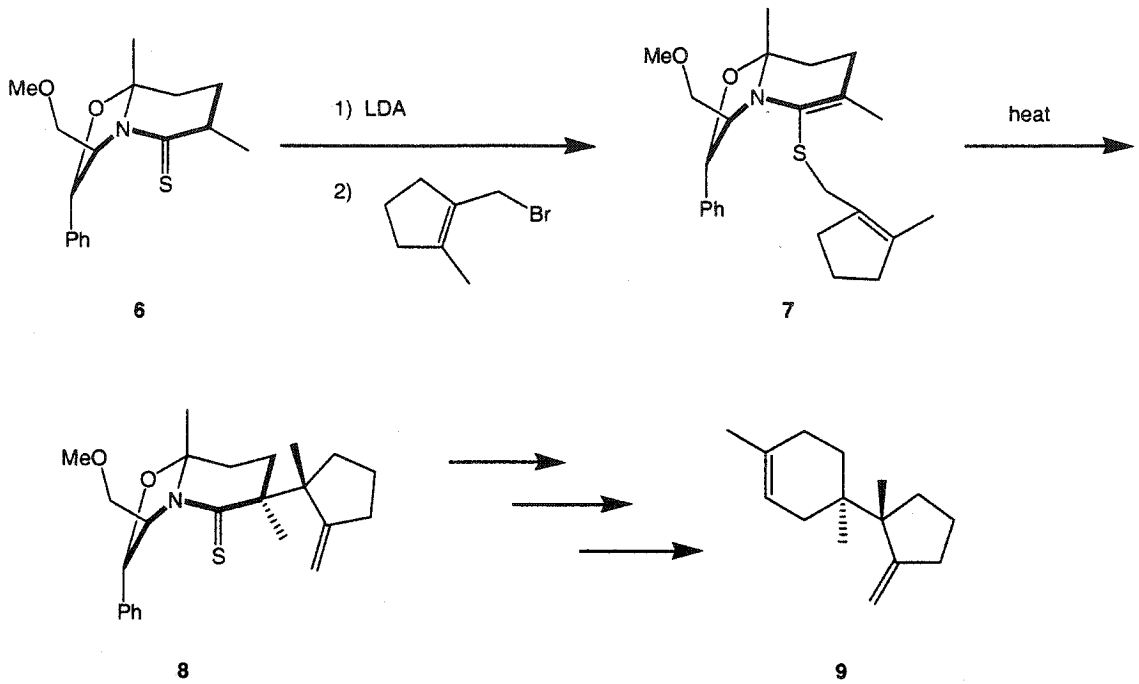
Entry	R_1	R_2	Base	Exo:Endo
1	Ph	Me	s-BuLi	96:4
2	Ph	Me	LDA	92:8
3	Me	Me	s-Buli	97:3

These chiral bicyclic lactams have also found important applications in pericyclic reactions.[5] Pericyclic reactions utilizing these lactam auxiliaries as chiral dieonophiles or dipolarophiles in cycloaddition reactions have shown great promise in the formation of carbocycles and heterocycles. The thio-Claisen rearrangement is another genre of pericyclic reactions where bicyclic lactams are used diastereoselectively. As an example, Scheme 1.2 illustrates the use of thio-lactam **6** in the synthesis of the sesquiterpene, trichodiene.[9] The parent bicyclic lactam is converted into the thio-lactam **6** by treatment with either Belleau's or Lawsson's reagent.[10] The thioenolate of **6** is formed by treatment with lithium diisopropylamide (LDA) and then trapped with the corresponding allylic halide. This produces substrate **7** which, upon heating, yields the alkylated thio-lactam **8**. In the synthesis of trichodiene **9**, the key transformation is the

[9] (a) Devine, P.N.; Meyers, A.I. *J. Am. Chem. Soc.* **1994**, 116, 2633. (b) Lemieux, R.M.; Meyers, A.I. *J. Am. Chem. Soc.* **1998**, 120, 5453. (c) Lemieux, R. M.; Devine, P.N.; Mechelke, M.F. Meyers, A.I. *J. Org. Chem.* **1999**, 64, 3585.

[10] (a) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, 24, 3815. (b) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, 62, 158.

installation of the vicinal quaternary centers via this thio-Claisen rearrangement of the bicyclic lactam.



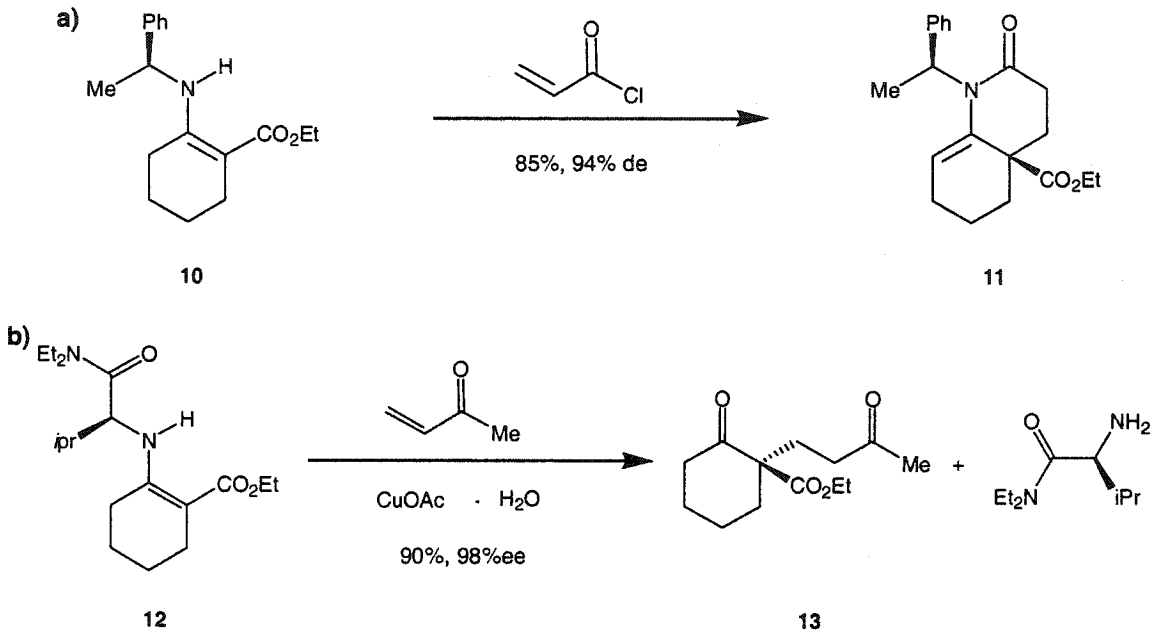
Scheme 1.2: Thio-Claisen rearrangement of a chiral bicyclic thio-lactam.

1–Phenylethylamine and α-Aminocarboxamides

Asymmetric Michael reactions assisted by chiral auxiliaries are of great utility and importance since the auxiliaries tolerate a vast range of functionalities and require comparatively mild conditions.[11] 1-Phenylethylamine is a common auxiliary used in these Michael reactions. The enamino ester **10**, for example, reacts with acryloyl chloride and a subsequent intramolecular enamine-Michael addition yields the δ-lactam derivative **11** with high diastereoselectivity (Scheme 1.3a).[12] As an alternative to phenylethylamine, α-aminocarboxamides are being launched as potential chiral

[11] Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051.
[12] Benovsky, P.;Stephenson, G.A.; Stille, J.R. *J. Am. Chem. Soc.* **1998**, 120, 2493.

auxiliaries in copper-catalyzed asymmetric Michael reactions (Scheme 1.3b).[13] Michael addition of methyl vinyl ketone to enamine **12** occurs in the presence of catalytic amounts of copper acetate monohydrate ($CuOAc \cdot H_2O$). The result is the functionalized chiral molecule **13**, achieved in high yield and enantiomeric purity; all of which occurs at ambient temperatures and under mild reaction conditions.



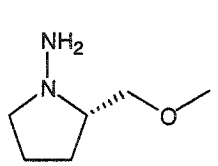
Scheme 1.3: Asymmetric Michael reactions with (a) Phenylethylamine and (b) α-aminocarboxamides as chiral auxiliaries.

Pyrrolidine-Based Chiral Auxiliaries

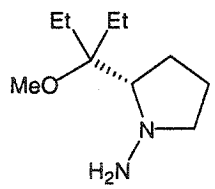
Sigmatropic rearrangements are an attractive option when testing the application of chiral auxiliaries to asymmetric reactions.[14] These rearrangements are advantageous as they usually proceed with high stereospecificity. Enders and co-workers have published asymmetric versions of the Carroll rearrangement and the [2,3] Wittig

[13] Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2000**, 39, 2752.
[14] Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, 7, 1847.

rearrangement using pyrrolidine-based chiral auxiliaries. (S)-N-amino-2-methoxymethylpyrrolidine (SAMP) **14** and (S)-N-amino-2-(1-ethyl-1-methoxypropyl)-pyrrolidine (SAEP) **15** are two such auxiliaries (Figure 1.1). SAMP is employed as the auxiliary for the Carroll rearrangement.[15] This specific auxiliary is one of several N-aminopyrrolidine derivatives developed by Enders and has various applications in C-C bond forming reactions.[16] SAMP hydrazone **16** underwent a [3,3] sigmatropic rearrangement upon treatment with LDA (Scheme 1.4). Reduction of the acid functionality with lithium aluminum hydride (LAH) gave compound **17**. Subsequent regeneration of the keto ester, via hydrolysis of the chiral auxiliary, afforded cyclohexanone **18** with quaternary α and tertiary β stereocenters. For the Wittig rearrangement, optically active SAEP was used to construct chiral α-hydroxy ketones.[17] Starting with α-allyloxycyclohexanone, SAEP hydrazone **19** was produced (Scheme 1.5).[18] After deprotonation with tert-butyllithium (tBuLi), the SAEP hydrazone underwent a Wittig rearrangement to yield the homoallyl alcohol **20** in good yield and excellent diastereoselectivity. Once again, after removal of the auxiliary, the product contains a quaternary center with a neighboring tertiary stereocenter.



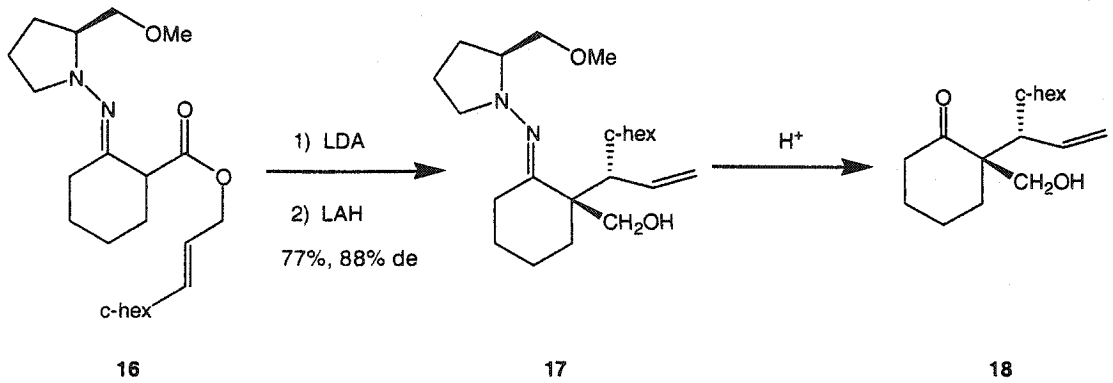
14



15

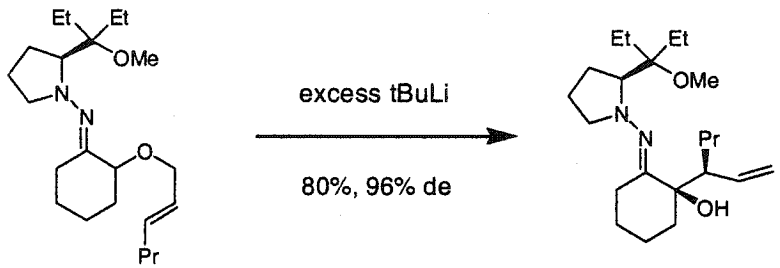
Figure 1.1: Structures of pyrolidine-based chiral auxiliaries SAMP and SAEP.

[15] (a) Enders, D.; Knopp, M.; Runsink, J.; Raabe, G. *Liebigs Ann.* **1996**, 1095. (b) Enders, D.; Knopp, M.; Runsink, J.; Raabe, G. *Ang. Chem. Int. Ed.* **1995**, 34, 2278.
[16] Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, 73, 573.
[17] (a) Enders, D.; Backhaus, D.; Runsink, J. *Angew. Chem. Int. Ed.* **1994**, 33, 2098. (b) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, 52, 1503.
[18] Enders, D.; Bartsch, M.; Backhaus, D.; Runsink, J.; Raabe, G. *Synthesis* **1996**, 1438.



16 17 18

Scheme 1.4: Carroll rearrangement with the chiral auxiliary SAMP.



19 20

Scheme 1.5: Wittig rearrangement with the chiral auxiliary SAEP.

Boronate Esters

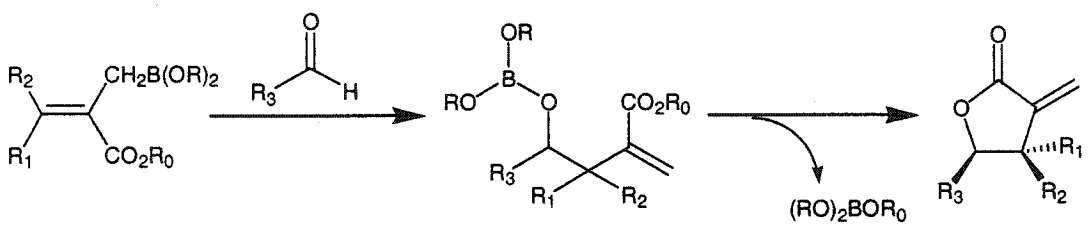
The allylation of aldehydes with allylboronates has been extensively used in the generation of homoallylic alcohols with tertiary centers.[19] Good examples involving the allylboration reaction with various aldehydes in the formation of quaternary centers are provided by Hall and Kennedy.[20] They had reported an efficient route for the synthesis of tetrasubstituted 2-alkoxycarbonyl boronate esters **21** as pure isomers. The allylboration of various aldehydes with **21** resulted in the diastereoselective formation of α-exomethylene γ-lactones **22**. In the process, the geometry of the allylboronate esters **21**

[19] (a) Metteson, D. S. *Stereodirected Synthesis with Organoboranes: Springer-Verlague: Berlin, Heidelberg*, **1995**, Chapter 7. (b) Roush, W.R. *Stereoselective synthesis, Houben-Weyl, 4th Ed.* Thieme: Stuggart, **1995**, Chapter 1.3.3.3.3 Vol. E21b.

[20] Kennedy, J. W.; Hall, D. J. *J. Am. Chem. Soc.* **2002**, 124, 898.

was transferred without losing stereochemical information (Entry 5 and 6). From entries 2 and 4 we can see that both electron donating and electron withdrawing groups give good yields and diastereomeric ratios. The results of a few selected examples are included in Table 1.2.

Table 1.2: The stereoselective synthesis of γ-lactones with quaternary centers in the β positon.



21 22

Entry	R_1, R_2	R_3	Conditions[a]	% Yield of 22[b]	dr[c]
1	Et, Me	C_6H_5	A	89	>20:1
2	Et, Me	p-MeO-C_6H_4	B	70	19:1
3	Et, Me	p-MeO-C_6H_4	C	55	20:1
4	Et, Me	p-NO_2-C_6H_4	B	81	>20:1
5	Bu, Me	p-NO_2-C_6H_4	B	76	>20:1
6	Me, Bu	p-NO_2-C_6H_4	D	67	>20:1

[a] reaction scale = 1 mmol [b] unoptimized yields [c] measured by HPLC or ^{1}H NMR
A: PhMe, rt, 12d B: PhMe, 80°C, 16-20h C: PhMe, 110°C, 18h D: CH_2Cl_2, 40°C, 48h

Hall and Kennedy also improved the reaction by testing the effects of Lewis acids.[21] They noticed a large rate increase (i.e. 6-24 hours versus 12 days) as well as a higher reactivity towards "non-reactive" aldehydes. In the paper, the authors reasoned

[21] Kennedy, J. W.; Hall, D. J. *J. Am. Chem. Soc.* **2002**, 124, 1586.

that the complexation of the metal from the Lewis acid could increase the acidity of boron in the transition state and thus strengthen its bond with the aldehyde (Figure 1.2).

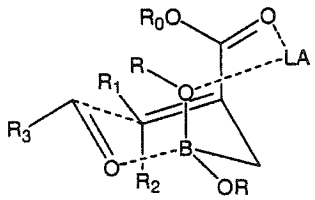


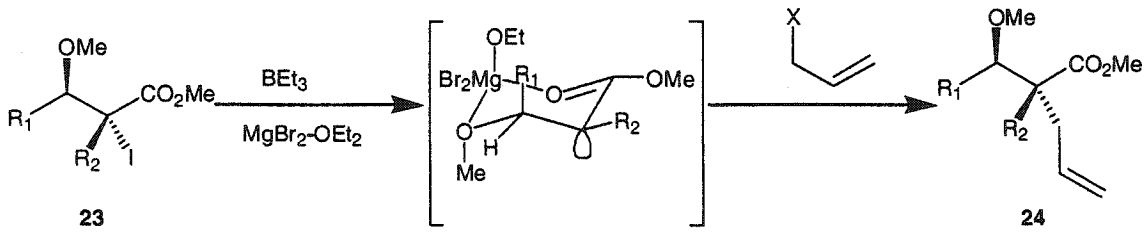
Figure 1.2: Transition state structure showing the effect of the Lewis acid on the allylboration reaction.

Radical Notions in Quaternary Center Formation

A big potential for quaternary center formation was demonstrated by Guindon and coworkers in 1995.[22] They reported a Diastereoselective chelation-controlled radical allylation reaction. In the sequence, α-iodo-β-methoxy esters **23** were treated with allyltrimethylsilane or allyltributyltin, magnesium bromide etherate and triethylborane in dichloromethane to produce esters **24** (Table 1.3). These reactions gave reasonably good yields and amazing diastereomeric ratios (>100:1). As pointed out by the table, better yields were obtained when allyltributyltin was used.

[22] (a) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W.; Mackintosh, N. *Synlett* **1995**, 449. (b) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, 118, 12528. (c) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W.; Mackintosh, N. *N. Can. J. Chem.* **2000**, 78, 852.

Table 1.3: Radical allylation under chelation control.



23 24

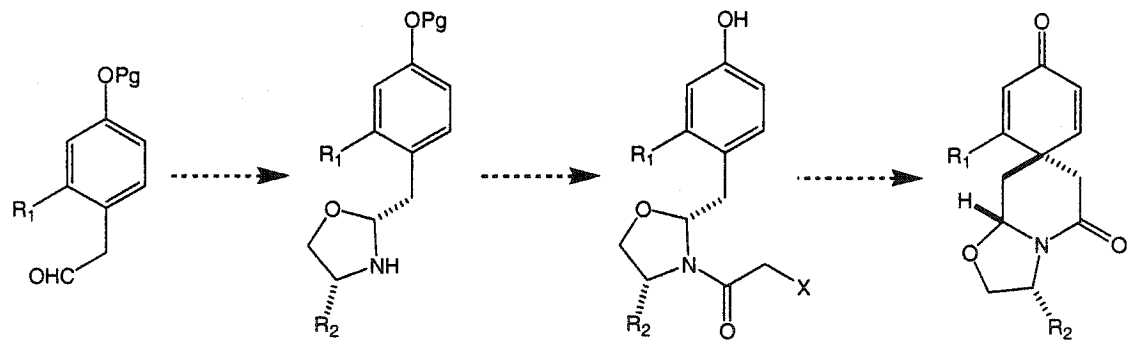
Entry	R_1, R_2	Anti : Syn	% Yield (X = TMS)	% Yield (X = $SnBu_3$)
1	Ph, Me	> 100:1	39	76
2	Me, Me	> 100:1	35	65
3	Et, Me	> 100:1	40	80

1.2 A Novel Para- and Ortho-C Alkylation of Phenols

Project Goals

In the first set of projects of this thesis, attempts were made to develop a novel method for the formation of quaternary carbons using an intramolecular para-C-alkylation. This would be the first asymmetric version of this reaction.

Protected 4-hydroxy-arylacetaldehydes **25** would be synthesized and used as starting materials for the projects (Scheme1.6). A variety of aryl appendages, R_1, were to be examined. Readily available chiral amino alcohols could be condensed with these aldehydes to give oxazolidines **26**, which would be used as the chiral auxiliaries. Acylation and deprotection of these oxazolidines was envisaged to give substrates **27**, the prescursors for the proposed methodology. Upon treatment with a hindered base, derivatives **27** should produce dienones **28** via the new asymmetric para-C-alkylation.

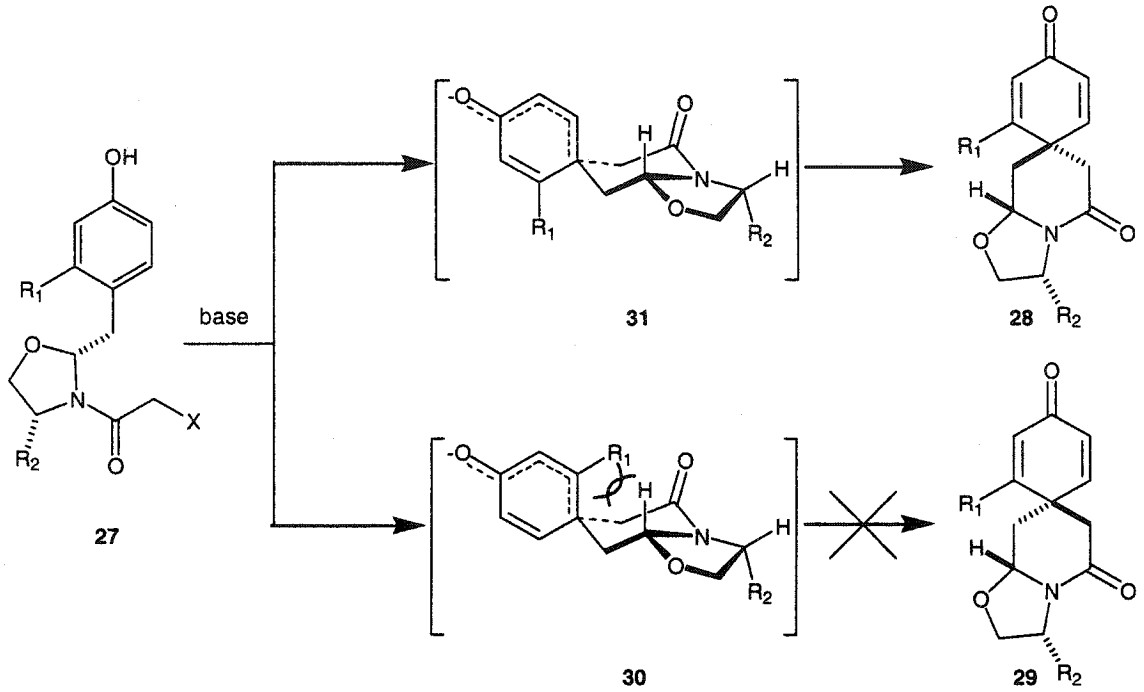


25 **26** **27** **28**

Scheme 1.6: Summary of the novel para-C-alkylation.

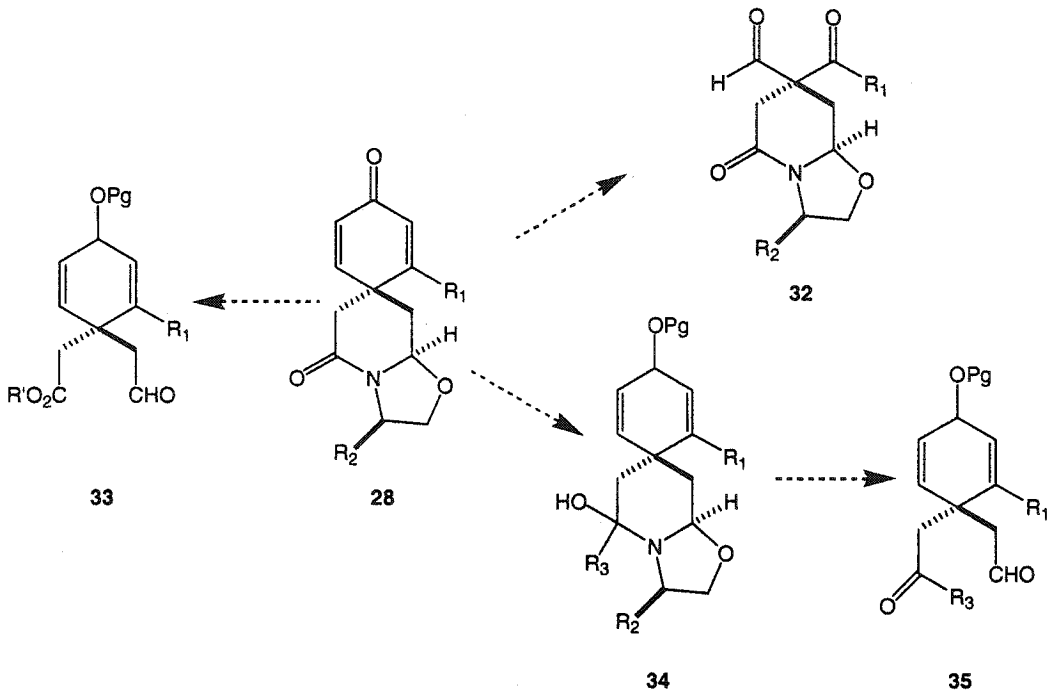
An examination of possible transition states for the para-C-alkylation provides a rational for the selective formation of dienone **28** over dienone **29** (Scheme 1.7 – the leaving group has been omitted for clarity). In transition state **30** the R_1 group would be extended over the incipient ring. Effectively, the resulting steric compression should

destabilize transition state **30** relative to **31**. Although boat-like transitions are possible, the severe steric interations would disfavor these transition states as compared to **31**.



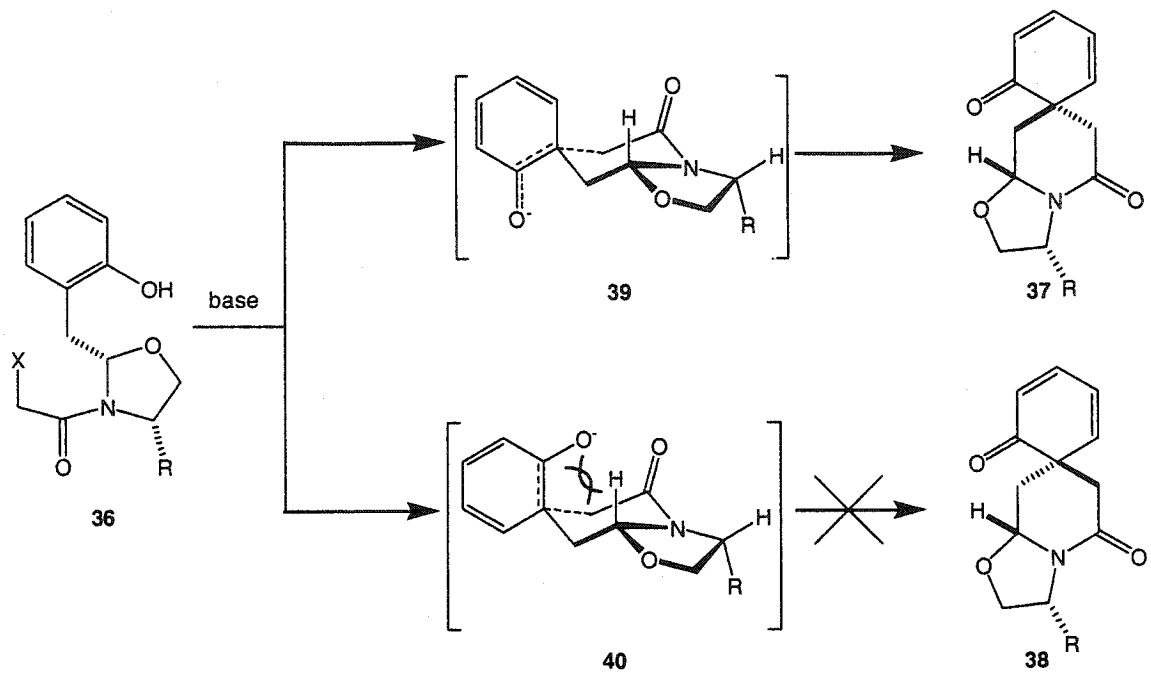
Scheme 1.7: Two chair-like transition states of para-C-alkylation reaction.

With dienones **28** in hand, a variety of functional group manipulations could be explored (Scheme 1.8). Oxidative cleavage of the dienone could yield differential carbonyl groups as in compounds **32**. Alternatively, removal of the auxiliary could be attempted using protected or reduced versions of the dienones. Hydrolysis to **33**, for example, may be problematic, however other bicyclic oxazolidines have been successfully hydrolyzed and so this transformation is not without precedent.[5] One last approach would involve the addition of organometallic reagents to the amide to produce aminals **34** which are easily hydrolyzed to derivatives **35**. Once the issues surrounding this novel methodology have been addressed, the synthesis of diverse natural and medicinal products containing quaternary centers will demonstrate the versatility of dienones **28**.



Scheme 1.8: Functionalization of the spirocyclic dienones.

In addition to the para version of the reaction, other variants of the reaction are proposed. The ortho-C-alkylation is an alternative to the para-C-alkylation that would be examined simultaneously. The same substrate for the alkylation reaction would be used except that the substituents on the phenyl ring would now be ortho to each other. Phenol **36** could be synthesized and upon treatment with a hindered base, the spirocyclic dienone **37** would result, not **38** (Scheme 1.9). Due to similar steric arguments as the para version of this reaction, transition state **39** would be favoured over **40**.



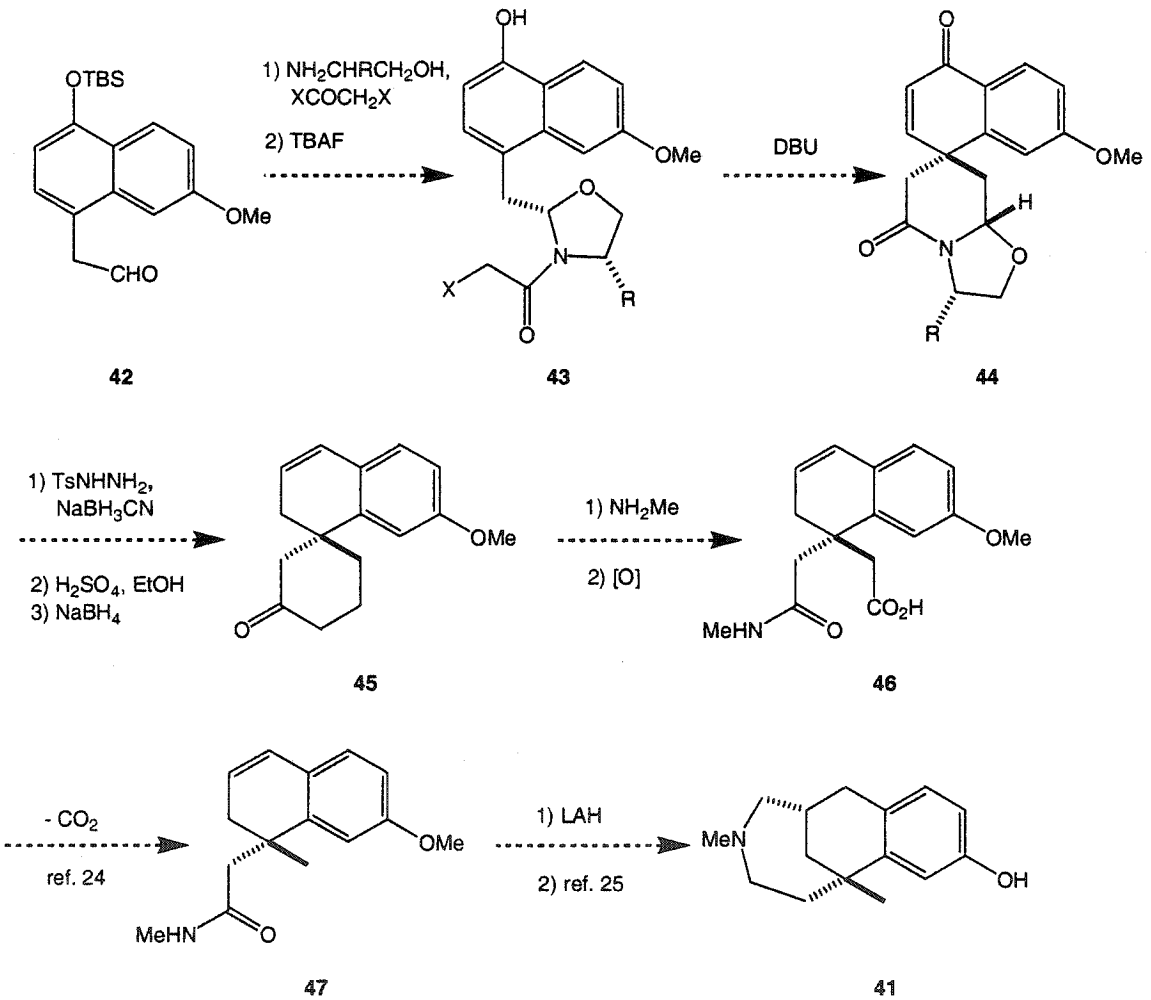
Scheme 1.9: Expected transition state for the ortho-C-alkylation.

Potential Applications of the Para-C-Alkylation

Several applications of this methodology to the synthesis of natural products and medicinal targets were envisioned. As an example, eptazocine **41** is a potent analgesic and shows narcotic antagonistic activity (Scheme 1.10).[23] Aldehyde **42** could be converted into oxazolidine **43** by treatment with the optimized amino alcohol, acylation and subsequent deprotection of the phenol. Via the proposed para-C-alkylation, the spirocyclic dienone **44** could be formed with the assistance of a hindered base. This key step would establish the correct configuration of the quaternary center in eptazocine. The α,β unsaturated ketone would be deoxygenated with tosylhydrazone to give a conjugated olefin. Hydrolytic removal of the auxiliary and successive reduction could be used to produce lactone **45**. Treatment of **45** with $MeNH_2$ would generate the open amide.

[23] Suzuki, T.; Shimizu, R.; Suganuma, T.; Nishino, J.-I.; Tomono, K.; Nanano, M.; Watanabe, J.; *Biol. Pharm. Bull.* **2000**, 23, 1504.

Oxidation of the revealed alcohol to its corresponding carboxylic acid yields compound **46**. In the next step, reductive carboxylation of **46** would be attempted.[24] During decarboxylation, a competing trans-annular radical reaction involving the double bond could crop up. If this is the case, conversion to the protected benzylic alcohol would allow for the final Mannich cyclization. Lastly, reduction of the amide **47** to the amine gives an intermediate that has been previously synthesized to eptazocine **41**.[25]

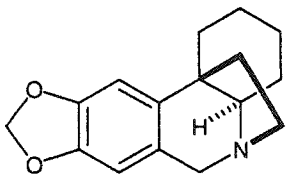


Scheme 1.10: Proposed synthesis of eptazocine.

[24] (a) Garner, P.; Anderson, J.T.; Dey, S.; Youngs, W.J.; Galat, K. *J. Org. Chem.* **1998**, 63, 732. (b) Barton, D.H.R.; Sarnadi, M. *Tetrahedron* **1992**, 48, 7083.

[25] Node, M.; Imazato, H.; Kurosaki, R.; Kawano, Y.; Inoue, T.; Nishide, K.; Fuji, K. *Heterocycles* **1996**,42, 811.

Other synthetic targets utilizing the para-C-alkylation include crinane,[26] the amaryllidaceae alkaloid **48** and nanaimoal,[27] the sesquiterpenoid aldehyde **49**.



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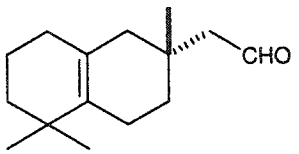

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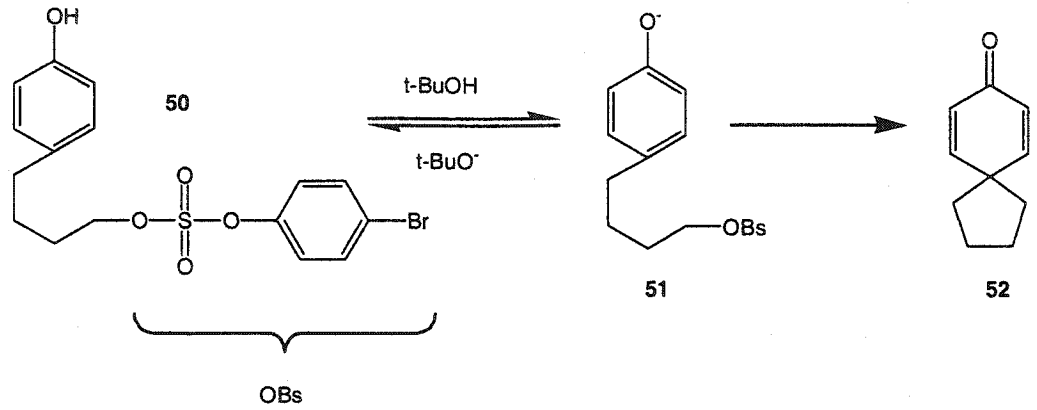
Figure 1.3: Structures of synthetic targets using para-C-alkylation methodology.

Literature Precedence

As mentioned previously, this would be the first asymmetric version of the para-C-alkylation. However, in the late 1950's, S. Winstein and R. Baird developed reaction conditions that allowed for the formation of spirocyclic dienones through the Ar-n-participation of a neighboring phenoxide group.[28] The nomenclature of the reaction was as follows: Ar symbolized the participation of the phenol (**A**romatic) and n represented the size of the spirocyclic ring being formed in the reaction. Using 4-p-hydroxyphenyl-1-butyl p-bromobenzenesulfonate **50**, Ar-5 participation was possible. Deprotonation of **50** gave the phenoxide **51.** Ar-5 participation of **51** led to the formation of spirodienone **52** (Scheme 1.11).[29] However, there were competing reactions like those leading to solvolysis products **53** and dimerization products **54** to be cautious of (Scheme 1.11). Another problem to be aware of was the dienone-phenol rearrangement of the formed spirodienone. This process involved the formation of a positively charged intermediate

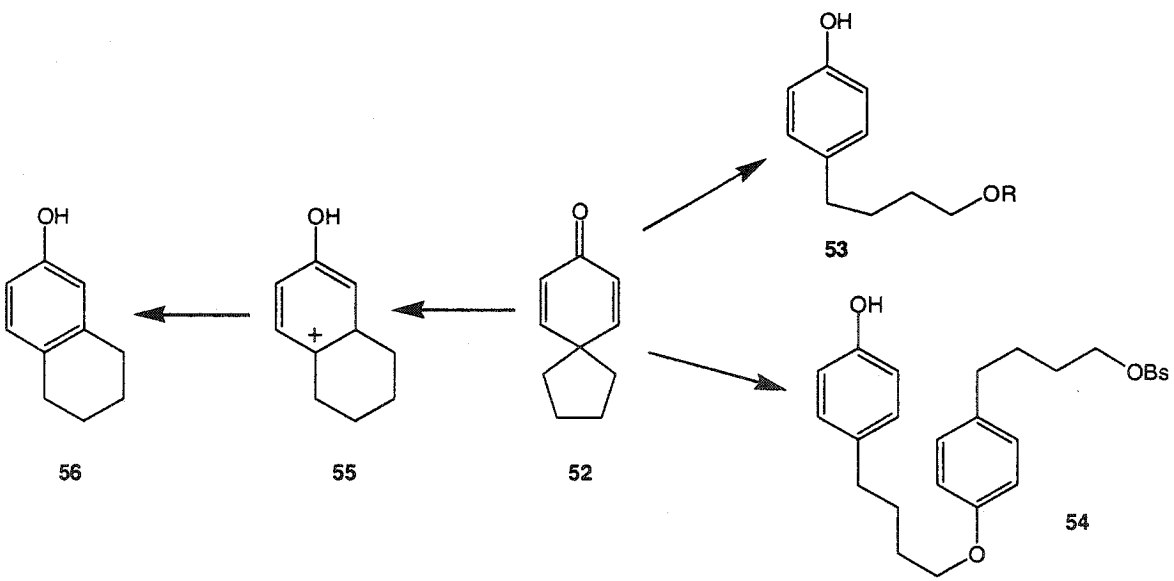
---

[26] Padwa, A.; Brodney, M.A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, 66, 3119.
[27] Ayer, S.W.; Hellou, J.; Tischler, M.; Andersen, R.J. *Tetrahedron Lett.* **1984**, 25, 141.
[28] (a) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, 79, 756. (b) Heck, R.; Winstein, S. *J. Am. Chem. Soc.* **1957**, 79, 3105.
[29] Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1962**, 84, 788.



Scheme 1.11: Formation of spirodienone via Ar-5 participation.

55 followed by the restoration of aromaticity to produce a tetralin-based product **56** (Scheme 1.12).[30] Through kinetic studies, Winstein and Baird were able to optimize the reaction conditions with regards to concentration, basicity and temperature to favor spirodienone formation. The best yield of spirodienone, 56%, was obtained when t-butanol salts were employed as base.



Scheme 1.12: Competing reactions for para-C-alkylation.

[30] Winstein, S.; Heck, R.; Lapporte, S.; Baird, R. *Experientia* **1956**, 12, 138.

The same authors also published an article describing the details of dienone formation from Ar-3 participation.[31] The formation of the three-membered spirodienone ring was found to be 100 times faster than the five-membered ring, which was 100 times faster than the formation of the corresponding six-membered ring analogue.[28] One last effect on Ar-n participation was phenyl ring substituents. Methoxy groups ortho to the incipient spiro center donate electron density and thus aid in spirodienone formation. The effect of electron donating groups was small but nonetheless was a contributing factor.[28]

More recent applications of this genre of alkylation are present in the literature. In 2000, Boger and coworkers published the synthesis of the DNA alkylating reagent, 1,2,9,9a-Tetrahydrocyclopropa[c]pyrido[3,2-e]indol-4-one-7-carboxylate, which relied on the para-C-alkylation developed by Winstein and Baird.[32] The synthesis necessitated the formation of a cyclopropyl ring from compound **57** (Scheme 1.13). **57** was consequently treated with the hindered base DBU to afford the dienone **58**. Although the yield of the reaction was 93%, the product was subjected to chiral resolution in order to separate the two possible enantiomers. In that same year, Boger and coworkers used a similar methodology in the synthesis of yet another DNA alkylating reagent, 1,2,8,8a-Tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one.[33]

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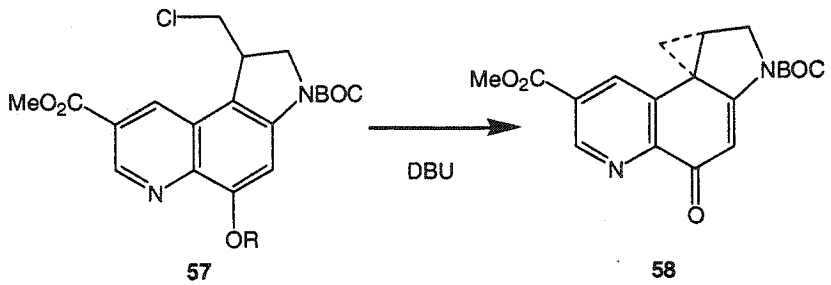
[31] Winsterin, S.; Baird, R. *J. Am. Chem. Soc.* **1963**, 85, 567.
[32] Boger, D.L.; Boyce, C. *J. Org. Chem.* **2000**, 65, 4088.
[33] Boger, D.L.; Santillan, A.Jr.; Searcey, M.; Brunette, S.R.; Wolkenberg, S.E.; Hedrick, M.P.; Jin, Q. J. Org. Chem. 2000, 65, 4101.

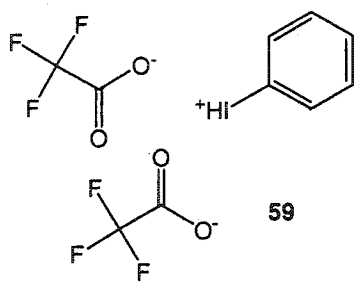


57 58

Scheme 1.13: Para-C-alkylation – Ar-3 participation.

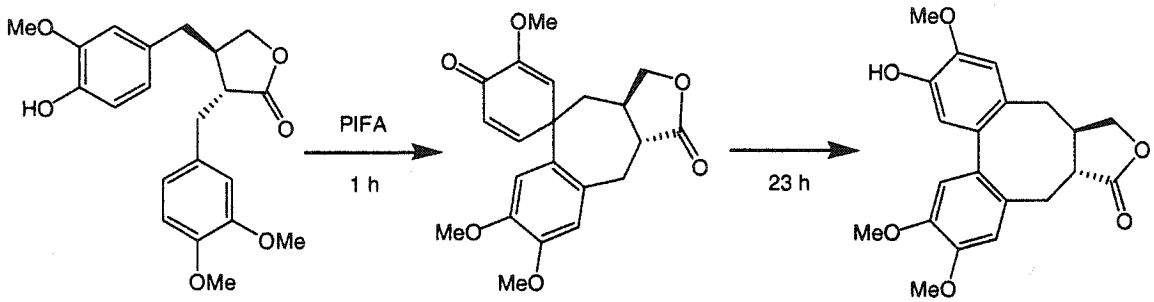
Another recent example involving a different mechanistic pathway for the formation of spirodienones was made available. Instead of the para-C-alkylation via Ar-n participation, an oxidative cyclisation using hypervalent iodine was performed.[34] The hypervalent iodine reagent used was phenyl iodonium bis(trifluoroacetate) (PIFA) **59** (Figure 1.4). In the publication, trans-2,3-dibenzylbutyrolactone **60** was treated with PIFA in trifluoroethanol (TFE) (Scheme 1.14). After 1h, the starting material disappeared and a polar product was formed in 46% yield. This product corresponded to the spirodienone **61**. When the reaction was allowed to stir for 24 hrs, the spirodienone intermediate disappeared and a new product **62** was formed in 58% yield. Once again, this corresponds to the dienone-phenol rearrangement product described for the Ar-n participation reaction. Thus, an alternate pathway is available for the formation of spirodienones. However, PIFA makes the phenol electrophilic, thus requiring a nucleophilic attack. In our project, the phenol acts as the nucleophile.

[34] Ward, R.S.; Hughes, D.D. *Tetrahedron* **2001**, 57, 5633.



59

Figure 1.4: Structure of phenyl iodonium bis(trifluoroacetate) (PIFA).



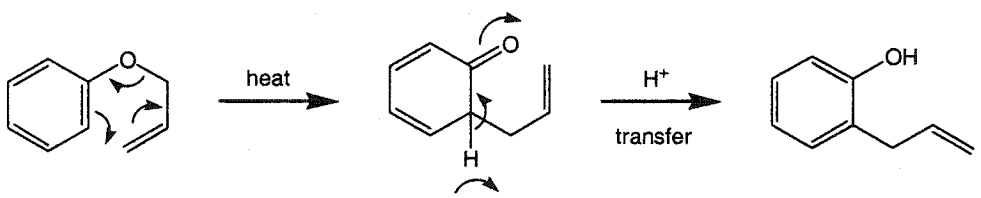
60 61 62

Scheme 1.14: Formation of the spirodienone with hypervalent iodine (PIFA).

1.3 The Aza-Ireland-Claisen Rearrangement

Sigmatropic Rearrangements – The Claisen Rerrangement

Sigmatropic reactions are a different type of pericyclic reaction that involve the breaking of both sigma and pi bonds. The Claisen rearrangement was the first of these sigmatropic reactions to be discovered.[35] It dates back to the year 1912, when L. Claisen heated allyl aryl ether **63** without solvent (Scheme 1.15). The product, to his fortunate surprise, was the ortho-allyl phenol **64**. The first step of the mechanism is pericyclic in nature and thus, no ionic intermediates are involved. The actual intermediate, **65**, easily loses a proton to regain its aromaticity. This particular reaction is designated a [3,3] sigmatropic rearrangement since the newly formed sigma bond is three atoms away from the old sigma bond in both directions. Today, the Claisen rearrangement is but one type of the several [3,3] sigmatropic rearrangements.



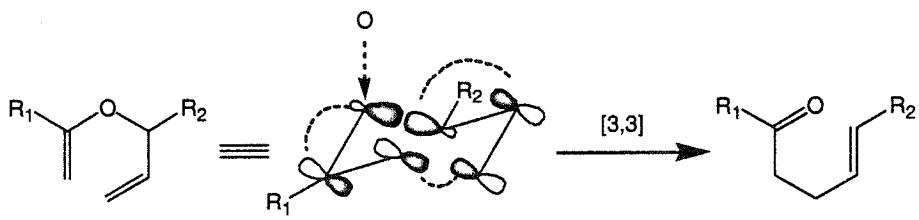
63 **65** **64**

Scheme 1.15: The mechanism of the Claisen rearrangement.

Since its discovery, much work has been put forth to explain the mechanistic pathway of the Claisen rearrangement.[36] The Claisen rearrangement is a reliable way to synthesize γ,δ-unsaturated carbonyl compounds. The reaction usually passes through a chair-like transition state, thus allowing for the stereochemistry of the product to be

[35] Claisen, L. *Ber.* **1912**, 45, 3157.

predicted and good orbital alignment to occur.[36] A negative value of entropy for the reaction demonstrates the high degree of order in the transition states.[37] If there are substituents involved, retention of stereochemistry is generally observed. The specific stereochemical information in the starting material is dependably transferred to the product.[38] In effect, the trans geometry of the alkene in the product **66** is already present, and consequently determined by the starting material **67** (Scheme 1.16). Furthermore, the new sigma bond is formed from two well-aligned p orbitals and the two new pi bonds are formed from two parallel orbitals.



67 66

Scheme 1.16: Orbital symmetry and stereochemistry of the Claisen rearrangement.

Many modifications to the Claisen rearrangement have since been developed. One of the earliest variants arose from the work of Carroll who investigated the reaction of acetoacetic ester with allylic alcohols under base-catalyzed conditions.[39] Specifically, the stereospecificity of the reaction was illustrated with the structural isomers cinnamyl alcohol (**68**) and phenylvinylcarbinol (**69**) (Scheme 1.17). Upon treatment with base, these substrates produced the γ,δ unsaturated methyl ketones **70** and **71**. Carroll proposed a Michael-type condensation that involved an S_N2' displacement of hydroxide by acetoacetate anion. However, Kimel and Cope interpreted the results in a different way.[40]

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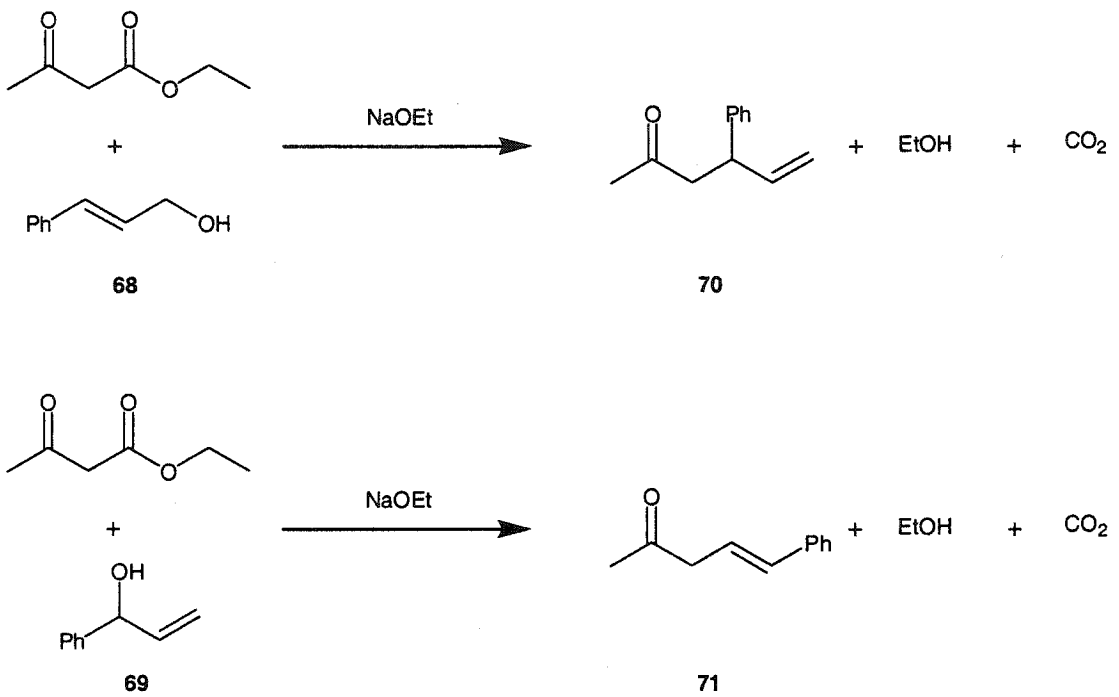
[36] Ziegler, F.E. *Chemical Reviews* **1988**, 88, 1423.
[37] Ziegler, F. E. *Acc. Chem. Res.* **1977**, 10, 227.
[38] Bartlett, P.A. *Tetrahedron* **1980**, 36, 2.
[39] (a) Carroll, M.F. *J. Chem. Soc.* **1940**, 704 and 1266. (b) Carroll, M.F. *J. Chem. Soc.* **1941**, 507.
[40] Kimel, W.; Cope, A.C. *J. Am. Chem. Soc.* **1943**, 65, 1992.

They corrected the mechanism by suggesting that the acetoacetic acid esters undergo the [3,3] sigmatropic rearrangement with their respective allylic alcohols to give methyl ketones **70** and **71**.

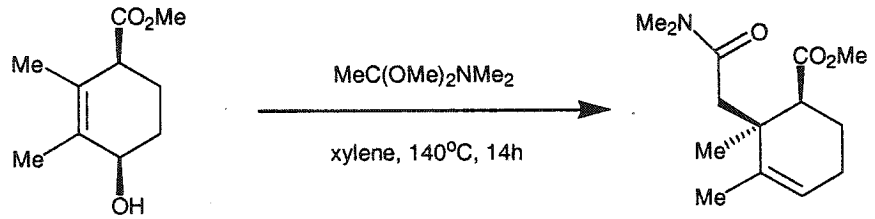


Scheme 1.17: Carroll's investigations of acetoacetic ester and allylic alcohols.

Two additional variations of the Claisen rearrangement came from the contributions of two independent chemists. The first, Eschenmoeser, realized the [3,3] sigmatropic rearrangement of amides.[41] In a typical example, substrate **72** underwent the rearrangement process to form the γ,δ unsaturated amide **73** (Scheme 1.18). The second, Johnson, examined the acid-catalyzed exchange of orthoesters with allylic alcohols and the ensuing sigmatropic rearrangement.[42] In the presence of ethyl orthoacetate and propionic acid, compound **74** underwent the rearrangement to produce the γ,δ unsaturated

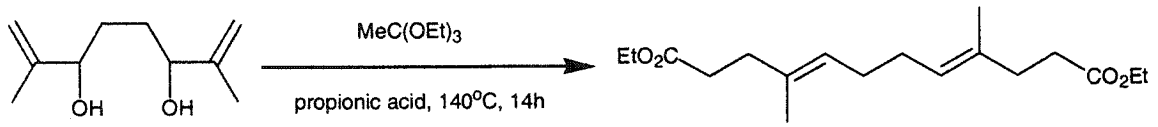
[41] (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, 47, 2425. (b) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, 52, 1030.
[42] Johnson, W.S.; Werthemann, L.; Bartlett, W. R.; Brocksom, R. J.; Li, T.; Faulkner, D.J.; Petersen, M. R. J. Am. Chem. Soc. **1970**, 92, 741.

amide **75** (Scheme 1.19). Fittingly, these reactions are currently referred to as the Eschenmoeser-Claisen and the Johnson-Claisen rearrangements.



72 **73**

Scheme 1.18: The Eschenmoeser-Claisen rearrangement.

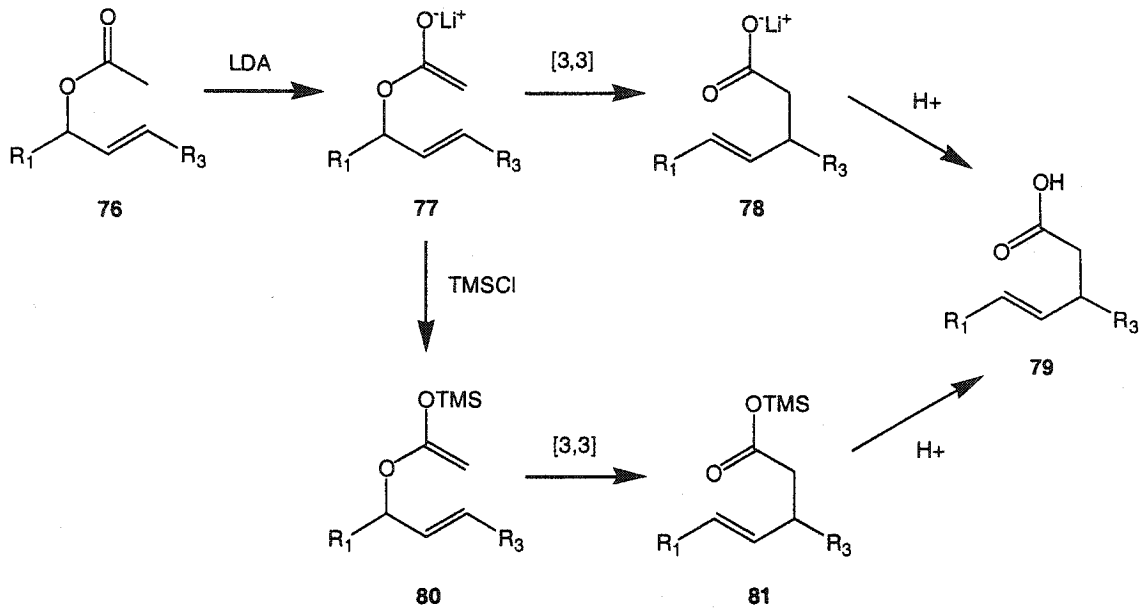


74 **75**

Scheme 1.19: The Johnson-Claisen rearrangement.

One of the most widely used adaptations is the Ireland-Claisen rearrangement.[43] It utilizes trapped ester enolates to accelerate the reaction. The generalized structure of unsaturated ester **76** can be deprotonated with LDA to give the trapped enolate **77** (Scheme 1.20). Lithium or potassium is often used as a counterion. This trapped enolate can then undergo the [3,3] rearrangement to form **78**, which can be hydrolyzed under acidic conditions to give **79**. Alternatively, silyl enol ethers can be used to trap the enolate. Enolate **77** can react with trimethylsilylchlroride (TMSCl) to give the trapped enolate **80**. Like **77**, this intermediate can similarly undergo a rearrangement to form **81**, which hydrolyzes to give **79**. Whether a metal or silyl group is used to trap the enolate, both pathways yield the same product.

[43] Ireland, R.E.; Mueller, R.H. *J. Am. Chem. Soc.* **1972**, 94, 5897.

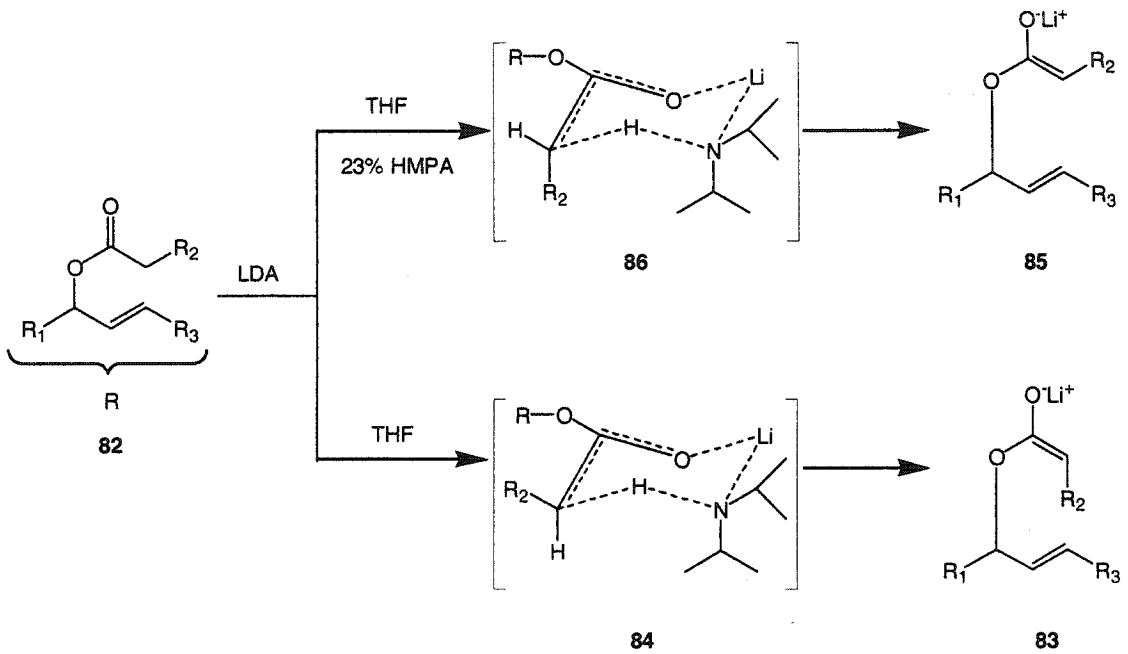


Scheme 1.20: The Ireland-Claisen rearrangement.

As previously mentioned, the relative configuration of the starting material, including the conformation of the enolate, dictates the relative stereochemistry of the product. As shown by Ireland and coworkers, enolate geometry can be controlled under kinetic conditions.[44] They showed that either enolate isomer of a propionate ester can be generated selectively by varying the choice of reaction solvent. Relevant steric interactions would then dictate the favored product, since they raise the energy level of one transition state compared to the other. In the case of ester **82** in THF, unfavorable non-bonded interactions arise between the isopropyl group of LDA and R_2, thus leading to preferential formation of the E-enolate **83** through a lower energy transition state **84** in which the R_2 group is equatorial (Scheme 1.21). When 23% HMPA in THF is used as the solvent, a reversal in selectivity is observed. That is, ester **82** leads to the preferential formation of the Z-enolate **85** through the lower energy transition state **86**. By using

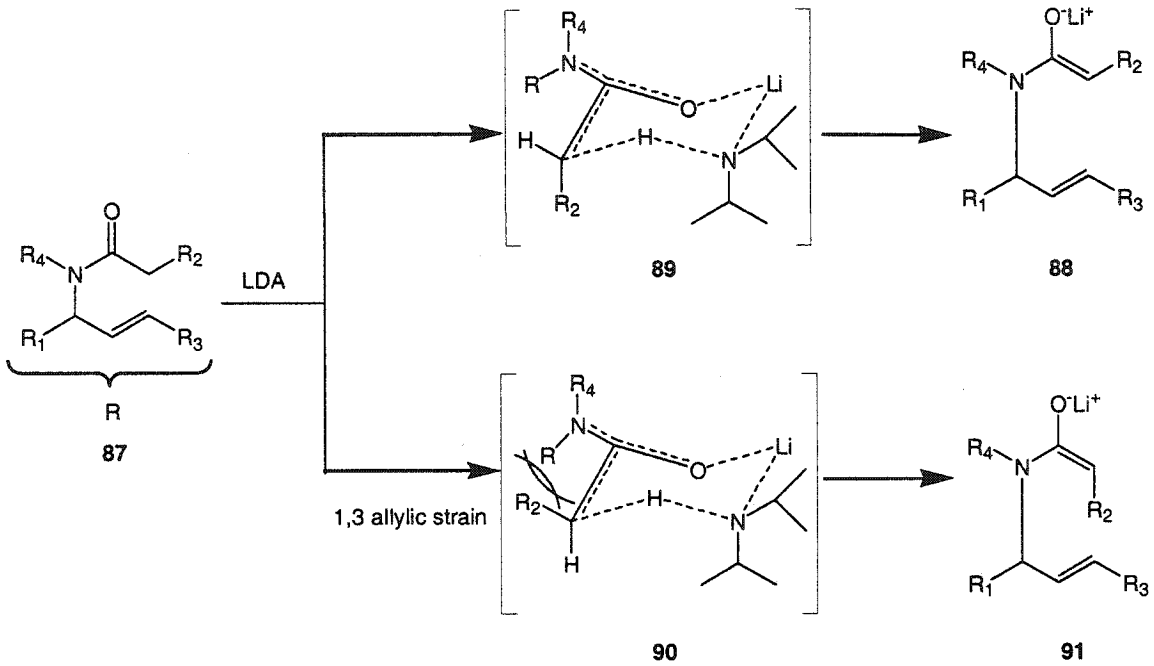
[44] (a) Ireland, R. E.; Wipf, P.; Armstong III, D. *J. Org. Chem.* **1991**, 56, 650. (b) Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, 56, 3572. (c) Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976**, 98, 2868.

HMPA and THF as solvent, the Li-O bond is considerably weaker. This results in a loosely held transition state which, in essence, makes the eclipsing interaction between OR and R_2 more important than the 1,3 diaxial interaction between R_2 and LDA. Thus, both E and Z enolates are accessible depending on the reaction conditions.



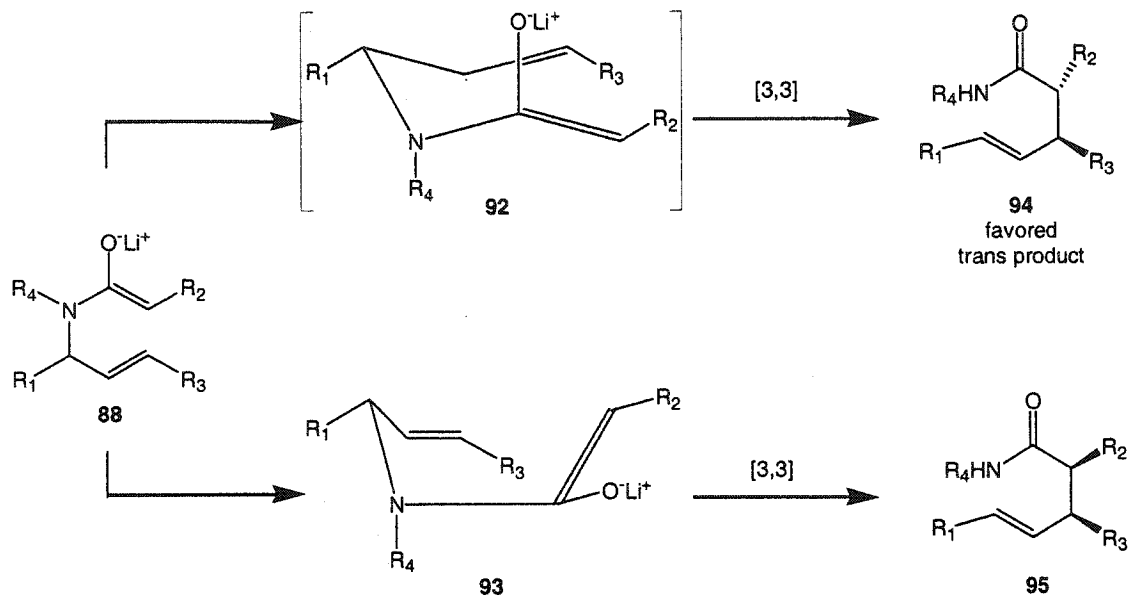
Scheme 1.21: Effect of changing solvent on the formation of Z and E enolates.

By replacing the ester with the tertiary amide **87**, a similar reaction, known as an aza-Ireland-Claisen rearrangement, occurs. In this case, however, there is exclusive formation of the Z-enolate **88** through a lower energy transition state **89** (Scheme 1.22). The amide functionality is essentially planar due to resonance between the nitrogen and the carbonyl group. With tertiary amides, this imposed rigidity results in high steric repulsion between R_2 and the nitrogen substituents. Accordingly, a higher energy transition state **90** is predicted for the E-enolate **91**. The interactions between R_2 and the base are less severe than this aforementioned 1,3 allylic strain.



Scheme 1.22: Exclusive formation of Z enolate in tertiary amides.

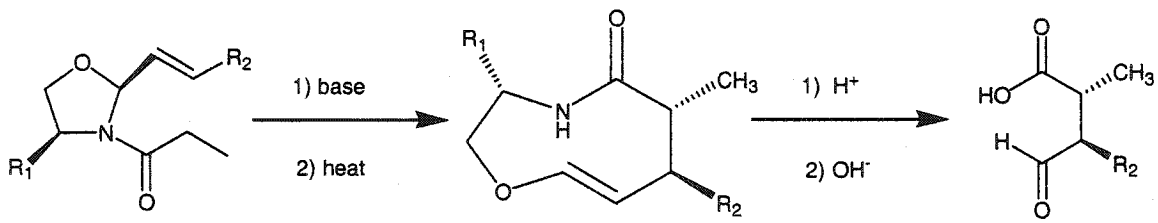
In addition to favored formation of the Z enolate **88** in tertiary amides, the diastereoselectivity of the reaction is enhanced if one looks at the possible chair and boat transition states of the rearrangement (Scheme 1.23). The chair transition state **92** is more stable because of the destabilizing eclipsing interactions between the R_2 and OLi groups present in the boat transition state **93**. Thus, along with the Z enolate formed from tertiary amides, the stable chair transition state drives the formation of a diastereoselective trans product **94** over the cis product **95**.



Scheme 1.23: Chair versus boat transition states in the aza-Ireland-Claisen rearrangement.

Project Goals

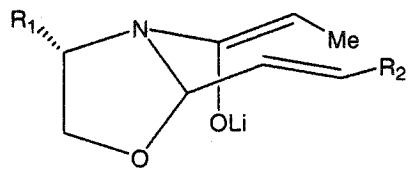
The major objective for this project was to determine the feasibility of the aza-Ireland-Claisen rearrangement on oxazolidine moieities (Scheme 1.24). Starting with chiral amino alcohols, oxazolidines **96** were to be synthesized. The rearrangement would then be evaluated under various conditions. A key feature of the rearrangement is the stereospecific formation of two new chiral centers in the product **97**, using the preexisting chiral center on the oxazolidine ring to determine the absolute configuration. Subsequent cleavage of the chiral auxiliary would yield highly functionalized subunits **98**, with two contiguous stereogenic centers.



96 97 98

Scheme 1.24: Aza-Ireland-Claisen rearrangement of oxazolidine moiety.

From the discussion above concerning enolate geometry and transition states, the rearrangement product **97** would be expected to pass through a transition state **99** as shown in Figure 1.5. Once again, due to eclipsing steric interactions, the boat transition state would be higher in energy.



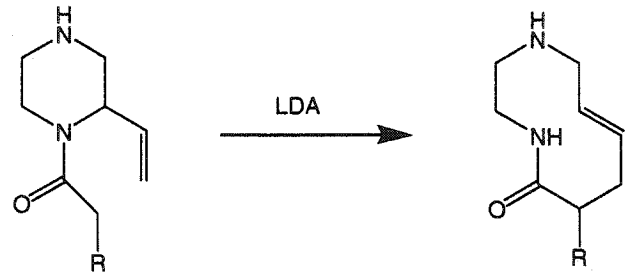
99

Figure 1.5: Expected transition state of aza-Ireland-Claisen rearrangement.

Literature Precedence

In 1996, Suh and coworkers performed a similar aza-Ireland-Claisen rearrangement on N-acyl-2-vinylpiperidines **100** but the reaction was not asymmetric (Scheme 1.25).[45] The result, upon treatment with LDA is the ten-membered ring macrocycle **101**.

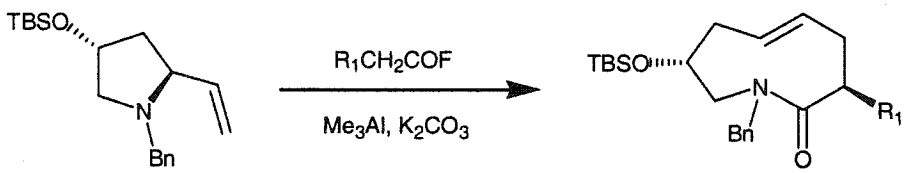
[45] Suh, Y-G.; Lee, J-Y.; Kim, S-A.; Jung, J-K. *Synth. Comm.* **1996**, 26, 1675.



100 101

Scheme 1.25: Aza-Ireland-Claisen rearrangement of N-acyl-2-vinylpiperidines.

A more recent example describes a diastereoselective zwitterionic aza-Claisen rearrangement of the vinyl pyrrolidine **102** with carboxylic acid fluoride derivatives (Scheme 1.26).[46] The reaction is carried out in dichloromethane in the presence of K_2CO_3 and trimethylaluminum. The result, in this case, is the nine-membered ring macrocycle **103** showing strong similarity to the one being attempted herein. The rearrangements described in this paper diastereoselectively led to products containing an E double bond as well as trans relationships between the OTBS and R_1 groups.



102 103

Scheme 1.26: A diastereoselective zwitterionic aza-Claisen rearrangement.

With this theory and background, both projects were attempted. The next section discusses the results obtained from both, the para- and ortho-C alkylations as well as the aza-Ireland-Claisen rearrangement.

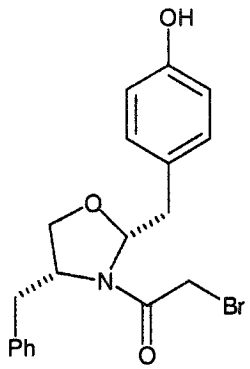
[46] Sudau, A.; Munch, W.; Nubbenmeyer, U. *J. Org. Chem.* **2000**, 65, 1710.

Chapter 2: Results and Discussion

2.1 Quaternary Centers by Para- and Ortho-C Alkylations

Synthesis of Spirodieones 113 and 123

With a plan in place, our first synthetic target was compound **104**. This would be the precursor required to test the potential success of the para-C-alkylation.



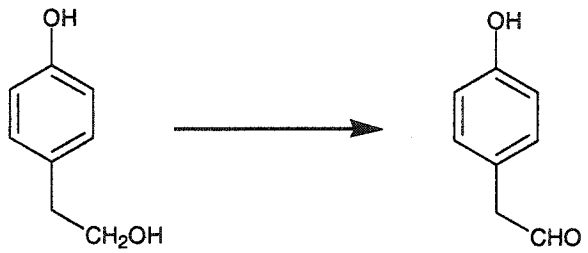
104

Figure 2.1: Precursor required in testing the para-C-alkylation.

Our initial attempts to synthesize **104** had explored the seemingly logical option of starting with the commercially available alcohol **105**. However, oxidation of the alcohol derivative **105** did not occur with any great success. As outlined in Table 2.1, numerous oxidations were attempted in order to obtain the aldehyde **106**. Swern (Entry 1) and Swern-like conditions (Entry 2[47] and 4) using dimethyl sulfoxide (DMSO), as well as catalytic conditions employing tetra-n-propylammonium perruthenate (TPAP) were tried and tested. Unfortunately, all efforts failed with the consequence of planning a different synthesis of precursor **104**. Already, a bump in the road!

[47] De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, 66, 7907.

Table 2.1: Oxidative conditions tested in an attempt to form aldehyde 106.

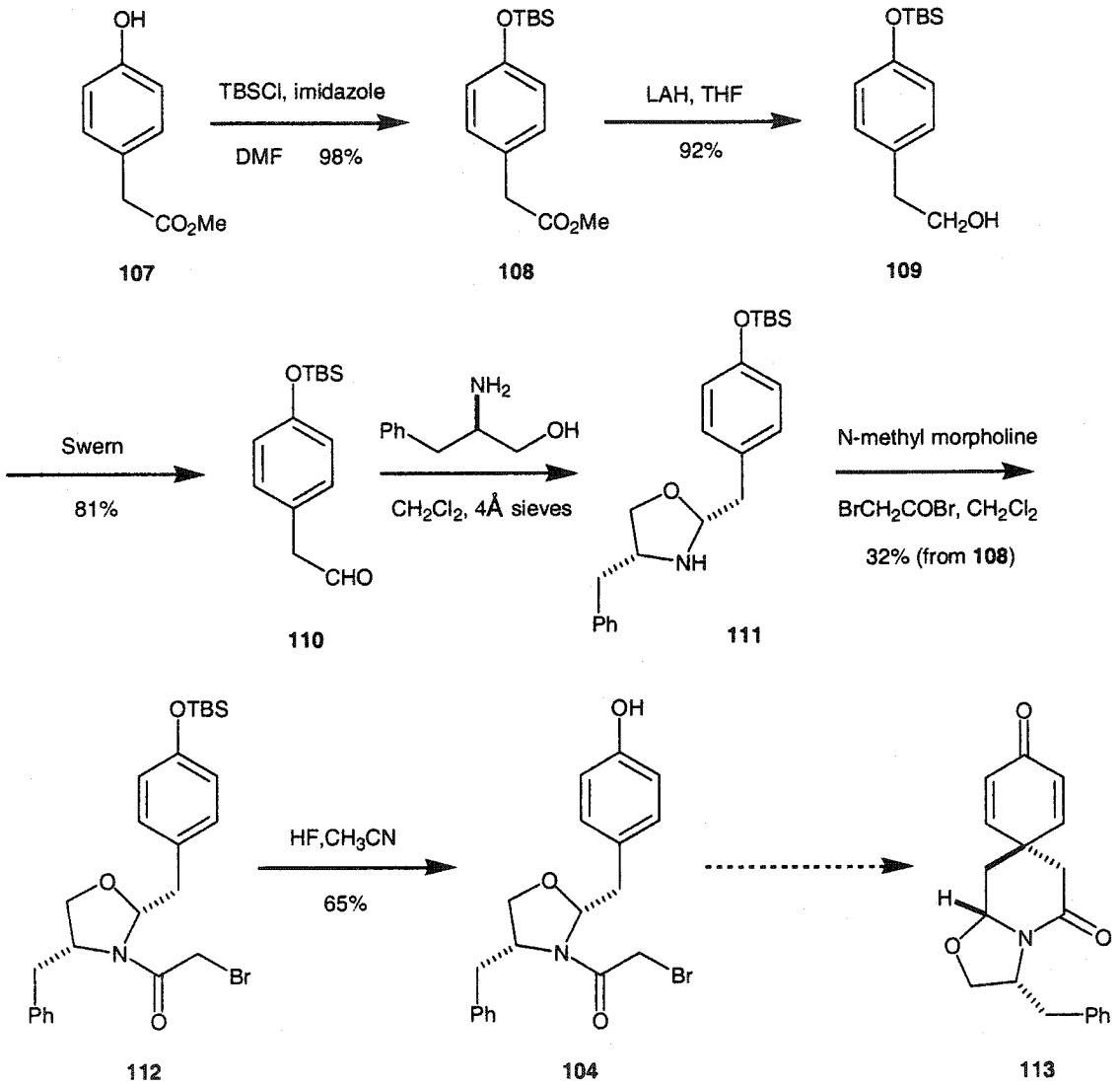


105 106

Entry	Oxidative conditions	Solvent	% Yield
1	DMSO, oxalyl chloride, triethylamine	CH_2Cl_2	0
2	DMSO, trichloro-triazole, triethylamine	THF	0
3	TPAP, N-methyl morpholine oxide	CH_2Cl_2	0
4	DMSO, SO_3-pyridine, triethylamine	CH_2Cl_2	0

The synthesis of the required aldehyde and ultimately precursor **104** was envisaged to occur following the pathway outlined in Scheme 2.1. The protection of phenol **107** proceeded smoothly to produce the tert-butyldimethylsilyl-protected phenol **108** in a near quantitative yield. With the protected ester **108** in hand, the reduction to alcohol **109** was easily performed, followed by Swern oxidation to give aldehyde **110**. The Swern protocol worked quite well on small scale. However, when a scale up would be attempted, the best yield for this reaction was 52% - a near 30% drop in yield. Accordingly, other possibilities for oxidative conditions were examined, such as those listed in Table 2.1 as well as a pyridinium dichromate oxidation. Unfortunately, none of

these showed improvement over the Swern. With aldehyde **110** in hand, the synthesis of the oxazolidine moiety **112** was undertaken.



Scheme 2.1: Synthetic route to test the para-C-alkylation.

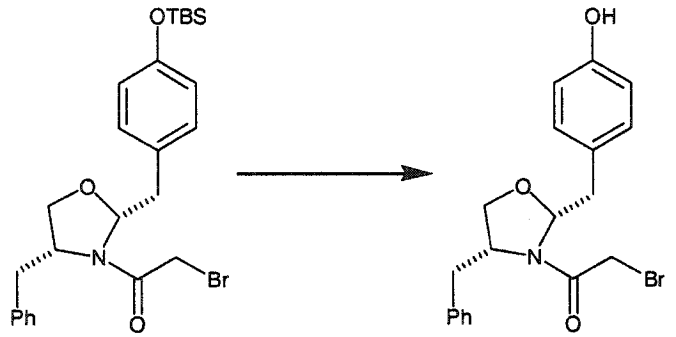
The selective formation of cis oxazolidines from aldehydes and amino alcohols is not without precedent and was not expected to be problematic.[48] However, this reaction turned out to be challenging as the trans product would always be formed along with the

[48] (a) Waldemar, A.; Peters, K.; Peters, E.-M.; Schambony, S.B. *J. Am. Chem. Soc.* **2000**, 122, 7610. (b) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *J. Org. Chem.* **1997**, 62, 2106.

cis. Even though reaction conditions were tweaked, the best yield for this reaction was 52% with the cis oxazolidine **112** accounting for 32% and the trans oxazolidine for 20%. Despite this low yield, the reaction sequence was carried forward since the para-C-alkylation could be tested after one more step.

Next, the deceivingly simple task of deprotecting the tert-butyldimethylsilyl (TBS) group was undertaken. Table 2.2 illustrates the numerous attempts made in order to remove this protective group. Initially, acidic conditions were used to obtain phenol **104**. These attempts (Entries 1 - 3) were either fruitless or extremely low-yielding. At low concentrations of HCl, the reaction was either incomplete or low yielding. A mixture of acetic acid, water and tetrahydrofuran (THF) was also tested (Entry 4) but starting material was the only product after 36 hrs. Deprotection with tetrabutyl-ammoniumfluoride (TBAF) was another dead end (Entry 5). After a reaction time of 15 minutes, the starting material had disappeared but nothing was visible on TLC except for a baseline spot. Increasing the polarity of the solvent system did not affect the mobility of this baseline product. It was originally predicted that the oxazolidine moiety may be a sensitive group. Next, HF·pyridine and HF·acetonitrile (HF·CH_3CN) deprotection conditions were used (Entries 6 and 7 respectively). Both reactions showed promise. The HF in CH_3CN gave a modest 32% yield the first time around but this was improved to 65% by decreasing the concentration of the 48% HF solution to 24%. Overnight reaction time was necessary to complete the reaction but nevertheless compound **104** was synthesized.

Table 2.2: Deprotection of TBS group to form 104.

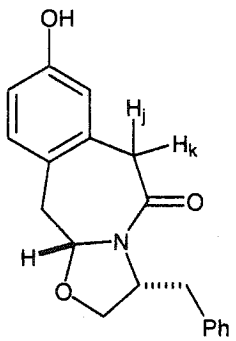


112 104

Entry	Reagents / Solvent	Conditions	% Yield
1	5% HCl / THF	RT, 48 hrs	All starting material
2	10% HCl / THF	RT, 30 hrs	6
3	10% HCl / THF	66 °C, 30 hrs	10
4	AcOH / H_2O, THF	RT, 48 hrs	All starting material
5	TBAF, THF	RT, 15 min.	Baseline spot
6	48% HF / pyr., THF	RT, overnight	30%
7	24% HF / CH_3CN	RT, overnight	65%

Finally, after some unpredicted problems along the way, the precursor **104** was employed to investigate the feasibility of the para-C-alkylation in the formation of the 6-membered ring spiro compound **113** (Table 2.3). Several reaction conditions were applied. The conditions used by Winstein and Baird[28] as well as those used more recently by Boger[32] were first attempted. Accordingly, the bases tert-butoxide (t-BuOK) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) were tested. With t-BuOK in t-BuOH, several products were visible on TLC but only one could be isolated after purification (Product X). The reaction with DBU in CH_3CN only gave one product, the same product

X that was isolated from the t-BuOK reaction. In their attempts, Winstein and Baird warned of a variety of side reactions. These included solvolysis reactions as well as a dienone-phenol rearrangement of the formed spirocycle. Initial analysis of the NMR spectra of our product X led to the presumption that the rearrangement product **114** was being isolated (Figure 2.2). This initial conclusion was supported by some of the spectral data. For example, the phenyl region of the ^{1}H NMR integrated for 8 protons, not 9. Also, protons j and k resonated much further downfield relative to their shifts in compounds **112** and **104**, which suggested that a new product had been formed.



114

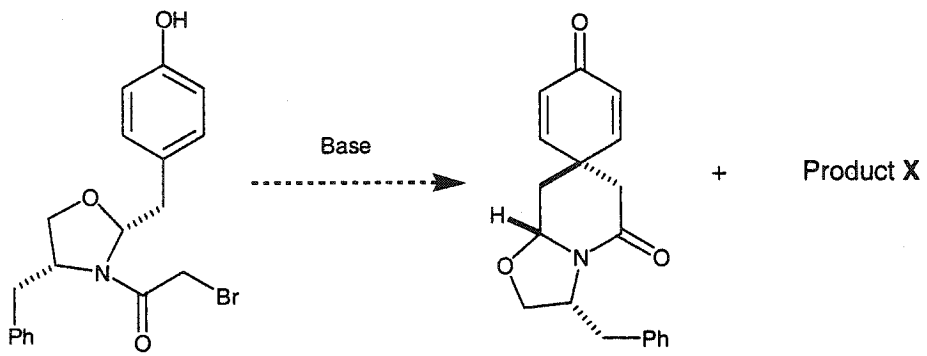
Figure 2.2: Structure originally suggested as the rearrangement product 114.

Besides DBU in CH_3CN and tert-butoxide in t-BuOH, several other base/solvent combinations were attempted with either starting material or the rearrangement product was the result. These bases included 1,4-Diazabicyclo[2.2.2]octane (DABCO), silver oxide and cesium carbonate (Table 2.3, entries 5-7). In all cases, either starting material or decomposition was realized.

As mentioned previously in the introduction, an alternative mechanistic pathway was examined. Ward and Hughes showed that an oxidative pathway for forming spirodienones was possible.[34] Thus, the use of the hypervalent iodine compound phenyl iodonium bis(trifluoroacetate) (PIFA) in trifluoroethanol (TFE) was used in an attempt to

oxidatively form the spirocyclic compound **113** (Entry 8). This attempt proved to be futile as only baseline polar products were observed.

Table 2.3: Various attempts in the formation of compound 113.

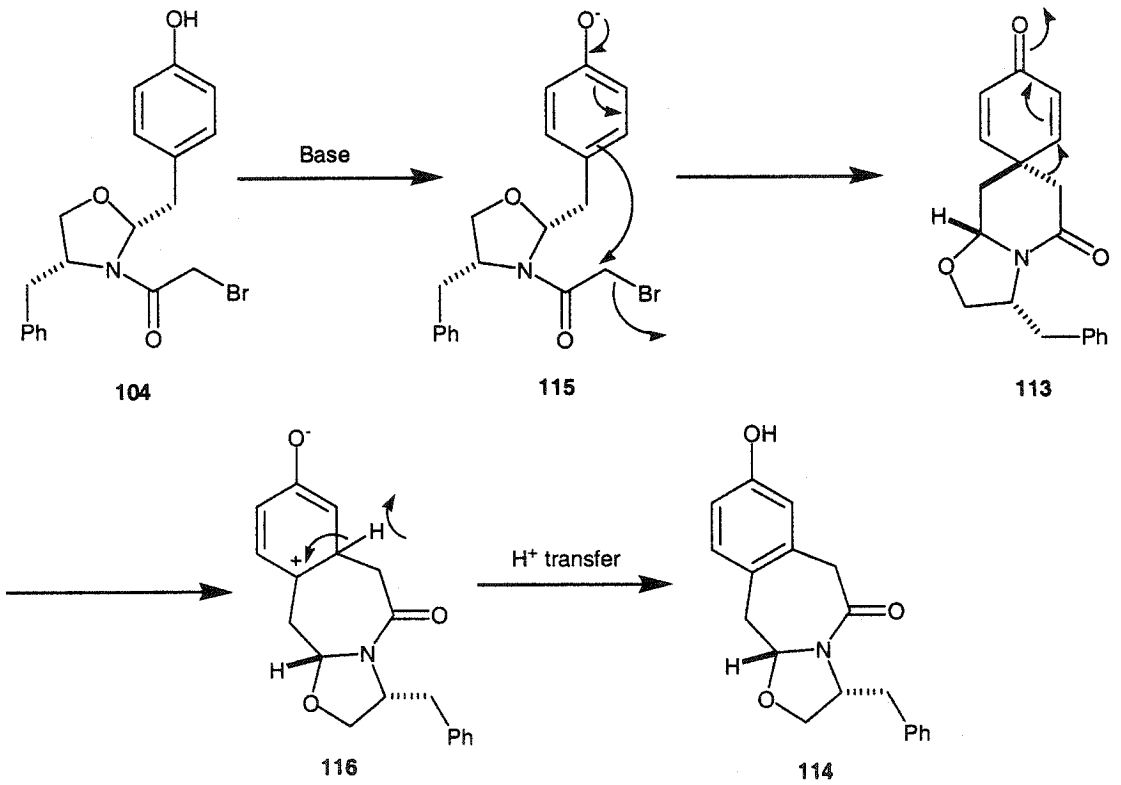


104 113

Entry	Base	Solvent	Conditions	% Yield of 113	% Yield of X
1	t-BuOK	t-BuOH	RT, 3h	0	20
2	t-BuOK	THF	0°C and RT, 3h	0	11
3	DBU	CH_3CN	RT, 3h	0	17
4	DBU	THF	RT, 3h	0	6
5	DABCO	CH_3CN	RT, 3h	0	0
6	Ag_2O	THF	RT, overnight	0	0
7	Cs_2CO_3	THF	RT, overnight	0	0
8	PIFA	TFE	RT, 30 min.	0	0

Hence, the results of the para-C-alkylation were interpreted in such a manner that rearrangement product **114** was thought to be forming. The mechanism of its formation is described in Scheme 2.2. Deprotonation of **104** would presumably form the phenoxide

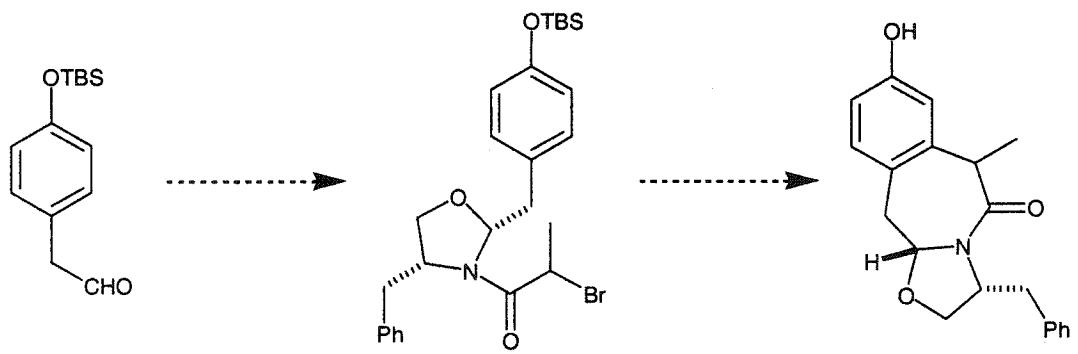
intermediate **115** which should go on to form the spirodienone **113**. Based on the mechanisms described by Winstein and Baird, it is believed that the dienone-phenol rearrangement would proceed through the spirocyclic intermediate **113**. This material contains a potent Michael acceptor and nucleophile in close proximity. Accordingly, the ionic intermediate **116** could be formed and the dienone-phenol rearrangement product **114** would result by regenerating aromaticity.



Scheme 2.2: Mechanistic pathway for the dienone phenol rearrangement product.

Since this product was thought to have been acquired, it was postulated that, under the right conditions, a new chiral center could be formed at the α position of the amide. As the rearrangement occurs, the chiral center will migrate to the expected α position. Consequently, we diverted our attention to the synthesis of oxazolidine **117** from aldehyde **110** in the hopes of synthesizing the rearrangement product **118**, with the

new chiral center in place (Scheme 2.3). However, attempts to form the oxazolidine **117** using similar reaction conditions to those described above were futile, leading to the decomposition of the oxazolidine into a side-product. The structure of the side product was elucidated by NMR interpretation to be compound **119**. As a whole, the ^{1}H NMR spectrum showed conclusively that a product other than the intended oxazolidine was being formed. The integration of the phenyl region was 5, there was a quartet at 5.3 ppm integrating for 1 (H_a), a multiplet around 4.4 ppm integrating for 4 protons (H_b, H_c, H_d and H_e) and two doublets further upfield each integrating for 3 protons indicating the presence of two methyl groups (Figure 2.3). Also, the ^{13}C showed two peaks in the amide region at 169 and 170 ppm respectively.



Scheme 2.3: Synthetic strategy for the formation of the rearrangement product 118.

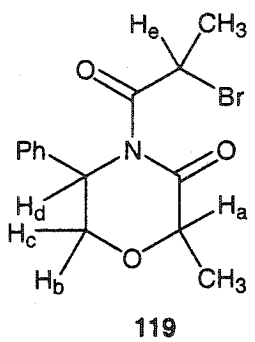
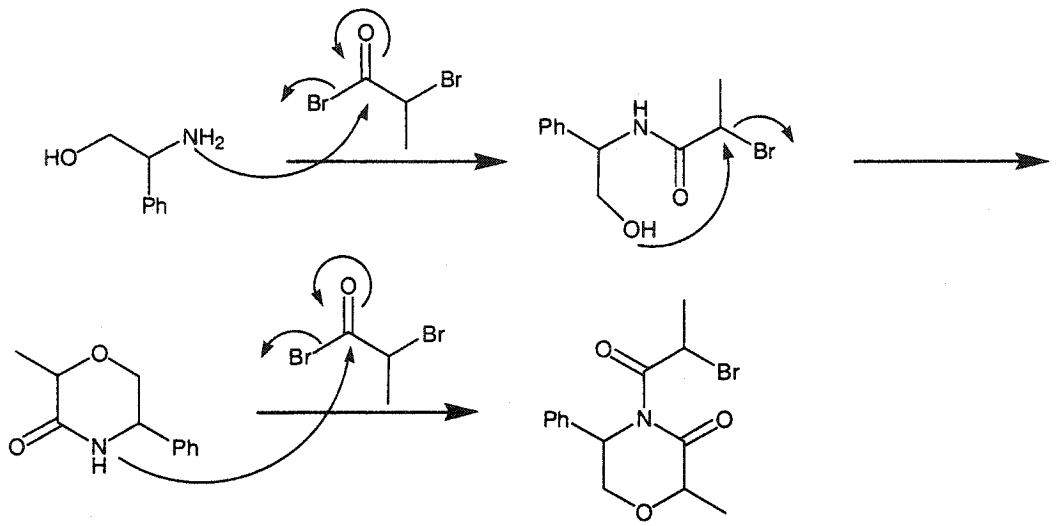


Figure 2.3: Side product 119 of an attempted oxazolidine-forming reaction.

The mechanism for the formation of this cleaved product is outlined in Scheme 2.4.

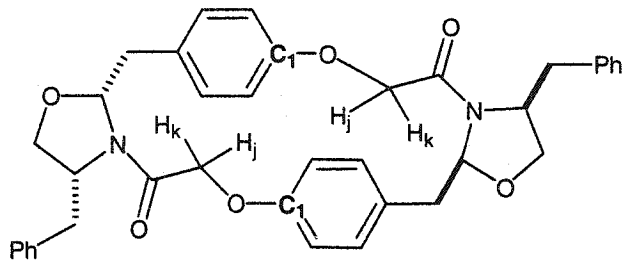


119

Scheme 2.4: Mechanistic pathway to the formation of the sideproduct 119.

Concurrently with the attempts to form oxazolidine **117**, we resubmitted the presumed rearrangement product for mass spectral analysis using a different ionization protocol (CI). Upon subsequent reanalysis of the spectra, we noticed that the mass spectrum contained a peak at 618 amu. The expected spirocyclic product would have had a mass of 309 amu. With this new information, a reevaluation of the NMR data was in order to determine whether our product X arose from a dimerization reaction or a dienone-phenol rearrangement. First of all, the ^{13}C NMR only showed 15 peaks. If the rearrangement product **114** was correct, we should expect a total of 17 different carbons, not 15. Initially, we had assumed that some resonances overlapped. Second, the fact that protons j and k are so far downfield would better be explained with the dimerization product since they would now be adjacent to an oxygen atom (Figure 2.4). Finally, the HMBC of product X showed that protons j and k "see" the carbonyl carbon of the amide

as well as the carbon of the aromatic group, C_1. From this, along with the new mass of 618 amu, we concluded that a dimerization reaction and not a dienone-phenol rearrangement was the dominant process. In other words, product X is the dimer **120** and not compound **114.**



120

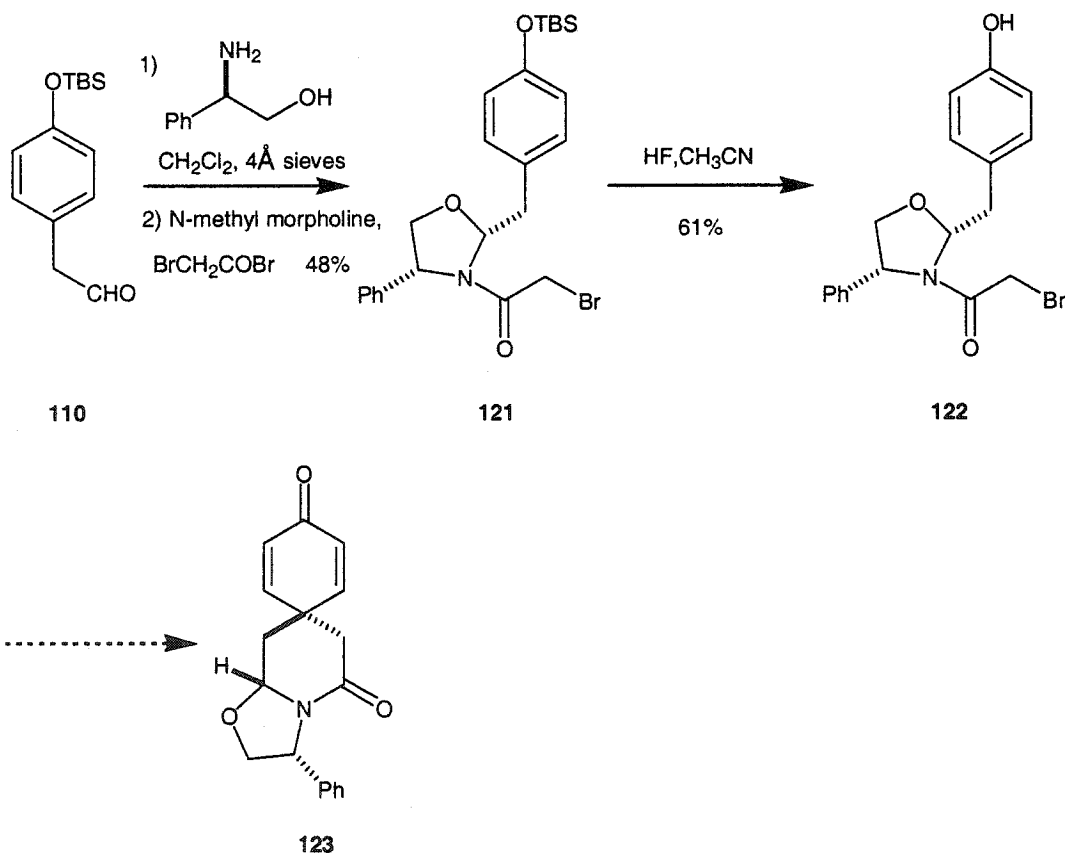
Figure 2.4: Structure of the dimerized product.

Dimerization was another side reaction that Winstein and Baird observed with their substrate. Despite future attempts to disfavor dimerization by using very dilute reaction conditions and the dropwise addition of substrate to the base, the spirocyclic compound **113** could never be observed (Table 2.4). Only dimerized product **120** could be isolated. Needless to say, attempts to form oxazolidine **117** ceased.

Table 2.4: Diluting the reaction mixture to disfavor dimerization.

Entry	Base (concentration)	Solvent	Conditions	% Yield of 113
1	DBU (0.03M)	CH_3CN	RT, 3h	0
2	DBU (0.001M)	CH3CN	RT, 3h	0
3	DBU (0.005M)	THF	RT, 3h	0
4	t-BuOK (0.005M)	t-BuOH	RT, 3h	0
5	t-BuOK (0.005M)	THF	RT, 3h	0

With aldehyde **110** in hand, other analogues of oxazolidine **112** were constructed to test the para-C-alkylation. First, S-phenylglycinol was used in place of S-phenylalaninol to produce the cis oxazolidine **121** (Scheme 2.5). This substrate would also be advantageous in that the ^{1}H NMR spectra of this and subsequent derivatives would be simplified. The trans and cis oxazolidines were synthesized once again, using N-methyl morpholine and bromoacetyl bromide. Subsequent deprotection of **121** with HF in acetonitrile gave the precursor **122**. Similar conditions to those discussed above in Table 2.3 and Table 2.4 were attempted. Once again, the spirodienone **123** was not observed as a product of the reaction.

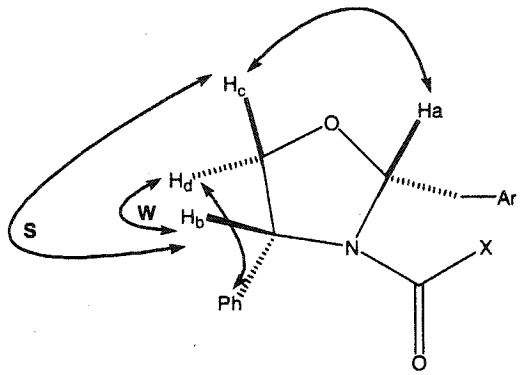


110 **121** **122**

123

Scheme 2.5: Formation of an analogous substrate to test the para-C-alkylation.

The cis oxazolidine stereochemistry was assigned with the help of nOe difference experiments. Figure 2.5 shows the distinguishing interactions. The cis geometry was reinforced by the strong interaction (S) between H_b and H_c as compared to the weak interaction between H_b and H_d (W) along with the fact that H_c also interacts with H_a.[49]

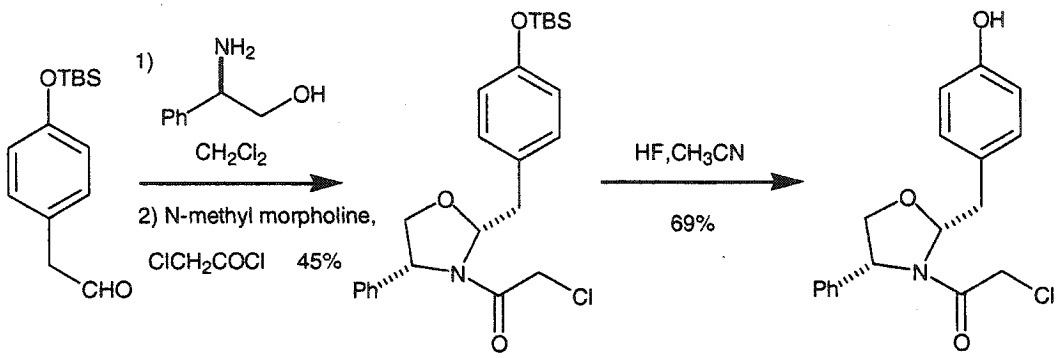


121

Figure 2.5: The important nOe interactions for the cis oxazolidine 121.

Since the dimer was forming, we decided to evaluate the effect of the leaving group on the reaction by substituting chlorine for bromine. Thus, we constructed the chloro analogue **124** (Scheme 2.6) using a similar sequence to that of the bromo analogue **121** (Scheme 2.5), by simply replacing bromoacetylbromide with chloroacetylchloride. Subsequent deprotection with HF in CH_3CN gave the cyclization precursor **125**. Unfortunately, the chloro analogue was found to be very unreactive under the same conditions listed in Tables 2.3 and 2.4 returning starting material time and time again.

[49] Bernstein, M.A.; Morton, H.E.; Guindon, Y. *J. Chem. Soc. Perkin Trans. II* **1986**, 8, 1155.



110 124 125

Scheme 2.6: Using chlorine as the leaving group to test the para-C-alkylation.

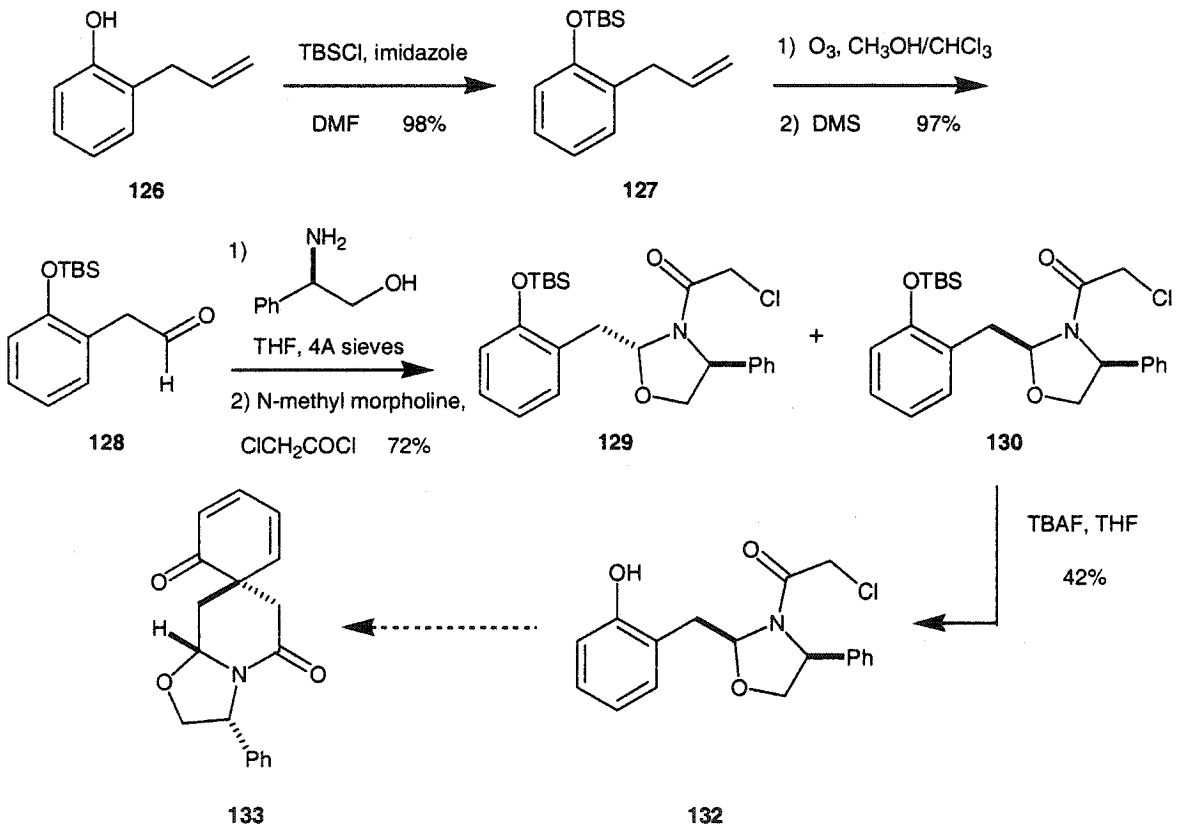
Synthesis of 133, the Ortho Derivative of Spirodienone 123

Several variations of the para-C-alkylation methodology were envisaged. At that point in time, we did not know that the dimerization would take place preferentially. Accordingly, the idea of alkylation through the use of a phenoxide ion was adapted to an ortho version. The ortho-C-alkylation synthetic route is delineated in Scheme 2.7 and was undertaken by an undergraduate student, Val Charbonneau, under my supervision. Since some of our target molecules necessitated this ortho substituent relationship, concurrent efforts were put forth to test the compatibility of this reaction.

Different pathways were explored but the best results were obtained when 2-allylphenol (**126**) was used as the starting material. The phenolic oxygen was successfully protected as the TBS silyl enol ether **127** as it was in the para-C-alkylation reaction scheme. Next, an ozonolysis of the allyl group followed by quenching with dimethyl sulfide (DMS) afforded aldehyde **128** in an excellent yield. Both of these reactions proceeded with greater than 95% conversion.

Next, we tried the oxazolidine-forming condensation reaction of aldehyde **128** with S-phenylglycinol. The trans and cis oxazolidines **129** and **130** were formed in a

similar manner as described for the para-C-alkylation. However, solvent and temperature optimization studies were carried out to establish reaction conditions that would favor the cis oxazolidine (Table 2.5). The effects of temperature and length of time using CH_2Cl_2 as solvent were examined (Entries 1-3). The results were not encouraging as the yield of the reaction decreased and the diastereoselectivity was not improved. It was consequently proposed to test the effects of changing solvent.

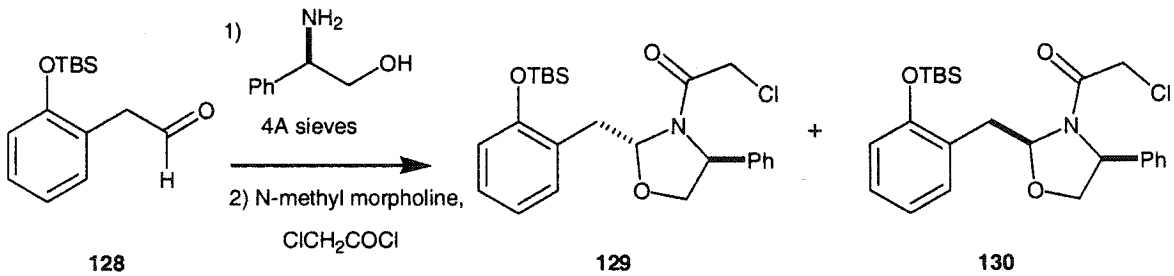


Scheme 2.7: Synthetic route to test the ortho-C-alkylation.

As seen by entry 4, switching to a more polar solvent like DMF resulted in 0 % formation of any oxazolidine product. With toluene as the solvent, a high diastereomeric ratio was obtained but the yield could never be brought higher than 12 % (Entry 5). Heating (Entry 6) the reaction and lengthening the reaction time (Entry 7) both increased the yield but

the diastereoselectivity was once again reduced to 1:1. Cooling the reaction to -78°C in toluene resulted in only a trace amont of oxazolidine being formed (Entry 8). Finally, by switching the solvent to THF (Entry 10), the ratios of cis to trans oxazolidine increased from 60:40 to 88:12. With xylene as the solvent (Entry 9), a favorable ratio was also obtained but for reasons of ease of purification, THF was chosen as the solvent. The optimum temperature for the cis oxazolidine formation was determined to be room temperature. Also worthy of mention is that 4 Å activated sieves were necessary for the success of the reaction.

Table 2.5: Optimization of reaction conditions to favor the formation of cis oxazolidines.

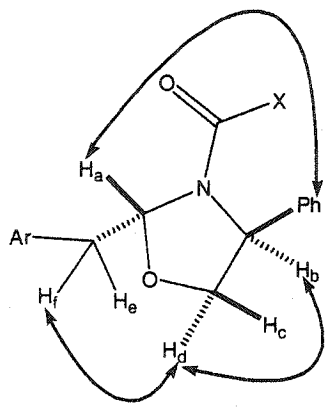


128 129 130

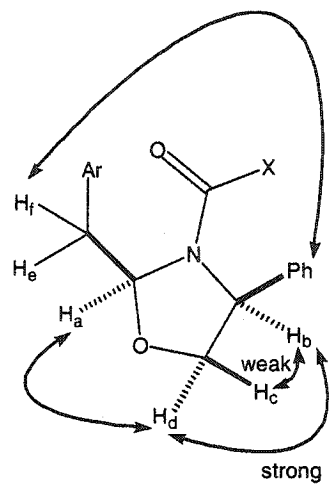
Entry	Solvent	Conditions	% Yield	Ratio (129:130)
1	CH_2Cl_2	RT, 3h	44	1:1.5
2	CH_2Cl_2	0 °C, 3h	25	1:1
3	CH_2Cl_2	RT, 24h	20	1:1
4	DMF	RT, 3h	0	n/a
5	Toluene	RT, 3h	12	1:30
6	Toluene	Reflux, 1.5h	52	1:1
7	Toluene	RT, 24h	60	1:1

8	Toluene	-78 °C, 3h	Trace	1:1
9	Xylene	RT, 3h	67	1:7
10	THF	RT, 3h	72	1:7

The stereochemistry of the oxazolidines formed was determined by through-space NMR experiments. In this case, a NOESY was used to verify the stereochemistry. Figure 2.6 shows two networks of the important nOe interactions for oxazolidines **129** and **130** that are consistent with the assigned relative stereochemistry. Although the spectra were similar in many respects, a few combined distinctions in the two spectra allowed us to distinguish the two isomers. For isomer **129**, the nOe interactions between H_b and H_f as well as the ones between H_a and the phenyl protons (Ph) support the trans relationship of the oxazolidine moiety. Noteworthy for the cis isomer **130** is the stronger interaction between protons H_b and H_d compared to the interaction between H_b and H_c coupled with the fact that H_a only interacts with H_d, and not H_c.[49] Also, H_f gave a cross peak with the phenyl (Ph) protons reinforcing the cis geometry assignment of oxazolidine **130**.



129

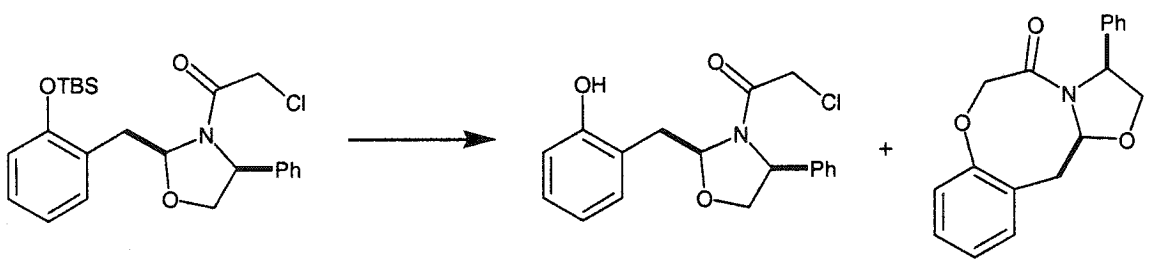


130

Figure 2.6: The nOe interactions of trans oxazolidine 129 and cis oxazolidine 130.

Once again, the deprotection of the TBS group proved to be a formidable challenge (Table 2.6). Several conditions were attempted, including a 10% HCl solution, HF in CH_3CN and NaF/HF buffer[50] solution (Entries 1-3). The best yields (42% and 43%) were obtained by the use of TBAF at -78 °C (Entry 5) and HF-pyridine (Entry 4) at RT respectively. A faster reaction time and less hazardous conditions prompted the adoption of the TBAF protocol. To our unfortunate surprise, a side product formed when TBAF was used at room temperature (Table 2.6 Entry 6). The product, **131**, was identified as the 8-membered ring lactam fused to the aromatic ring. This reaction is the result of a direct Sn2 displacement of the chlorine by the oxygen nucleophile. If this reaction occurs without the presence of a base, one could imagine that the ortho-C alkylation will probably not be favored when a base is added.

Table 2.6: Deprotection of the TBS protected phenol 130.



130 132 131

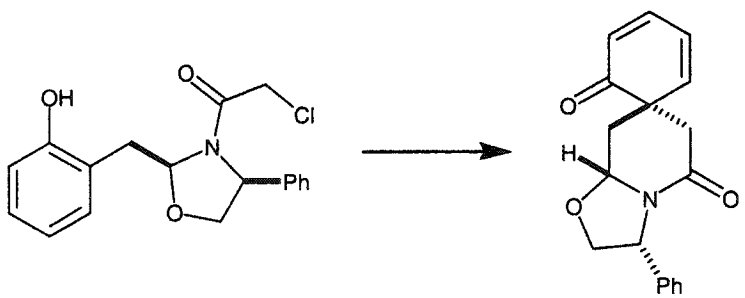
Entry	Reagent	Solvent	Conditions	% Yield 132
1	10% HCl	THF	RT, overnight	14
2	HF	CH_3CN	RT, 3h	7
3	NaF/HF (pH=5)	THF	RT, overnight	21

[50] Kandall, P.M.; Johnson, J.V.; Cook, C.E. *J. Org. Chem.* **1979**, 44, 1421.

4	HF-pyridine	THF	RT, 1h	43
5	TBAF	THF	-78 °C, 15 min.	42
6	TBAF	THF	RT, 15 min.	9% of **131**

Despite this fact, the ortho-C alkylation of **132** was attempted with a number of different bases in an effort to synthesize the spirocyclic product **133**. However, none of this product was observed (Table 2.7). In each case, only compound **131** could be isolated.

Table 2.7: Attempted formation of spirocyclic product via ortho-C-alkylation.

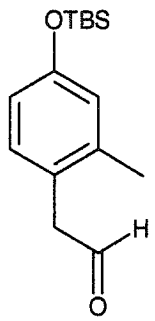


132 **133**

Entry	Base	Solvent	Conditions	% Yield of 133
1	NEt_3	THF	RT, overnight	0
2	$NaHCO_3$	THF	RT, 20 min.	0
3	DABCO	THF	RT, 10 min.	0
4	DBU	THF	RT, 25 min.	0
5	Cs_2CO_3	THF	RT, 45 min.	0

Synthesis of Spriodienone 150, an Analogue of 123

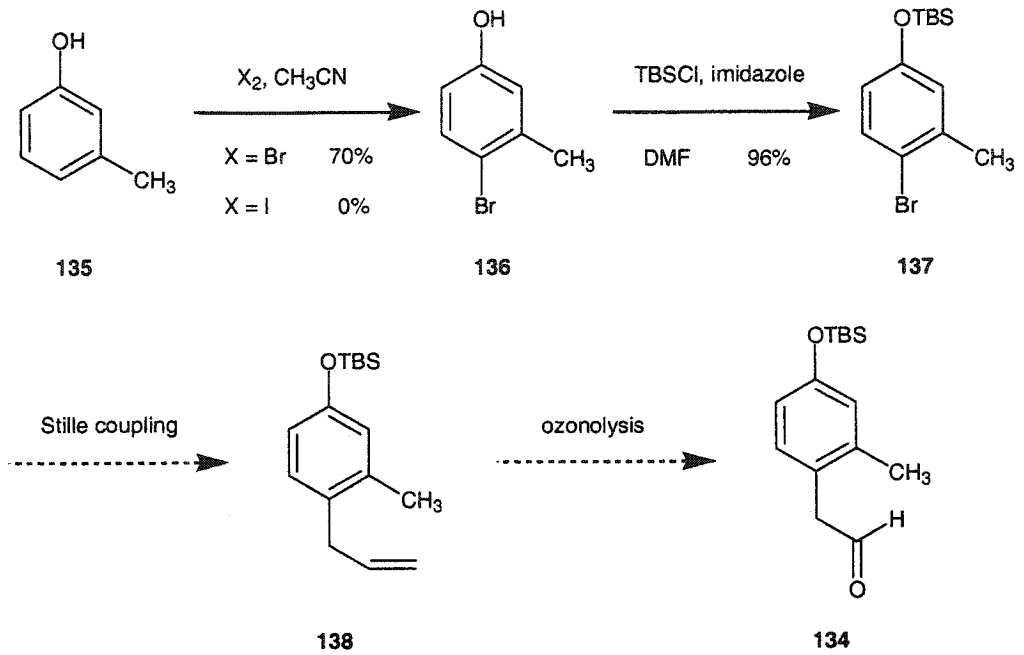
The last substrate that we attempted to synthesize through this diastereoselective alkylation reaction was very similar to compound **123** except that there was an extra methyl substituent meta to the carbonyl functionality of the dienone group. This substrate was being tested since some of our target molecules have a substituent on the phenyl ring in that position. Several synthetic strategies were evaluated and implemented to obtain aldehyde **134** (Figure 2.7).



134

Figure 2.7: Common aldehyde target of several synthetic plans.

Initially, the fastest synthetic route envisaged a Stille coupling of an aromatic bromide or iodide with a vinyl or allyl tin reagent, followed by oxidative reactions to obtain aldehyde **134**. This synthetic route is outlined in Scheme 2.8.



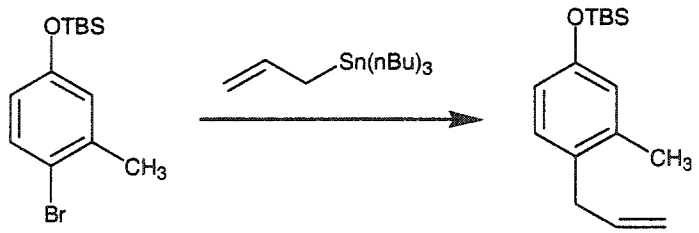
Scheme 2.8: Proposed synthesis of aldehyde 134 via Stille coupling of aryl bromide.

The readily available starting material **135** was utilized as follows. The first step required a halogenation of the aromatic ring at the para position with respect to the hydroxyl group. The bromination was successful in creating the brominated product **136**, with the correct regiochemistry as the major product. nOe studies performed to ensure correct regiochemistry are discussed below for the iodinated product (see p. 55-56). Based on the spectral similarity between those products, we were confident that we had **136** in hand. The corresponding iodination was surprisingly unsuccessful. There was only starting material visible after several attempts – or so it seemed. We were hoping to proceed with the iodinated benzene ring because, in general, iodides undergo Stille couplings with more ease than their bromo analogues. As previously done, TBS protection of **136** occurred in high yield to give the Stille precursor **137**.

The Stille couplings attempted on this substrate were numerous and utilized varying reaction conditions. Table 2.8 summarizes these futile, yet valiant efforts. A

variety of catalysts, solvents, temperatures and additional reagents were tested, however none were successful. The effect of changing the palladium ligands was tested by using $AsPh_3$[51] and $P(t\text{-}Bu)_3$[52] (Entries 1, 2, 6). However, no product was observed. The use of BHT as a radical scavenger was of no consequence (Entries 3-5, 7). Also, the addition of CuI in hopes of it acting as a scavenger for free ligands and a transmetalating agent did not coax the formation of any product (Entries 1, 2, 6, 8, 13, 14).[53] A recent modification to the Stille reaction proposed by Corey offered no improvement to the reaction (Entries 8-14).[54] Vinyl tributyltin was also looked at as a replacement for allyl tributyltin and still no product was observed. Most of the reactions returned starting material. Heating above 90 °C was attempted but definite decomposition of the catalyst was observed as it turned black. Copper iodide was purified in boiling aqueous sodium iodide and then stored in the glove box. Both, nitrogen and argon atmospheres were evaluated, however, the carbon-carbon bond never formed. If the Stille coupling with allyltributyltin would have worked, ozonolysis of **138** could have lead to the the formation of aldehyde **134**.

Table 2.8: Attempted Stille couplings on the aryl bromide substrate.



137 138

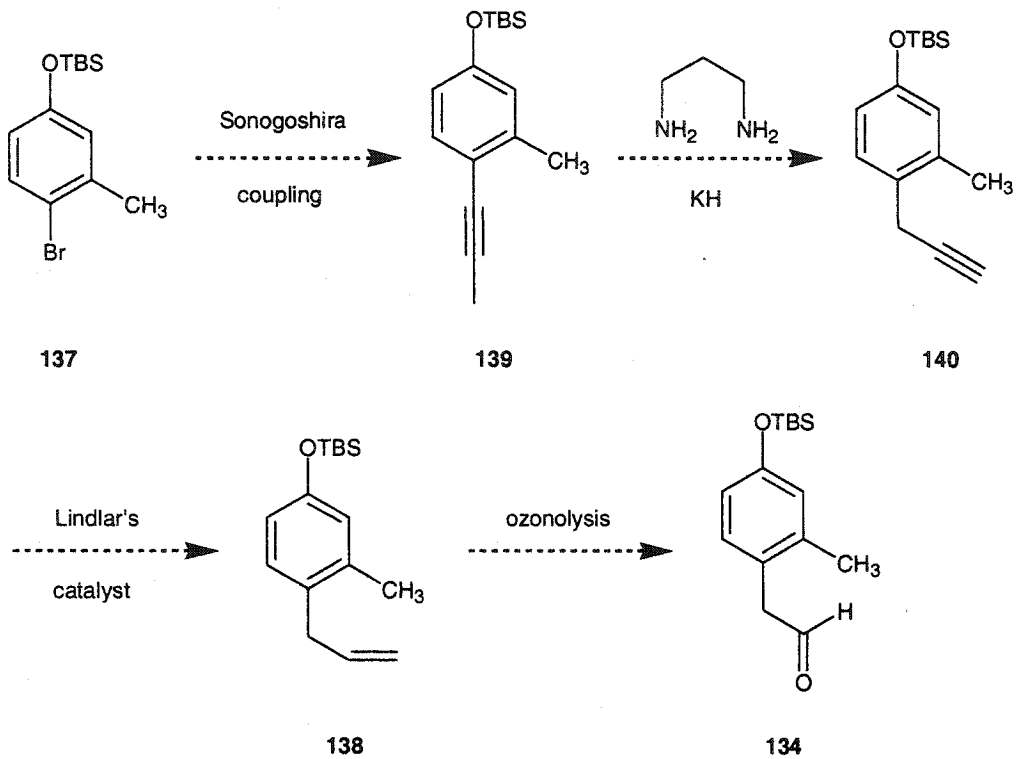
Entry	Reagents	Solvent	Conditions	% Yield

[51] Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585.
[52] Littke, A.F., Schwarz, L.; Fu, G. *J. Am. Chem. Soc*. **2002**, 124, 6343.
[53] Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. *J. Org. Chem.* **1994**, 59, 5905.
[54] Xiaojun, H.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 7600.

1	10% Pd/C, CuI, $AsPh_3$	DMF	25°C, 6h	no reaction
2	$Pd_2(dba)_3$, CuI, $AsPh_3$	DMF	25°C, 6h	no reaction
3	Pd(II)dppf, BHT	DMF	25°C, 6h	no reaction
4	Pd(II)dppf, BHT	DMF	115°C, 24h	no reaction
5	$Pd(PPh_3)_4$, BHT	DMF	115°C, 24h	no reaction
6	$Pd_2(dba)_3$, CuI, P(t-Bu)$_3$	DMF	80°C, 24h	no reaction
7	$Pd(PPh_3)_4$, BHT	DMF	80°C, 72h	no reaction
8	Pd(II)dppf, CuI, LiCl	DMF	80°C, 72h	no reaction
9	$Pd(PPh_3)_4$, CuBr, LiCl	DMSO	72°C, 72h	no reaction
10	Pd(II)dppf, CuBr, LiCl	DMSO	72°C, 72h	no reaction
11	$Pd(PPh_3)_4$, CuBr, LiCl	NMP	80°C, 72h	no reaction
12	Pd(II)dppf, CuBr, LiCl	NMP	80°C, 72h	no reaction
13	$Pd(PPh_3)_4$, CuI, LiCl	DMSO	75°C, 72h	no reaction
14	$Pd_2(dba)_3$, CuI, LiCl	DMSO	75°C, 72h	no reaction

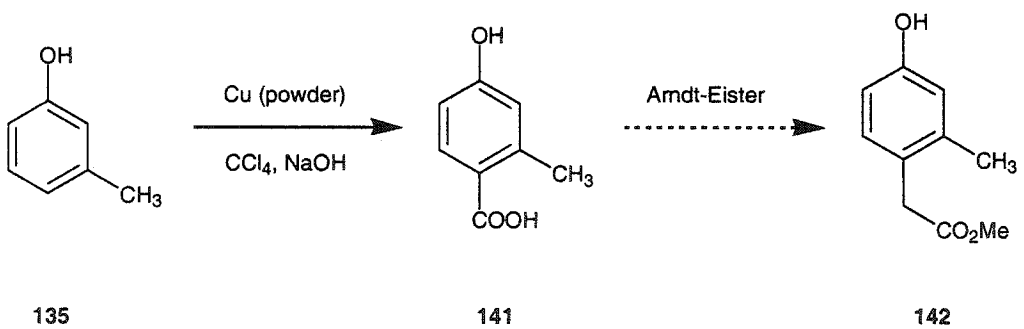
A Sonogoshira coupling of the aryl bromide with propyne was next attempted. This also proved to be fruitless, yielding only the starting material **137**. This strategy anticipated that upon successful coupling of propyne to form **139**, migration of the triple bond to the terminal position with 1,3 diamino propane and potassium hydride (KH) could produce compound **140** (Scheme 2.9).[55] The terminal alkyne could then be reduced to the alkene **138** using Lindlar's catalyst and subsequent ozonolysis would provide aldehyde **134**.

[55] Brown, C.A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, 97, 891.



Scheme 2.9: Proposed synthesis of aldehyde 134 via Sonogoshira coupling.

Since the coupling reactions were fruitless, a second route was visualized. This approach is delineated in Scheme 2.10.



Scheme 2.10: Proposed synthesis of aldehyde 134 via Arndt-Eister extension.

The carboxylation reaction was quite problematic, leading to several spots being observed on TLC.[56] Purification attempts were made on the more polar spots, however, the products proved to be impossible to isolate. Product **141** was never observed cleanly,

[56] Cox, E.H. *J. Am. Chem. Soc.* **1927**, 49, 1028.

consequently, the Arndt-Eister extension to form the ester **142** could not be tested. This ester could have been easily reduced to the alcohol using LAH and then oxidized to aldehyde **134**.

As the Arndt-Eister sequence was problematic, a novel method for making aryl iodides became available to us. A reagent by the name of benzyltrimethyl ammonium dichloro iodate (BTMA ICl_2) has been previously used to synthesize aryl iodides similar to our target (Figure 2.8).[57] Initially, the reaction of m-cresol (**135**) with BTMA ICl_2 (**143**) was attempted twice with only starting material being observed after overnight stirring. The TLC was also left on the bench top overnight. Upon reentering the lab in the morning, I noticed that my TLC plate was very different. The spot corresponding to the starting material had disappeared but the co-spot and the reaction mixture spot had become bright yellow. Upon quenching the reaction, NMR analysis showed conclusively that the compound had indeed been iodinated to product **144** (Figure 2.8). The R_f values of the two spots were identical. Looking back, the iodination probably worked with I_2 in CH_3CN as well. The correct regiochemistry of the iodination reaction was verified by NMR experiments. The proton NMR consisted of an ortho-coupled doublet at 7.58 ppm, a meta-coupled doublet at 6.74 ppm, a doublet of doublets (ortho and meta coupling) at 6.40 ppm and a large singlet at 2.34 ppm representing the protons of the methyl group. An nOe irradiation of the methyl protons led to the enhancement of only the meta-coupled doublet at 6.74 ppm. This would indicate that the iodine must occupy the position para to the hydroxyl group (Figure 2.8).

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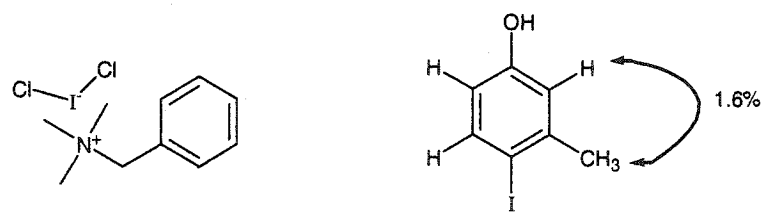
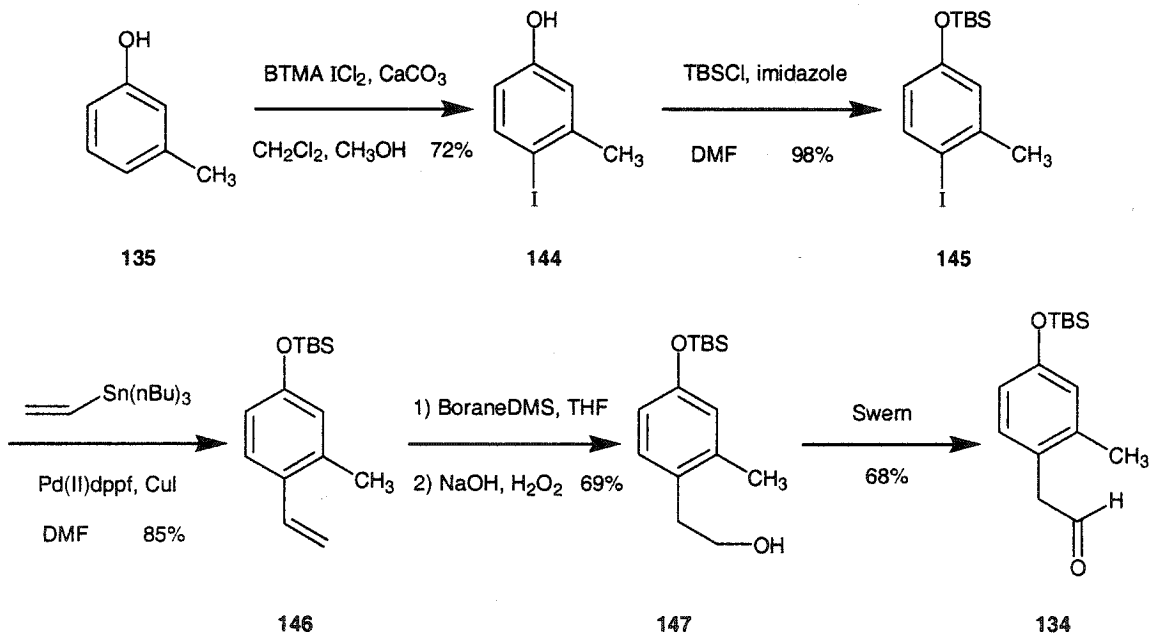
[57] Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. *Chem. Letters* **1987**, 2109.



143 144

Figure 2.8: Structure of BTMA ICl_2 (left) and the nOe interaction resulting from the irradiation of the benzyl protons (right).

Consequently, a similar reaction sequence to that of the aryl bromide was planned (Scheme 2.11). With **144** in hand, protection of the phenol as the TBS ether was uneventful, forming product **145** without any trouble.



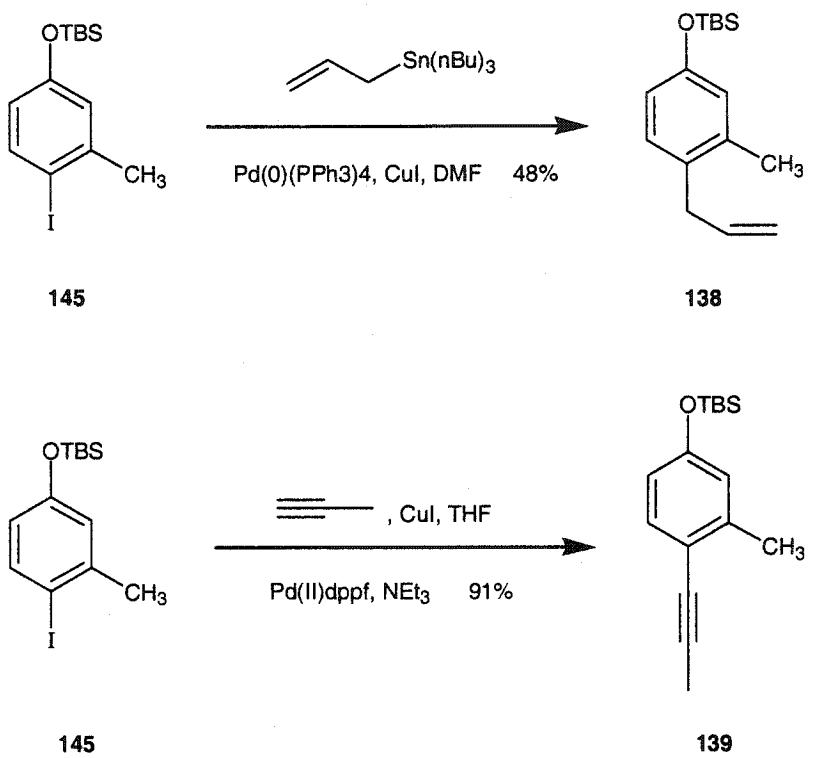
135 144 145

146 147 134

Scheme 2.11: Completed synthesis of aldehyde 134 via Stille coupling of aryl iodide.

Next, each of the Stille and Sonogoshira couplings were attempted. Both coupling reactions worked beautifully with the aryl iodides yielding products **138** and **139** respectively (Scheme 2.12). Compound **139** from the Sonogoshira coupling did not require any purification and the yield was an astounding 91%. The Stille coupling with allyl tributyltin did not have such a good yield nor was it a clean reaction, but it was

chosen to be carried forward in the reaction pathway since compound **138** requires only an ozonolysis to form aldehyde **134**. Compound **138** was extremely non-polar and so purification was quite difficult with the presence of the n-butyl groups from the tin reagent.



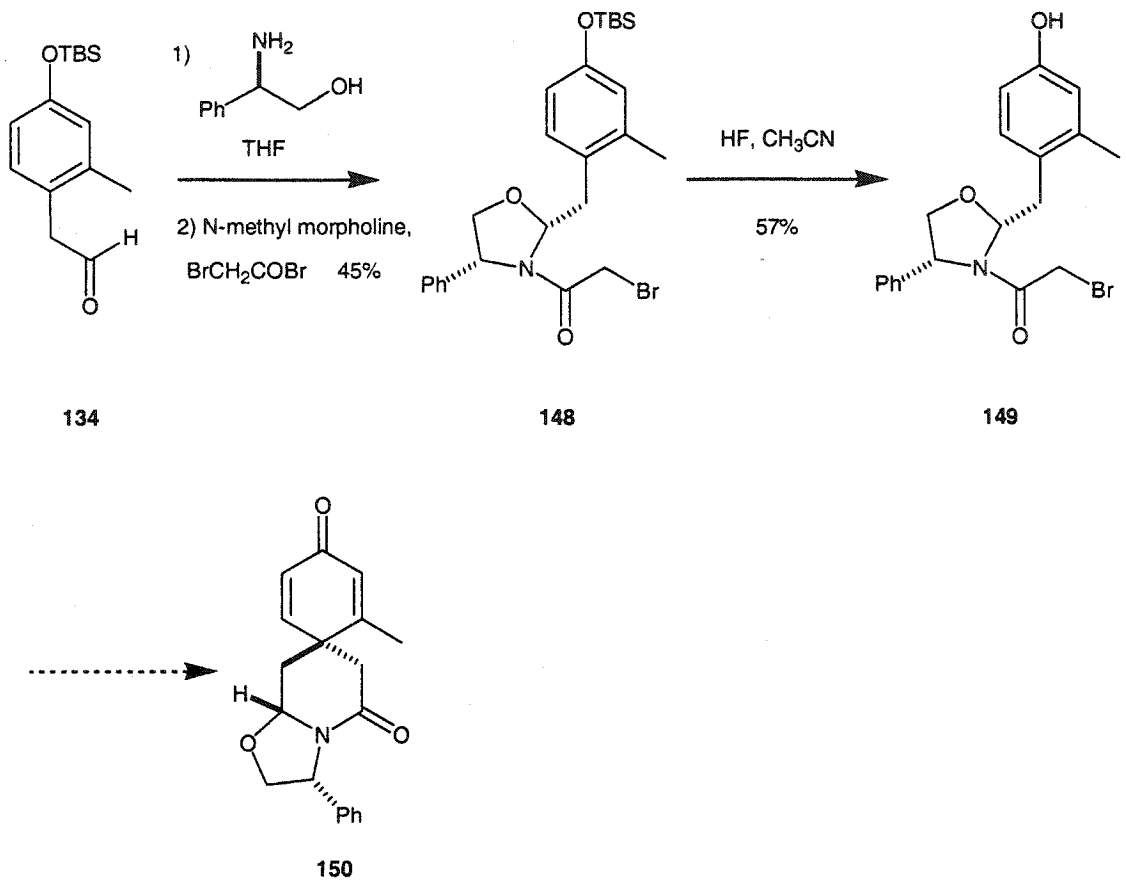
Scheme 2.12: Successful Stille and Sonogoshira couplings of the aryl iodide.

The Stille coupling was even more successful when vinyl tributyltin replaced allyl tributyltin. With the use of vinyl tributyl tin, the styrene derivative **146** was formed instead of the allyl compound **138** (Scheme 2.11). The vinyl compound **146** underwent hydroboration quite effectively to yield alcohol **147** which was then oxidized via a Swern reaction to give the aldehyde **134**. The hydroboration gave multiple products when 9-borabicyclononane (9-BBN) or just borane (BH_3) in THF were used. The purification of the products from the Stille couplings and even after the hydroboration reaction was always difficult, with the butyl groups of the tin by-products constantly plaguing the

spectra. A clean spectrum could only be obtained after aldehyde **134** was synthesized and purified.

There were two steps left to complete before the para-C-alkylation could be tested (Scheme 2.13). The first was the oxazolidine-forming reaction of aldehyde **134** with S-phenylglycinol and acylation of the secondary amine with bromoacetylbromide and N-methyl morpholine. The cis-oxazolidine **148** could be formed in 45% yield. The last step to form the precursor was the deprotection of the TBS group with HF and CH_3CN. This reaction was once again sluggish but the deprotected product **149** could be obtained.

At this point, realizing that the para-C-methodology was not working, we decided to cut our losses and move on. Few attempts were made to form the spirodienone **150**. These attempts included DBU in CH_3CN, t-BuOK in tBuOH, NaH in THF and PIFA in trifluoroethanol. Not surprisingly, these reactions were fruitless.



Scheme 2.13: Completion of synthesis of the precursor for the para-C-alkylation.

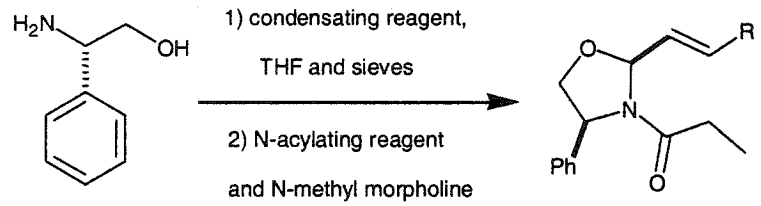
While completing this previous synthesis, continuous efforts were being put forth to construct spirodienone **123** (Scheme 2.5). These attempts were unsuccessful; however, a new oxidative condition to obtain the required aldehydes was discovered. The swern was replaced by pyridinium dichromate (PDC) oxidation. These conditions are much more user friendly and gave similar, if not better yields.

2.2 Quaternary Centers by an aza-Ireland-Claisen Rearrangement

Synthesis of 6,7-Dimethyl-3-phenyl-3,4,6,7-tetrahydro-2H-[1,4]-oxazonin-5-one

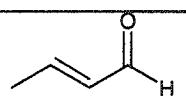
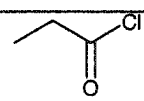
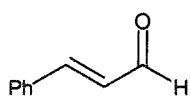
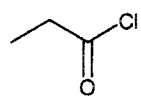
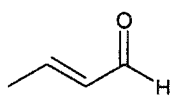
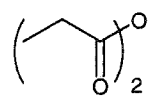
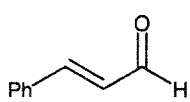
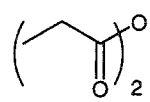
Our later efforts were concentrated on forming quaternary centers via an aza-Ireland-Claisen rearrangement. The goal of this project was to form a small, useful functionalized intermediate containing a quaternary center via a short, efficient synthesis. The synthesis begins with the need to form an N-acylated oxazolidine ring with substituents in the 2 and 5 positions (Table 2.9). Starting with S-phenylglycinol (**151**), different reagents were tested in the synthesis of oxazolidine moieties **152** and **153**.

Table 2.9: Attempts at making the oxazolidine precursor for the aza-Ireland-Claisen rearrangement.

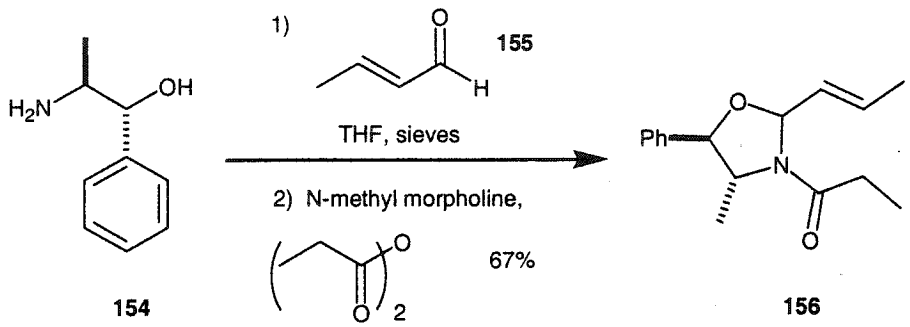


151

152 R = Me
153 R = Ph

Entry	Condensating reagent	N-acylating reagent	Product	% Yield
1			R = Me	32
2			R = Ph	27
3			R = Me	67
4			R = Ph	74

When propionyl chloride was used, a significant amount of the trans oxazolidine was also formed. However, with propionic anhydride, only the cis oxazolidine was obtained as the product. Before moving on however, the oxazolidine resulting from the reaction of norephedrine (**154**) with crotonaldehyde (**155**) was also tested. Again, only one major isomer (**156**) was observed in a yield of 78% (Scheme 2.14).

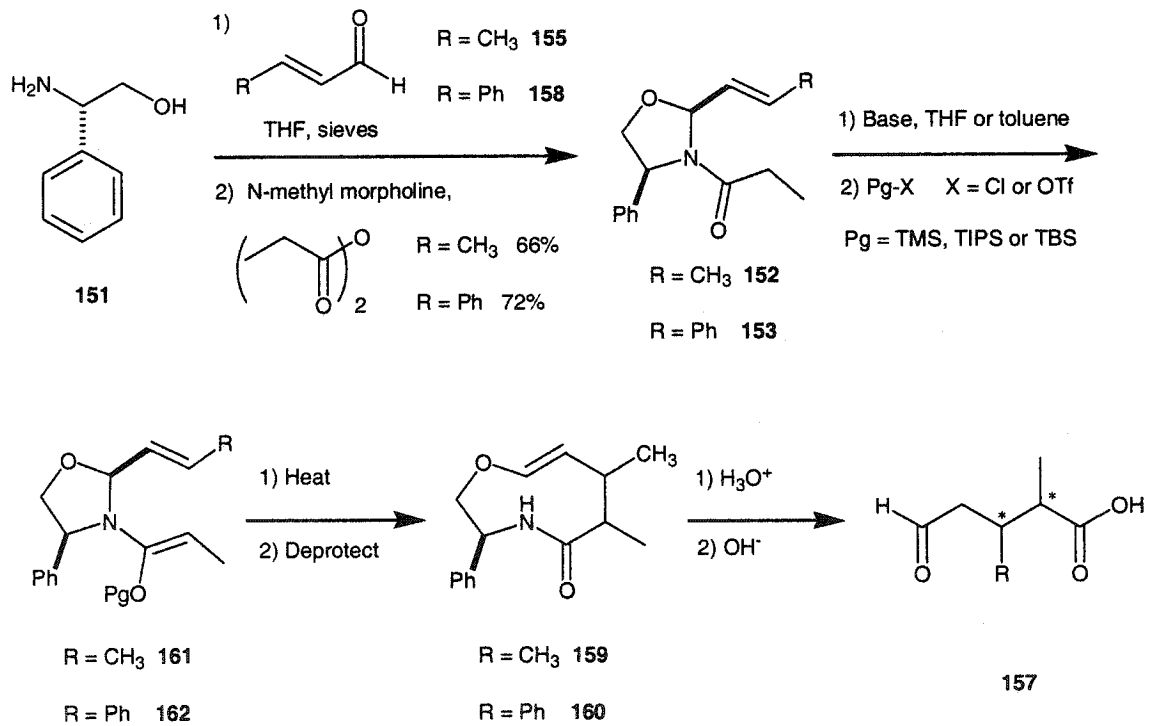


Scheme 2.14: Oxazolidine formation using norephedrine as the substrate.

The spectra of these oxazolidines were especially difficult to interpret because of the presence of the tertiary amide. Tertiary amides have a slow rotation about the C-N bond due to partial double bond character imparted by resonance. The multiple peaks found on these spectra were a consequence of two different amide rotamers present in solution. In effect, the interconversion of these rotamers was slow enough on the NMR time scale that the proton resonances of both were observed. Variable temperature NMR experiments verified this presumption. Upon heating, all peaks corresponding to the same protons of each of the rotamers coalesced. The temperature at which this occurs, known as the coalescence temperature, was found to be 55 °C. From this value, we were able to calculate that the barrier for rotation ($\Delta G^{\ddagger}$) had a value of approximately 23 kcal mol^{-1}. The formula for calculating the barrier of rotation is $\Delta G^{\ddagger} = 22.96 + \ln(T_c/\Delta\upsilon)$; where Tc is the coalescence temperature and $\Delta\upsilon$ is the difference in chemical shift between the same proton on the two rotamers. Furthermore, we were able to estimate the

actual ratio of these rotamers and it was determined to be 45:55. This was calculated by measuring the ratios of the integration peaks of the corresponding protons.

With appropriate yields of the oxazolidine reaction being observed, a synthetic plan was put in place to test the aza-Ireland-Claisen rearrangement, with the eventual formation of intermediate **157** (Scheme 2.15). As mentioned previously, the oxazolidines **152** and **153** were successfully synthesized with the use of crotonaldehyde **155** and trans cinnamaldehyde **158** respectively.

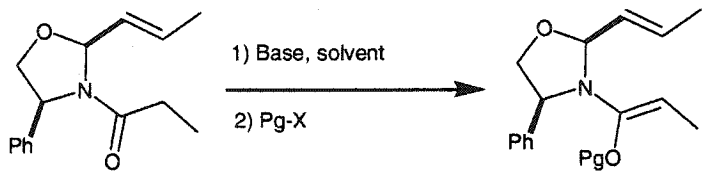


Scheme 2.15: Synthetic route undertaken to synthesize intermediate 157.

These oxazolidines were essentially the precursors for the rearrangement. Initially, we suggested that the deprotonation with LDA (or other bases) and the aza-Ireland-Claisen rearrangement could be done in tandem to produce **159** or **160** directly (Table 2.10, Entry 3). After realizing that this protocol was not conducive to the isolation of the nine-membered ring product, we decided to evaluate both reactions separately.

The enolates formed from the deprotection reaction would first be trapped as silyl enol ethers **161** and **162**. Once these silyl enol ethers would be obtained, the rearrangement would then be attempted. The variety of conditions attempted to form and isolate the trapped enolate **161** are shown in Table 2.10.

Table 2.10: Attempted formation of trapped enolate 161.



152 161

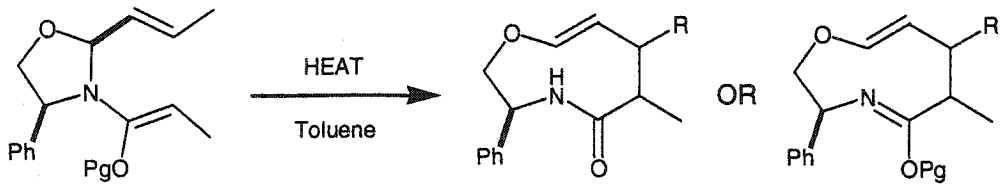
Entry	Base	Solvent	Pg-X	% Yield
1	LDA	THF	TIPSOTf	?
2	LDA	Toluene	TIPSOTf	?
3	LDA	Toluene	n/a	?
4	LDA	Ether	TIPSOTf	?
5	KHMDS	Toluene	TIPSOTf	?
6	LHMDS	Toluene	TIPSOTf	?
7	LDA	THF	TMSCl	?
8	LDA	THF	TBSCl	?
9	LDA	Toluene	TBSCl	?

As you can see from every entry, the yields, or the product for that matter, were not identified. The NMR spectra were not clean even after several purifications. The effect of the solvent was evaluated for the reaction (Entries 1, 2, 4). THF, toluene and ether all gave very complicated spectra. No significant change in the reaction was

observed when bases like KHMDS and LHMDS were used instead of LDA (Entries 2, 5, 6). The use of various trapping agents (TIPSOTf, TBSCl, TMSCl) was investigated but to no avail (Entries 1, 7, 8).

The products of these reactions, although inconclusive, had the potential of being the trapped enolate. Consequently, the rearrangement was attempted with these products (Table 2.11). Those deprotonation reactions performed in THF or ether were evaporated and then the residues dissolved in toluene for the rearrangement reactions. Despite the variety of conditions, the medium sized nine-membered ring product **163** or its' protected version **164** were never observed. Even in those cases where the enolate was not trapped, **163** was not isolated. Each time, the starting material would disappear but either the original oxazolidine **152** was recovered or nothing was visible on TLC.

Table 2.11: Attempted aza-Ireland-Claisen rearrangement.

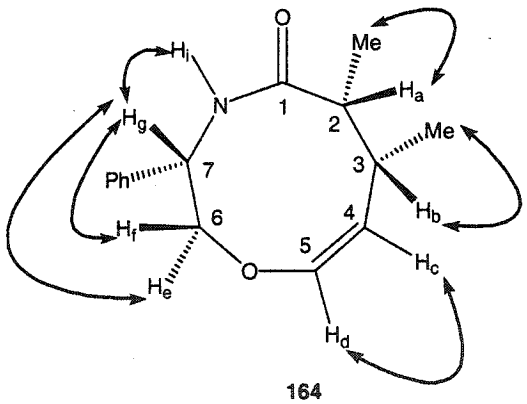


161 163 164

Entry	Heat source	Temperature (°C)	Time (min.)	% Yield
1	Microwave	210	60	0
2	Microwave	210	45	0
3	Microwave	180	60	0
4	Seal tube	Reflux	60	0
5	Seal tube	Reflux	30	0

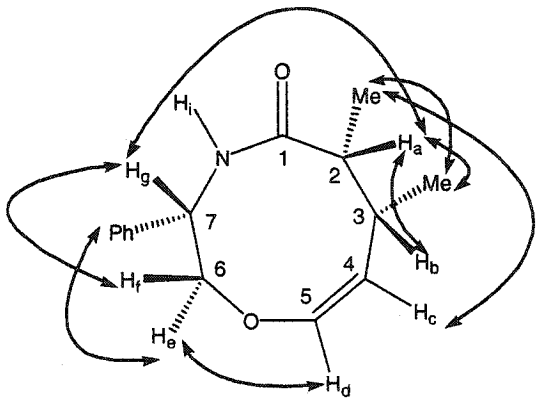
Along with my help, this project was worked on by an undergraduate student, Myra Bertrand. She had managed to isolate a very small amount of an isomer of the nine-membered ring macrocycle **163** but unfortunately these results could not be reproduced. The spectra of this compound (**164**), although not clean, showed that the compound was indeed isolated. The ^{1}H NMR fit very well with the structure of the macrocycle **164**. Of special note was the appearance of a doublet of quartets that appeared around 2.6 ppm, which strongly indicated that a bond between C_2 and C_3 had indeed been made (Figure 2.9). In identifying the structure, a COSY was used to make structural inferences. The important correlations are summarized in Figure 2.9. First, H_g had correlations with H_i, H_e and H_f. Second, the two new olefinic protons H_c and H_d were strongly interacting. Also, each of protons H_a and H_b were coupled with the

appropriate methyl group. The only important interaction that was missing was that between H_a and H_b. It was proposed that these two protons could be at right angles to each other, and so no coupling was observed. The geometry of the double bond was concluded to be cis since the coupling constant between H_c and H_d was determined to be 5.9 Hz. Furthermore, initial nOe studies seemed to indicate a syn relationship between the two methyl groups. Figure 2.10 shows the important nOe reactions that led to these conclusions. Of worthy note was the cross peak between H_a and H_g, which indicated that these protons were on the same side of the ring. Since the absolute stereochemistry of H_g was known, these two protons can be drawn as shown in Figure 2.10. The syn relationship between the two methyl groups was then established by the enhancement between H_a and H_b combined with the lack of interaction between H_b and the methyl group on C_2.



164

Figure 2.9: Proton correlations from COSY spectrum of 164.



164

Figure 2.10: nOe interactions for the protons of macrocycle 164.

However, one important observation was that this undergraduate student was working with the trans oxazolidine (trans isomer of **152**). For the oxazolidine-forming reaction, she used propionyl chloride instead of propionic anhydride.

If the formation of this nine-membered ring substrate would have been successful, application of this methodology to the formation of quaternary centers would have been a relatively simple task. The only change would be to add an extra substituent on the aldehyde or on the acyl portion of the amide in the oxazolidine-forming reaction.

Chapter 3: Conclusions and Future Work

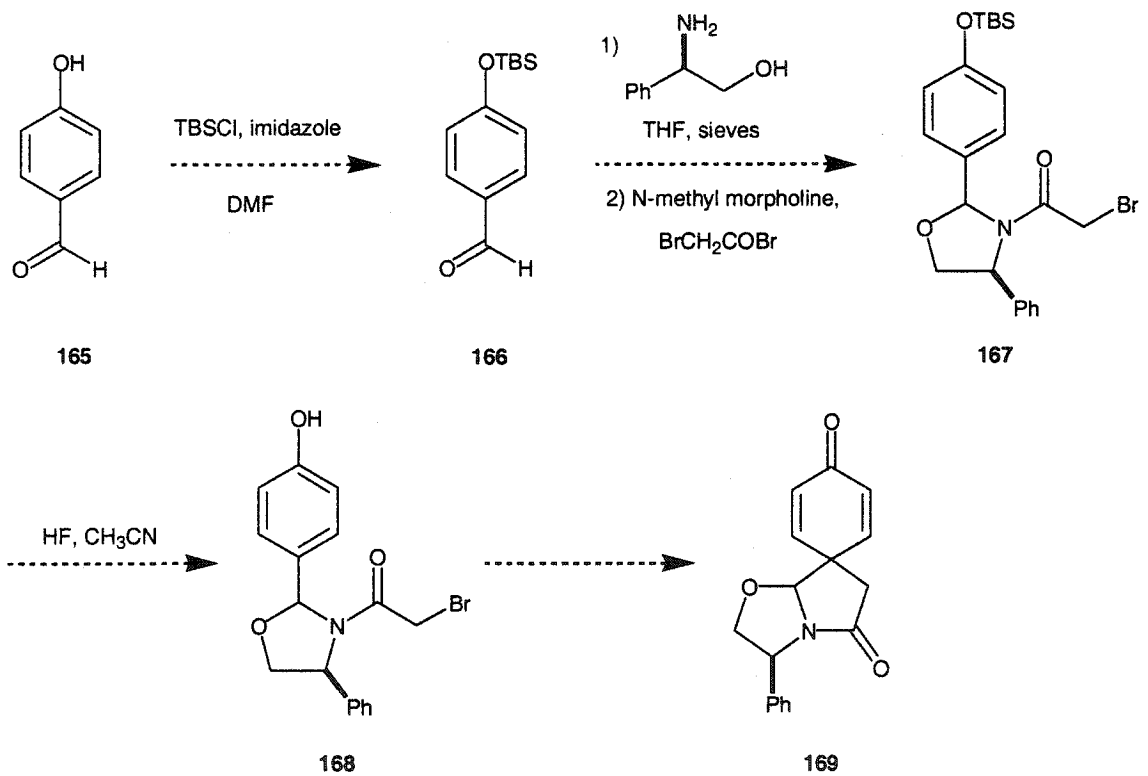
3.1 Para-C-Alkylation

Unfortunately, the quaternary centers were not synthesized via the newly proposed para-C-alkylation. In each case, the precursor was successfully synthesized but the formation of the 6-membered spirocycle was never observed. Despite this lack of success, a paramount breadth of information has been acquired by the candidate.

Often, when doing intensive research, one stumbles upon critical pieces of information that cause another idea to sprout. While reading through some articles, I recently stumbled upon such a piece of information. The previous work done by Winstein, Baird and Heck on the Ar-5 and Ar-3 phenoxide participation, referenced one of their original publications on the subject.[29] In that paper, a small section addressed the topic of Ar-n participation and ring size.[28] Remember that the nomenclature was based on the size of the incipient ring being formed. Hence, in our case, the reaction would be called Ar-6 participation. Here is a quote from the paper concerning Ar-6 participation: "...it is clear that rates associated with Ar-6 participation are much lower than those associated with Ar-5. Consequently, it will be more difficult to arrange conditions of structure and solvent so as to have Ar-6 participation dominate..." The authors base their conclusion on various kinetic studies which determine the rate constants for the different possible outcomes of the reaction (i.e. Ar-6 participation product, solvolysis product, dimerization product and the dienone phenol rearrangement product).

Although this was quite disappointing to discover, new ideas have been developed in an attempt to test the para-C-alkylation via an Ar-5 participation methodology. The precursor can be synthesized in half the number of steps than the precursor for the Ar-6

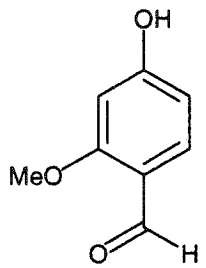
participation (Scheme 3.1). First, a protection of commercially available 4-hydroxy benzaldehyde **165** is in order. This should proceed smoothly as it has not previously been problematic. The TBS-protected benzaldehyde **166** could be transformed into oxazolidine **167**. Although this reaction has been bothersome, the conditions using THF as a solvent have given some promising results. Subsequent deprotection of **167** using HF/CH_3CN will yield precursor **168** for the para-C-alkylation. Several conditions could once again be considered in an attempt to form spirodienone **169**.



Scheme 3.1: Proposed formation of 169 via Ar-5 participation.

Another potential idea that stems from previous research would explore the effect of electron donating substituents (i.e. OMe) on the Ar-5 participation reaction. Also in their original publication on Ar-n participation, Winstein and Heck tested the effect of the methoxy group on the reaction. It was found that, although the effect was slight, the electron donating group nonetheless aided in the formation of the spirodienone product.

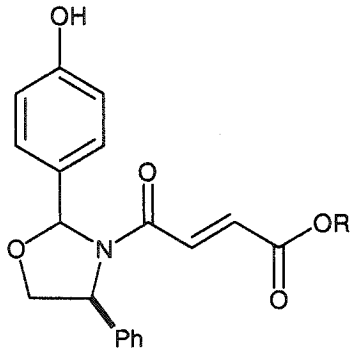
They predicted that the increased electronic nature of the phenyl ring further favored the Ar-5 participation reaction. This idea could be tested starting with the commercially available substrate **170** (Figure 3.1). A similar reaction sequence to that demonstrated in Scheme 3.1 could then be applied.



170

Figure 3.1: Potential substrate to test the effects of electron donating substituents on the para-C-alkylation.

One last potential pathway would be to decrease the hardness of the electrophilic site of our precursor. Since the delocalized phenoxide anion system would be considered a soft nucleophile, perhaps a softer electrophile would help the reaction along. This could also help to explain the dominance of the dimerization reaction. The electrons on the phenoxide oxygen would rather attack the hard electrophile directly than proceed through the phenyl ring. A potential precursor **171** to test the para-C-alkylation is revealed in Figure 3.2. The same reaction sequence proposed in Scheme 3.1 could be applied. The only adaptation would be to use a fumaric ester derivative instead of the bromoacetyl bromide in the N-acylation step of the oxazolidine-forming reaction.



171

Figure 3.2: A potentially softer electrophilic precursor to test the para-C-alkylation.

3.2 Aza-Ireland-Claisen Rearrangement

This project has worked once but the 9-membered ring product could not be resynthesized. The oxazolidine-forming reaction was optimized quite nicely to form the cis product, exclusively, in very good yield. However, the rearrangement product was not observed.

In hindsight, there may be a difference when a trans oxazolidine is used. The one time we did observe a rearrangement product was when the trans oxazolidine was used. This would prompt the idea that the sequence should be reexamined using the minor product of the oxazolidine reaction, the trans isomer.

3.3 Personal Reflection

As an undergraduate in Biochemistry, I came to this school with very little theoretical knowledge of organic chemistry and an infinitesimal small amount of practical experience. Although the projects were not successful, the plethora of knowledge and experience gained over these last two years is unconscionable. This is a victory in itself... "From our withering failures, our successes will flourish".

3.4 Claims to Original Research

1. Investigated the selective formation of cis oxazolidines over trans oxazolidines.
2. Prepared several substrates in order to test the feasibility of the proposed para-C-alkylation as a novel Ar-6 participation reaction.
3. Explored the possibility of forming medium-sized rings through an aza-Ireland-Claisen rearrangement.

Chapter 4: Experimental Procedures

Reactions were performed in heat-gun or oven-dried evacuated flasks under dry N_2 atmosphere equipped with a magnetic stir bar and a rubber septum unless otherwise noted. THF and Et_2O were freshly distilled from sodium/benzophenone, while dichloromethane and DMF were freshly distilled from CaH_2. Reagents were purchased from Sigma Aldrich, Fluka and Lancaster companies and used without purification. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F254 precoated 0.25 mm thick aluminum plates. TLCs were developed using ultraviolet light and iodine, potassium permangate, ninhydrin, ceric ammonium molybdate, or p-anisaldehyde stains. When necessary, products were purified using flash chromatography on silica gel 60 (230-400 mesh), a chromatotron, or preparatory glass TLC plates precoated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

The CuI used in Stille Couplings were purified in the following manner. The CuI was dissolved in a boiling, saturated solution of NaI for 1 hr. The mixture was then diluted with water and allowed to cool. The white powder was filtered and washed with water, EtOH, EtOAc and Et_2O/pentane. It was then dried in vaccuo for 24 hours and stored in a glove box.

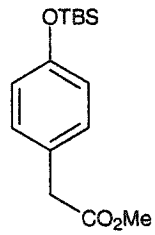
Ag_2O was prepared as follows. In a foil-wrapped 25 mL flask, $AgNO_3$ (0.1000g, 0.5882 mmol) was dissolved in water. Potassium hydroxide (0.0658g, 1.1765 mmol) was added to the flask and, after 5 minutes, Ag_2O precipitated out as a brown solid. The product was filtered and washed with water, acetone and ether. It was then dried in vaccuo for 24 hours and stored in a foil-wrapped vial.

Diazomethane was prepared from commercially available N-nitroso-N-mehtyl urea. To a 250 mL plastic bottle was added 30 mL of a 40% solution of KOH and the solution was cooled to 0°C. 100 mL of ether was then transferred to the flask. After stirring for 5 minutes, 7 grams of N-nitroso-N-methyl urea was added in 4 portions over a 15 minute period. After an additional 5 minutes of stirring, the ether layer was decanted into a plastic bottle and cooled to -78°C so that any remaining water would freeze. The cooled mixture was filtered through cotton into a 100 mL plastic bottle containing KOH pellets. The yellow diazomethane mixture was stored in the freezer.

When HF was used in deprotecting the TBS groups, no glass could be used. Plastic containers replaced round bottom flasks and plastic pipettes were used.

The base n-butyllithium (n-BuLi) was titrated using the following procedure. To a 10 mL flask, 100mg of BHT and 5 mg of Fluorene were dissolved in THF. The reaction mixture was cooled to 0°C and nBuLi was added dropwise until a yellow color persisted.

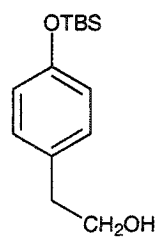
^{1}H and ^{13}C NMR spectra were acquired using a Bruker Avance 300 MHz (^{1}H) and 75 MHz (^{13}C). IR spectra were recorded on a Bomem Michaelson 100 FTIR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques.



108

[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-acetic acid methyl ester (108). In a 250 mL flask, (4-Hydroxy-phenyl)-acetic acid methyl ester (10.00 g, 60.24 mmol) and imidazole (8.19 g, 120.48 mmol) were dissolved in anhydrous DMF (150 mL). TBSCl (13.64 g, 90.36 mmol) was added and allowed to stir for 2 hours. The reaction mixture was extracted in ether and washed three times with water, followed by brine. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified by flash chromatography (5% EtOAc in hexanes) to yield **108** as a pale yellow oil in 98% yield.

IR (neat) 3050, 1738, 1255, 1155; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 3.67 (s, 3H), 3.54 (s, 2H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 172.7, 155.1, 130.6, 127.0, 120.5, 52.3, 40.7, 26.1, 18.6, -4.1; MS (EI) m/z 280 (M+), 223 (M-tbutyl).

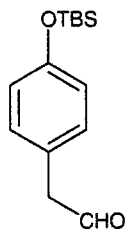


109

2-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-ethanol (109). To a 500 mL flask was added LAH (4.88 g, 128.43 mmol) and it was dissolved in anhydrous THF (100 mL). To a 100 mL flask was added **108** (18.00 g, 64.21 mmol) which was dissolved in anhydrous

THF (30 mL). This mixture was cannulated into the LAH solution, allowed to stir for 2.5 hours and then cooled to 0°C. The reaction was first quenched with the slow addition of 5 mL of water (followed by 15 minutes of stirring), then with the slow addition of 5 mL of 3N NaOH (followed by 15 minutes of stirring) and finally with another addition of 15 mL of water. This reaction was stirred until a white precipitate formed. The white aluminum salts were separated by vacuum filtration and the filtrate was extracted in ether, and then washed with brine. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to yield **109** as a colourless oil in 92% yield.

IR (neat) 3296, 3050, 1046; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 3.77 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 6.6 Hz, 2H), 1.95 (broad s, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 154.6, 131.4, 130.3, 120.5, 64.2, 38.7, 26.1, 18.6, -4.0; MS (EI) m/z 252 (M+), 195 (M-tbutyl).

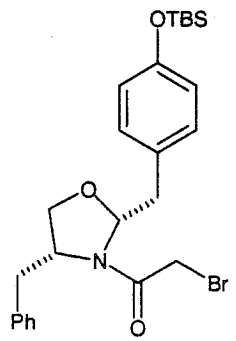


110

[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-acetaldehyde (110). In a 500 mL flask equipped with a 3-way adapter leading to a N_2 outlet, $(COCl)_2$ (6.23 mL, 71.34 mmol) was dissolved in CH_2Cl_2 (190 mL) and brought to -78°C. DMSO (10.12 mL, 142.69 mmol) was added dropwise to the solution. After stirring for 15 minutes, **109** (15.00 g, 59.45 mmol) in CH_2Cl_2 (10 mL) was slowly added to the mixture. After another 15 minutes of stirring, triethylamine (39.78 mL, 285.37 mmol) was added slowly. The

mixture turned orange and this precipitate was filtered. The filtrate was extracted twice in ether and each ethereal layer was washed with HCl, $NaHCO_3$ and brine. The organic phases were dried over magnesium sulphate, filtered and concentrated. The black residue was purified by flash chromatography (5% EtOAc in hexanes) to yield **110** as an orange oil in 57% yield.

IR (neat) 3037, 2840, 2753, 1727; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.69 (t, J = 2.5 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 3.58 (d, J = 2.5 Hz, 2H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 200.0, 155.4, 131.0, 124.8, 120.9, 50.1, 26.1, 18.6, -4.1; MS (EI) m/z 250 (M+), 193 (M-tbutyl).



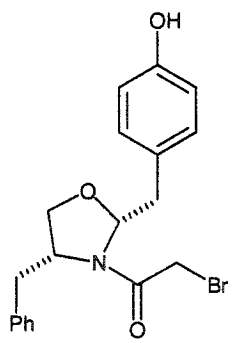
112

1-{4-Benzyl-2-[4-(tert-butyl-dimethyl-silanyloxy)-benzyl]-oxazolidin-3-yl}-2-bromo-ethanone (112). In a 100 mL flask, 4 Å molecular sieves were activated with a heat gun for 10 minutes. S-Phenylalaninol (1.14 g, 7.53 mmol) was added to the flask and dissolved in freshly distilled CH_2Cl_2 (30 mL). In a separate 100 mL flask, **110** (1.79 g, 7.17 mmol) was dissolved in CH_2Cl_2 (10 mL) and cannulated into the phenylalaninol mixture. After 3.5 hours, freshly distilled N-methyl morpholine (1.57 mL, 14.34 mmol) was added and this was allowed to stir for 10 minutes. Bromoacetyl bromide (0.94 mL, 10.76 mmol) was transferred to the reaction vessel. After 35 minutes of stirring, the sieves were filtered from the reaction mixture into a separatory funnel. $NaHCO_3$ was

added to the reaction and this was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with brine and then dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (8% EtOAc in hexanes followed by 15% EtOAc in hexanes) to produce **112** as a reddish oil in 32% yield.

IR (neat) 3068, 1666, 1261; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 3H), 7.16 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 6.8 Hz, 2H), 6.79 (d, J = 8.3 Hz, 2H), 5.31 (d, J = 4.0 Hz 1H), 4.03 (m, 1H), 3.88 (d, J = 8.8 Hz, 1H), 3.72 (dd, J = 8.8 Hz, J = 5.3 Hz, 1H), 3.48 (d, J = 10.8 Hz, 1H), 3.31 (d, J = 10.8 Hz, 1H), 3.29 (d, J = 14.0 Hz, 1H), 3.15 (dd, J = 14.1 Hz, J = 5.7 Hz, 1H), 2.55 (dd, J = 13.7 Hz, J = 6.6 Hz, 1H), 2.20 (dd, J = 13.7 Hz, J = 8.2 Hz, 1H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 165.2, 155.0, 137.5, 131.9, 129.6, 129.4, 129.1, 127.5, 120.2, 91.9, 70.2, 59.8, 39.9, 38.8, 27.7, 26.1, 18.6, -4.1; MS (EI) m/z 503 (M+), 505 (M+2), 426 (M-Br), 282 and 284 (M-[CH_2PhOTBS]).

*** The cis and trans isomers were differentiated by 2D NOESY.

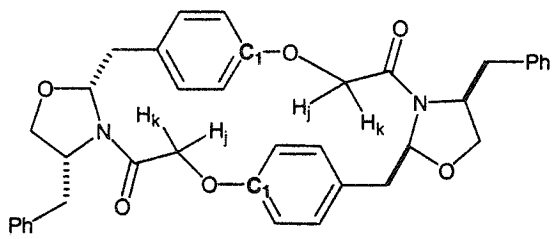


104

1-[4-Benzyl-2-(4-hydroxy-benzyl)-oxazolidin-3-yl]-2-bromo-ethanone (104). In a plastic vessel, **112** (0.2000 g, 0.3971 mmol) was dissolved in CH_3CN (7mL). Using a plastic pipette, a solution of 24% HF (0.5 mL) was added dropwise to the mixture. After

24 hours of stirring, the mixture was poured into a separatory funnel containing a solution of $NaHCO_3$. Ether was used to extract the product, followed by a brine wash. The organic phase was dried over magnesium sulphate, filtered and concentrated. The remaining product was purified by flash chromatography (35% EtOAc in hexanes) to give **104** as a clear oil in 65% yield.

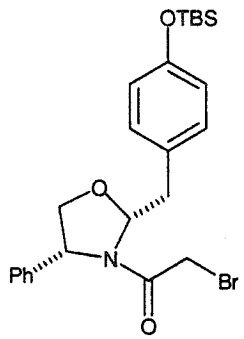
IR (neat) 3431, 3064, 1654, 1275; ^{1}H NMR (acetone-d6, 300 MHz) δ 8.25 (s, 1H) 7.25 (m, 7H), 6.81 (m, J = 8.1 Hz, 2H), 5.31 (d, J = 4.0 Hz, 1H), 4.15 (m, 1H), 3.83 (d, J = 8.4 Hz, 1H), 3.66 (m, 2H), 3.33 (d, J = 10.5 Hz, 1H), 3.16 (m, 1H), 3.07 (d, J = 10.1 Hz, 1H), 2.82 (dd, J = 13.6 Hz, J = 5.7 Hz, 1H), 2.38 (dd, J = 13.7 Hz, J = 6.8 Hz, 1H); ^{13}C (acetone-d6, 75 MHz) δ 164.8, 156.6, 138.3, 131.8, 130.3, 129.8, 129.1, 127.7, 115.2, 91.7, 69.8, 59.4, 39.4, 38.7, 28.7; MS (CI) m/z 390 (MH+), 392 (MH+2), 310 (M-Br), 282 and 284 (M-[CH_2PhOH]).



120

(120). 4 Å molecular sieves were activated with a heat gun for 10 minutes in a 25 mL flask. To this was added **104** (0.0300 g, 0.0771 mmol) and tert-butanol (8 mL). Tert-butoxide in tert-butanol (0.1 mL of 1.0 M, 0.1157 mmol) was added and the mixture was allowed to stir for 3 hours. The reaction was quenched with NH_4Cl, extracted in EtOAc and washed with brine. The organic phases were dried over magnesium sulphate, filtered and concentrated. The oily residue was purified by flash chromatography (20% EtOAc in hexanes, followed by 50% EtOAc in hexanes) to yield **120** in 17% yield.

IR (neat) 3050, 1685, 1158; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, J = 7.6 Hz, 2H), 6.96 (m, 5H), 6.55 (d, J = 7.8 Hz, 2H), 5.31 (d, J = 2.3 Hz, 2H), 4.85 (d, J = 15.8 Hz, 1H), 4.51 (d, J 15.8 Hz, 1H), 3.98 (m, 1H), 3.55 (m, 2H), 3.34 (m, 1H), 3.09 (d, J = 15.0 Hz, 1H), 1.55 (d, J = 13.0 Hz, 1H), 1.07 (dd, J = 13.0 Hz, J = 12.8 Hz, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 169.9, 157.5, 137.8, 132.7, 129.3, 129.0, 128.6, 126.0, 91.9, 71.5, 69.0, 59.5, 37.5, 36.8; MS (EI) m/z 618 (M+).

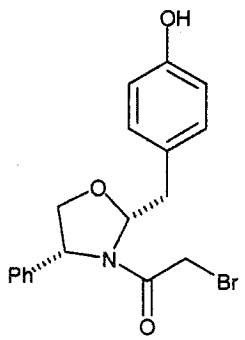


121

2-Bromo-1-{2-[4-(tert-butyl-dimethyl-silanyloxy)-benzyl]-4-phenyl-oxazolidin-3-yl}-ethanone (121). In a 250 mL flask, 4 Å molecular sieves were activated with a heat gun for 10 minutes. S-Phenylglycinol (0.9376 g, 6.83 mmol) was added to the flask and dissolved in freshly distilled THF (50 mL). In a separate 100 mL flask, **110** (1.4874 g, 5.94 mmol) was dissolved in THF (10 mL) and cannulated into the phenylglycinol mixture. After 3 hours, freshly distilled N-methyl morpholine (1.30 mL, 11.89 mmol) was added and this was allowed to stir for 10 minutes. Bromoacetyl bromide (0.78 mL, 8.91 mmol) was transferred to the reaction vessel. After 45 minutes of stirring, the sieves were filtered from the reaction mixture into a separatory funnel. $NaHCO_3$ was added to the reaction and this was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with brine and then dried over magnesium sulfate, filtered and

concentrated. The brown residue was purified by flash chromatography (5% EtOAc in hexanes followed by 10% EtOAc in hexanes) to yield **121** as a reddish oil in 48% yield. IR (neat) 3050, 1657, 1257; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 4H), 7.18 (m, 3H), 6.78 (d, J = 8.4 Hz, 2H), 5.49 (broad d, J = 7.0 Hz, 1H), 5.06 (dd, J = 6.5 Hz, J = 4.7 Hz, 1H), 4.30 (dd, J = 8.9 Hz, J = 6.9 Hz, 1H), 4.03 (dd, J = 8.9 Hz, J = 4.5 Hz, 1H), 3.50 (m, 3H), 3.06 (dd, J = 13.9 Hz, J = 8.1 Hz, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 165.7, 155.0, 139.4, 131.4, 129.7, 129.5, 128.9, 126.5, 120.3, 93.1, 74.3, 61.2, 38.8, 28.5, 26.1, 18.6, -4.0; MS (CI) m/z 490 (MH+), 492 (MH+2), 268 and 270 (M-[CH_2PhOTBS]).

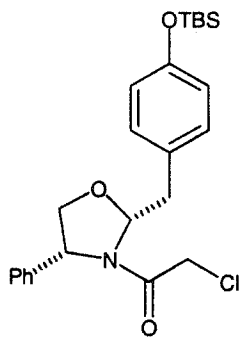
*** The cis and trans isomers were differentiated by a network of 1D nOe experiments.



122

2-Bromo-1-[2-(4-hydroxy-benzyl)-4-phenyl-oxazolidin-3-yl]-ethanone (122). In a plastic vessel, **121** (0.2500 g, 0.3971 mmol) was dissolved in CH_3CN (8mL). Using a plastic pipette, a solution of 24% HF (0.5 mL) was added dropwise to the mixture. After 24 hours of stirring, the mixture was poured into a separatory funnel containing a solution of $NaHCO_3$. Ether was used to extract the product, followed by a brine wash. The organic phase was dried over magnesium sulphate, filtered and the solvent reduced by rotary evaporation. The product was purified by flash chromatography (25% EtOAc in hexanes) to give **122** as a clear oil in 61% yield.

IR (neat) 3338, 3050, 1654, 1197; ^{1}H NMR (acetone-d6, 300 MHz) δ 8.22 (s, 1H), 7.35 (m, 5H), 7.12 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.74 (dd, J = 6.7 Hz, J = 2.3 Hz, 1H), 5.10 (d, J = 5.9 Hz, 1H), 4.31 (dd, J = 8.8 Hz, J = 6.2 Hz, 1H), 3.78 (m, J = 11.8 Hz, 2H), 3.50 (d, J = 11.8 Hz, 1H), 3.07 (m, 1H), 2.84 (d, J = 10.0 Hz, 1H); ^{13}C (acetone-d6, 75 MHz) δ 164.2, 156.6, 142.4, 131.3, 129.5, 128.5, 128.0, 126.2, 115.4, 92.6, 73.7, 60.4, 36.8, 28.5; MS (CI) m/z 376 (MH+), 378 (MH+2), 268 and 270 (M-[CH_2PhOH]).



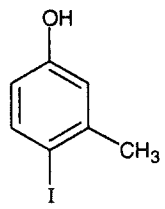
124

2-Chloro-1-{2-[4-(tert-butyl-dimethyl-silanyloxy)-benzyl]-4-phenyl-oxazolidin-3-yl}-ethanone (124). In a 25 mL flask, 4 Å molecular sieves were activated with a heat gun for 10 minutes. S-Phenylglycinol (0.1261 g, 0.9189 mmol) was added to the flask and dissolved in freshly distilled THF (6 mL). In a separate 10 mL flask, **110** (0.2000 g, 0.7991 mmol) was dissolved in THF (2 mL) and cannulated into the phenylglycinol mixture. After 3 hours, freshly distilled N-methyl morpholine (0.18 mL, 1.5981 mmol) was added and this was allowed to stir for 10 minutes. Chloroacetyl chloride (0.10 mL, 1.1984 mmol) was transferred to the reaction vessel. After 45 minutes of stirring, the sieves were filtered from the reaction mixture into a separatory funnel. $NaHCO_3$ was added to the reaction and this was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with brine and then dried over magnesium sulfate, filtered and concentrated. The brown residue was purified by flash chromatography

(10% EtOAc in hexanes followed by 15% EtOAc in hexanes) to give **124** as a yellow oil in 45% yield.

IR (neat) 3061, 1659, 1243; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 4H), 7.19 (m, 3H), 6.78 (d, J = 8.5 Hz, 2H), 5.52 (broad d, J = 7.2 Hz, 1H), 4.99 (broad m, 1H), 4.29 (broad t, J = 6.8 Hz, 1H), 4.06 (m, 1H), 3.84 (d, J = 13.1 Hz, 1H), 3.67 (d, J = 13.1 Hz, 1H), 3.48 (d, J = 14.1 Hz, 1H), 3.06 (dd, J = 13.9 Hz, J = 8.1 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 164.9, 154.8, 140.8, 131.3, 129.6, 129.2, 128.7, 126.0, 120.2, 92.4, 74.1, 60.2, 42.8, 37.2, 25.9, 18.4, -4.3; MS (CI) m/z 446 (MH+), 448 (MH+2), 224 and 226 (M-[CH_2PhOTBS]).

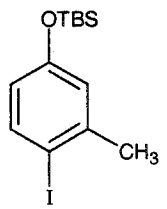
*** The cis and trans isomers were differentiated by a network of 1D nOe experiments.



144

4-Iodo-3-methyl-phenol (144). To a 250 mL flask was charged m-cresol (4.8356 mL, 46.23 mmol) and a 30% CH_3OH in CH_2Cl_2 (155 mL) solution. To this was added benzyltrimethylammonium dichloroiodate (16.8977 g, 48.54 mmol) and $CaCO_3$ (10.2635 g, 101.72 mmol). After 5 hours of stirring, excess $CaCO_3$ was filtered and reaction quenched with excess 10% HCl. The mixture was extracted with EtOAc three times; the organic layers were combined and washed with $NaHCO_3$ and then brine. The organic layers were dried over magnesium sulphate, filtered and solvent removed. The remainder was purified by flash chromatography (5% EtOAc in hexanes) to produce **144** in 72% yield. The substitution of the phenyl ring was verified by 1D nOe.

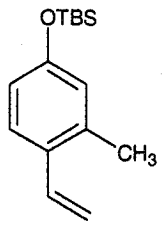
IR (neat) 3375, 1445, 1032; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.40 (dd, J = 7.9 Hz, J = 2.0 Hz, 1H), 4.74 (broad s, 1H), 2.34 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 155.9, 143.2, 140.0, 117.5, 115.3, 90.2, 28.5; MS (EI) m/z 234 (M+), 107 (M-I).



145

tert-Butyl-(4-iodo-3-methyl-phenoxy)-dimethyl-silane (145). In a 250 mL flask, **144** (3.60 g, 15.39 mmol) and imidazole (2.09 g, 30.79 mmol) was dissolved in anhydrous DMF (60 mL). While stirring, TBSCl (3.4864 g, 23.09 mmol) was added and allowed to stir for 2 hours. The reaction mixture was extracted in ether and washed three times with water, followed by brine. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified by flash chromatography (100% hexanes) to yield **145** as a yellow oil in 98% yield.

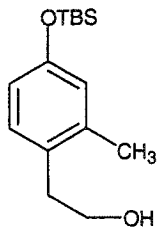
IR (neat) 3063, 1463, 1290; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 2.1 Hz, 1H), 6.40 (dd, J = 8.5 Hz, J = 2.3 Hz, 1H), 2.36 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 156.4, 142.7, 139.7, 122.4, 119.3, 91.1, 28.5, 26.1, 18.6, -4.0; MS (EI) m/z 348 (M+), 291 (M-tbutyl), 164 (M-I-tbutyl).



146

tert-Butyl-dimethyl-(3-methyl-4-vinyl-phenoxy)-silane (146). To a 50 mL flask was charged **145** (0.8500 g, 2.4425 mmol), CuI (0.0464 g, 0.2443 mmol) and freshly distilled DMF (20mL). The lot was degassed for 5 minutes, followed by the addition of Pd(II)dppf (0.0894 g, 0.1221 mmol) and subsequent degassing for 5 minutes. The vinyl tributyl tin (0.8556 mL, 2.9310 mmol) was added to the flask and the reaction was stirred for 30 hours at 80 °C. The mixture was filtered through a pad of Celite, extracted in ether and washed three times with water. The organic phase was dried over magnesium sulphate, filtered and concentrated. The purification of the residue by flash chromatography (100% hexanes) was not successful as the n-butyl groups consistently appeared in the spectra. Compound **146** was obtained as an orange oil in 85% yield.

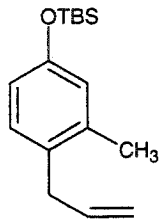
IR (neat) 3078, 1644, 1110; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, J = 8.1 Hz, 1H), 6.84 (dd, J = 17.5 Hz, J = 11.0 Hz, 1H), 6.63 (m, 2H), 5.51 (dd, J= 17.4 Hz, J = 1.4 Hz, 1H), 5.15 (dd, J = 11.0 Hz, J = 1.5 Hz, 1H), 2.27 (s, 3H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 155.8, 137.2, 134.6, 130.4, 126.73, 122.0, 118.1, 113.5, 26.1, 20.2, 18.6, -4.0; MS (EI) m/z 248.



147

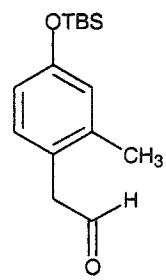
2-[4-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-phenyl]-ethanol (147). In a 25 mL flask, **146** (0.1150 g, 0.4637 mmol) was dissolved in THF (5 mL) at 0°C. A 5.0 M solution of borane dimethylsulfide (0.0927 g, 0.4637 mmol) in diethyl ether was transferred to the flask and allowed to stir for 2 hours. 3N NaOH (0.8387 mL) and 30% H_2O_2 (0.191 mL, 1.8548 mmol) were added at 0°C. After 1 hour of stirring, a white precipitate formed and the mixture was extracted in ether, followed by a brine wash. The organic phase was dried over magnesium sulphate, filtered and concentrated to yield the crude alcohol. Subsequent purification of the alcohol by flash chromatography (10% EtOAc in hexanes followed by 20% EtOAc in hexanes) gave pure **147** as a yellow oil in 69% yield.

IR (neat) 3361, 3050, 1045; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.60 (dd, J = 8.1 Hz, J = 2.6 Hz, 1H), 3.76 (td, J = 6.8 Hz, J = 6.0 Hz, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.25 (s, 3H), 1.50 (broad t, J = 5.8 Hz, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 154.5, 138.1, 130.8, 129.3, 122.4, 117.7, 63.1, 36.1, 26.1, 20.0, 18.5, -4.0; MS (EI) m/z 266 (M+), 209 (M-tbutyl), 191 (M-tbutyl-H_20).



138

(4-Allyl-3-methyl-phenoxy)-tert-butyl-dimethyl-silane (138). To a 10 mL flask was charged **145** (0.1323 g, 0.3802 mmol), CuI (0.0072 g, 0.0380 mmol) and freshly distilled DMF (4 mL). The mixture was degassed for 5 minutes, followed by the addition of $Pd(0)(PPh_3)4$ (0.0220 g, 0.0190 mmol) and subsequent degassing for 5 more minutes. The allyl tributyl tin (0.1414 mL, 0.4562 mmol) was added to the flask and the reaction was stirred for 3 days at 80 °C. The mixture was filtered through Celite pad, extracted in ether and washed three times with water. The organic phase was dried over magnesium sulphate, filtered and concentrated. The purification of the residue by flash chromatography (100% hexanes) was not successful as the n-butyl groups and other impurities consistently plagued the spectra. Compound **138** was crudely obtained as an orange oil in 48% yield. This compound was carried through to the ozonolysis reaction. Please see compound **134** below for spectral data.



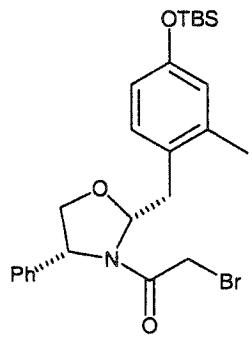
134

[4-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-phenyl]-acetaldehyde (134). In a 25 mL flask equipped with a 3-way adapter leading to a N_2 outlet, $(COCl)_2$ (0.0353 mL, 0.4040

mmol) was dissolved in CH_2Cl_2 (6 mL) and brought to -78°C. DMSO (0.0573 mL, 0.8081 mmol) was added dropwise to the solution. After stirring for 15 minutes, **147** (0.0900 g, 0.3367 mmol) in CH_2Cl_2 (1 mL) was slowly added to the mixture. After another 15 minutes of stirring, triethylamine (0.2253 mL, 1.6162 mmol) was added slowly. The mixture turned orange/brown and the precipitate was filtered. The filtrate was extracted twice in ether and each ethereal layer was washed with HCl, $NaHCO_3$ and brine. The organic phases were dried over magnesium sulphate, filtered and concentrated. The black residue was purified by flash chromatography (5% EtOAc in hexanes) to yield **134** as an orange oil in 68% yield.

Alternatively, crude **138** was dissolved in a 1:1 mixture of CH_2Cl_2:MeOH (10 mL) and ozone was bubbled into the solution at -78°C until it was blue (45 min.). The reaction was quenched with excess dimethyl sulfide and allowed to stir an additional 1 hour at room temperature. The mixture was extracted in ether and washed with water. The organic layer was dried over magnesium sulphate, filtered and rotovaped. The product was purified by flash chromatography (100% hexanes followed by 5% EtOAc in hexanes) to give pure aldehyde **134** in an overall yield of 26% from the aryl iodide **145**.

IR (neat) 3025, 2804, 2719, 1719, 1281; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.64 (s, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.97 (s, 1H), 6.67 (d, J = 8.3 Hz, 1H), 3.59 (s, 2H), 2.18 (s, 3H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 200.1, 155.5, 138.9, 131.8, 123.5, 122.6, 118.2, 48.4, 26.0, 20.2, 18.6, -4.0; MS (EI) m/z 264 (M+), 265 (M-H), 207 (M-tbutyl-H).

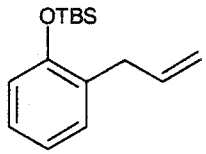


148

2-Bromo-1-{2-[4-(tert-butyl-dimethyl-silanyloxy)-2-methyl-benzyl]-4-phenyl-oxazolidin-3-yl}-ethanone (148). In a 25 mL flask, 4 Å molecular sieves were activated with a heat gun for 10 minutes. S-Phenylglycinol (0.0347 g, 0.2529 mmol) was added to the flask and dissolved in freshly distilled THF (4 mL). In a separate 5 mL flask, **134** (0.0610 g, 0.2299 mmol) was dissolved in THF (1 mL) and cannulated into the phenylglycinol mixture. After 3 hours, freshly distilled N-methyl morpholine (0.0505 mL, 0.4599 mmol) was added and this was allowed to stir for 10 minutes. Bromoacetyl bromide (0.0300 mL, 0.3449 mmol) was transferred to the reaction vessel. After 45 minutes of stirring, the sieves were filtered from the reaction mixture into a separatory funnel containing $NaHCO_3$. This was extracted three times with CH_2Cl_2 and the combined organic phases were washed twice with brine; then dried over magnesium sulfate, filtered and concentrated. The dark residue was purified by flash chromatography (5% EtOAc in hexanes followed by 10% EtOAc in hexanes) to yield **148** as a reddish oil in 45% yield.

IR (neat) 3033, 1649, 1278; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5H), 7.30 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 2.2 Hz, 1H), 6.60 (dd, J = 8.2 Hz, J = 2.1 Hz, 1H), 5.85 (dd, J = 7.2 Hz, J = 2.0 Hz, 1H), 4.90 (broad d, J = 6.1 Hz, 1H), 4.22 (dd, J = 8.7 Hz, J = 6.3 Hz, 1H),

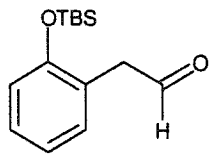
3.85 (dd, J = 8.7 Hz, J = 1.0 Hz, 1H), 3.50 (d, J = 11.3 Hz, 1H), 3.43 (d, J = 11.3 Hz, 1H), 3.35 (dd, J = 14.3 Hz, J = 1.9 Hz, 1H), 2.93 (dd, J = 14.2 Hz, J = 7.2 Hz, 1H), 2.37 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 165.2, 154.8, 141.4, 138.9, 132.3, 129.8, 128.9, 128.0, 126.1, 122.2, 117.7, 92.5, 73.8, 60.6, 34.1, 28.5, 26.1, 20.4, 18.6, -4.0; MS (CI) m/z 503 (MH+), 505 (MH+2), 268 and 270 (M-[CH_2ArOTBS]).



127

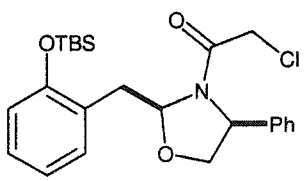
(2-Allyl-phenoxy)-tert-butyl-dimethyl-silane (127). In a 500 mL flask, 2-allyl-phenol (5.01 g, 37.34 mmol) and imidazole (4.86 g, 74.68 mmol) was dissolved in anhydrous DMF (200 mL). While stirring, TBSCl (8.46 g, 56.01 mmol) was added and allowed to stir for 3 hours. The reaction mixture was extracted in ether and washed three times with water, followed by brine. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified by flash chromatography (5% EtOAc in hexanes) to yield **127** as a pale yellow oil in 98% yield.

IR (neat) 3053, 1668, 1155; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (ddd, J = 7.5 Hz, J = 5.1 Hz, J = 1.7 Hz, 1H), 7.14 (dd, J = 7.6 Hz, J = 1.8 Hz, 1H), 6.97 (ddd, J = 7.4 Hz, J = 1.2 Hz, 1H), 6.87 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.05 (m, 1H), 5.15-5.08 (m, 2H), 3.45 (d, J = 6.5 Hz, 2H), 1.10 (s, 9H), 0.31 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 153.8, 137.5, 131.1, 130.6, 127.5, 121.5, 118.9, 115.9, 34.9, 26.3, 18.7, -3.7; MS (EI) m/z 248 (M+), 191 (M-tbutyl).



128

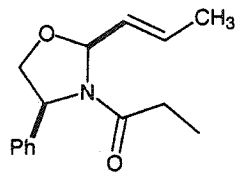
[2-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-acetaldehyde (128). **127** (1.10 g, 4.40 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2:MeOH (40 mL) and ozone was bubbled into the solution at -78°C until a blue colour appeared (1 hour). The reaction was quenched with excess dimethyl sulfide and allowed to stir an additional 1 hour at room temperature. The mixture was extracted in ether and washed twice with water. The organic layer was dried over magnesium sulphate, filtered and rotovaped. The product was purified by flash chromatography (100% hexanes followed by 5% EtOAc in hexanes) to give aldehyde **128** in 97% overall yield.



130

1-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-benzyl]-4-phenyl-oxazolidin-3-yl}-2-chloro-ethanone (130). In a 500 mL flask, 4 Å molecular sieves were activated with a heat gun for 10 minutes. S-Phenylglycinol (4.76 g, 34.65 mmol) was added to the flask and dissolved in freshly distilled THF (1800 mL). In a separate 100 mL flask, **128** (7.92 g, 31.49 mmol) was dissolved in THF (20 mL) and cannulated into the phenylglycinol mixture. After 3 hours, freshly distilled N-methyl morpholine (6.91 mL, 63.00 mmol) was added and this was allowed to stir for 15 minutes. Chloroacetyl chloride (3.76 mL, 47.25 mmol) was transferred to the reaction vessel. After 3 hours of stirring, the sieves were filtered from the reaction mixture into a separatory funnel. $NaHCO_3$ was added to

the reaction and this was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with brine and then dried over magnesium sulfate, filtered and concentrated. The brown residue was purified by flash chromatography (5% EtOAc in hexanes followed by 15% EtOAc in hexanes) to yield **130** as a reddish oil in 48% yield.

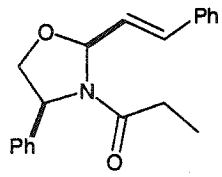


152

1-(4-Phenyl-2-propenyl-oxazolidin-3-yl)-propan-1-one (152). In a 100 mL flask, 4 Å molecular sieves were activated with a heat gun. S-phenylglycinol (0.4893 g, 3.5663 mmol) in THF (25 mL) was charged to the flask, followed by the addition of freshly distilled crotonaldehyde (0.2914 mL, 3.5663 mmol) in THF (5 mL). After 2.5 hours of stirring, N-methyl morpholine (0.7830 mL, 7.1327 mmol) was added. This was allowed to stir for 5 minutes followed by the addition of propionic anhydride. After 1.5 hours of stirring, the mixture was filtered from the sieves into a separatory funnel containing $NaHCO_3$. The lot was extracted three times in dichloromethane and the organic layers were washed twice with brine. The organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to yield **152** as a colourless oil in 66% yield. The spectra of this compound are particularly complicated by the slow rotation about the amide bond.

IR (neat) 3067, 1698, 1668, 1171; ^{1}H NMR (DMSO at 80°C, 300 MHz) δ 7.29 (m, 5H), 5.93 (m, 1H), 5.65 (m, 2H), 5.13 (broad t, 1H), 4.24 (broad t, J = 9.1 Hz, 1H), 3.87 (broad dd, J = 8.9 Hz, J = 2.7 Hz, 1H), 2.32-1.90 (m, 2H), 1.90-1.68 (broad d, J = 6.8 Hz, 3H),

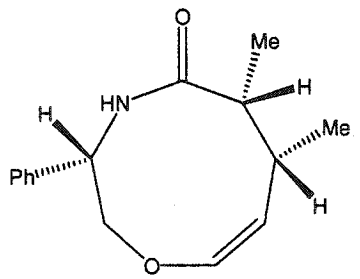
0.91 (broad t, J = 5.3 Hz, 3H); ^{13}C (DMSO 100°C, 75 MHz) δ 172.5, 141.9, 129.7, 129.3, 128.0, 127.1, 127.0, 90.1, 73.6, 60.4, 28.2, 17.8, 9.3; MS (EI) m/z 245 (M+).



153

1-(4-Phenyl-2-styryl-oxazolidin-3-yl)-propan-1-one (153). In a 100 mL flask, 4 Å molecular sieves were activated with a heat gun for 10 minutes. S-Phenylglycinol (0.2595 g, 1.8911 mmol) was added to the flask and dissolved in freshly distilled THF (13 mL). In a separate 10 mL flask, freshly distilled cinnamaldehyde (0.2381 mL, 1.8911 mmol) was dissolved in THF (3 mL) and cannulated into the phenylglycinol mixture. After 3.5 hours, freshly distilled N-methyl morpholine (0.4152 mL, 3.7821 mmol) was added and this was allowed to stir for 10 minutes. Propionic anhydride (0.3690 mL, 2.8366 mmol) was transferred to the reaction vessel. After 1 hour of stirring, the sieves were filtered from the reaction mixture into a separatory funnel. $NaHCO_3$ was added to the reaction and this was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with brine and then dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes followed by 25% EtOAc in hexanes) to produce **153** as a clear oil in 72% yield.

IR (neat) 3070, 1695, 1642, 1158; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48-7.09 (m, 10H), 6.93 (d, J = 16.0 Hz, 1H), 6.50 (dd, J = 15.9 Hz, J = 4.5 Hz, 1H), 6.14 (d, J = 4.1 Hz, 1H), 4.88 (broad t, 1H), 4.37 (broad t, 1H), 4.02 (m, 1H), 2.22 (m, 2H), 0.99 (broad t, J = 7.0 Hz, 3H); ^{13}C $CDCl_3$, 75 MHz) δ 173.3, 140.2, 136.6, 133.5, 129.5, 129.0, 128.5, 127.4, 127.2, 126.7, 125.8, 90.3, 74.9, 61.2, 28.6, 9.0; MS (EI) m/z 307 (M+).

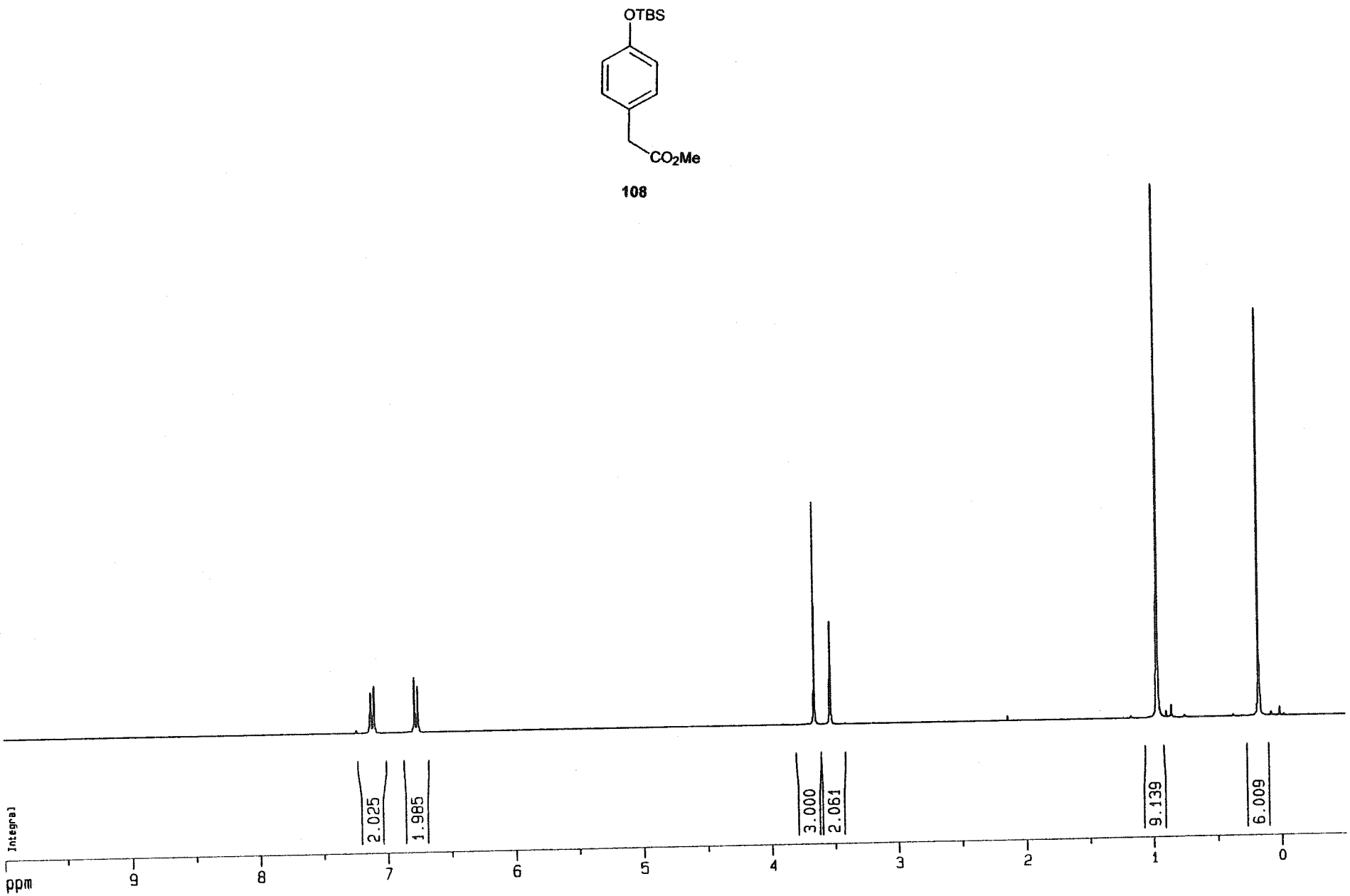


164

6,7-Dimethyl-3-phenyl-3,4,6,7-tetrahydro-2H-[1,4]oxazonin-5-one (164). In a 10 mL flask, was dissolved dry diisopropylamine (0.06 mL, 0.40 mmol) in 3 mL THF. The mixture was cooled to 0 °C and n-butyllithium (0.03 mL, 0.40 mmol) was added. After 15 minutes, the flask was cooled to -78 °C and the trans oxazolidine of **152** (0.103 g, 0.4 mmol) dissolved in 2 mL of THF was added dropwise. The enolate was given 30 minutes to form and then neat triisopropylsilyltriflate (0.11 mL, 0.4 mmol) was charge to the flask. The reaction was allowed to warm to room temperature over 4 hours and then was extracted in ether. The salts were filtered through a pad of Celite and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc in hexanes, 3% NEt_3) to give the amide silyl acetal. This product was then dissolved in 20 mL of toluene and heated to 210 °C for 1 hour in a microwave. The residue was concentrated and purified by preparative thin layer chromatography (25% EtOAc in hexanes, 3% triethylamine) to give 157 in < 5% yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.28 (m, 6H), 6.15 (d, J = 5.9 Hz, 1H), 5.61-5.45 (m, 1H), 5.36 (d, J = 10.4 Hz, 1H), 4.50-4.41 (m, 2H), 3.34 (t, J = 10.9 Hz, 1H), 3.25-3.18 (m, 1H), 2.62-2.55 (m, 1H), 1.17 (d, J = 7.2 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H); ^{13}C $CDCl_3$, 75 MHz) δ 180.1, 148.9, 129.1, 128.1, 126.3, 116.1, 100.3, 76.3, 56.3, 47.9, 34.4, 30.0, 19.9, 8.8.

Appendix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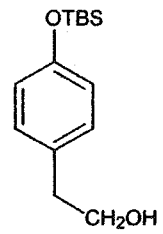
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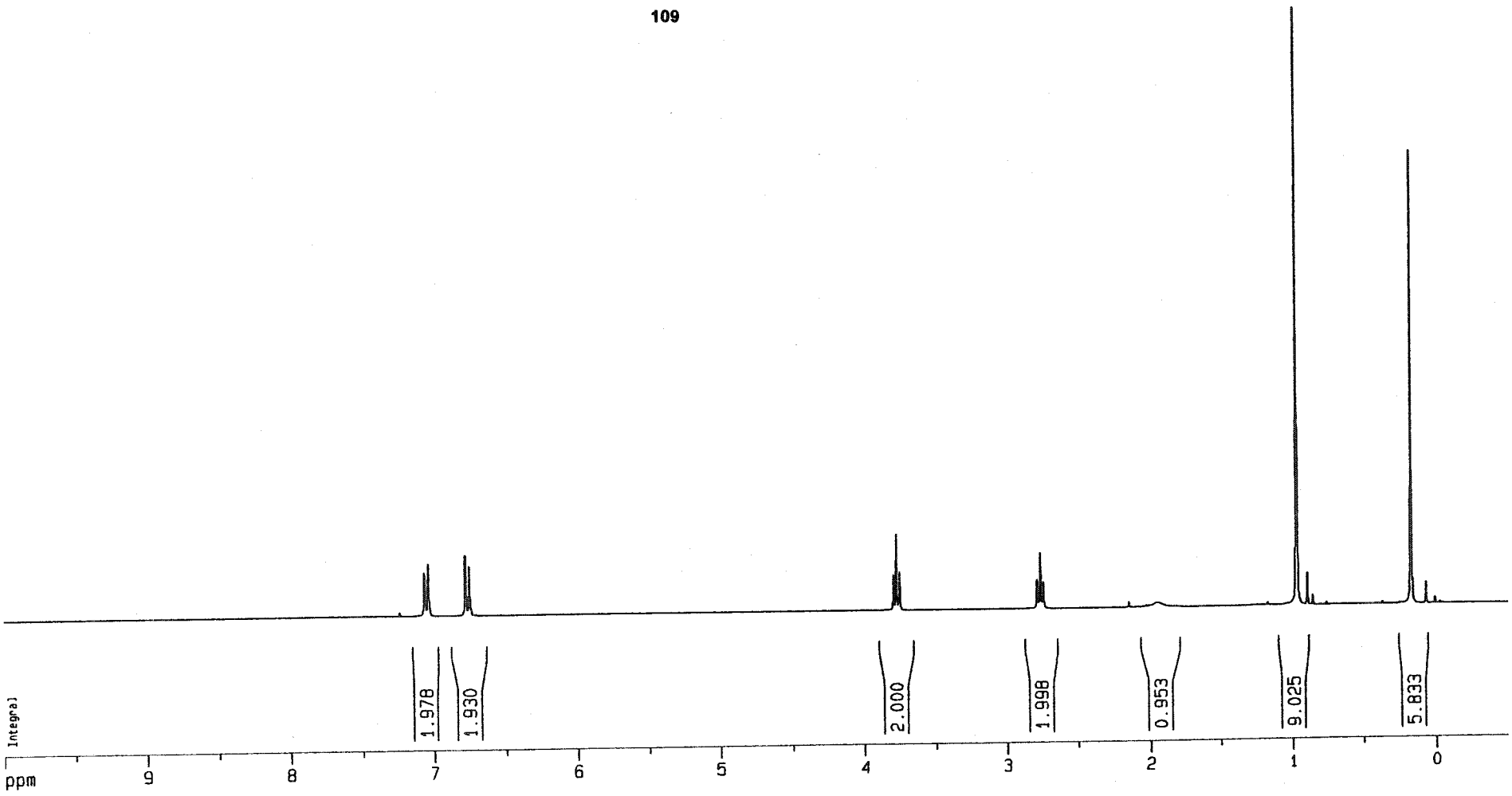
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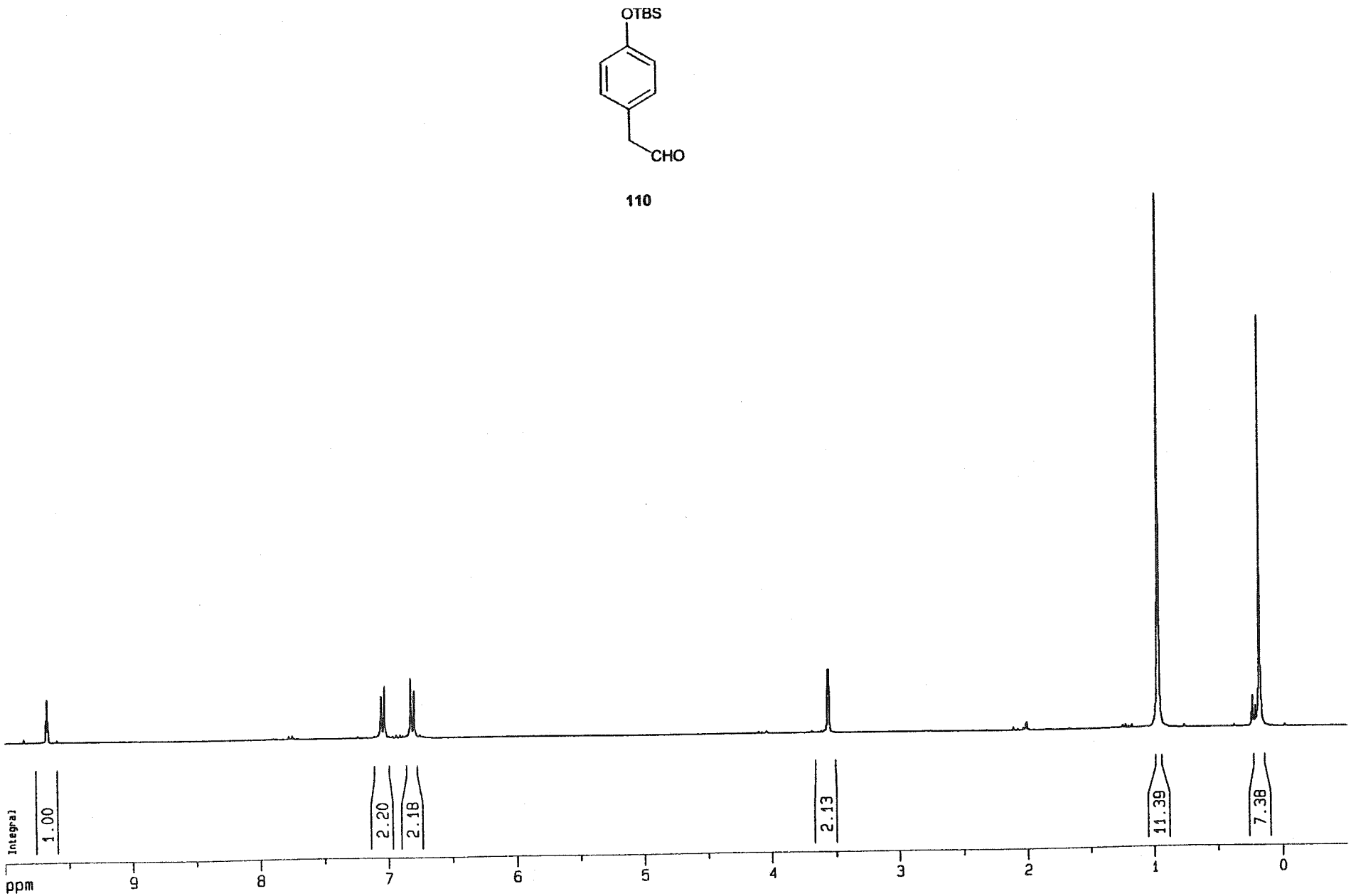
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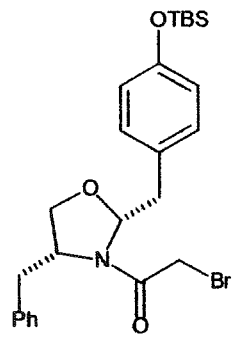

112


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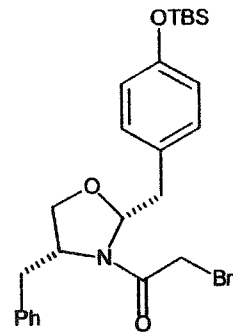

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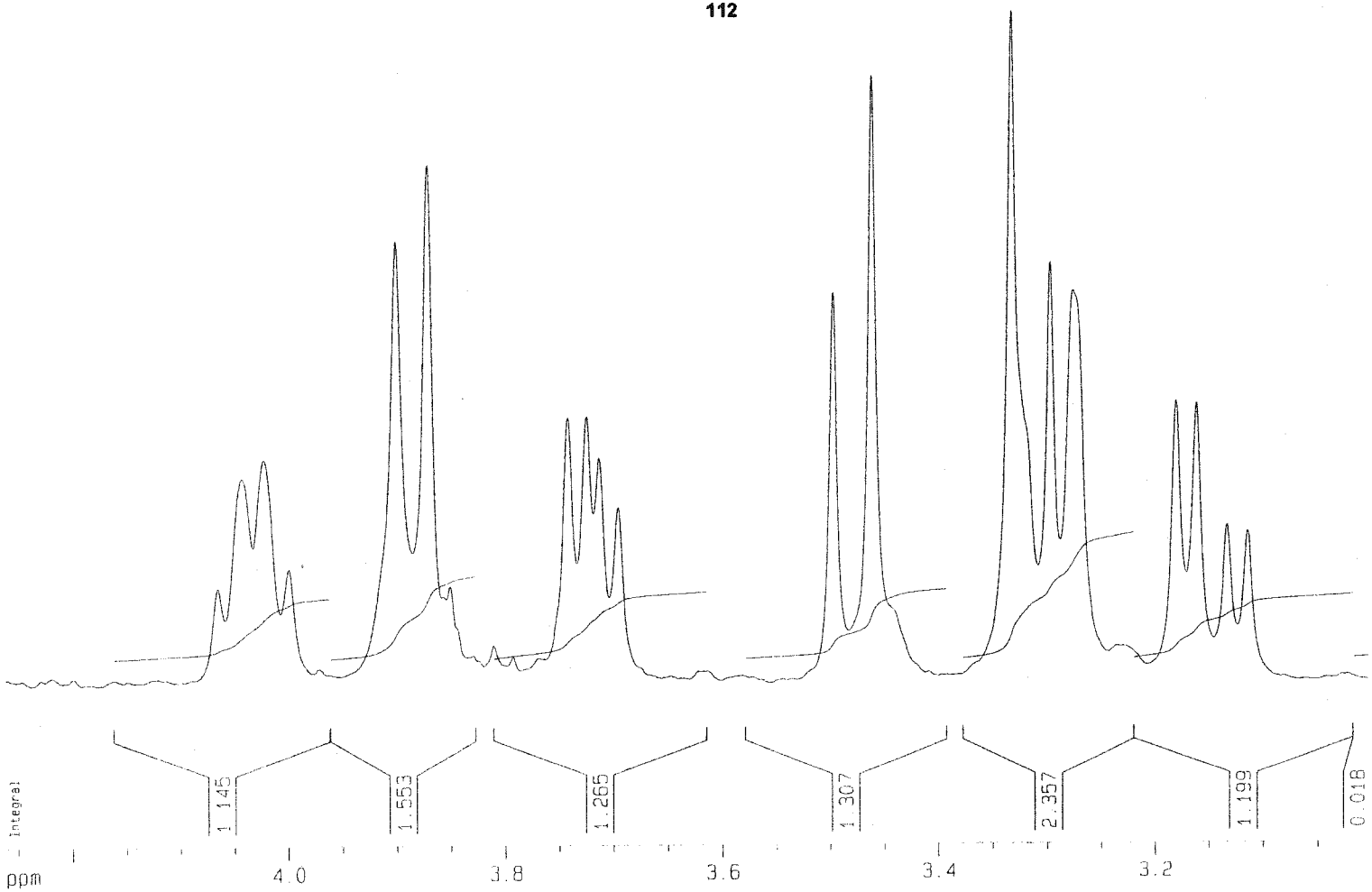


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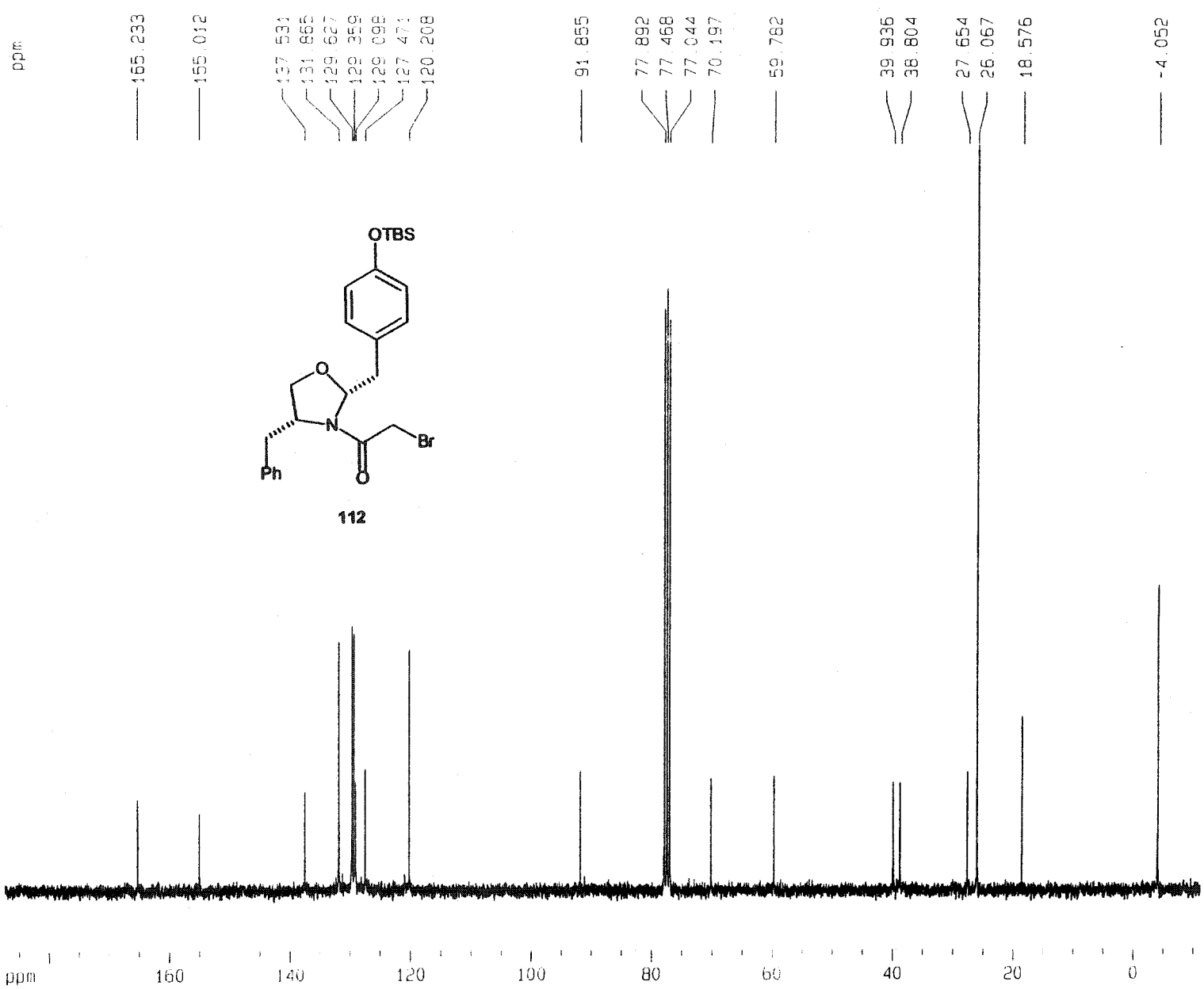

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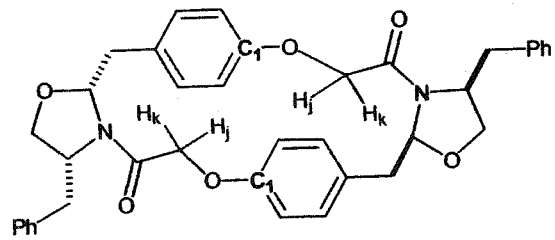
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Ph

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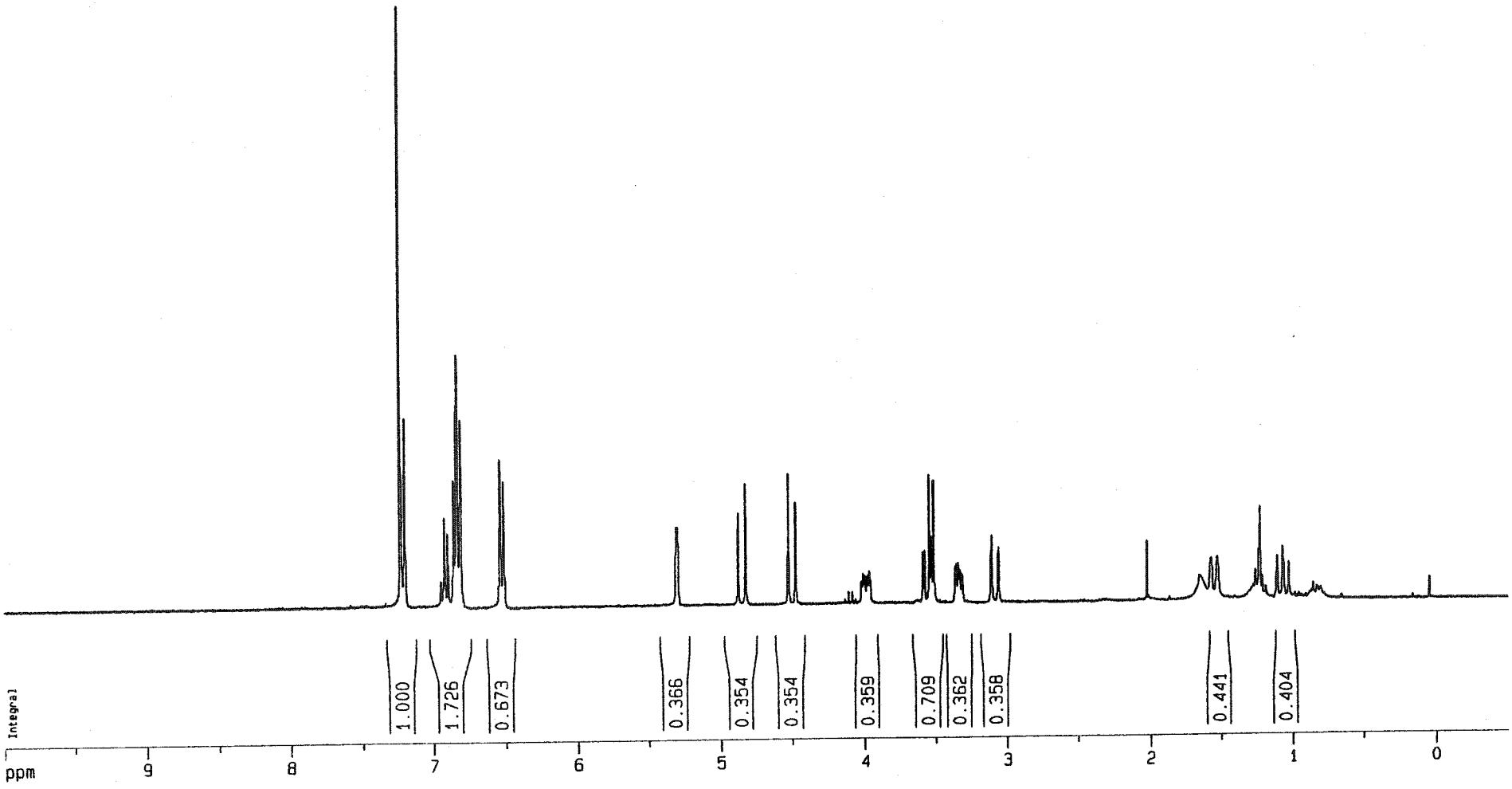
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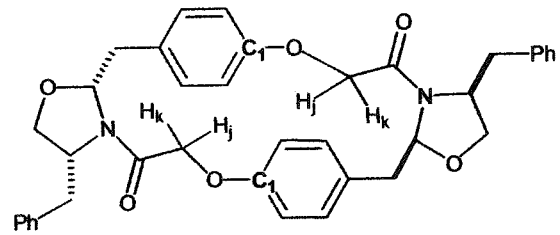
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Ph

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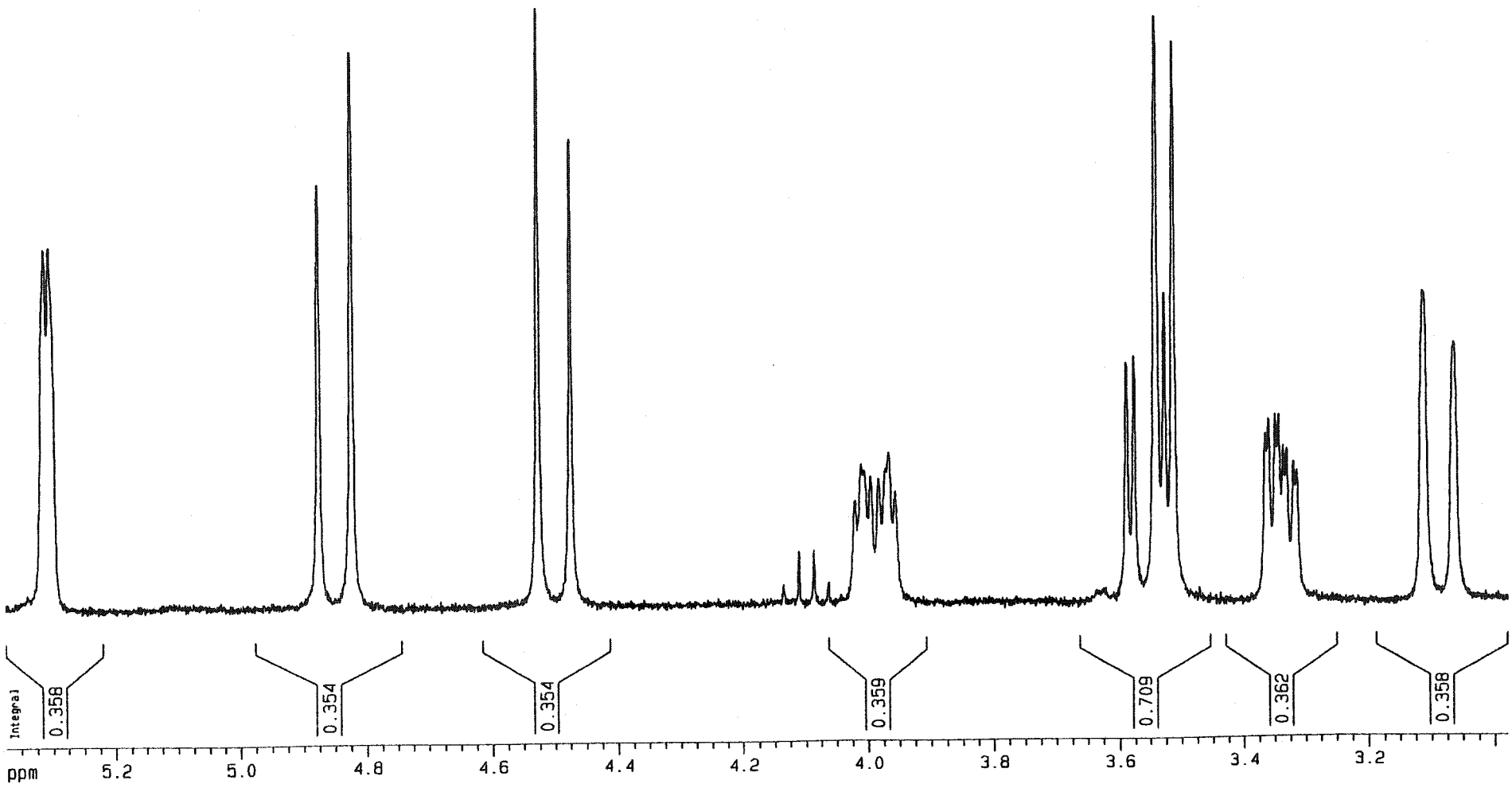
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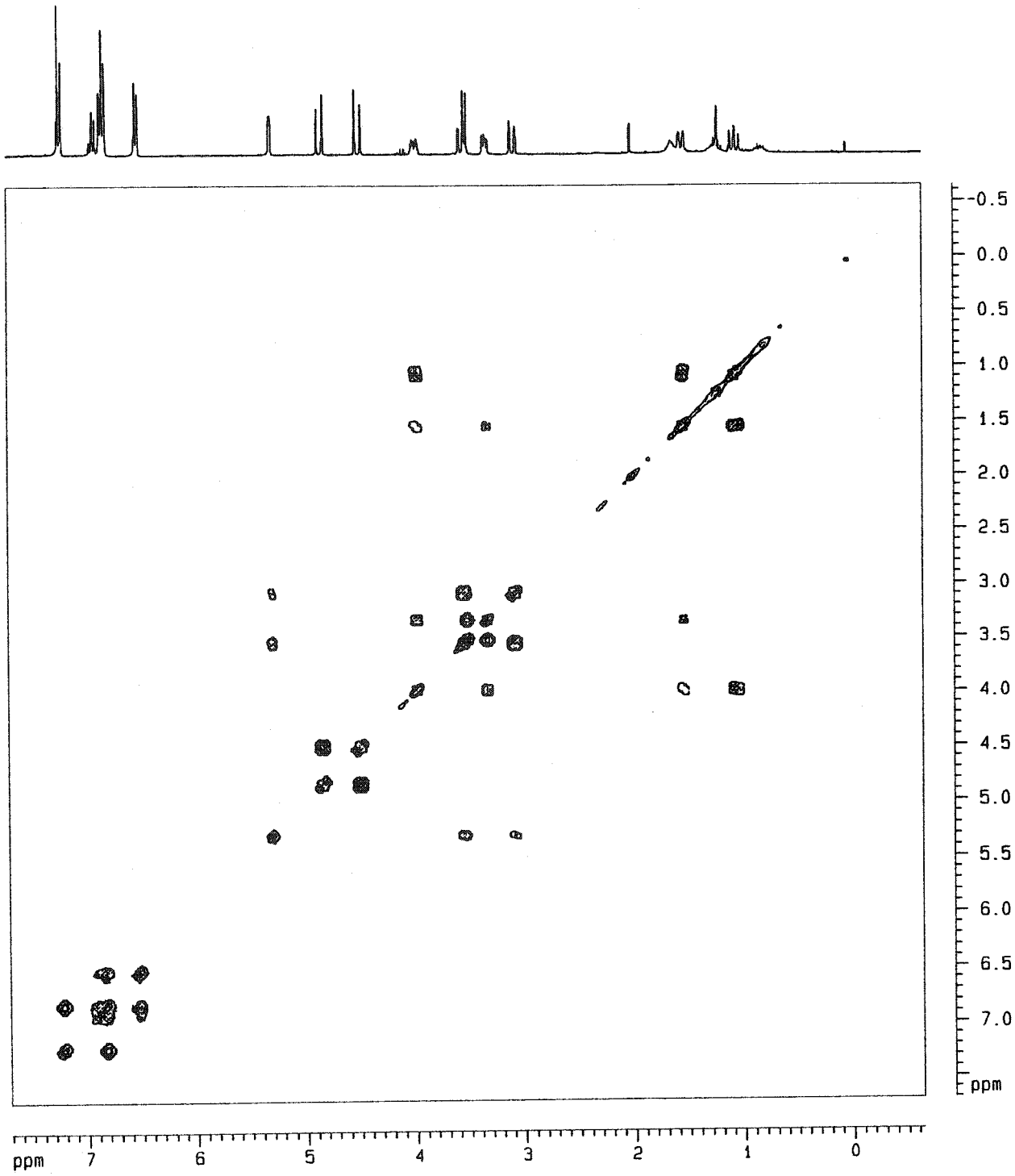
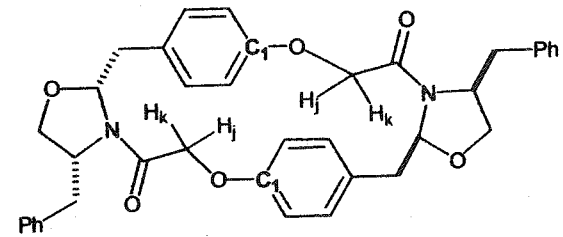
3.2

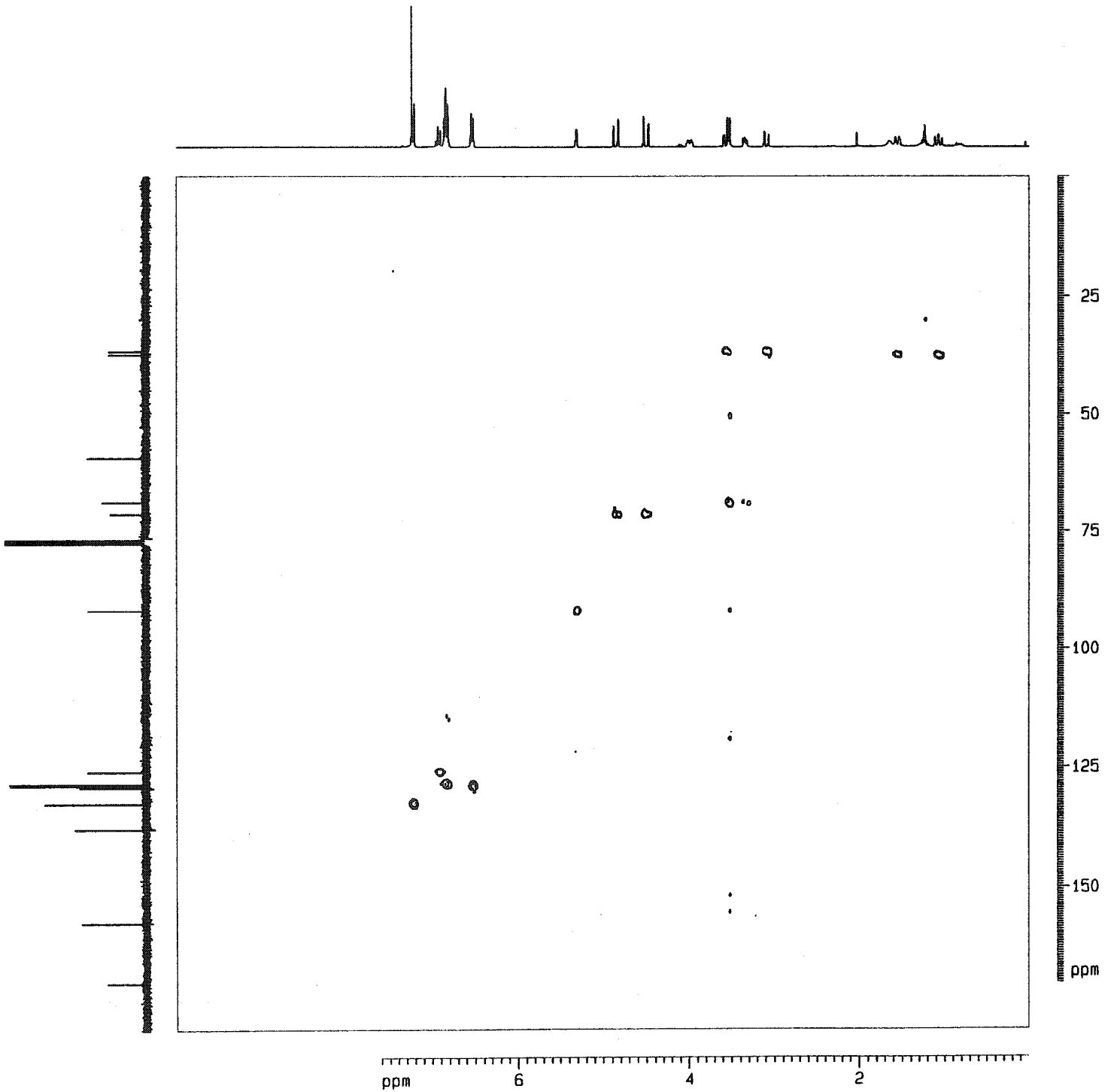
1H COSY

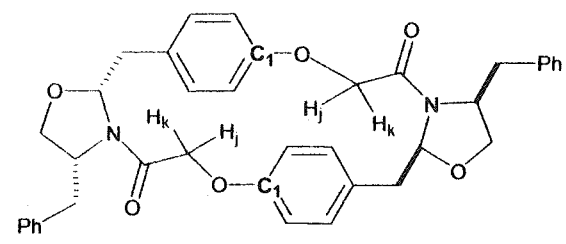

-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
ppm
ppm 7 6 5 4 3 2 1 0


O
C1
O
O
N
Ph
Hj
Hk
Hk
Hj
N
O
O
C1
Ph

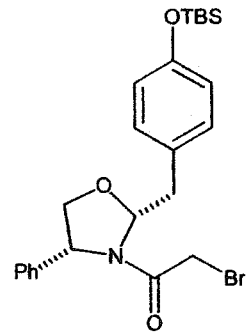
120

1H 13C HMQC

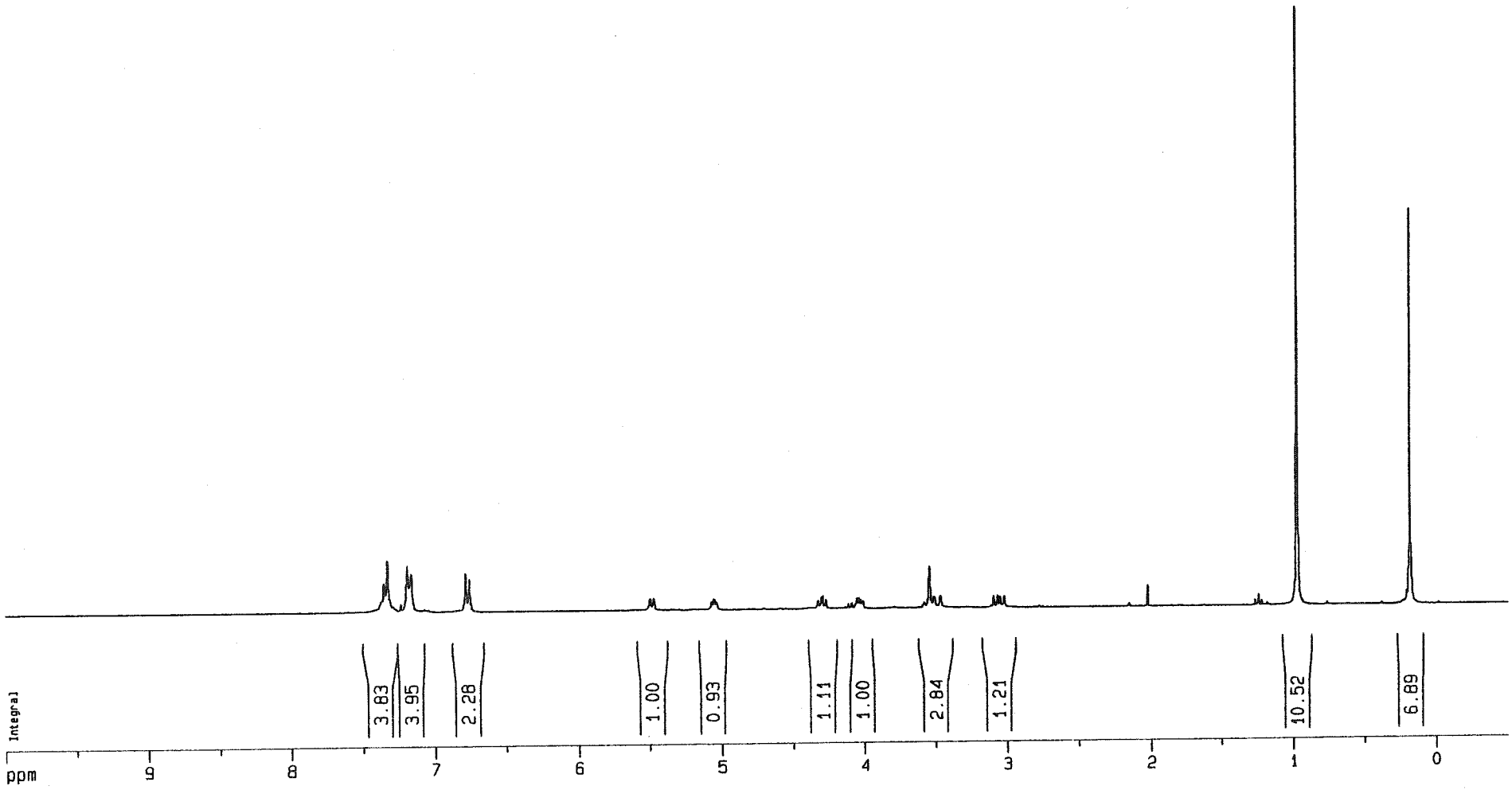




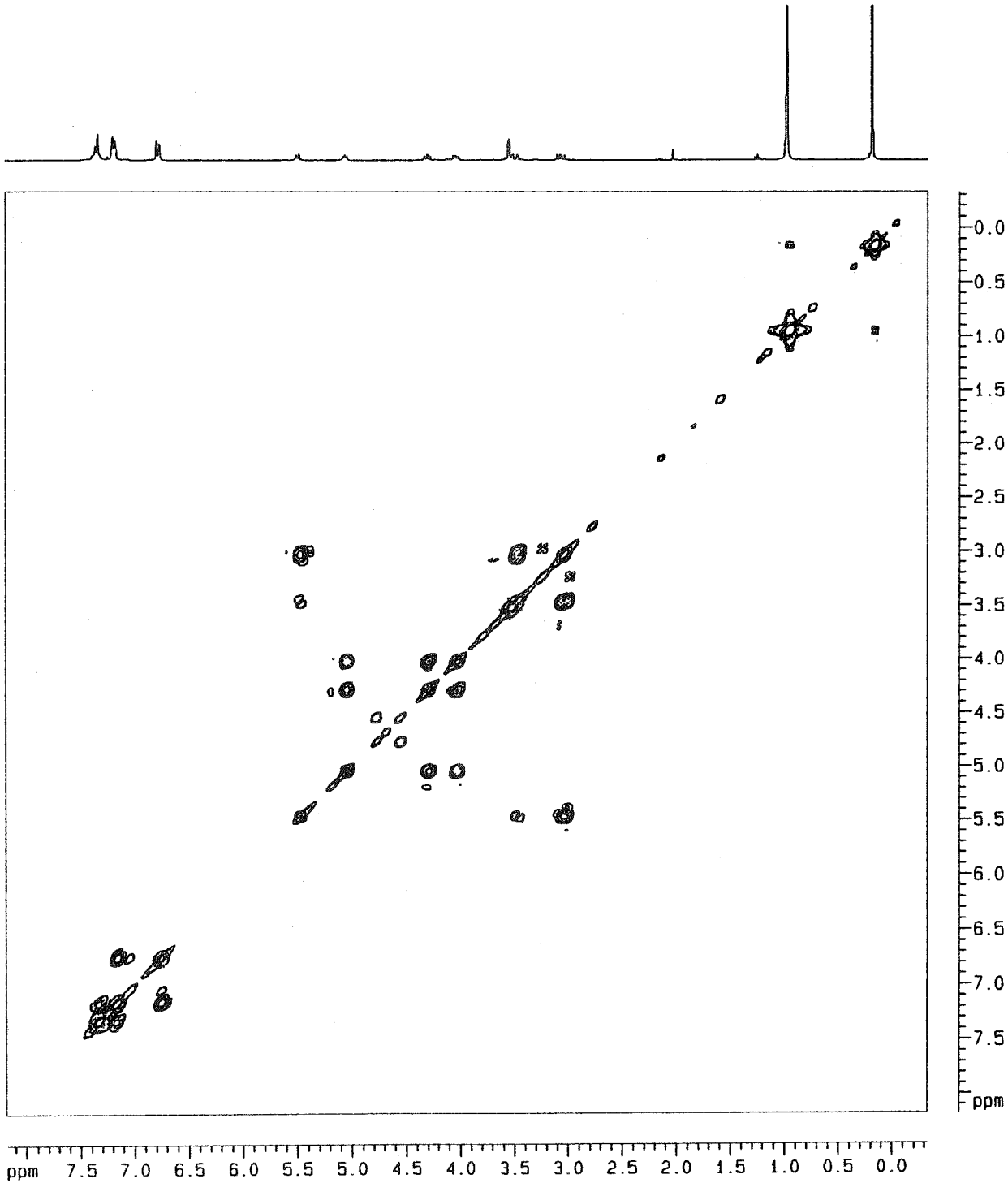
120

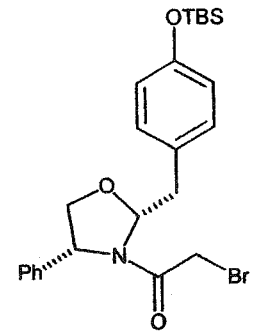

OTBS
O
Ph
N
Br
O

121

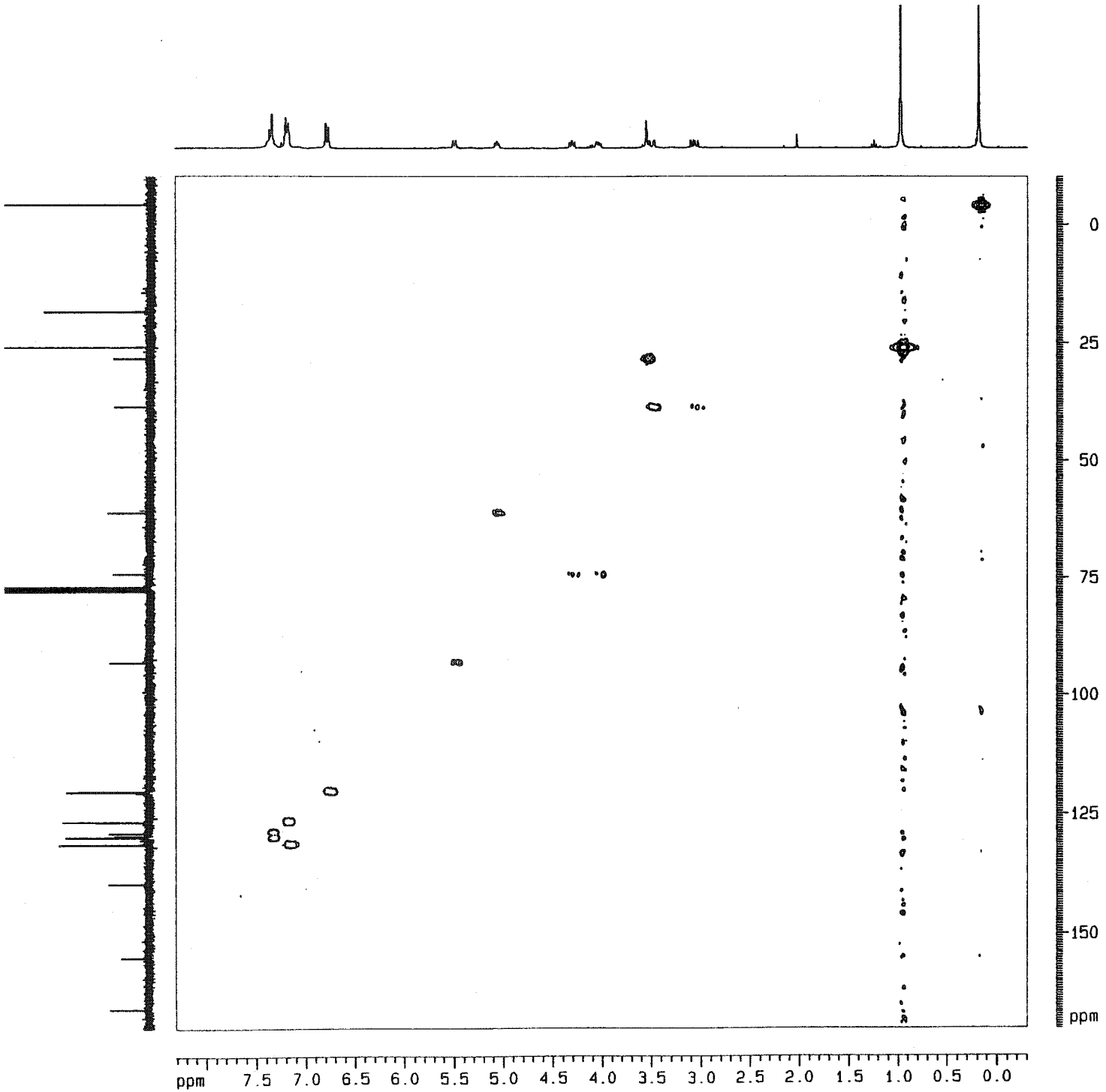

Integral
3.83
3.95
2.28
1.00
0.93
1.11
1.00
2.84
1.21
10.52
6.89
ppm
9
8
7
6
5
4
3
2
1
0

1H COSY

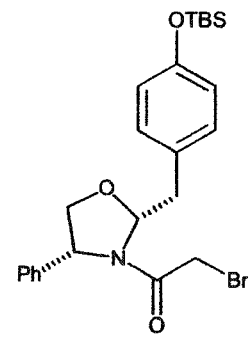

0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
ppm
ppm 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


OTBS
O
N
Ph
Br
O

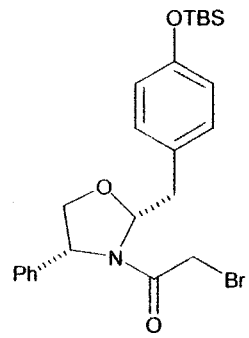
121



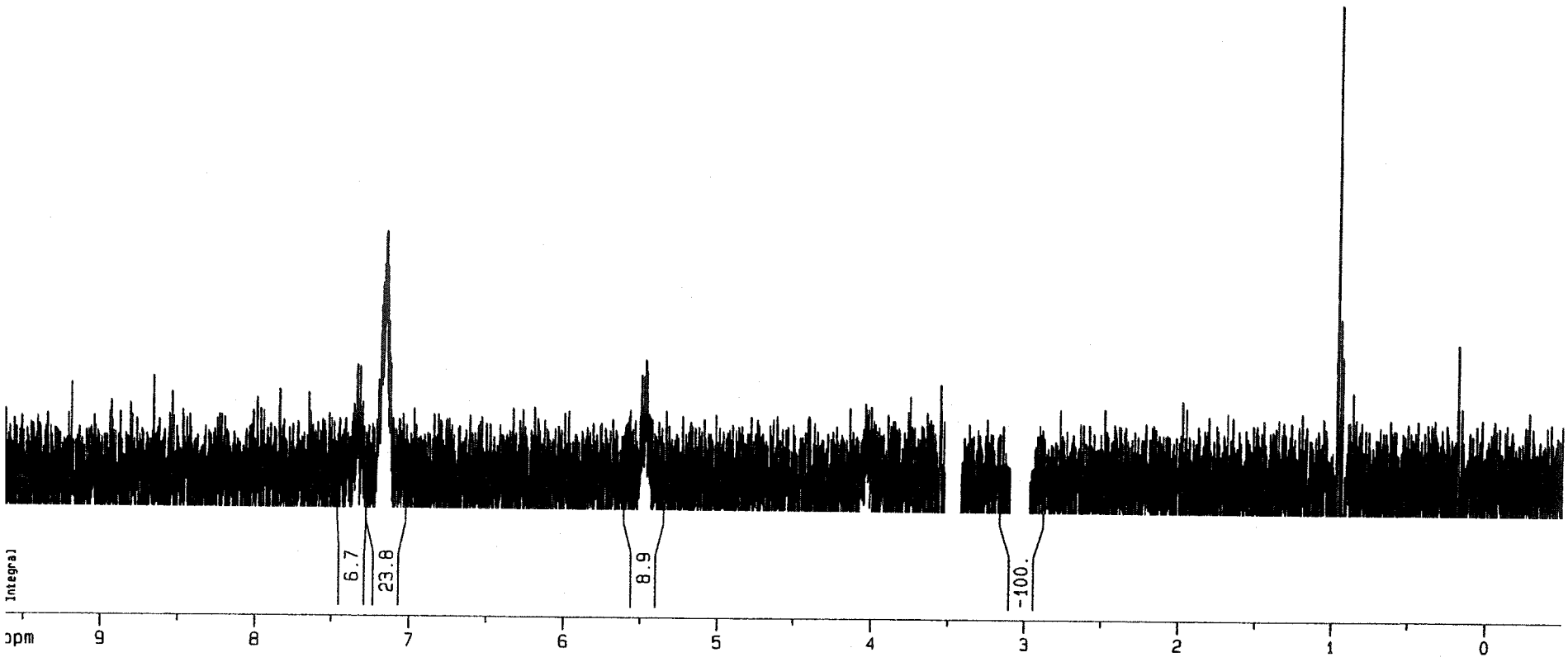
1H 13C HMQC

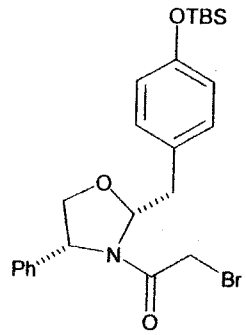


121

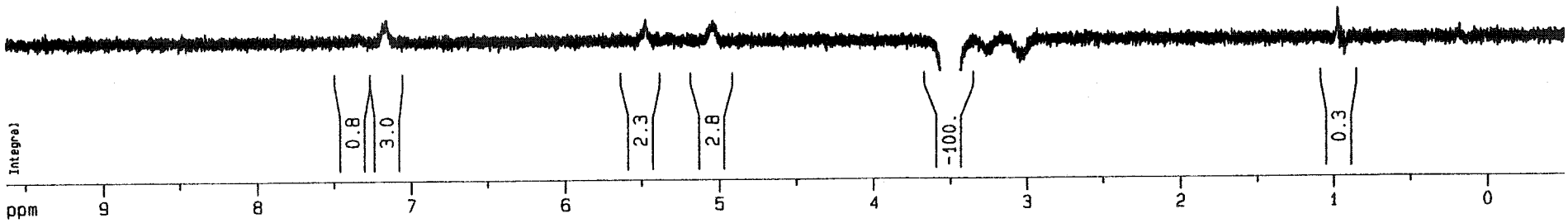


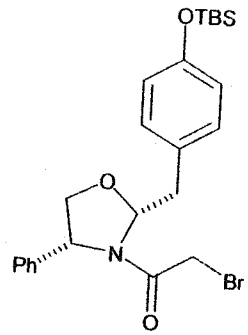
121



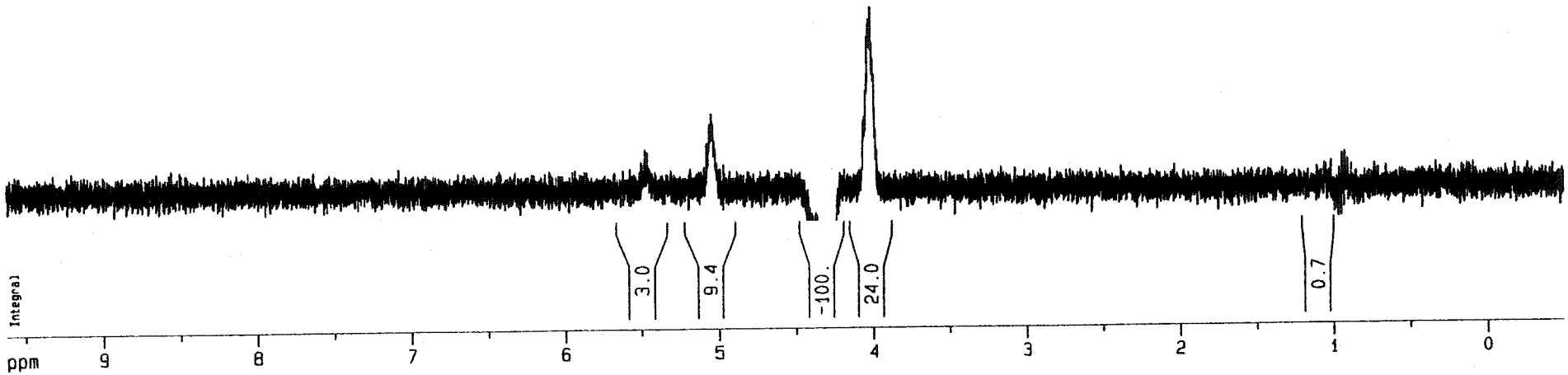


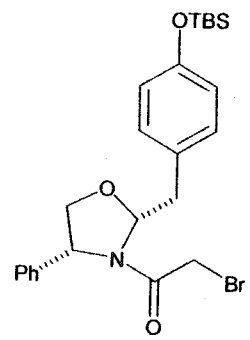
121





121





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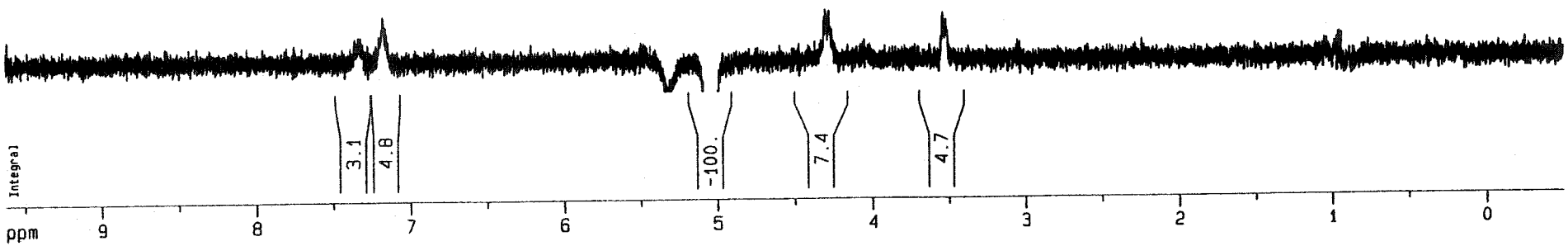
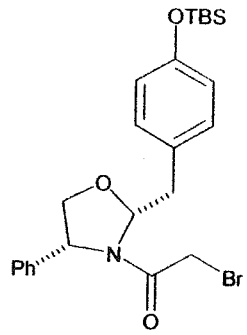
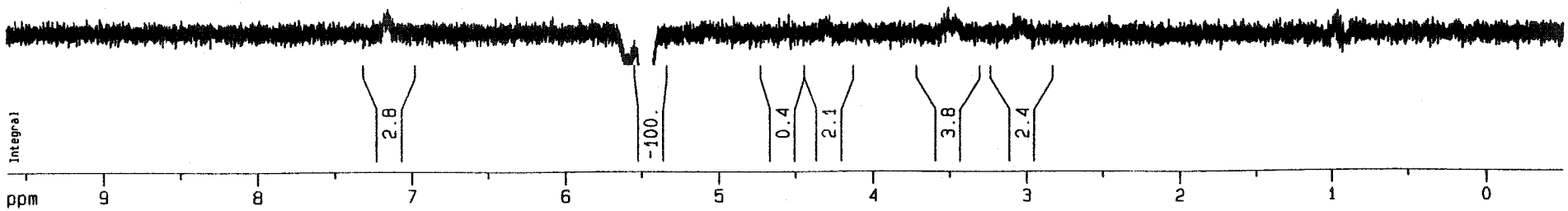
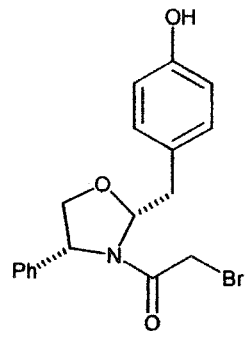


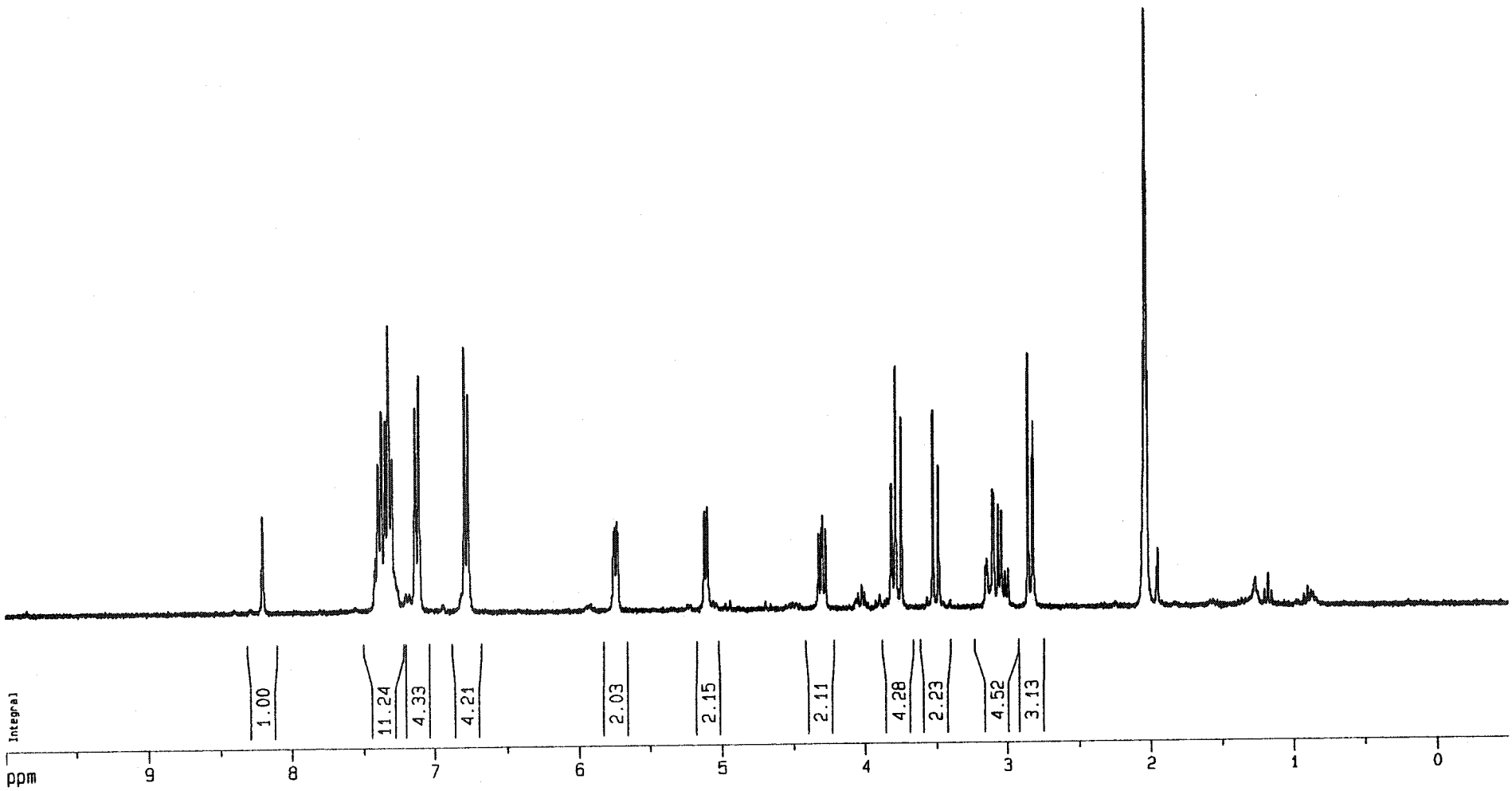


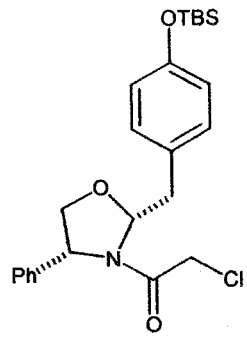
121



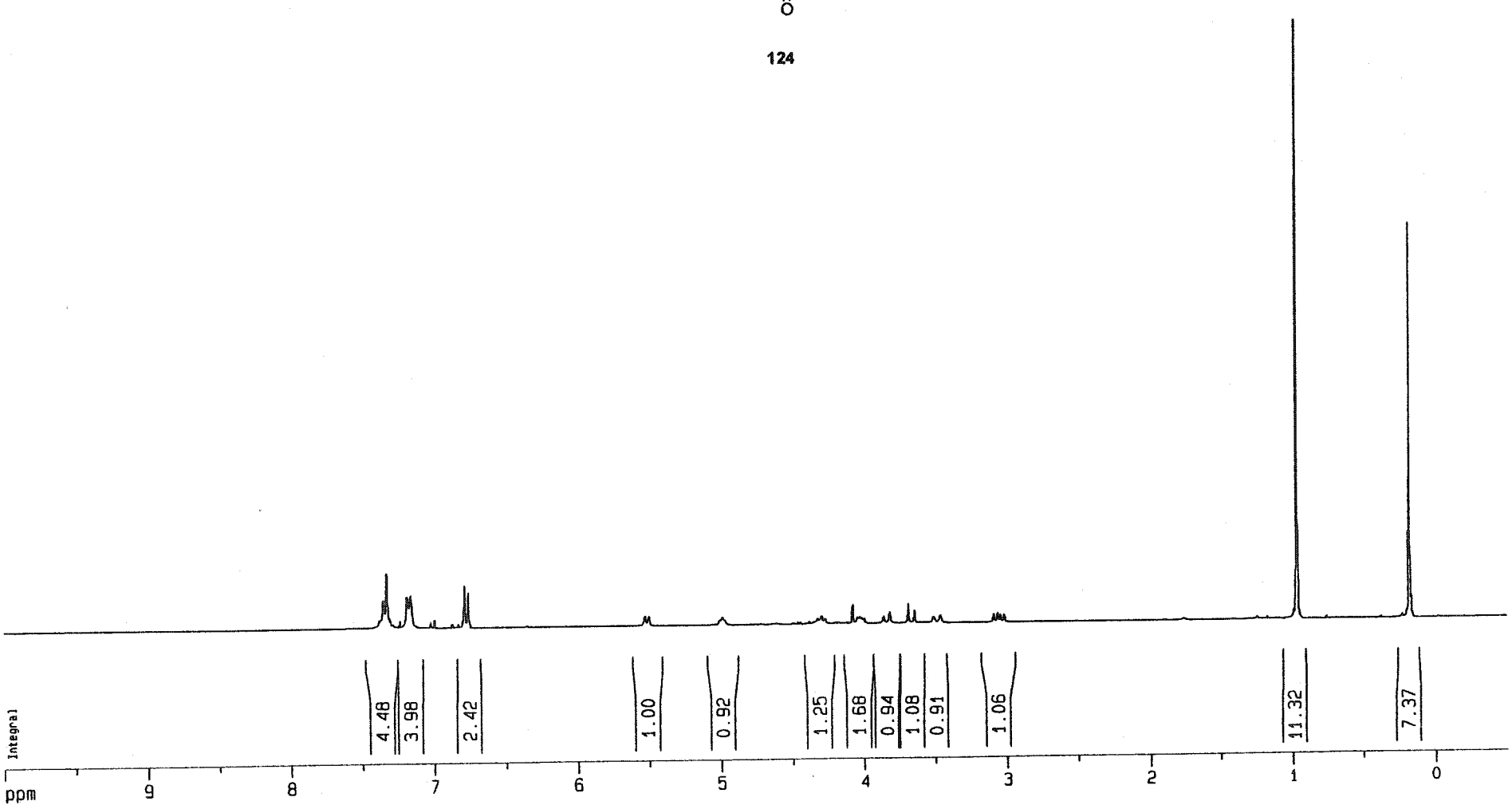

OH
O
Ph
N
Br
O

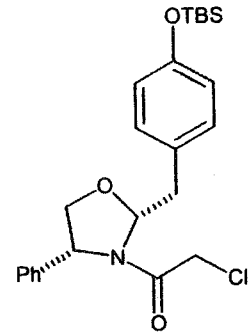
122


Integral
1.00
11.24
4.33
4.21
2.03
2.15
2.11
4.28
2.23
4.52
3.13
ppm
9
8
7
6
5
4
3
2
1
0

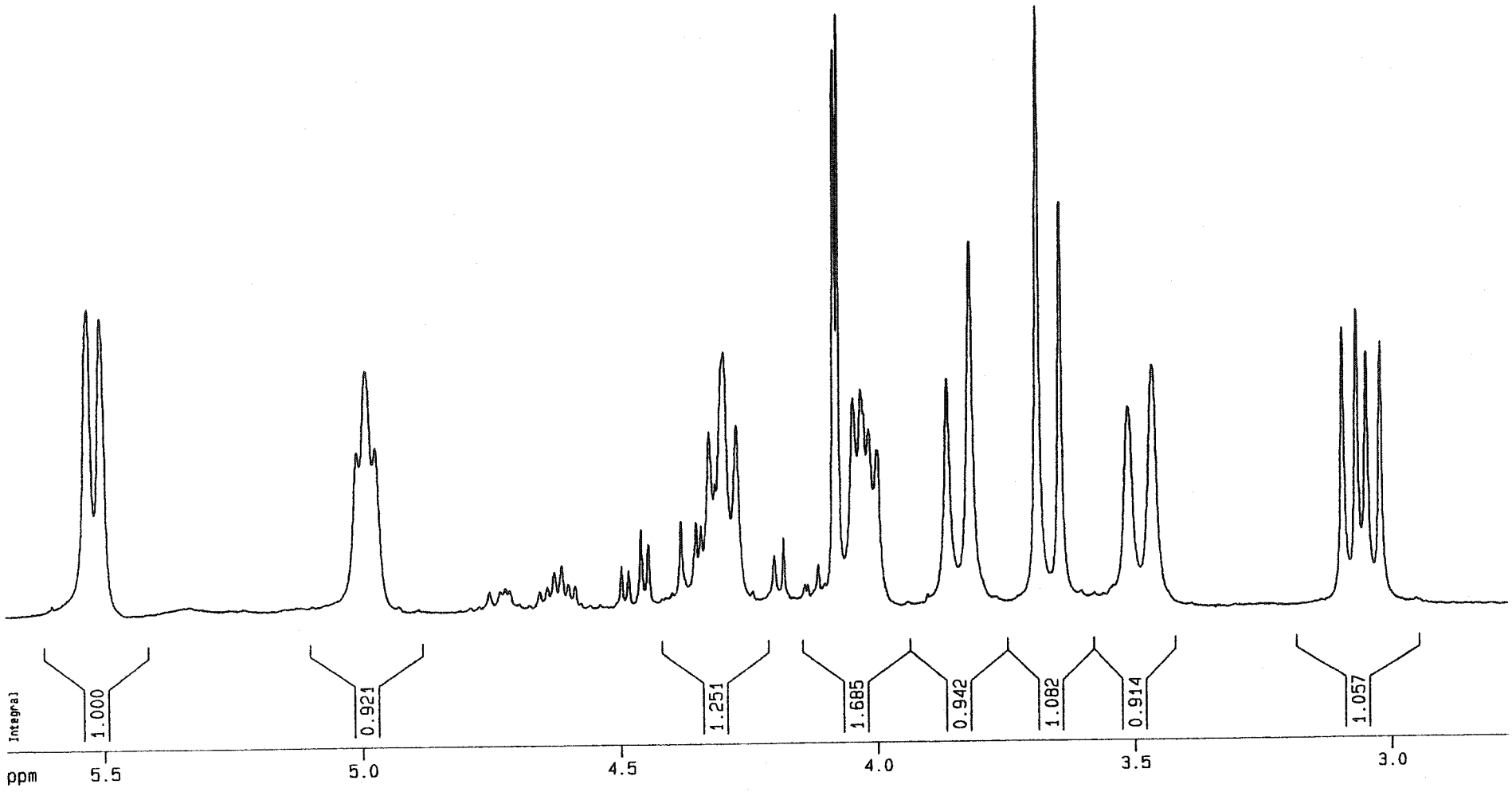

OTBS
O
Ph
N
Cl
O

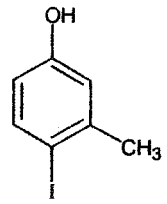
124


Integral
4.48
3.98
2.42
1.00
0.92
1.25
1.68
0.94
1.08
0.91
1.06
11.32
7.37
ppm
9
8
7
6
5
4
3
2
1
0

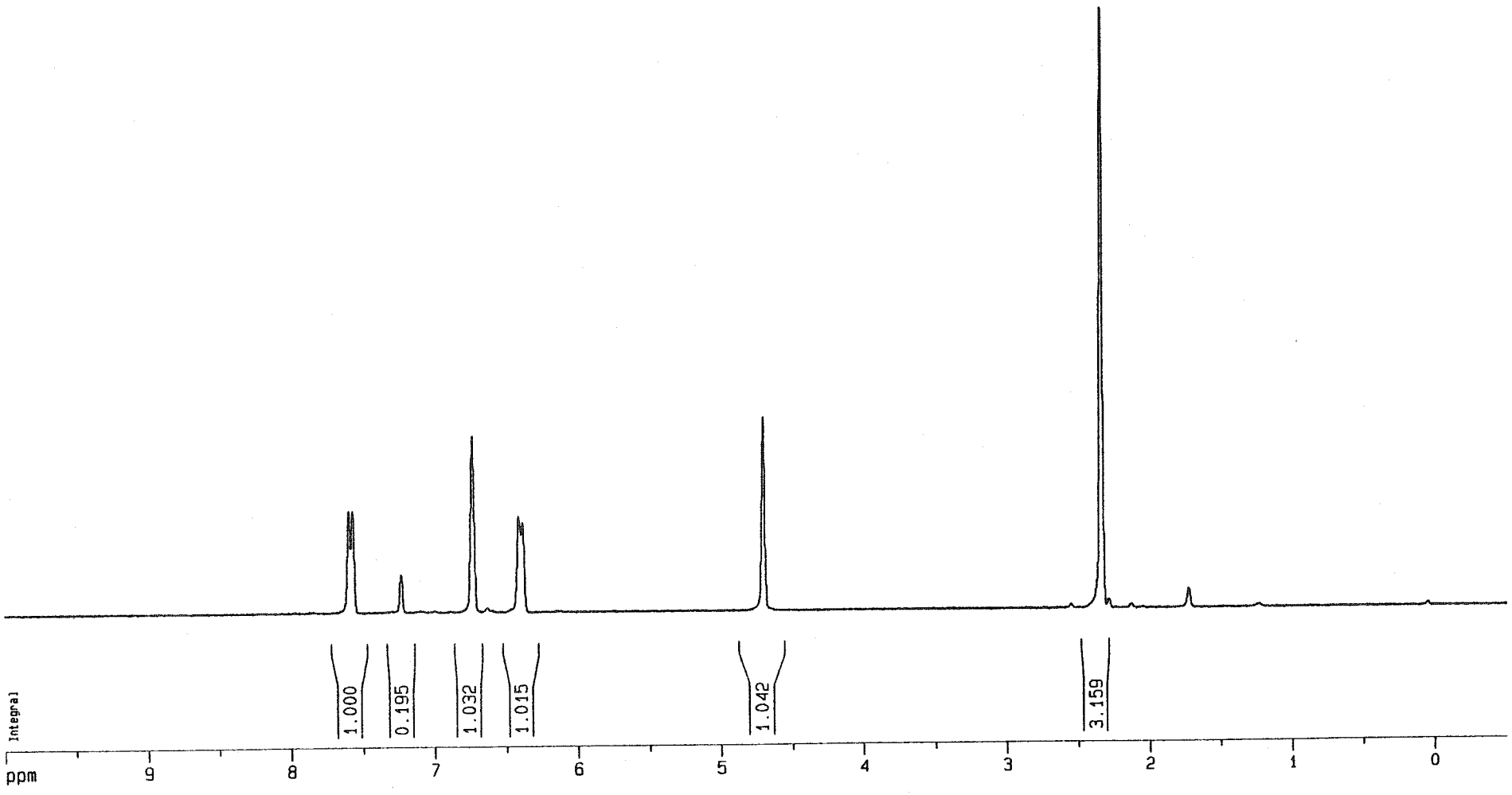

OTBS
O
Ph
N
Cl
O

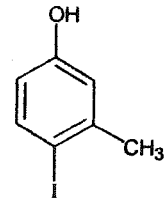
124


Integral
1.000
0.921
1.251
1.685
0.942
1.082
0.914
1.057
ppm
5.5
5.0
4.5
4.0
3.5
3.0

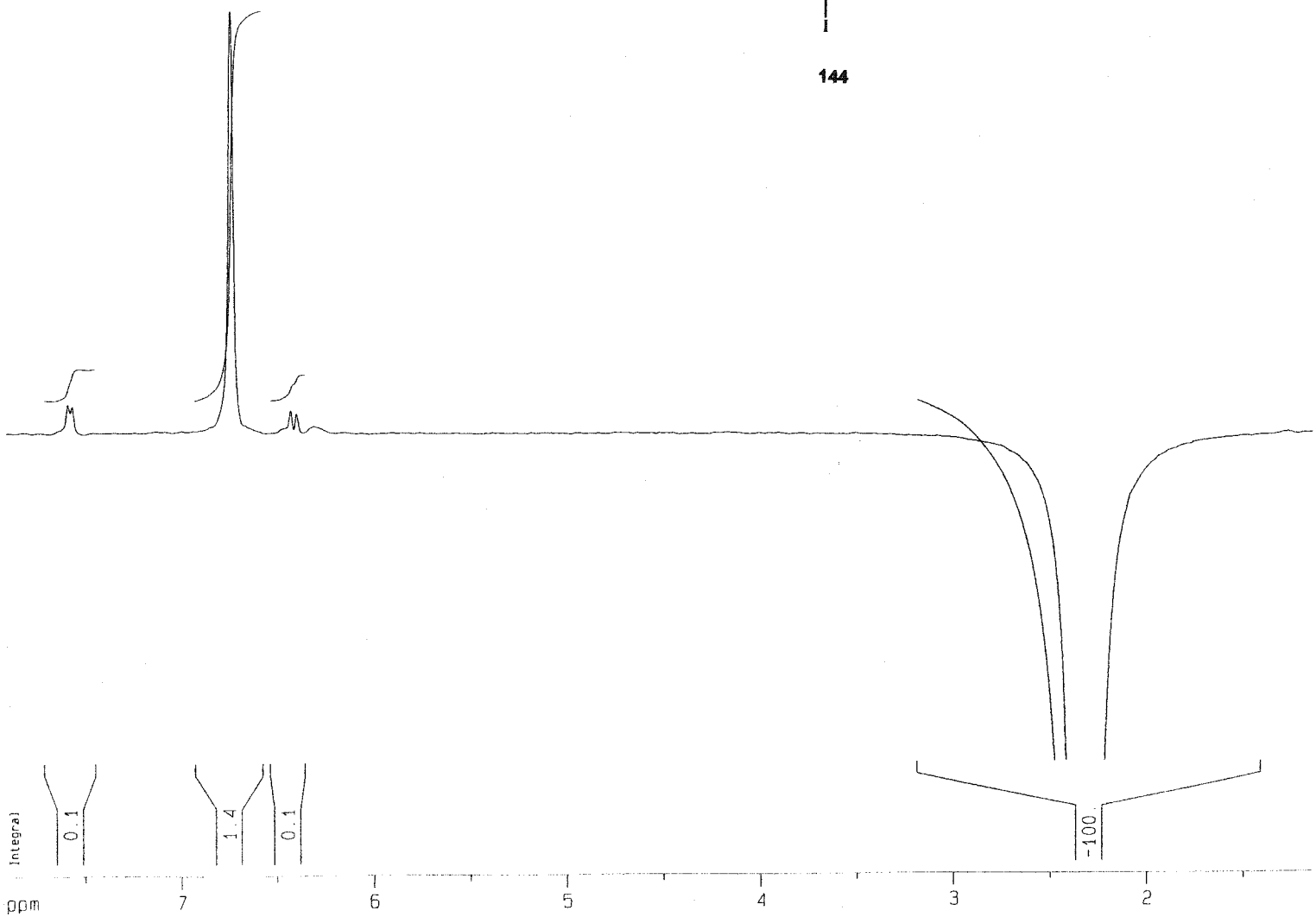

OH
CH3
I

144

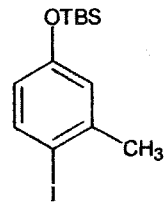

Integral
1.000
0.195
1.032
1.015
1.042
3.159
ppm
9
8
7
6
5
4
3
2
1
0



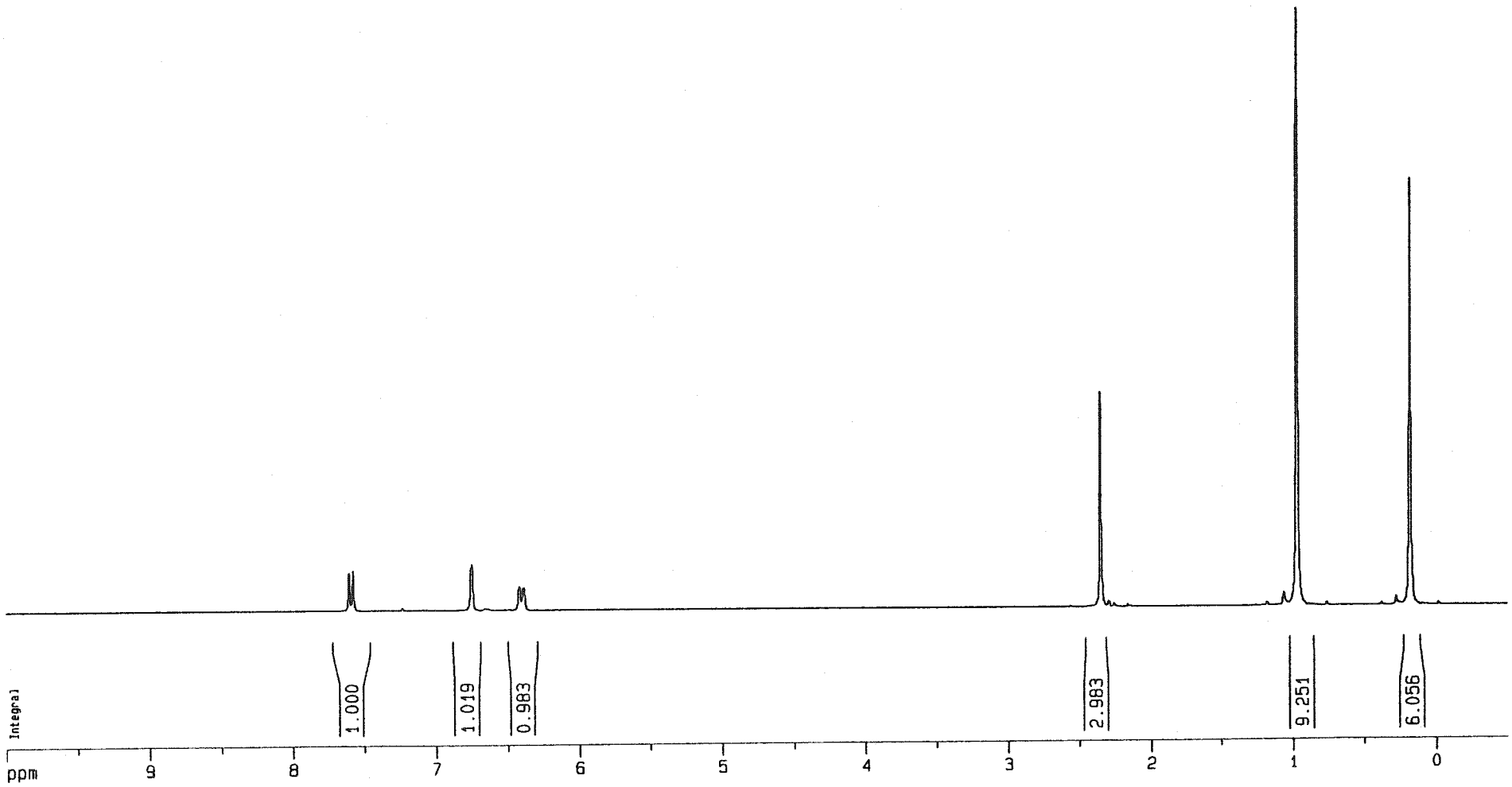
144

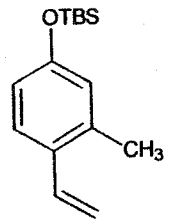



```
Current Data Parameters
NAME                  jj02_noe
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_              20020823
Time                    12.47
INSTRUM                 av300
PROBHD   5 mm QNP  1H/1
PULPROG                selnogp
TD                       30720
SOLVENT                  CDCl3
NS                          48
DS                           2
SWH                 5081.301 Hz
FIDRES                 0.165407 Hz
AQ                  3.0228980 sec
RG                       456.1
DW                      98.400 usec
DE                        6.00 usec
TE                       300.0 K
D1                  1.00000000 sec
D8                  1.00000000 sec
D16                 0.00010000 sec
d20                 0.49890000 sec

============ CHANNEL f1 =============
NUC1                        1H
P1                        8.00 usec
p2                       16.00 usec
P12                 215498.30 usec
PL0                      120.00 dB
PL1                       -3.00 dB
SFO1                300.1319477 MHz
SP2                       66.61 dB
SPNAM2                 guass.1k
SPOFF2                -1251.05 Hz

============ GRADIENT CHANNEL ========
GPNAM1                 SINE.100
GPNAM2                 SINE.100
GPNAM3                 SINE.100
GPNAM4                 SINE.100
GPX1                      0.00 %
GPX2                      0.00 %
GPX3                      0.00 %
GPX4                      0.00 %
GPY1                      0.00 %
GPY2                      0.00 %
GPY3                      0.00 %
GPY4                      0.00 %
GPZ1                     11.00 %
GPZ2                     17.00 %
GPZ3                     40.00 %
GPZ4                    -40.00 %
P16                   1000.00 usec

F2 - Processing parameters
SI                       65536
SF                300.1300000 MHz
WDW                         EM
SSB                          0
LB                        5.00 Hz
GB                           0
PC                        1.00

1D NMR plot parameters
CX                       20.00 cm
CY                      600.00 cm
F1P                       7.912 ppm
F1                     2374.54 Hz
F2P                       1.140 ppm
F2                      342.02 Hz
PPMCM                  0.33861 ppm/cm
HZCM                 101.62602 Hz/cm
```

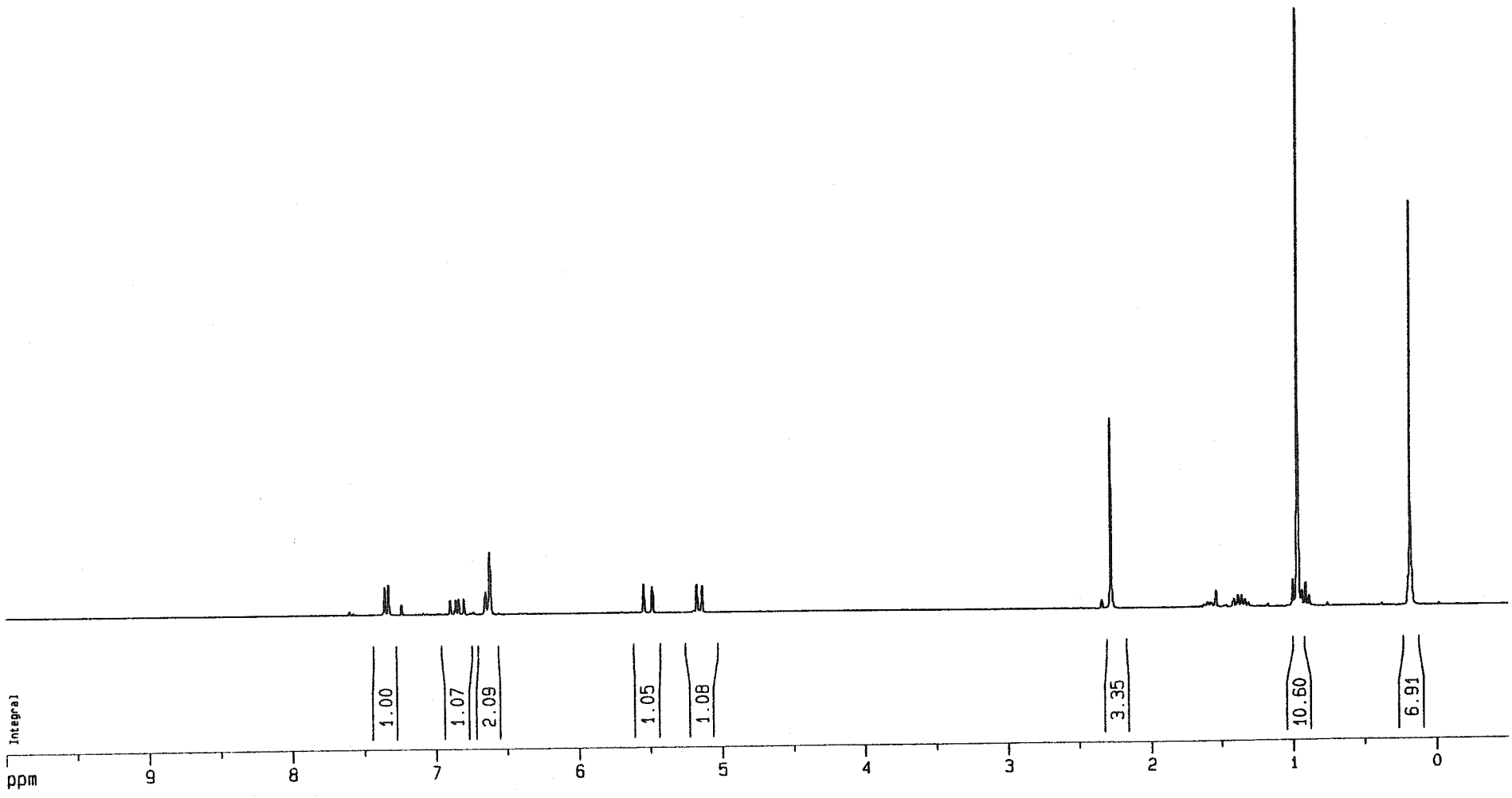

OTBS
CH3
I

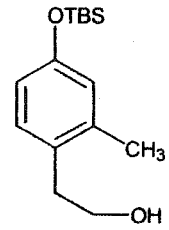
145


Integral
1.000
1.019
0.983
2.983
9.251
6.056
ppm
9
8
7
6
5
4
3
2
1
0

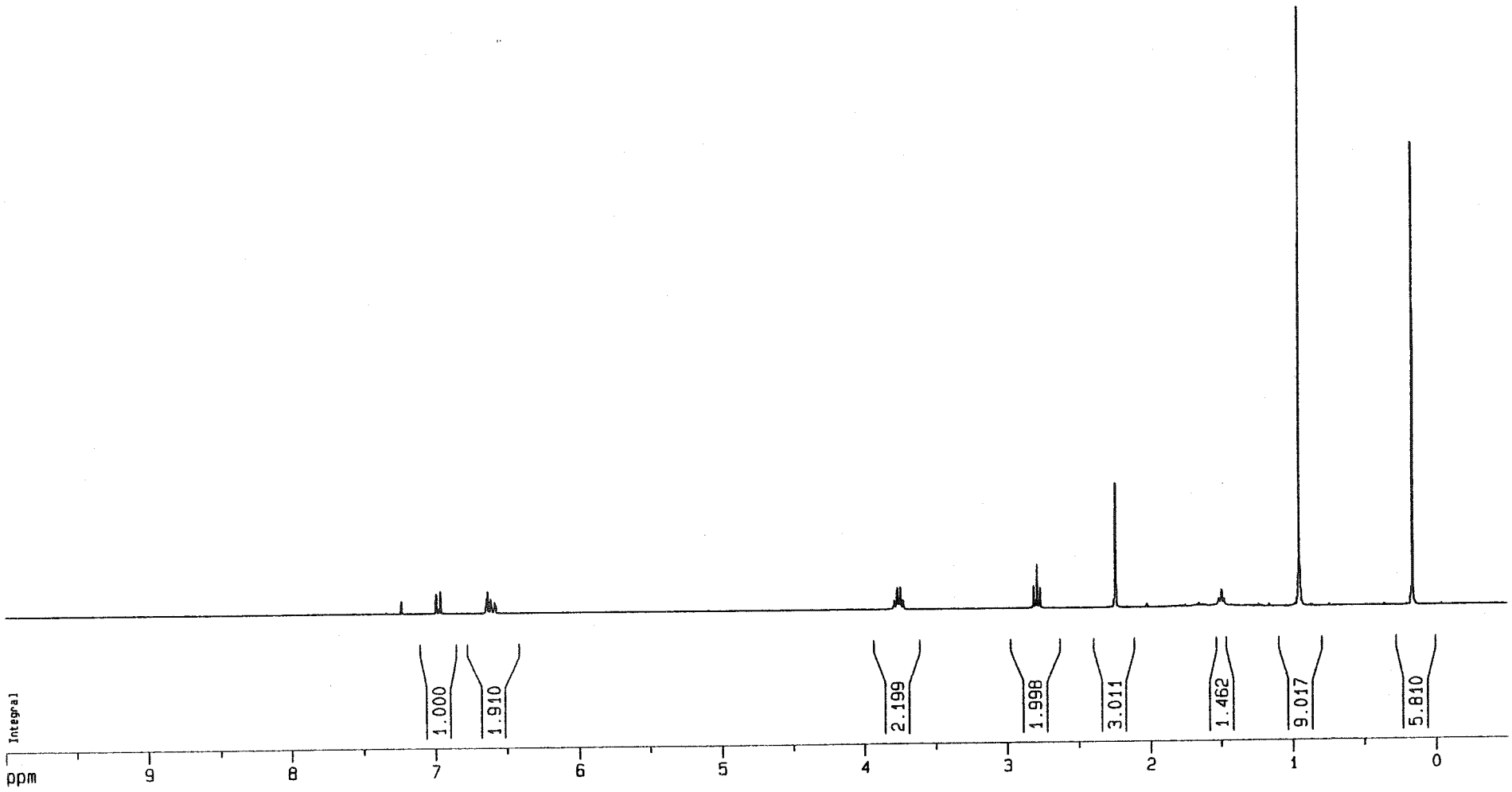

OTBS
CH3

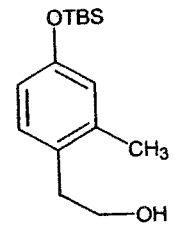
146


Integral
1.00
1.07
2.09
1.05
1.08
3.35
10.60
6.91
ppm
9
8
7
6
5
4
3
2
1
0

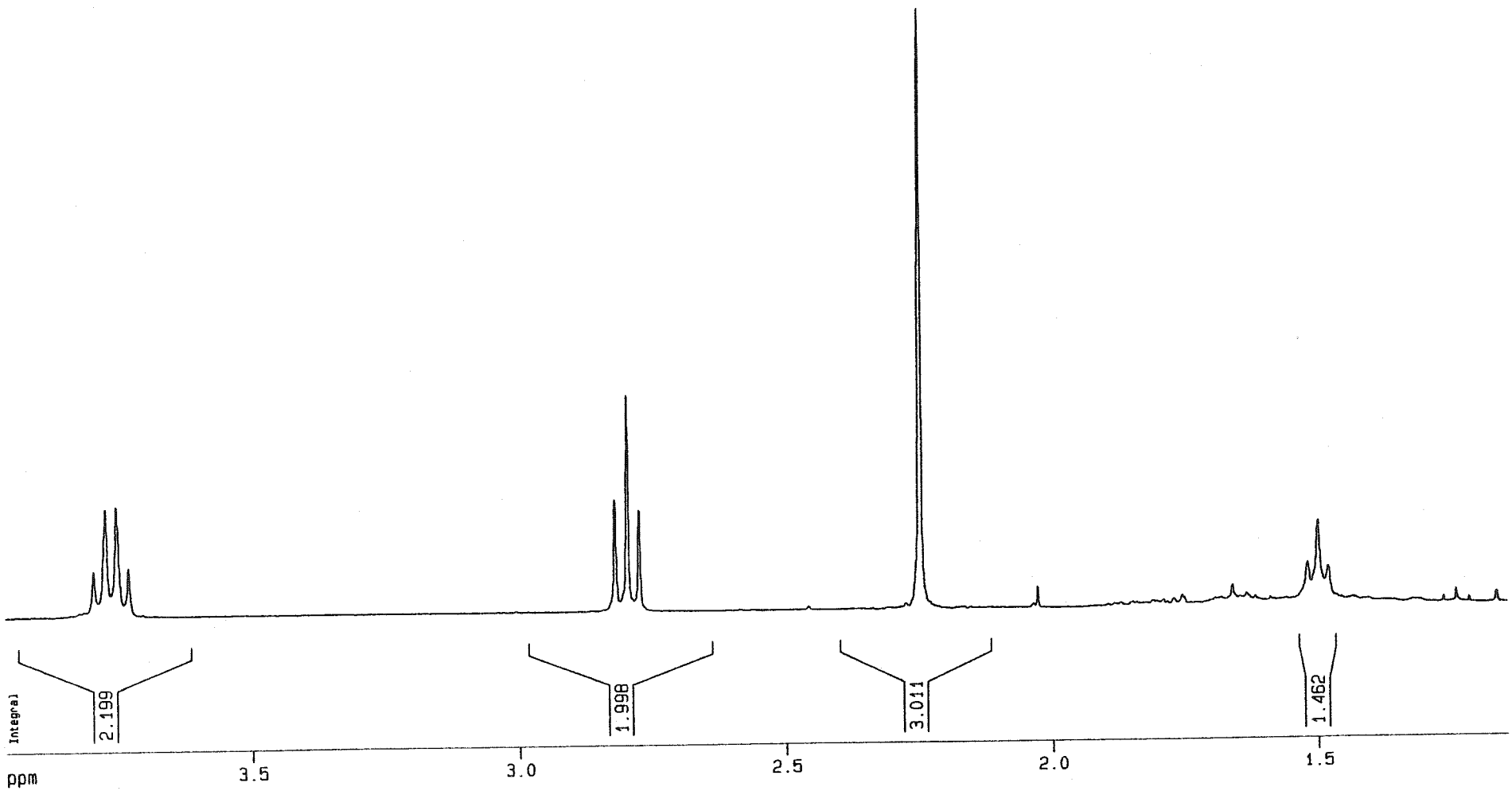

OTBS
CH3
OH

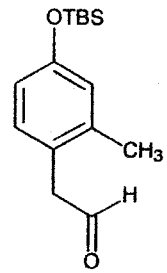
147


Integral
1.000
1.910
2.199
1.998
3.011
1.462
9.017
5.810
ppm
9
8
7
6
5
4
3
2
1
0

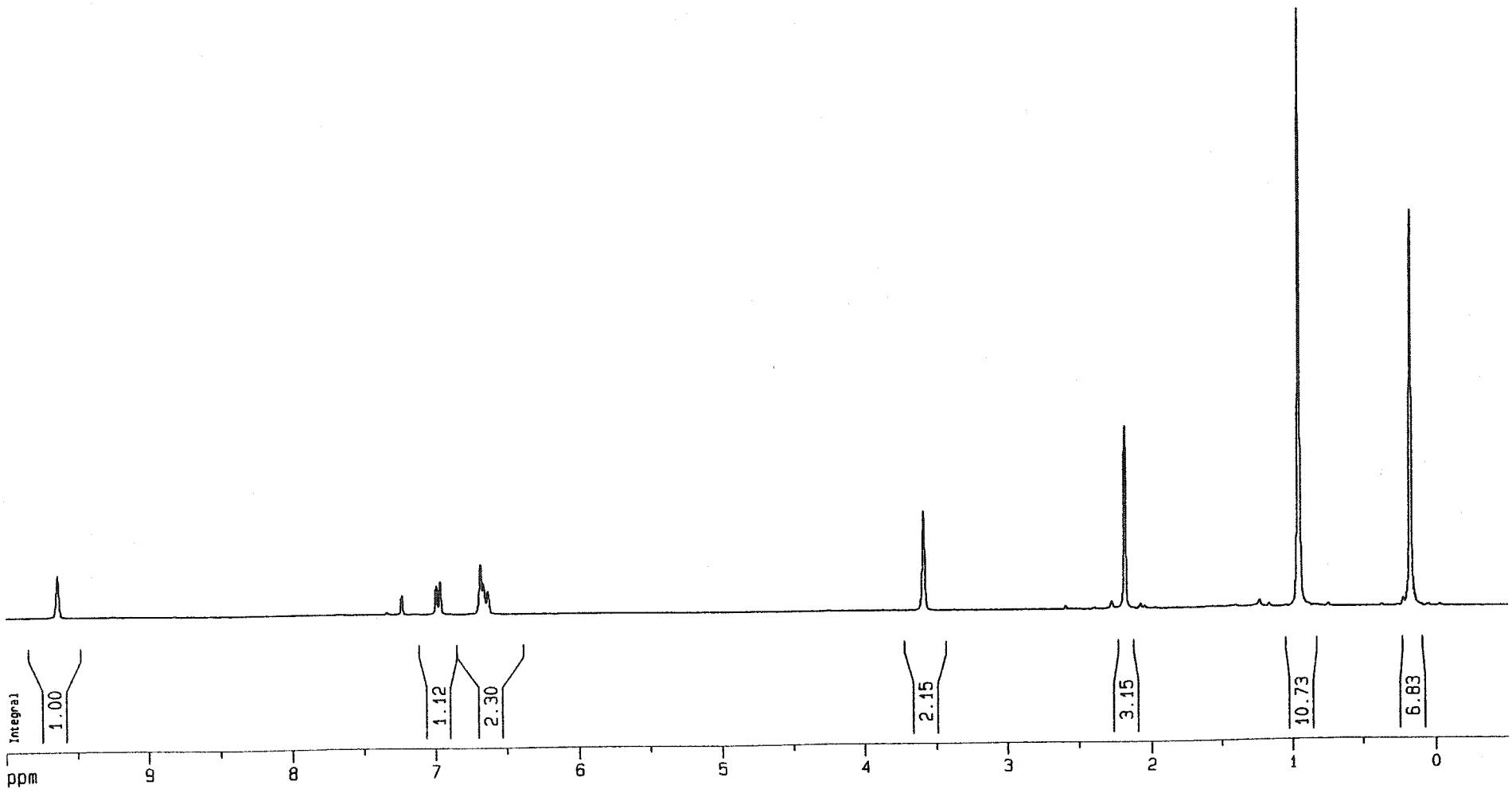


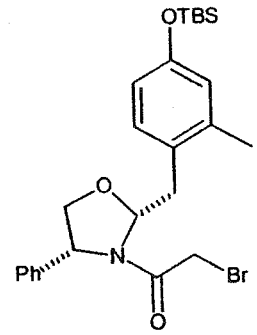
147



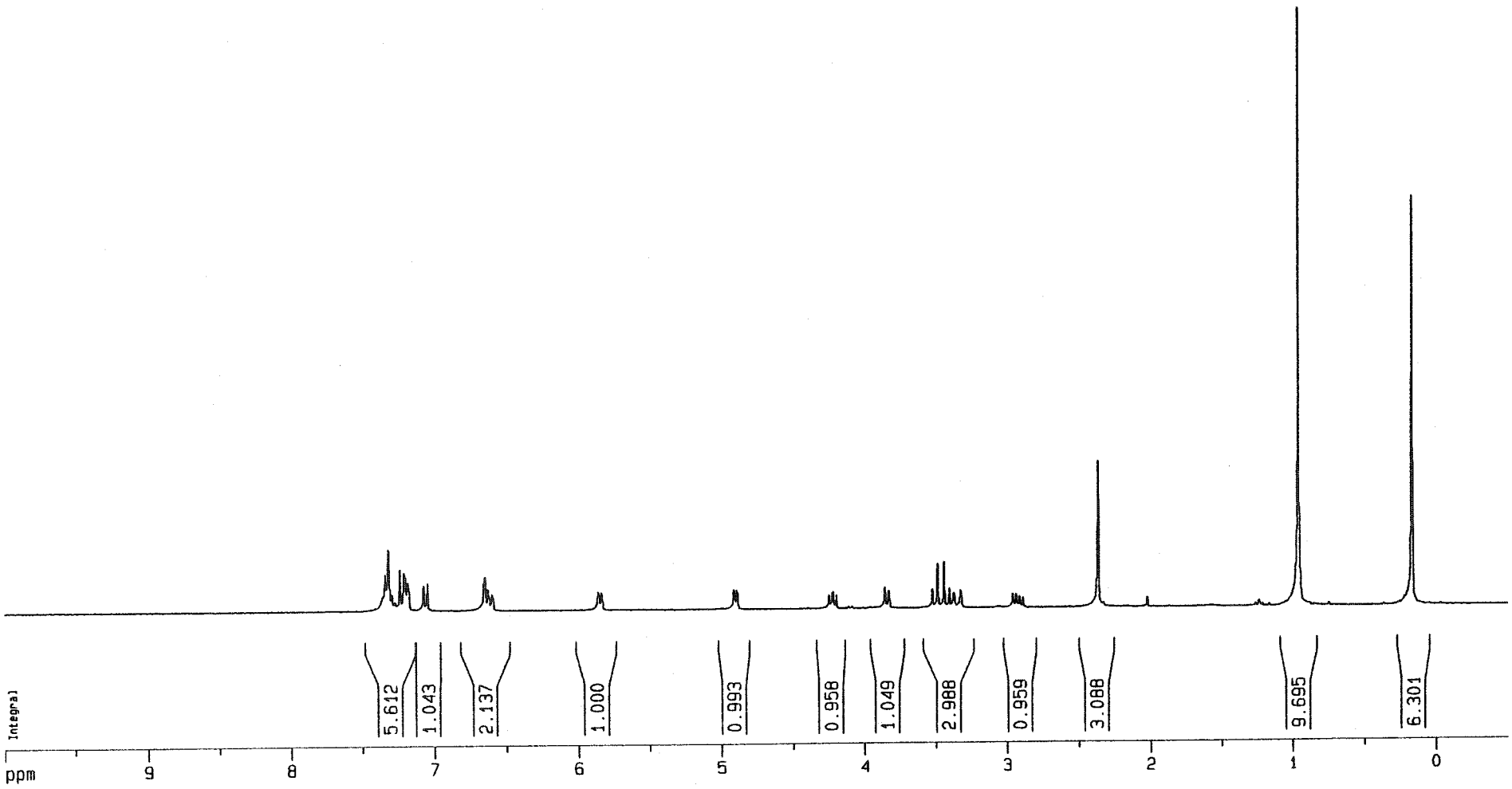

OTBS
CH3
H
O

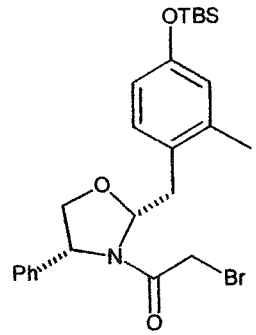
134


Integral
1.00
1.12
2.30
2.15
3.15
10.73
6.83
ppm
9
8
7
6
5
4
3
2
1
0

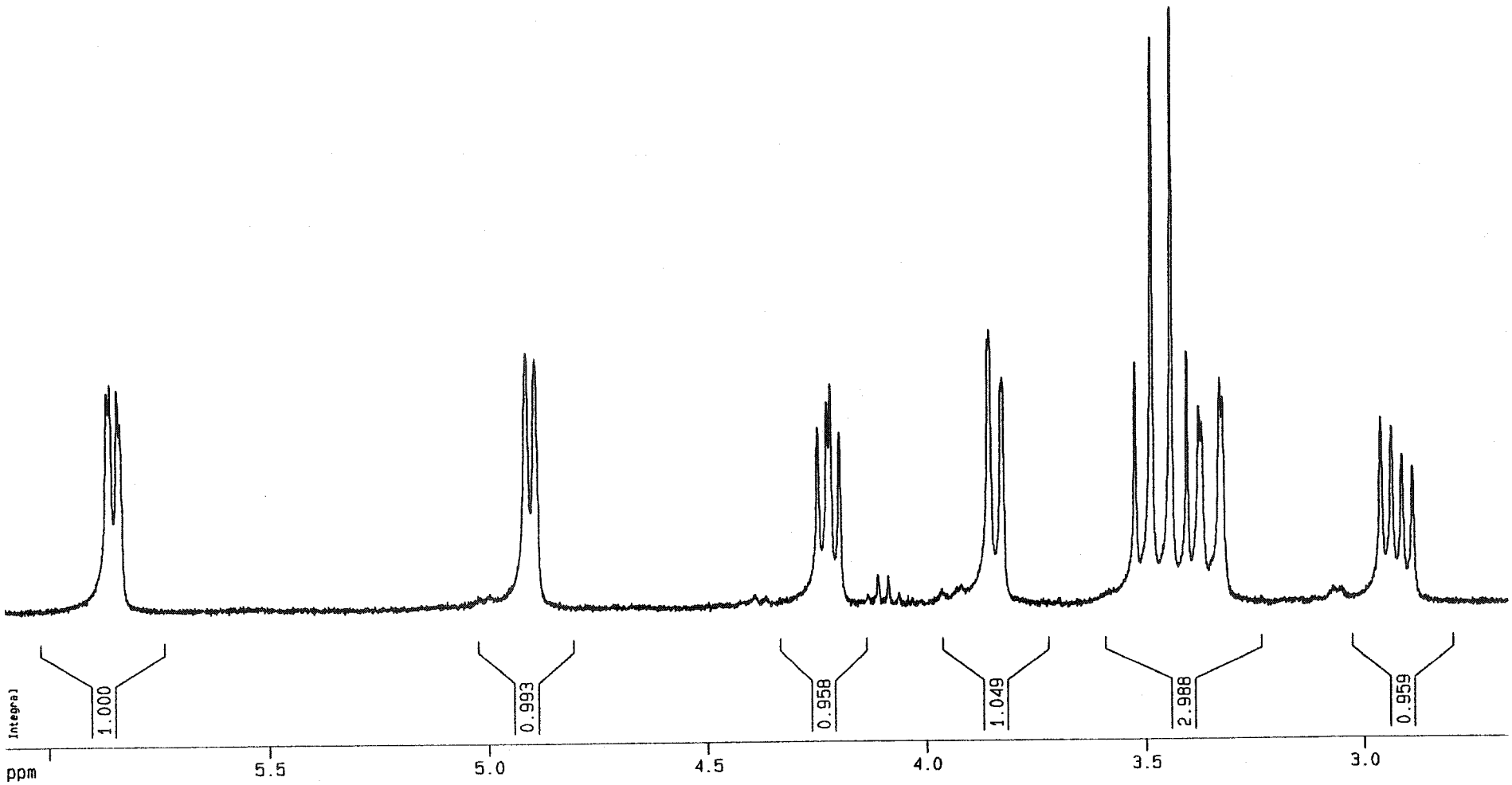

OTBS
O
N
Ph
Br
O

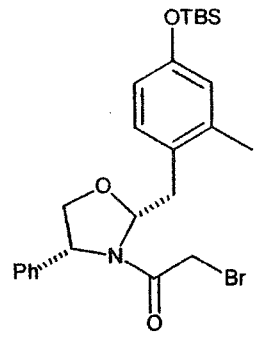
148


Integral
5.612
1.043
2.137
1.000
0.993
0.958
1.049
2.988
0.959
3.088
9.695
6.301
ppm
9
8
7
6
5
4
3
2
1
0

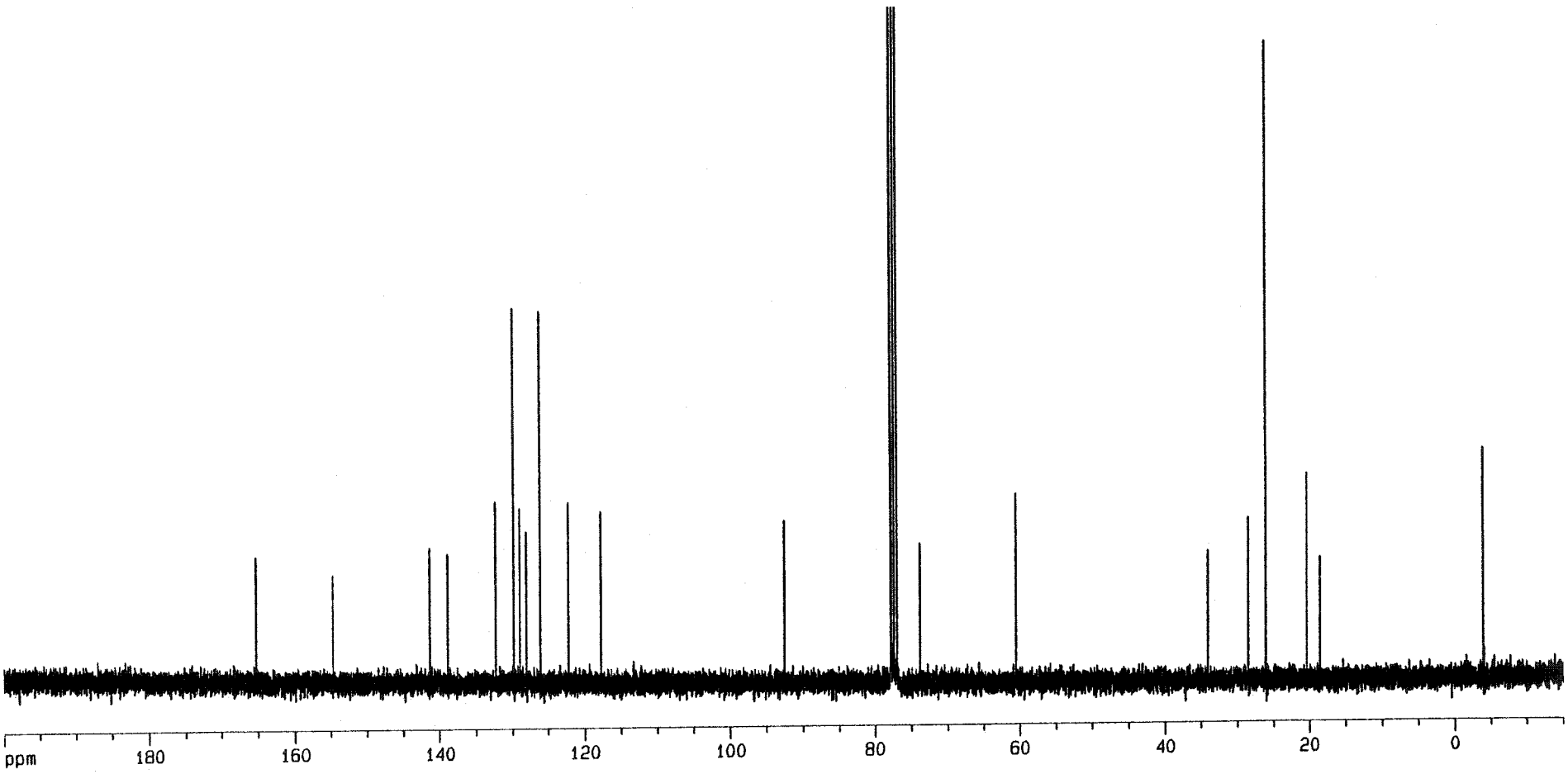

OTBS
O
Ph
N
Br
O

148

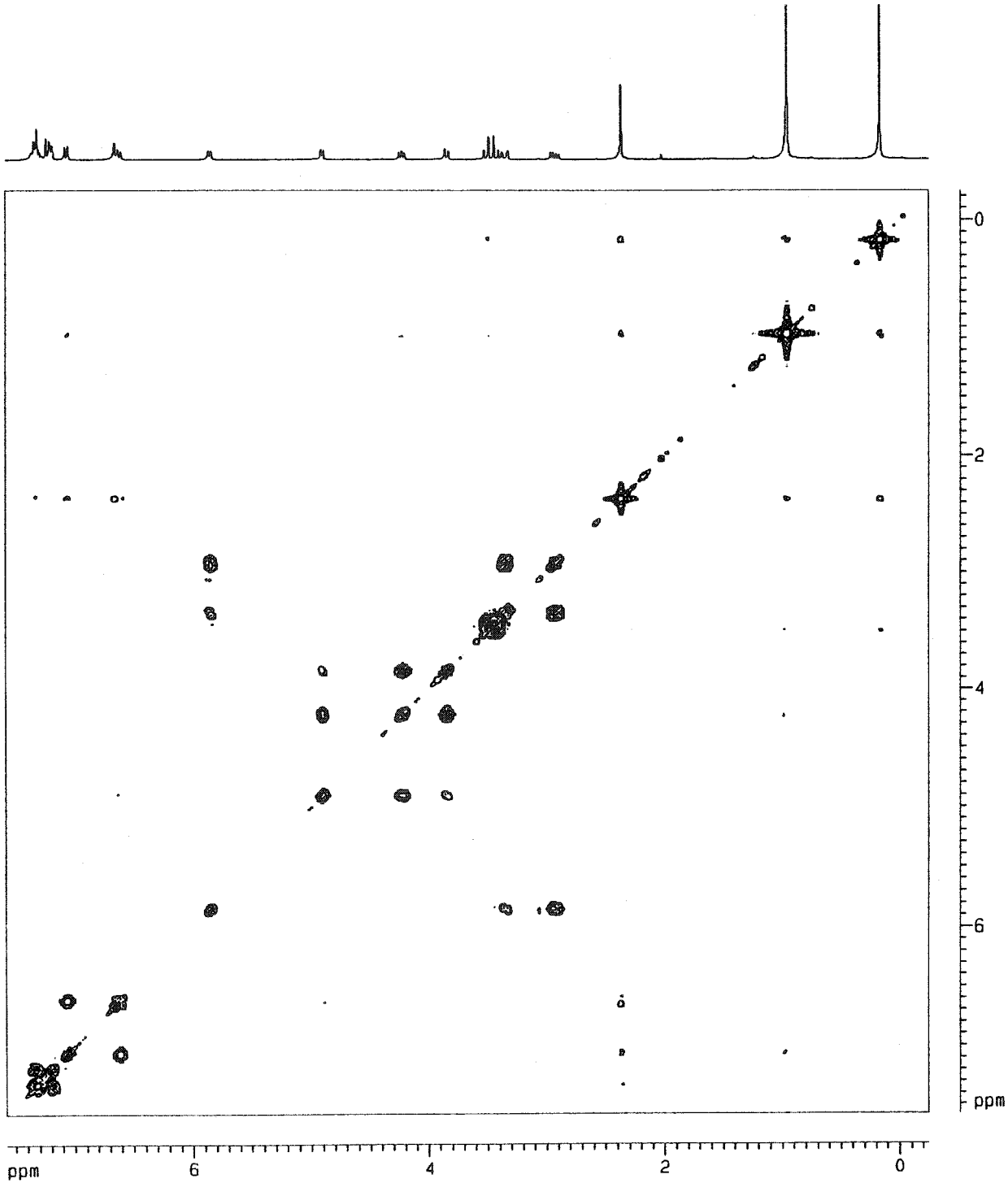

Integral
1.000
0.963
0.958
1.049
2.988
0.959
ppm
5.5
5.0
4.5
4.0
3.5
3.0

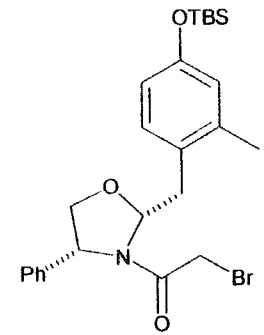


148

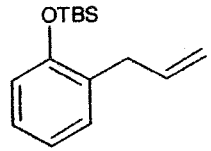


1H COSY

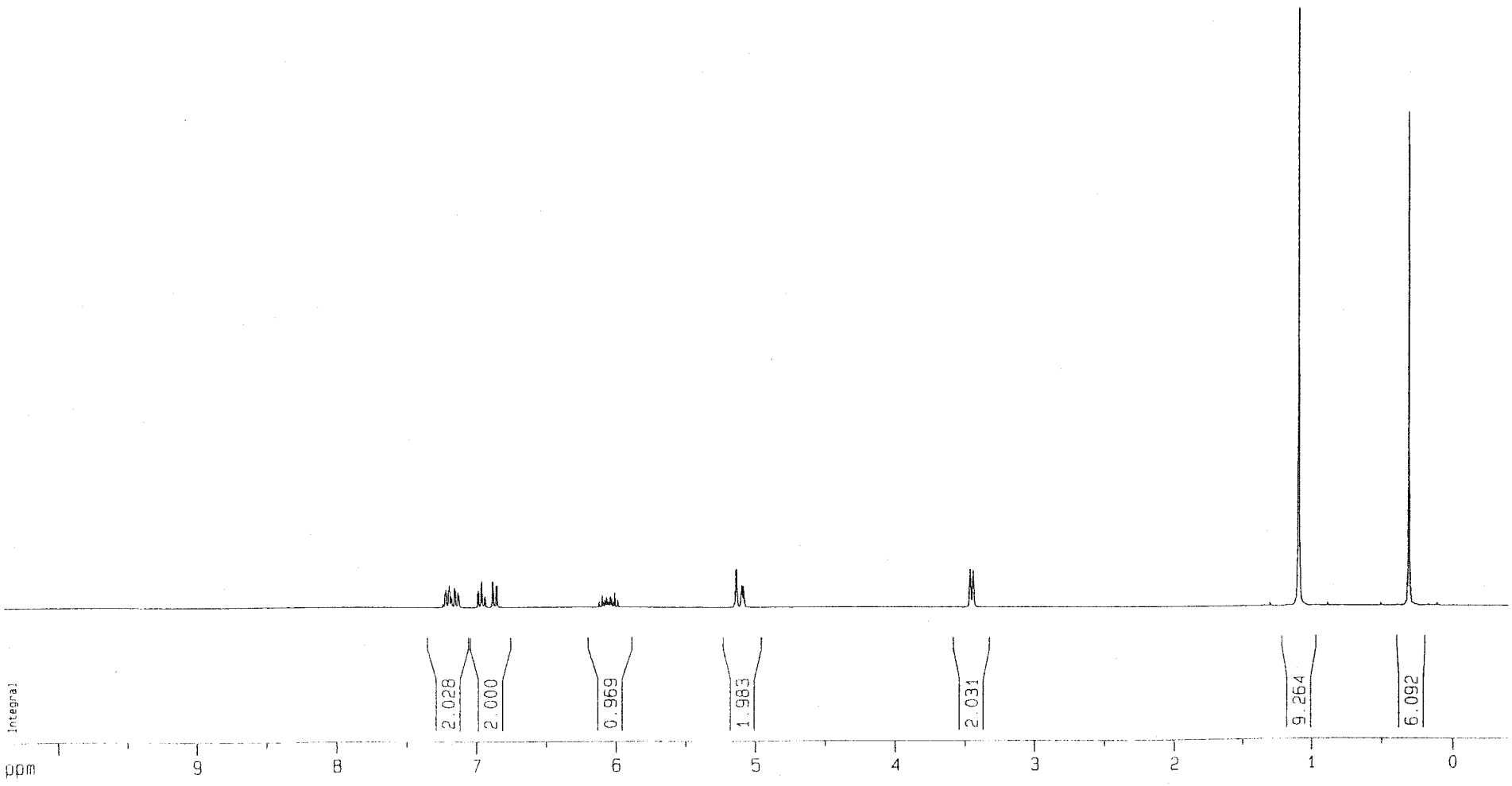


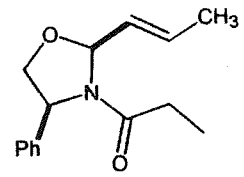


148

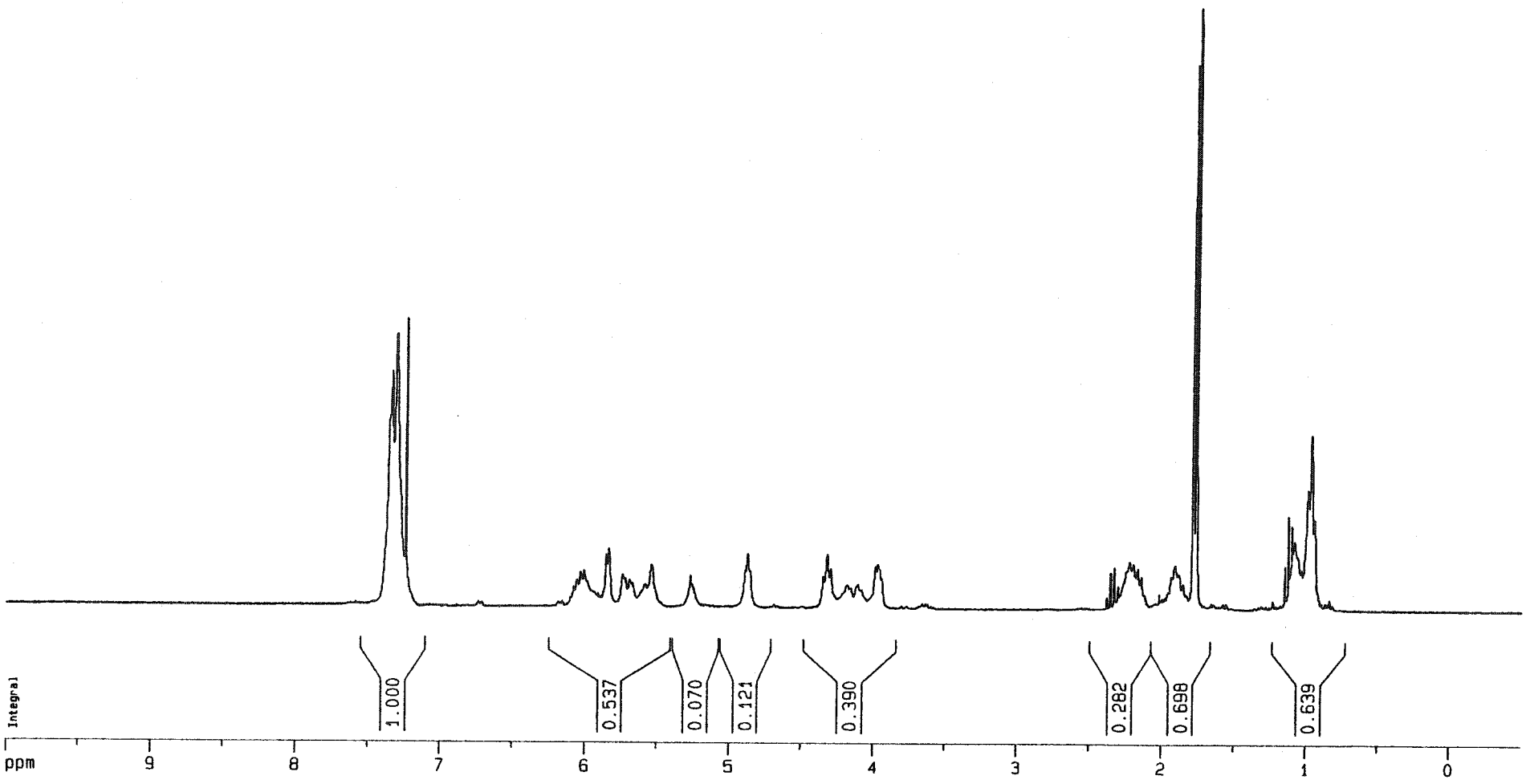

OTBS

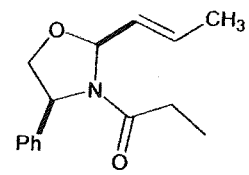
127


Integral
2.028
2.000
0.969
1.983
2.031
9.264
6.092
ppm
9
8
7
6
5
4
3
2
1
0


CH3
O
N
Ph
O

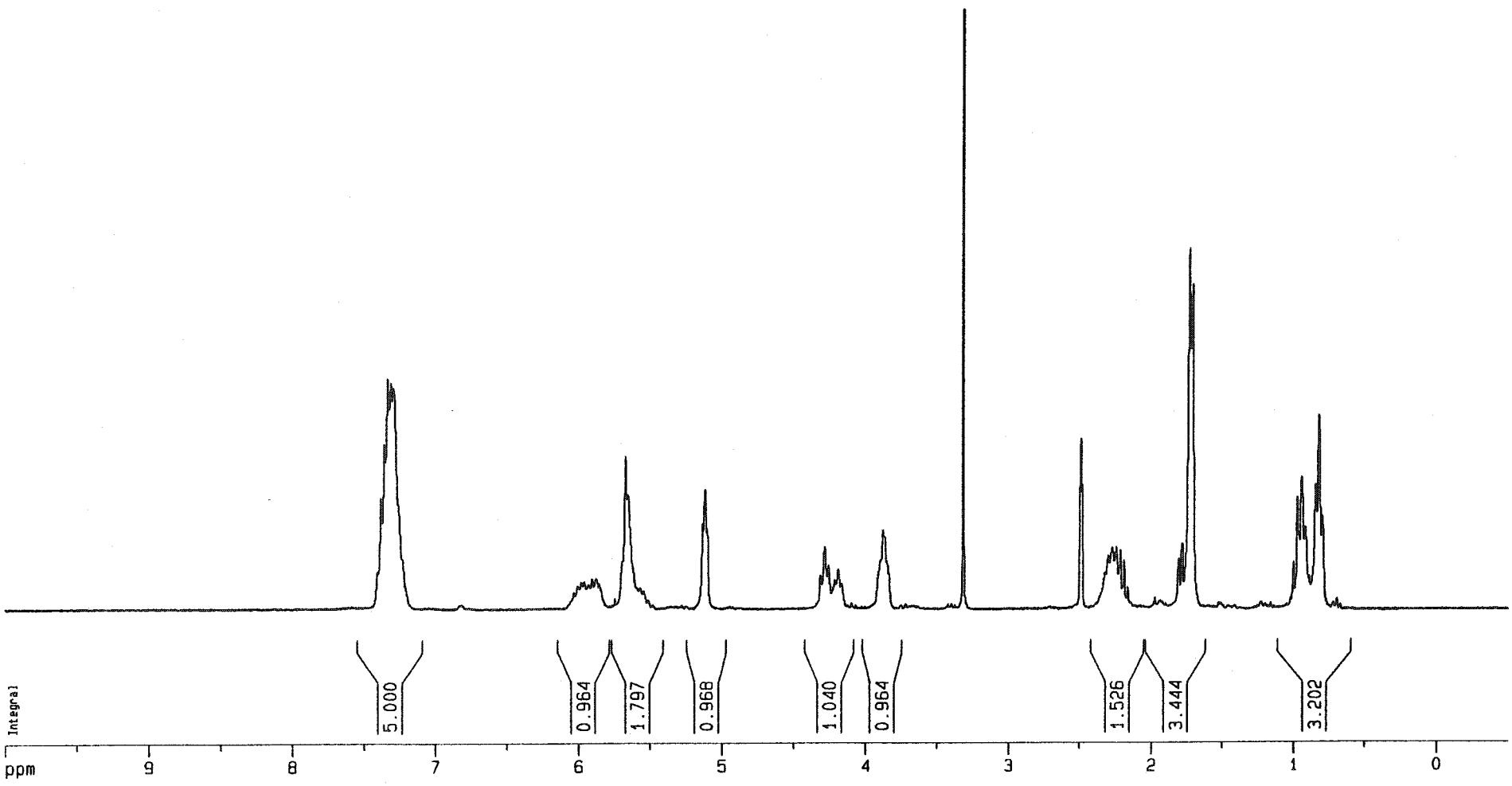
152

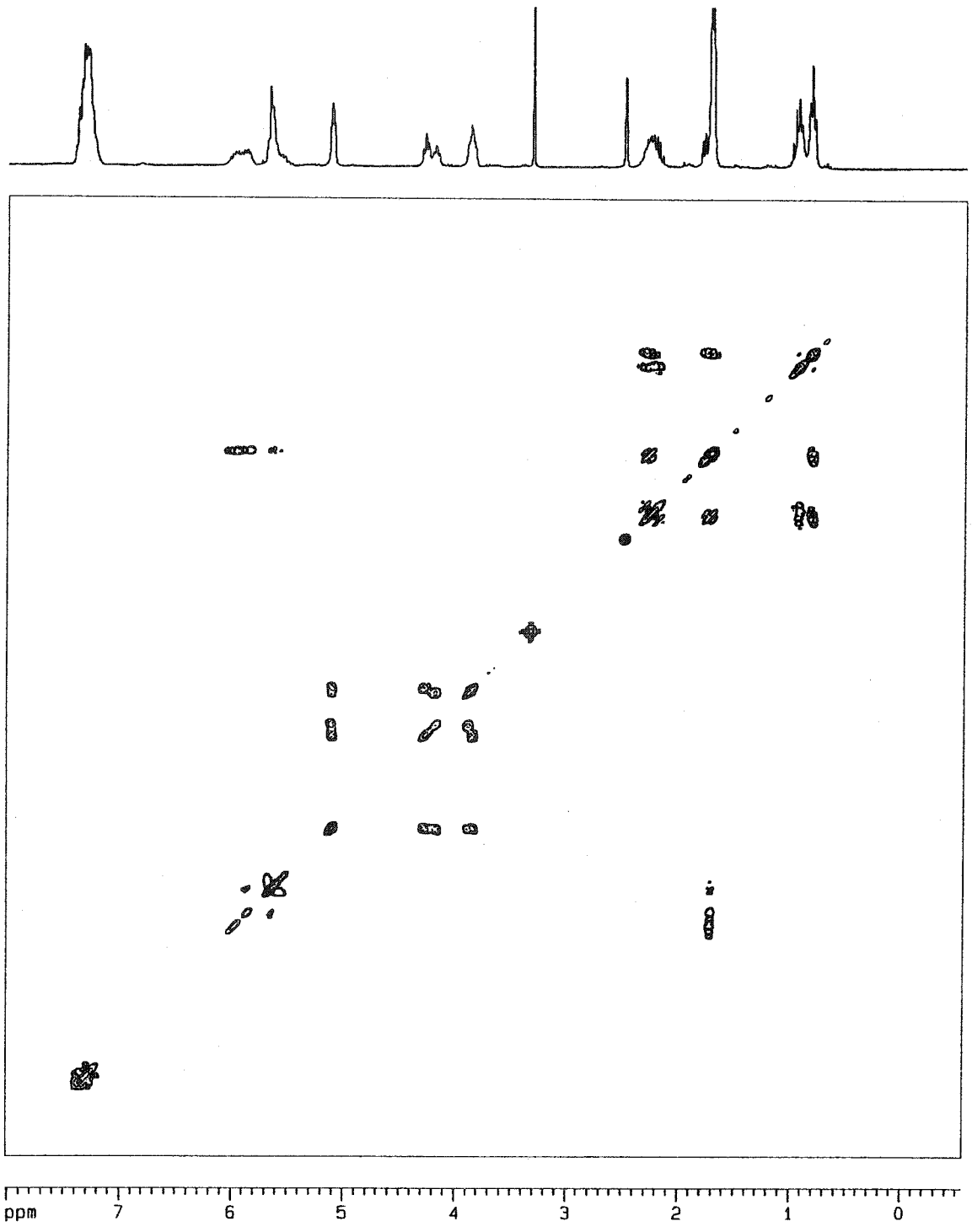

Integral
1.000
0.537
0.070
0.121
0.390
0.282
0.698
0.639
ppm
9
8
7
6
5
4
3
2
1
0



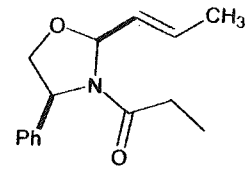
152

Solvent: DMSO



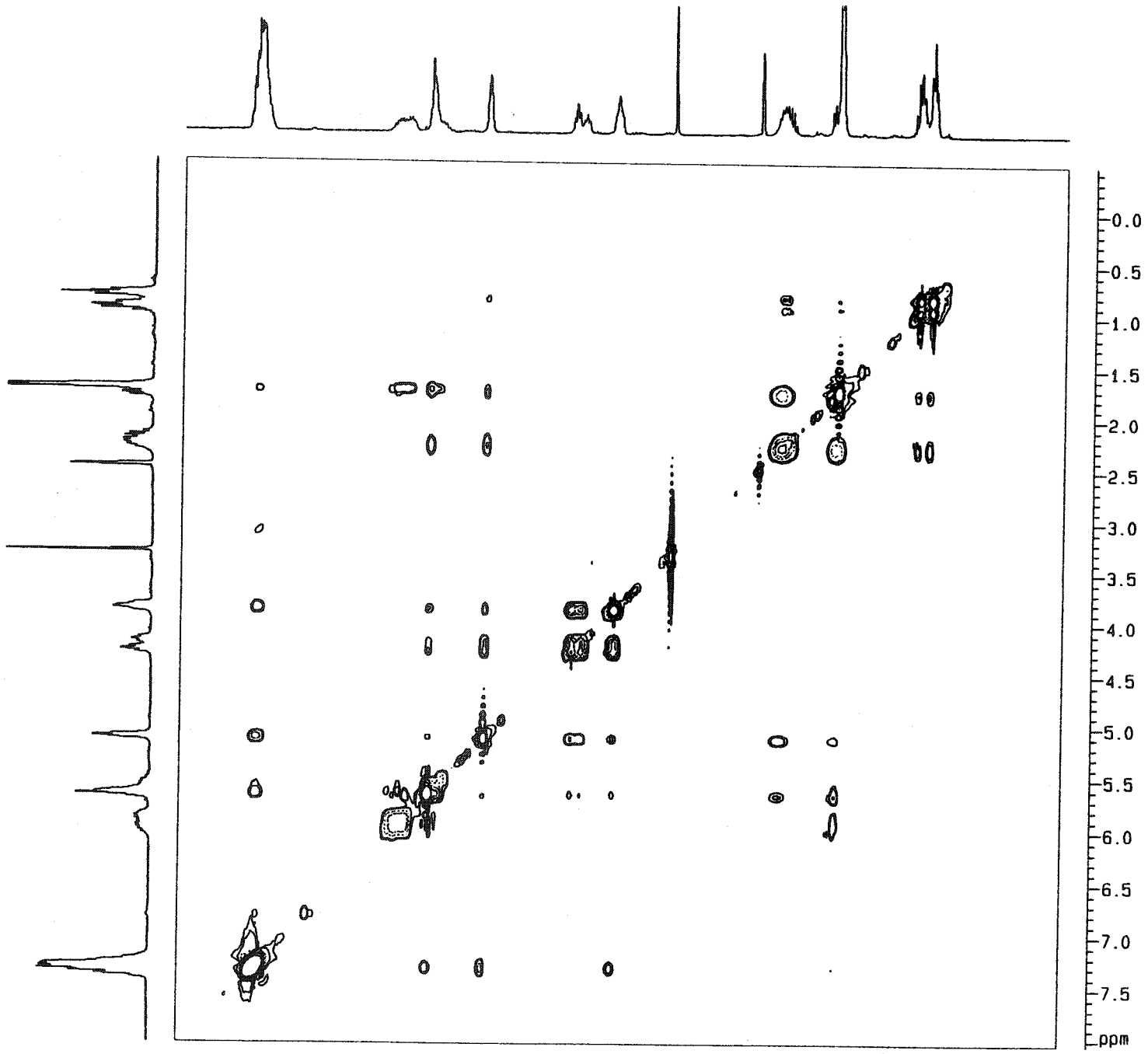


1H COSY

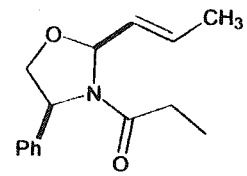


152

Solvent: DMSO

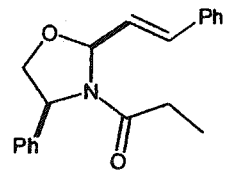


1H NOESY

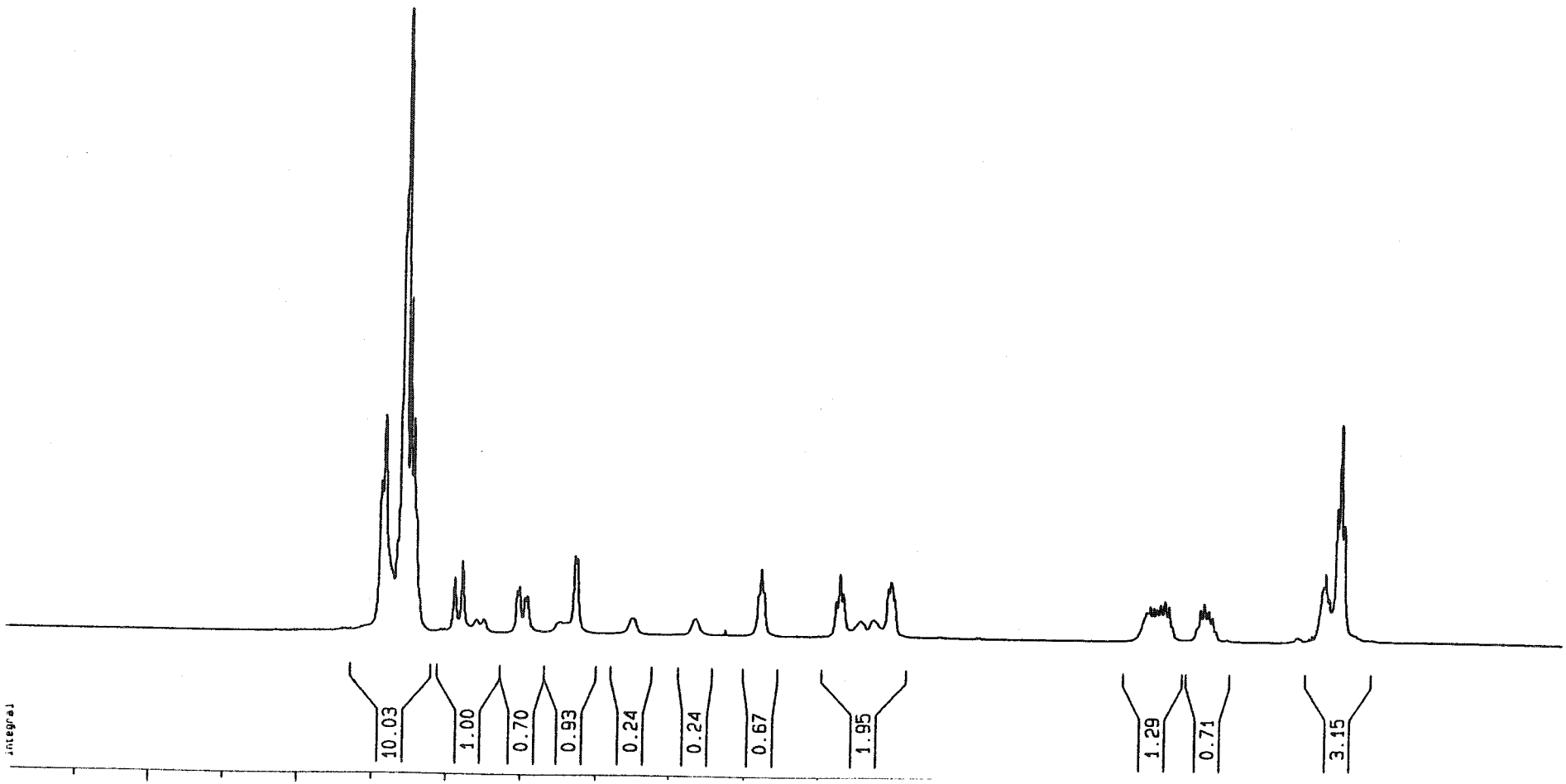


152

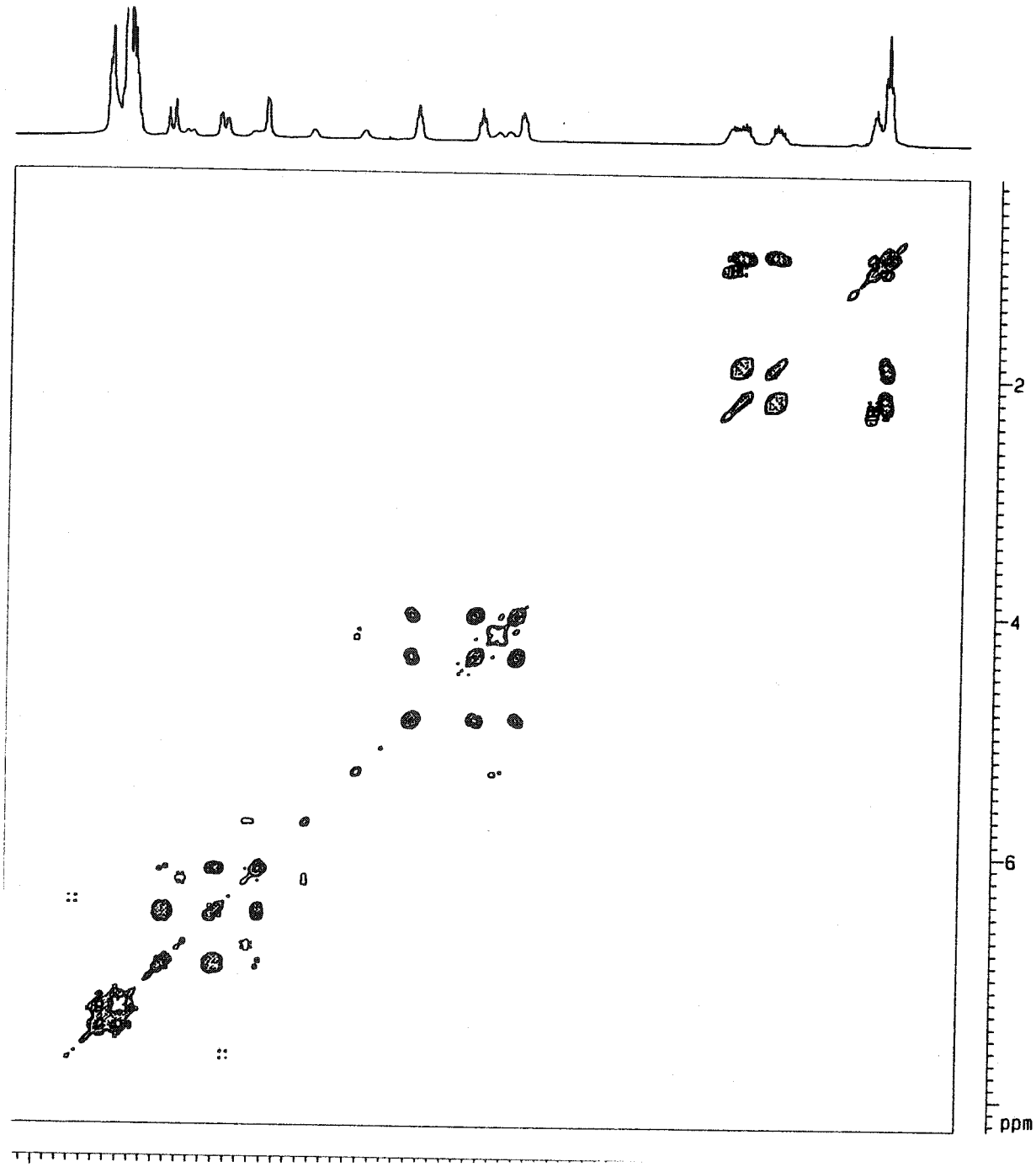
Solvent: DMSO

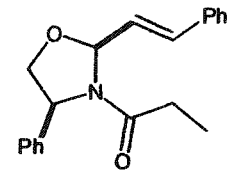


153



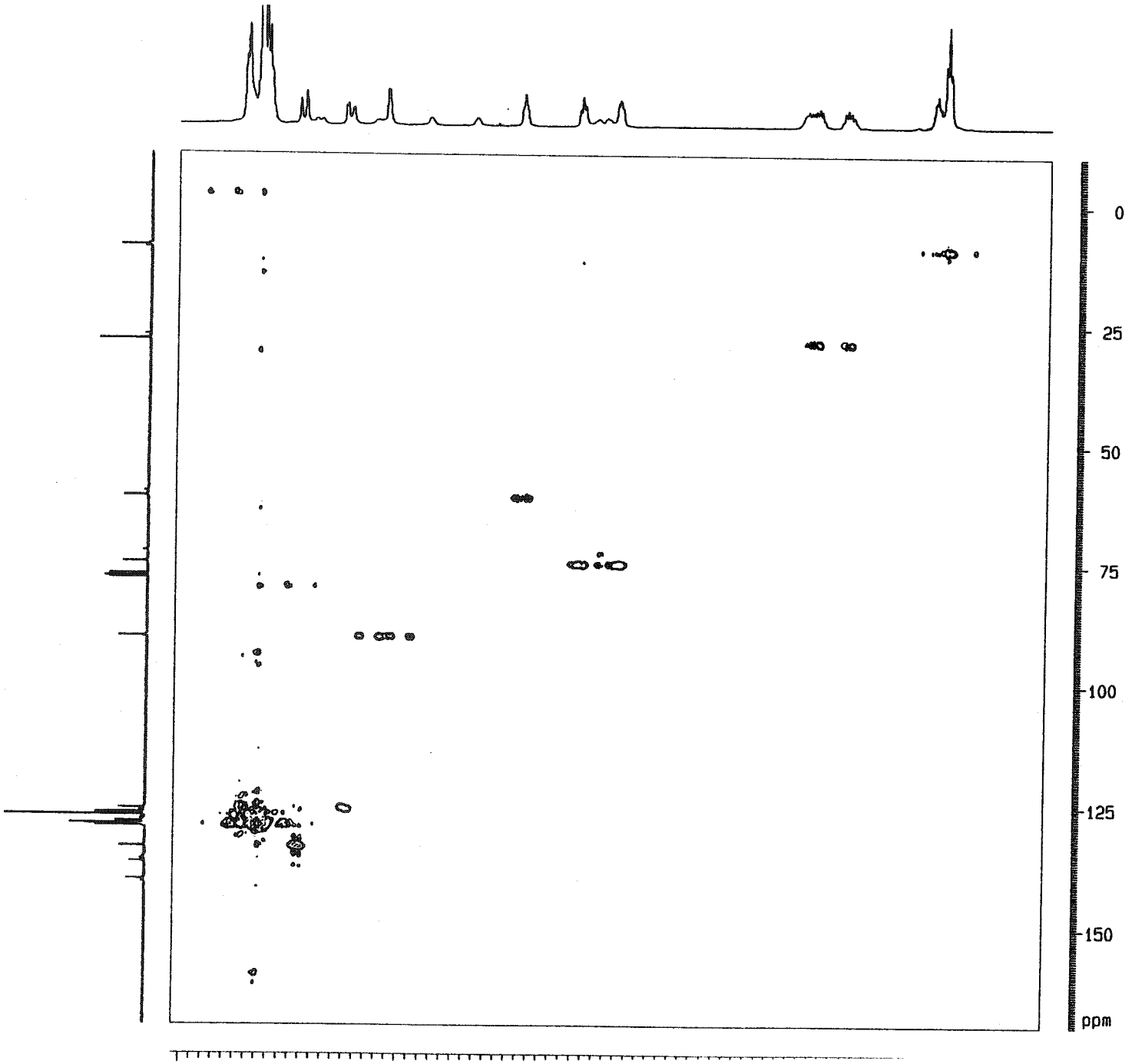
1H COSY

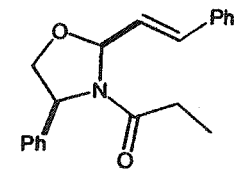




153

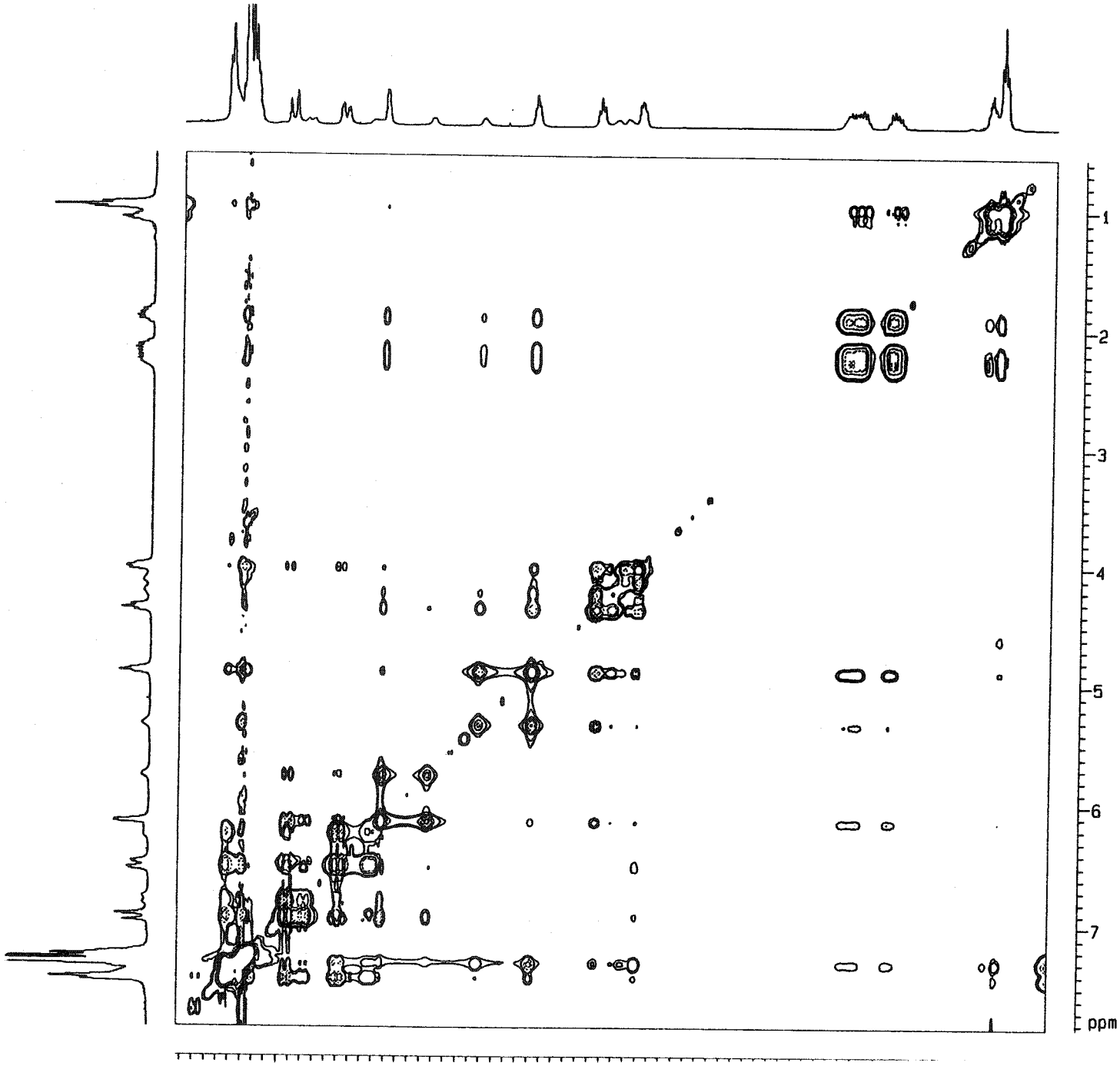
1H 13C HMQC

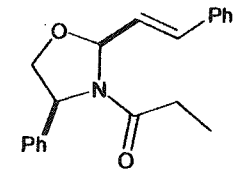




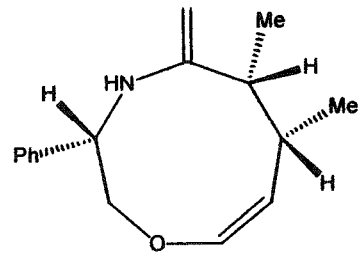
153

1H NOESY

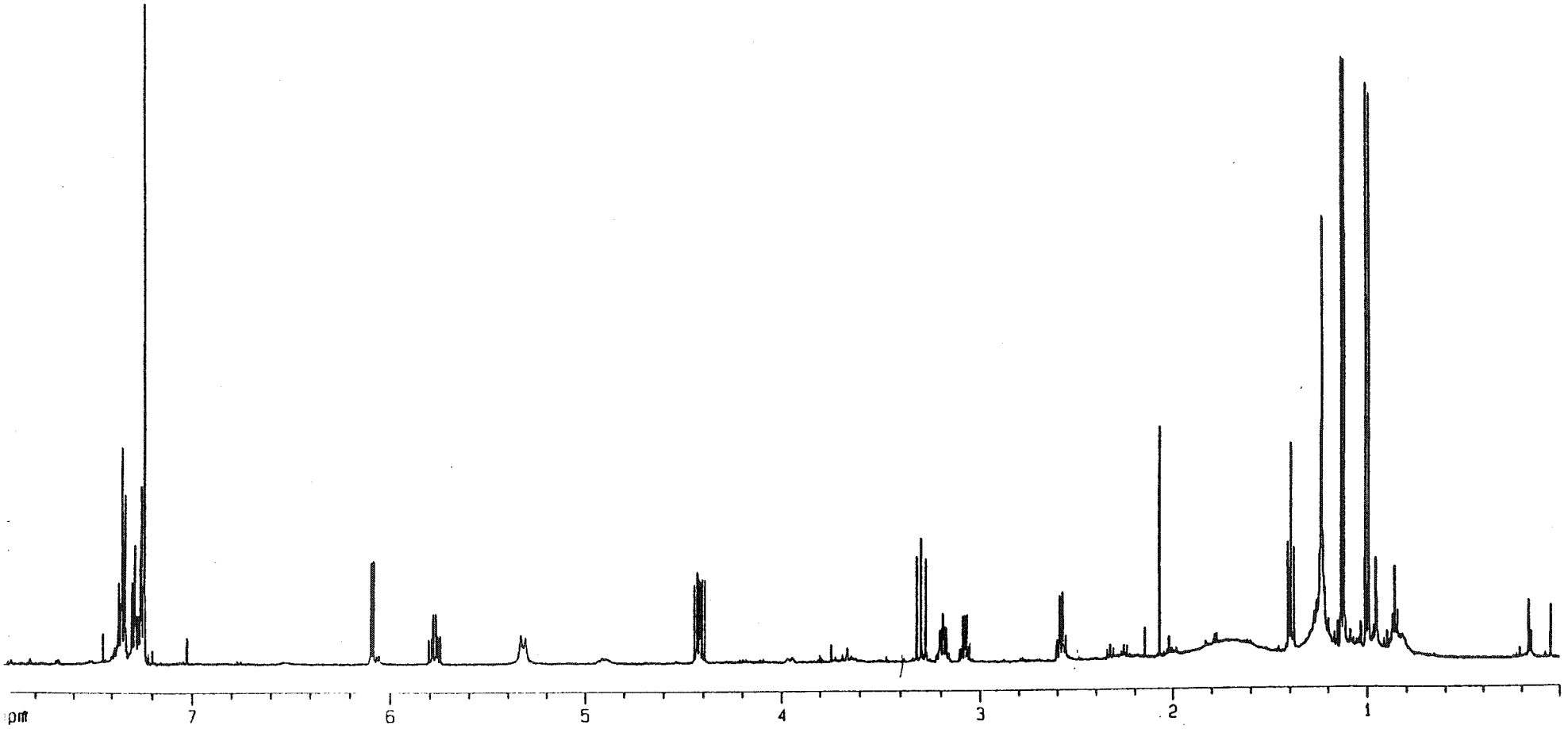




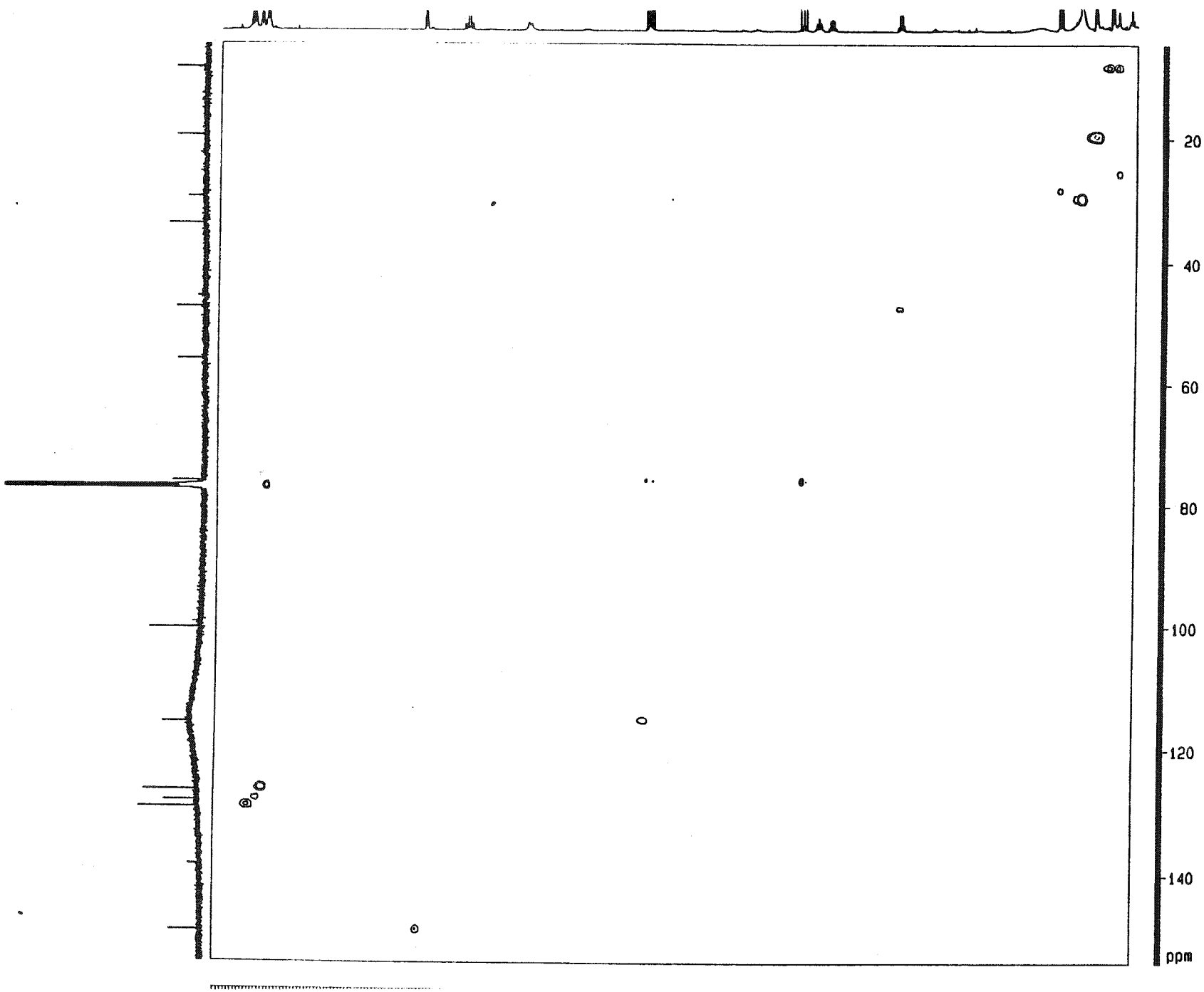
153

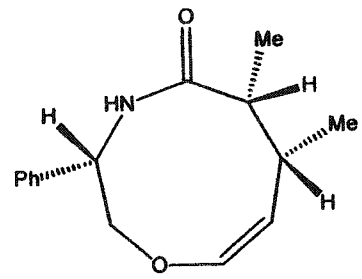


164

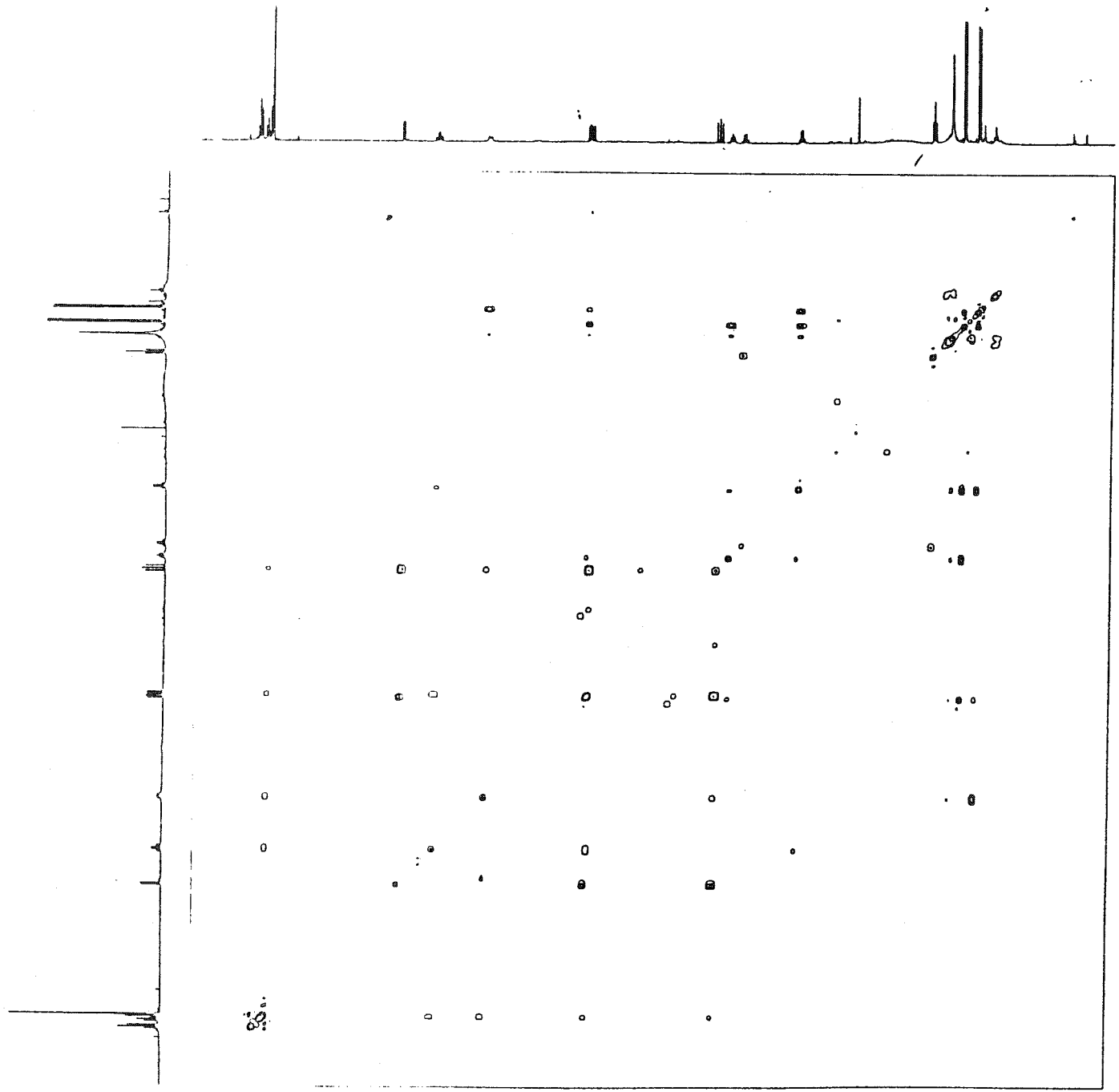


164

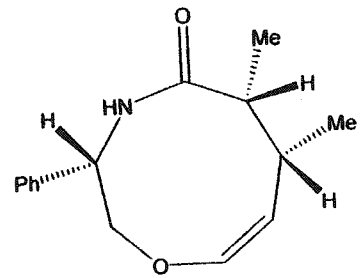




164



1H NOESY/EXSY
All positive contours
showing NOE's



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```
-------- CHANNEL f1 --------
NUC1                      1H
P1                      9.00 usec
P2                     18.00 usec
PL1                     3.00 dB
SFO1           500.1319200 MHz

====== GRADIENT CHANNEL =====
GPNAM1                sine.100
GPNAM2                sine.100
GPZ1                    0.00 %
GPX2                    0.00 %
GPY1                    0.00 %
GPY2                    0.00 %
GPZ1                   40.00 %
GPZ2                  -40.00 %
P16                 1000.00 usec

F1 - Acquisition parameters
NOO                        1
TD                       256
SFO1             500.1319 MHz
FIORES           15.601982 Hz
SW                   8.086 ppm
FnMODE                TPPI

F2 - Processing parameters
SI                      1024
SF             500.1300000 MHz
WDW                   QSINE
SSB                        2
LB                    0.00 Hz
GB                         0
PC                      1.00

F1 - Processing parameters
SI                      1024
MC2                   TPPI
SF             500.1300000 MHz
WDW                   QSINE
SSB                        2
LB                    0.00 Hz
GB                         0

2D NMR plot parameters
CX2                   15.00 cm
CX1                   15.00 cm
F2PLO                 7.883 ppm
F2LO               3942.67 Hz
F2PHI                -0.205 ppm
F2HI               -102.63 Hz
F1PLO                 7.883 ppm
F1LO               3942.67 Hz
F1PHI                -0.205 ppm
```