STUDIES IN STEREOSELECTIVE SYNTHESIS VIA REISSERT COMPOUND CHEMISTRY

by

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Chemistry

(ABSTRACT)

Isoquinoline alkaloids have long been known for their biological activity. Many of the isoquinoline alkaloids have been made as racemic mixtures. The present investigation was aimed at developing methodology for the asymmetric synthesis of some isoquinoline alkaloids through Reissert compound chemistry.

The stereochemistry of lepidine and isoquinoline Reissert compounds has not been reported. To better understand the stereochemistry of these compounds, selected Reissert compounds were synthesized and subsequently studied by proton NMR. The two types of isomerism studied were amide isomerism and aryl / carbonyl rotation. In at least some cases, both amide isomers and restricted aryl / carbonyl rotamers were observed. For other cases only the restricted aryl / carbonyl rotamers were observed. The presence of ortho substituents on the aroyl moiety was found to greatly

increase the chance amide isomerism on the NMR time scale.

(-)-Menthyl chloroformate, (+)-menthyl chloroformate, and (-)-menthoxyacetyl chloride have been utilized as chiral acyl auxiliaries to induce the stereochemistry at C_1, resulting in diastereomeric isoquinoline Reissert compounds.

By reaction of a mixture of the diastereomeric Reissert anions of 2-(l)-(menthoxycarbonyl)-1,2-dihydroisoquinaldonitrile (**110**) with pivaldehyde we were able to form the resulting distereomeric carbonates of 1-isoquinolyl-t-butyl carbinyl menthyl carbonate (**120**) in a 77:23 ratio by NMR [82 : 18 ratio by HPLC]. After obtaining the major diastereomer of the carbonate in pure form, hydrolysis yielded the enantiomerically pure (S)-(-)-1-isoquinoyl t-butyl carbinol (**121**).

The proton NMR spectra of the diastereomeric Reissert compounds led to elucidation of the stereochemistry. The diastereomeric ratios were determined for both **110** and 2-(l)-menthoxyacetyl-1,2-dihydroisoquinaldonitrile (**125**). Amide isomerism was observable in the case of **110** but not in the case of **125**. Aromatic solvent induced shift (ASIS) studies of the compound **125** showed the s-trans amide to be predominant. The reaction of the diastereomeric Reissert anion of **110** with CS_2 and partial conversion with pivaldehyde allowed us to determine that the Reissert anion equilibrates.

Reaction of the anion of **125** with pivaldehyde gave 1-isoquinolyl t-butyl carbinyl menthyl acetate (**127**) in quantitative yield and 0 % de. However, the diastereomers are easily separated using simple silica gel column chromatography.

DEDICATION

I would like to dedicate this thesis first of all to my parents, Bill and Karen Clifton. They gave me the emotional support and courage necessary to make the completion of this thesis possible. They have always supported my educational endeavors and gave me the dream to be anything I set my sights on.

Second, I would like to dedicate this thesis to my husband, Steve Bullock. Without his patience, love, and support the completion of this thesis would not have been possible.

ACKNOWLEDGMENTS

I would like to acknowledge my research director, Dr. Gibson, for always being there and for his never ending patience. Dr. Gibson has also given me a love of organic chemistry and instilled in me the value of hard work and good chemistry.

I would like to acknowledge my program chairman, Dr. Teates, for his understanding and kindness. Dr. Teates has also taught me the importance of preparation and vision in teaching the next generation of scientists. He has also been of tremendous help in putting together the unit of study which I have also submitted.

I would like to acknowledge Dr. Wolfe and Dr. Burton as special friends and colleagues who often helped me to keep things in perspective.

Last, but most, I would like to acknowledge, Drs. Y. Jois and Pierre Lecavalier, for many helpful research discussions. Jois was also an invaluable editor for my thesis and publications. I would like to thank Mike Berg for being a good friend and co-worker on the chiral Reissert compound project. I would also like to thank all of the other Reissert coworkers (Ashish, Brad, Mel, Roger, and Kim) for all the helpful suggestions and going through this with me.

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Introduction / Objectives

1,2-Dihydroisoquinolines are very interesting species due to both their chemical reactivity centered at C_1 and their potential as building blocks in the synthesis of alkaloids and medicinal agents. The chemistry of 2-acyl-1,2-dihydroisoquinaldonitriles (isoquinoline Reissert compounds) and their analogs have been exhaustively studied and well documented.[2-6] However, little was known about the stereochemistry of these compounds. A brief review concerning the synthesis of Reissert compounds, their stereochemical aspects and reactions is given in the first part of the thesis. The next section deals with the study of the stereochemistry of 2-acyl-1,2-dihydroisoquinaldonitriles as well as 1-acyl-1,2-dihydro-4-methylquinaldonitriles to investigate their possible utility as asymmetric reagents.

Subsequently, the focus of this work shifted to the use of chiral acid chlorides and chiral chloroformates as chiral acyl auxiliaries in the formation of diastereomeric Reissert compounds.

The diastereomeric " Reissert anions " were found to react diastereoselectively with aldehydes, thus producing enantiomerically pure isoquinoline based 1,2-aminoalcohols. This methodology opens the door for the enantioselective synthesis via Reissert chemistry of a number of isoquinoline based alkaloids and 1,2-aminoalcohols. Stereoselective synthesis of both biologically active isoquinoline alkaloids and 1,2-aminoalcohols (effective asymmetric catalysts) are very important.

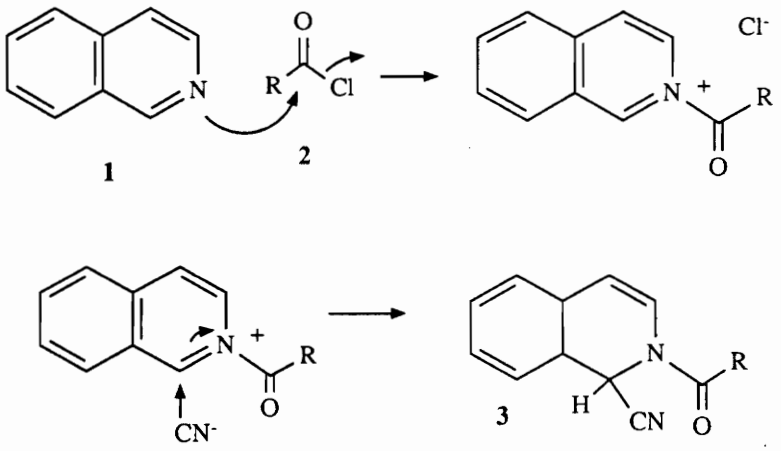
BACKGROUND

A: Reissert Compounds

1. Reissert Compound Synthesis

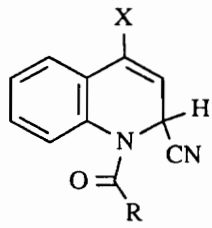
Reissert compounds have been known since 1905[1] and their chemistry is well documented.[2-6] They are generally formed by the reaction of a nitrogen heterocycle such as isoquinoline (**1**) with an acyl chloride (**2**) and a cyanide source by formal addition of the acyl cyanide across the C=N bond (Scheme 1). Several excellent reviews of the synthesis and reactions of Reissert compounds are available.[2-6]

Scheme 1

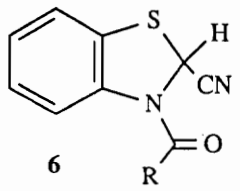


For example, 2-acyl-1,2-dihydroisoquinaldonitrile (**3**), 1-acyl-1,2-dihydroquinaldonitriles (**4, 5**), 3-acyl-2-cyano-2,3-dihydrobenzothiazole (**6**), 3-acyl-2-cyano-2,3-dihydrobenzoxazole (**7**), 2-cyano-1,3-diacyl-1,2-dihydrobenzimidazole (**8**), 1-acyl-2-cyano-1,2-dihydropyridine (**9**), and 5-acyl-5,6-dihydro-6-phenanthridinecarbonitrile (**10**) are all Reissert compounds formed from the

appropriate heterocycle.



4. X = H
5. X = Me



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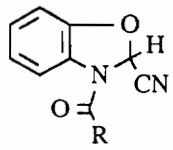

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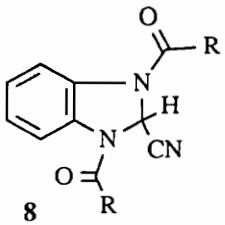

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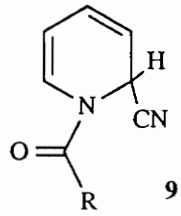

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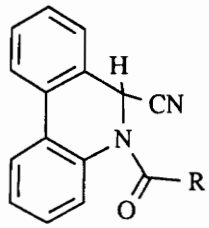

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Several methods have become available for the synthesis of Reissert compounds. The first of these methods was the aqueous method. The heterocycle was added to the water and mixed with potassium cyanide (3 equivalents) and the acid chloride (2 equivalents). The aqueous method

utilized conditions similar to those of the Schotten - Baumann reaction; that is, the aqueous solution of KCN was forcefully mixed with the heterocycle and the acid chloride.[2] Although this method gave reasonable yields, in some cases hydrolysis of the acid chloride was faster than the reaction with the heterocycle, resulting in low yields of Reissert compound.

To combat this problem the dual phase method was developed. This method involves the use of methylene chloride and water as solvents. The heterocycle was dissolved in the methylene chloride, and KCN (2-3 equivalents) was dissolved in the water layer and the two phases were mixed with vigorous stirring. This was followed by the addition of the acyl chloride (1-2 equivalents) dropwise over a two to three hour period. The reaction was allowed to stir vigorously for four to eight hours. The phase transfer catalyst, trimethylbenzylammonium chloride, was found to increase the yield as much as 10 %.[2]

The first single phase method utilized benzene as the solvent and HCN gas as the cyanide source. The impracticality of the use of cyanide gas limits the utility of this method.

A recent technique was found by Ruchirawat *et al.*[7], developed and utilized by Popp *et al.*[8] especially for the synthesis of pyridine Reissert compounds and other reactions which utilize expensive or hydrolytically unstable acid chlorides. The main advantage of this system was the absence of water. This method utilized dry methylene chloride under nitrogen to which the heterocycle, acid chloride and trimethylsilyl cyanide (TMSCN) were added consecutively. A catalytic amount of aluminum trichloride generally increased the yield.[8] In fact, in the case of the Reissert reaction on pthalazine with benzoyl chloride by the aqueous method gave only 0.5 - 3.0 % yield; the dual phase method without the phase transfer catalyst gave 55 - 65 % yield; the two phase method with the phase transfer catalyst gave 65 - 70 % yield; and the single phase method with TMSCN as a cyanide source gave 88 - 90 % yield.[8] Selected examples of the synthesis of Reissert compounds by these methods are shown in Table 1.

Table 1

Comparison of Reissert Compound Yields by Different Methods

Reissert Compound	R	% Yield (by method)			Ref
		a	**b**	**c**	
3	C_6H_5-	58	84(2)[d]	69[e]	18, 7, 10
3	CH_3-		85(1)	87[e]	19, 10
			84(2)		7
3	C_6H_5CH=CH-		91(1)		14
3	$(CH_3)_3C$-	36			14
3	C_6H_4O-	trace	99(1)	96	5
3	CH_3CH_2O-	43	88(2)[d]	57[e]	5,7, 16
4	C_6H_5-	94	96(1)	70	1,5
			89(2)[d]		5
4	4-$NO_2C_6H_4$-			3	5
4	4-ClC_6H_4-	26	77(1)	20[e]	5,19
4	2-$OCH_3C_6H_4$-	51	88(1)	80[e]	17, 12, 10
4	C_6H_5CH=CH-	34	76(3)		14
4	CH_3-		74(1)	50	14, 10
4	$(CH_3)_3C$-	36			14
4	$CH_3(CH_2)_2$-		10(1)	12	5, 14
4	CH_3CH_2O-	43		65	5
5	C_6H_5-	32		71	15, 13

9	C_6H_5-	0	3.5(2)[d]	0	22
10	C_6H_5-		94(1)		5
10	C_6H_5CH=CH-		86(1)		5

a. aqueous method

b. nonaqueous method: (1) HCN/benzene, (2) TMSCN/CH_2Cl_2, (3) SO_2

c. two phase (CH_2Cl_2/ water)

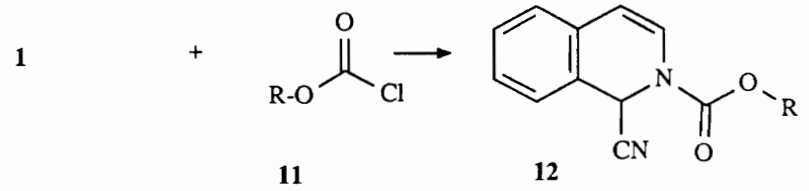
d. use of $AlCl_3$ as catalyst

e. use of trimethyl benzyl ammonium chloride as phase transfer catalyst (PTC)

2. Reissert Compound Analogs

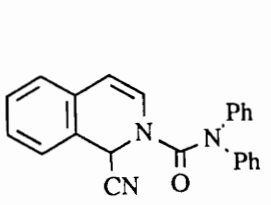
Three types of Reissert analogs have been synthesized and will be discussed here.[4] The urethane Reissert analogs **12** were formed from the heterocycle **1** and a chloroformate **11** (Scheme 2). These analogs were generally formed in high yield (> 90 %) by the trimethylsilyl cyanide method.[8]

Scheme 2



The second analog is formed from the reaction of isoquinoline with N,N-diphenylcarbamoyl chloride and a cyanide source to give the compound **13**. 1,6-Napthyridine analogously gave the compound **14** upon reaction with N,N-diphenyl carbamoyl chloride.[4]

The third analog is from the reaction of isoquinoline and potassium cyanide with a dialkylchlorophosphate to form the Reissert compound **15**. A pthalazine Reissert compound **16** was also formed.[4]



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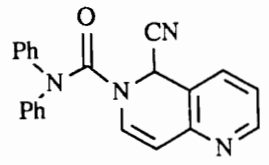

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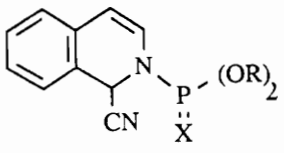
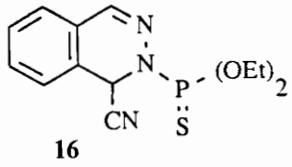


15 X = O, S



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3. Stereochemistry of Reissert Compounds

The major part of my research work is on the stereochemistry of Reissert compounds. A detailed account of stereochemical aspects of Reissert chemistry available in the literature will be presented here. The first part is the study of the stereochemistry of 2-acyl-1,2-dihydroisoquinaldonitriles (isoquinoline Reissert compounds) **3** and 1-acyl-1,2-dihydroquinaldonitriles (quinoline Reissert compounds) (**4, 5**).

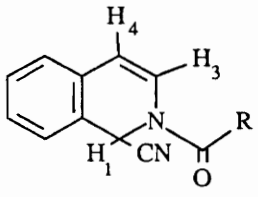
Gibson *et al*,[23-25] have studied the stereochemistry of isoquinoline Reissert compounds **3** by considering the following: nitrogen inversion, ring inversion, amide isomerism and restricted aryl / carbonyl rotation.

One of the best tools for stereochemical studies is NMR spectroscopy.[26] Several conditions must be met before a particular form of isomerism is visible by NMR. The first condition is that the free energy of activation must be high enough that the relaxation time of the isomers is within the time scale of the NMR. Otherwise, the isomers will not be observed independently, but will be observed in their time averaged form. The minimum free energy of activation for isomerization to be observed on a 270 mHz NMR instrument is 5.1 kcal / mol. The second condition is that the free energy between isomers be small enough that both isomers are present in large enough quantities to be detectable by the NMR. If there is less than 5 % of the minor isomer quantitative evaluation of the isomer ratios is not possible, and the minor isomer may not be visible at all in the NMR spectrum. The third condition is that the stereoisomers must possess sufficiently different chemical shifts such that they can be detected.

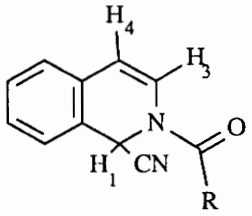
The proton NMR studies performed also depend on the correct identification of the protons involved. The H_1 proton of the isoquinoline ring (α to the cyano group) can be assigned by reacting the Reissert compound with CS_2 and NaH in a solution of dimethylformamide and quenching with deuterium oxide, thus eliminating CS_2 and forming the 1-deutero derivative **18** of the Reissert compound.[6] This reaction will be discussed in a later section in more detail. The cyano group is larger than the hydrogen and prefers the less hindered psuedoaxial position. The H_3 and H_4 protons

on the isoquinoline ring can be identified by coupling constant studies. The coupling constant $J_{3,4}$ is generally found to be 8.0 Hz.

Two types of isomerism were found to be important. Amide configuration is the first type of isomerism that I would like to discuss. The s-trans (**3a**) and s-cis (**3b**) moieties as defined with respect to R and H_1 can both be present as illustrated for isoquinoline.



3a (s-trans)

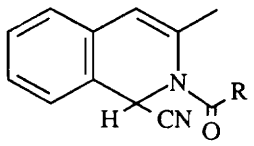


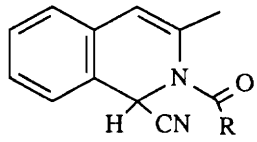
3b (s-cis)

This type of isomerism is due to the partial double bond character of the carbon - nitrogen bond in amides via resonance contribution of " $^{+}$N=C(R)O^{-} ". The activation energies for the interconversion of amide isomers have generally been found to be 15-25 kcal / mol at room temperature (25 °C).[26] The presence of s-cis and s-trans isomers can be detected by ^{1}H NMR.[26]

Aromatic solvent induced shift (ASIS) effects were studied to determine the presence of one or more of the amide isomers. The ASIS involves examining the shift differences in a nonaromatic solvent versus an aromatic solvent.[26] The shift from carbon tetrachloride to benzene caused a number of shifts, the most important of which are summarized below for the isoquinoline Reissert compound **3**.[23]

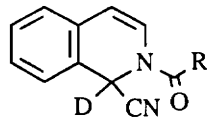
s-cis	s-trans
large upfield shift in H_1	small downfield shift in H_1
small downfield shift in	large upfield shift in
H_3 and H_4	H_3 and H_4





17a (s-trans) **17b (s-cis)**

The 3-substituted isoquinoline Reissert compounds in the study can also exist in the s-trans **17a** and s-cis **17b** conformation as defined with respect to R and H_1. The s-cis and s-trans amide isomers showed the approximate shifts as mentioned above. The ratios of the amide populations can be measured on the basis of integration of the two signals observed for each of the protons H_1, H_3, and H_4. The ASIS results show the s-trans product to predominate.



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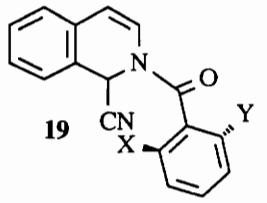
Another interesting type of isomerism is restricted aryl / carbonyl rotation of the acyl group where R is an aryl group. This rotation depends on the steric nature of the acyl chloride used to form the Reissert compound. Reissert compounds with bulky groups at the ortho positions on the aroyl moiety would be expected to exhibit this type of isomerism. Gibson has studied the Reissert compound 2-(2,6-dimethylbenzoyl)-1,2-dihydro-3-methylisoquinaldonitrile.[23] In this case both amide isomerism and restricted rotation were detected in the proton NMR by the examination of the

methyl groups. Four methyl signals are observed, one pair for each amide isomer in a ratio of 3 : 1 (s - trans : s - cis). For each amide isomer the restricted aryl carbonyl rotation makes the ortho methyl groups anisochronous.

The restricted rotational isomerism, however, in the case of the isoquinoline Reissert compounds with two different ortho substituents gives rise to more complicated NMR spectra.[23-25] There are four possible isomers (**19**, **20**, **21**, **22**) of the Reissert compound visible by NMR.



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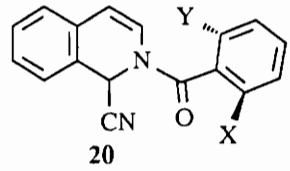

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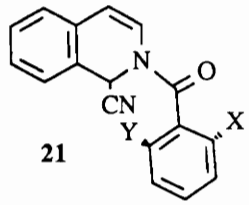

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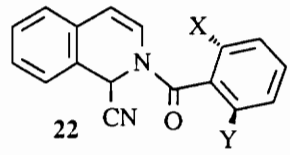

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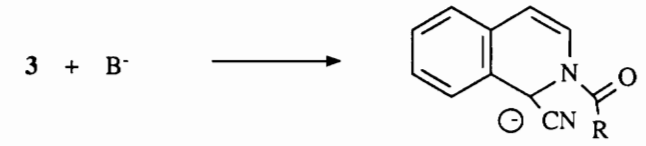
4. Reactions of the Reissert Anion

Useful reactions arise from the acidic hydrogen alpha to the cyano group of the Reissert compound. The reaction of Reissert compounds with bases such as sodium hydride or phenyllithium to remove the acidic proton results in the formation of the "Reissert anion" (**23**). This anion undergoes several nucleophilic reactions which are of interest.[2-6]



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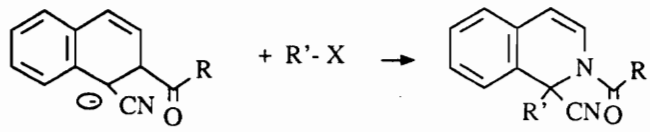
a. Reaction With Alkyl Halides

The reaction of the anion **23** with alkyl halides has been of synthetic utility in the synthesis of substituted quinolines and isoquinolines.[25-27] More importantly this reaction has been utilized in the synthesis of several alkaloids.[28] Upon reaction with alkyl halides the 1-alkyl derivatives **24** of the Reissert compounds are produced from the anion **23** (Scheme 3) and some examples are cited in Table 2.

Scheme 3



23 **24**

Table 2

Alkylation of Reissert Anion **23** to Produce **24**

Reissert Compound / R	R'X	% Yield	ref.
3, Ph	Ph-CH_2-Cl	46[a]	29
3, Ph	Ph-CH_2-Cl	83[b]	29
3, Ph	Ph-CH_2-Cl	85[c]	29
3, Ph	o-NO_2-Ph-CH_2-Cl	36[a]	29
3, Ph	o-NO_2-Ph-CH_2-Cl	91[b]	29
3, Ph	o-NO_2-Ph-CH_2-Cl	95[c]	29
3, Me	$(CH_3)_2$CH-I	81[d]	24
3, Ph	$(CH_3)_2$CH-Br	83[d]	24
3, i-Pr	$(CH_3)_2$CH-I	100[d]	24
3, Me	$CH_2C_6H_5$-Cl	83[d]	24
3, Ph	$CH_2C_6H_5$-Cl	83[d]	24
3, Me	CH_3-I	19[d]	24

[a]LDA, THF - HMPA

[b]50 % NaOH in H_2O / benzene

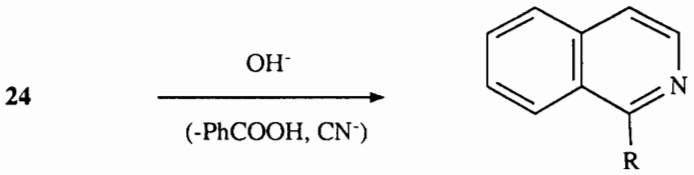
[c]KOH, 18 - crown - 6, benzene

[d]NaH / DMF

b. Basic Hydrolysis

The reaction of the anion **23** has been of interest mainly as a route to the synthesis of alkylated isoquinolines which can be further reacted to yield isoquinoline based alkaloids. Basic hydrolysis of the 1-alkylated Reissert compound **24** results in the elimination of benzoyl cyanide to form the 1-alkylisoquinolines (**25**) (Scheme 4).

Scheme 4

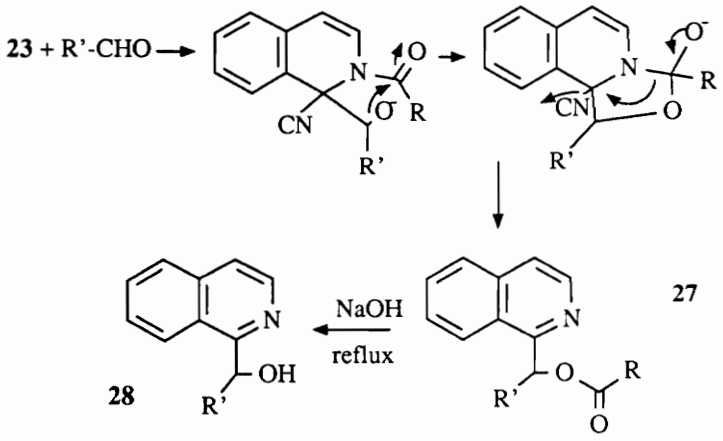


25

c. Reaction With Aldehydes

Generally, aldehydes react with the Reissert anion **23** to produce the ester **27** via rearrangement of intermediate **26** (Scheme 5). Upon hydrolysis of the ester the 1,2-aminoalcohol **28** is formed. Reaction of the anion **23** with aldehydes has led to the synthesis of several benzylisoquinoline alkaloids.[28,37] Papaverine and papaverinol are two examples discussed in more detail in a later section. The aforementioned reaction of aldehydes with Reissert compounds was initially investigated by McEwen *et al.*[5]

Scheme 5



Joncyzk[30] has reported a two phase method of condensation of the Reissert compound **3** using benzene or acetonitrile as the organic phase and an aqueous solution of 50% NaOH with phase transfer catalysis. This reaction proceeds directly to the 1,2-aminoalcohol **28**. We have utilized this approach to asymmetric induction by the chiral phase transfer method in our laboratory.[31]

Of interest in this thesis is the reaction of Reissert compounds **23** and their urethane analogs **29** with aldehydes as reported by Rozwadowska.[32-34] The formation of the ester **32**, carbonate **33**, and cyclic urethane **34** all proceed through the five membered cyclic intermediates **30** and **31** (Scheme 6).The esters **32** and carbonates **33** form in nearly quantitative yield at -40 °C. At temperatures 0 °C or above elimination of alkoxide or phenoxide anion from the intermediate **31** produces the cyclic urethane **34** Some examples are shown in Table 3.

Table 3

Reaction of Reissert Compounds With Aldehydes

Reissert Compound/R	Aldehyde	Base	Ester	% Yield
3, Ph	benzaldehyde	PhLi[b]	**32**	89
5, Ph	veratraldehyde	PhLi[b]	**32**	86(67)[a]
5, Ph	benzaldehyde	PhLi[b]	**32**	88
12, Ph	benzaldehyde	OH^- [c]	**34**	96
12, Ph	piperonal	OH^- [c]	**34**	32
12, Ph	benzaldehyde	NaH[d]	**34**	96(68)[a]
47, Ph	veratraldehyde	NaH[d]		67[a]

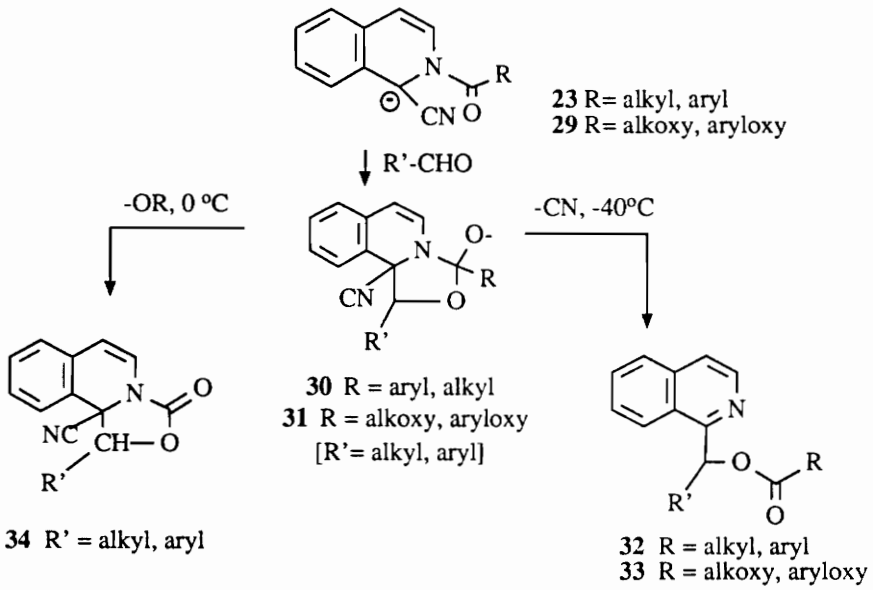
a. yield of alcohol upon hydrolysis of the ester

b. THF as solvent, -78 °C, reference 28

c. 50 % aq. NaOH / benzene as solvent system at 25 °C catalyzed by triethylbenzylammonium chloride, reference 30

d. DMF as solvent, -40 °C reference 32

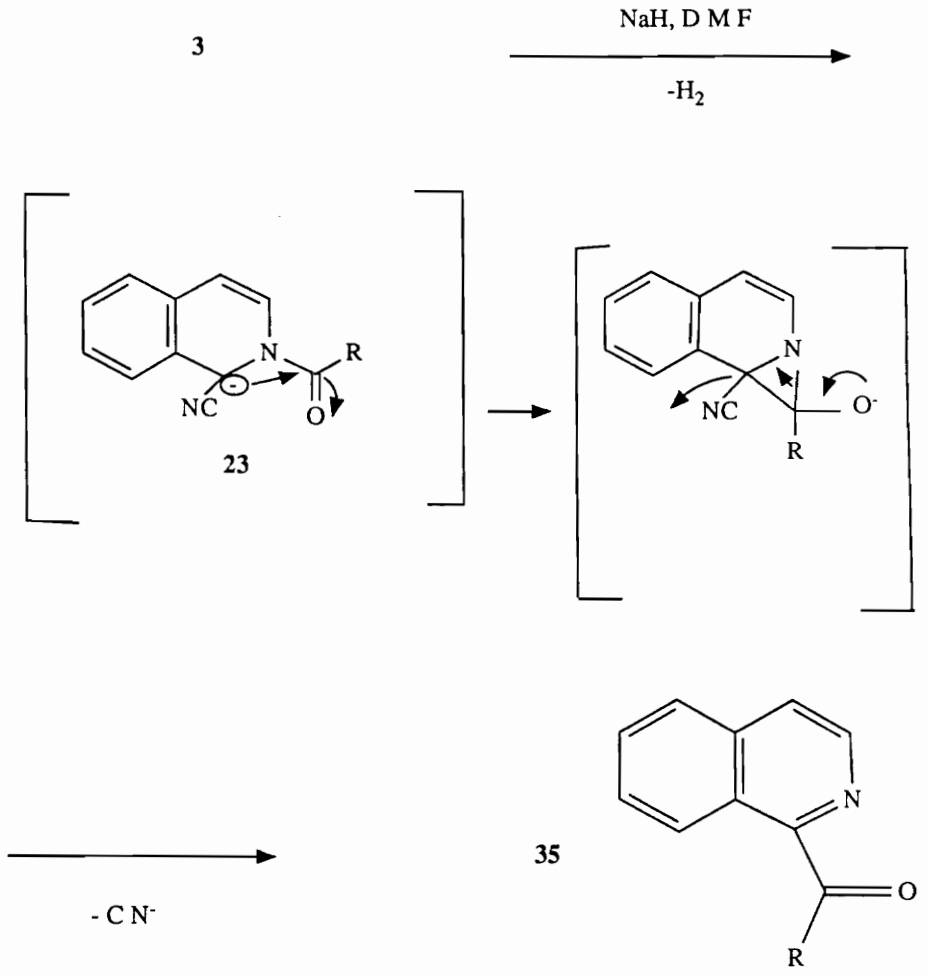
Scheme 6


23 R= alkyl, aryl
29 R= alkoxy, aryloxy
R'-CHO
-OR, 0 °C
-CN, -40°C
30 R = aryl, alkyl
31 R = alkoxy, aryloxy
[R'= alkyl, aryl]
34 R' = alkyl, aryl
32 R = alkyl, aryl
33 R = alkoxy, aryloxy

d. Rearrangement of Reissert Compounds

The anion **23** in the absence of an electrophile will rearrange in most cases to form the ketone **35** (Scheme 7)[5].

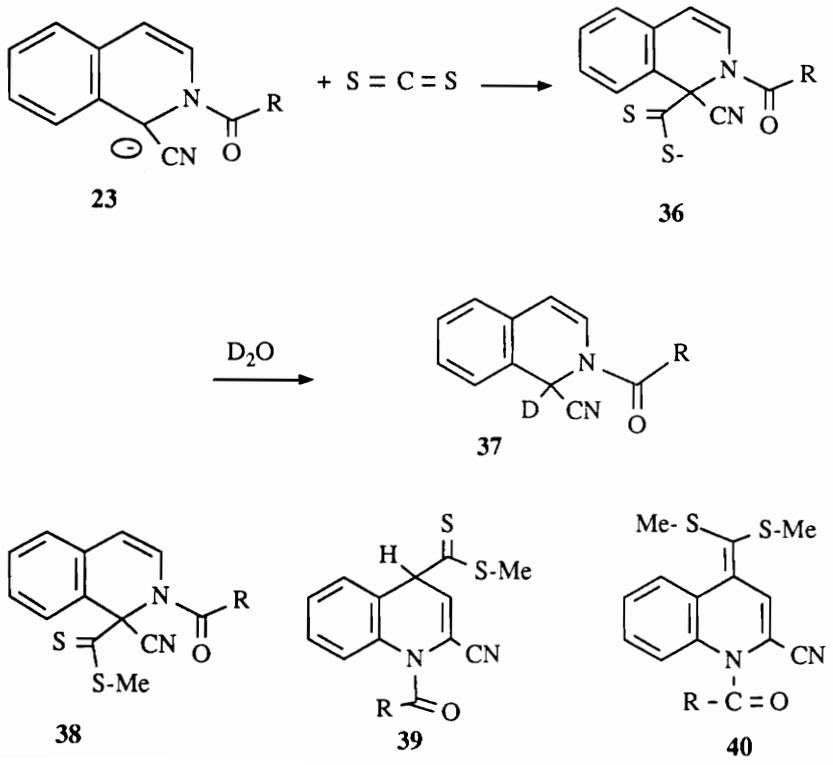
Scheme 7



e. Reaction With Carbon Disulfide

The Reissert anion **23** reacts with carbon disulfide to form an anion **36** which can then be quenched with water to give back the starting Reissert compound or with D_2O to give the corresponding deuterated derivative **37**.[6] Addition of methyl iodide to the anion **36** gave compound **38** in the isoquinoline case and a 4-substituted quinoline derivative **40** in the quinoline case via the intermediate **39** (Scheme 8).

Scheme 8

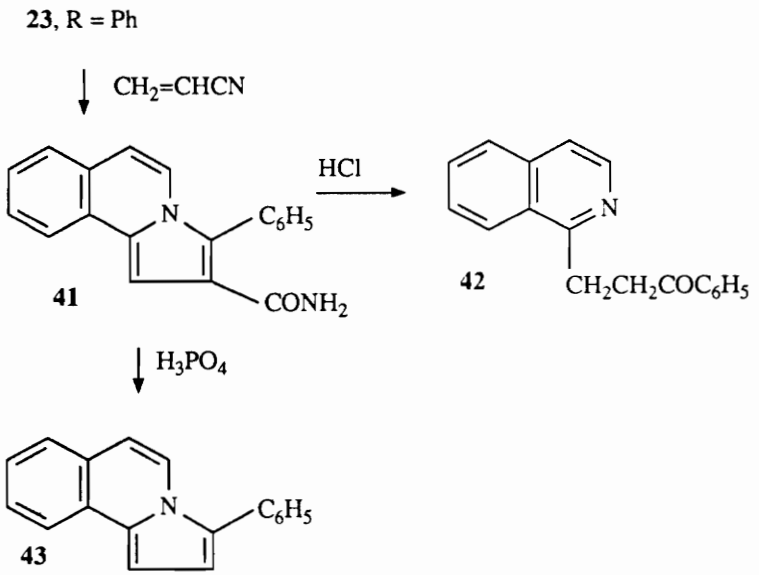


5. Miscellaneous Reactions of Reissert Compounds

The Reissert anion has been found to undergo Michael addition with acrylonitrile, 2-vinylpyridine and ethyl acrylate as well as other similar compounds.[5] These reactions are, however, complex because of further reaction of the original adduct.

Reaction of the Reissert anion with acrylonitrile gave 3-phenyl-2-formamido-7,8-benzopyrrocoline (**41**) in 76 % yield. Treatment of the pyrrocoline product with HCl gave phenyl β-(1-isoquinolyl)ethyl ketone (**42**), and treatment of the pyrrocoline with H_3PO_4 gave 3-phenyl-7,8-benzopyrrocoline (**43**) (Scheme 9).

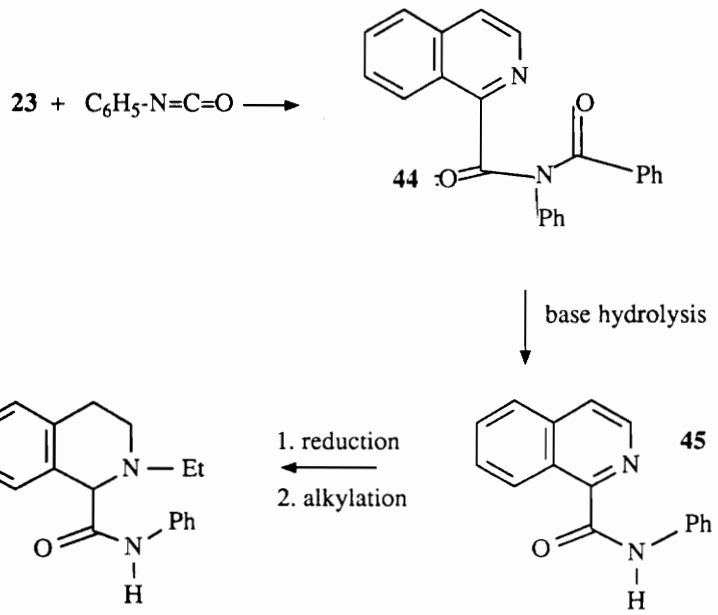
Scheme 9



The Reissert anion **23** has also been reacted with phenyl isocyanate to form N-phenylisoquinaldamide (**45**) upon hydrolysis of the condensation product **44**.[35] Catalytic hydrogenation and subsequent alkylation with ethyl iodide gave

N-phenyl-2-ethyl-1,2,3,4-tetrahydroisoquinalamide (**46**) as an analog of the local anesthetic lidocaine (Scheme 10).

Scheme 10



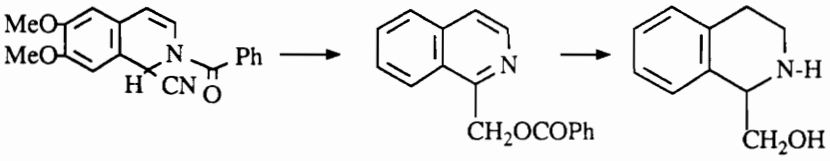
Reaction of the Reissert anion with ketones[36] gave the ester analogously to the reaction of the anion with aldehydes. However, in most cases the reaction with aldehydes gives higher yields than the reaction with ketones.

B: Isoquinoline Alkaloids Derived from Reissert Chemistry

It is of importance to synthesize many of the naturally occuring isoquinoline alkaloids due to their biological activity. For example, the alkaloid bulbocampine (an aporphine alkaloid) has CNS activity (catatonia), boldine has sedative and diuretic activity, and apomorphine has been found to be

a dopamine agonist and thus a possible drug for the treatment of Parkinson's disease. Brossi[37] in the series "The Alkaloids" describes the racemic synthesis of several classes of the isoquinoline alkaloids via Reissert chemistry. Popp[28] has written an excellent review on the early work of isoquinoline alkaloid synthesis from Reissert compounds. The Reissert compound, 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (**47**) was found to be an important starting compound for the synthesis of isoquinoline alkaloids by Reissert chemistry. Popp and Gibson[38] reacted the Reissert compound **47** via its anion with formaldehyde to form the ester **48** which was then hydrogenated to form the alkaloid calycotomine (**49**) (Scheme 11).

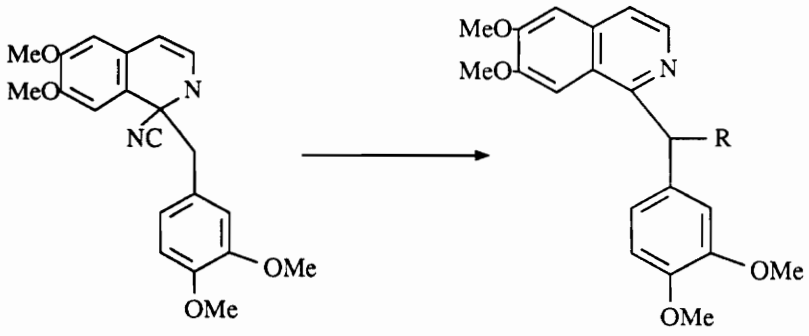
Scheme 11



47 **48** **49**

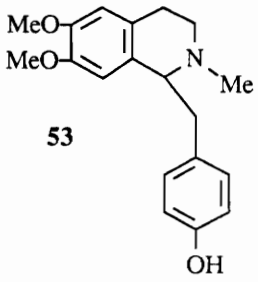
Popp and McEwen[39] synthesized papaverine (**51**) and papaverinol (**52**) via the intermediate **50** from the reaction of the anion of Reissert compound **47** with veratraldehyde (Scheme 12). Popp and Gibson[40] have also prepared armepavine (**53**) from the anion of Reissert compound **47** in 44 % yield by reaction with p-benzyloxybenzaldehyde.

Scheme 12



50

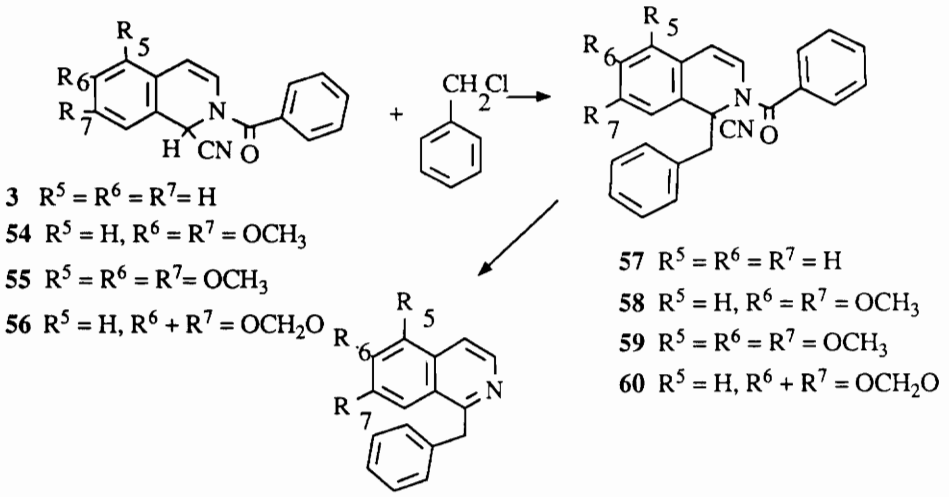
51. R = H
52. R = OH



53

The synthesis of the 1-benzylisoquinoline alkaloid skeleton has been reported by Uff et al.[41] starting from isoquinoline and benzyl chloride. The substituted N-benzoyl-1-cyano-1,2-dihydro-isoquinoline Reissert compounds **3**, **54**, **55**, **56** were synthesized. This was followed by reaction of the Reissert compounds with benzyl chloride and a base, NaH in DMF, to form **57** - **60**. Hydrolysis of compound **57** gives the 1-benzylisoquinoline **61** in 75 - 84 % yield (Scheme 13).[42]

Scheme 13



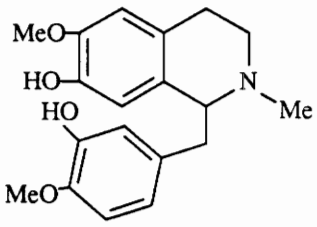
3 $R^5 = R^6 = R^7 = H$
54 $R^5 = H, R^6 = R^7 = OCH_3$
55 $R^5 = R^6 = R^7 = OCH_3$
56 $R^5 = H, R^6 + R^7 = OCH_2O$

57 $R^5 = R^6 = R^7 = H$
58 $R^5 = H, R^6 = R^7 = OCH_3$
59 $R^5 = R^6 = R^7 = OCH_3$
60 $R^5 = H, R^6 + R^7 = OCH_2O$

61 $R^5 = R^6 = R^7 = H$

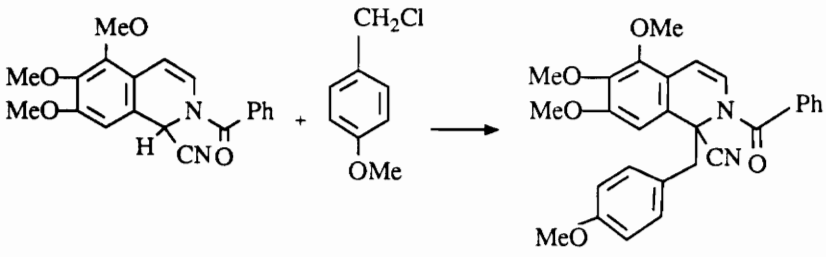
Skiles *et al.*[29] utilized several methods for the alkylation of Reissert compounds. The methods were: (a) LDA in THF / HMPA (b) KOH with benzene in the presence of dicyclohexyl-18-crown-6 (c) 50 % aqueous NaOH with benzene in the presence of phase transfer catalyst. Methods (b) and (c) were found to be more advantageous in general (i. e., the 1,2-aminoalcohols were produced in higher yield) and method (c) in particular could be easily modified by use of chiral phase transfer catalysts as opposed to achiral phase transfer catalysts. Reticuline (**62**), in particular, has been synthesized using this methodology. Reticuline is an important intermediate in the synthesis of several opium alkaloids.[43] Escholamine (**67**) is also biologically active as a vasodialation agent.[43] Several other alkaloids have been synthesized by this route. Some examples are shown in Scheme 14.

Scheme 14

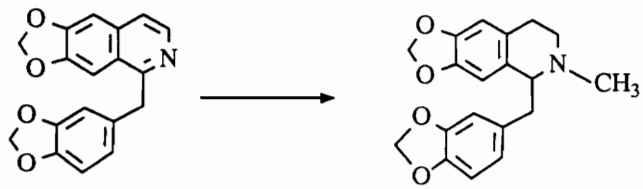


Reticuline

62

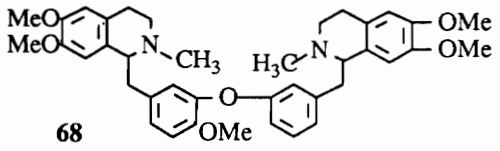


63 **64** **65**



66 **67** Escholamine

Another related class of alkaloids are the bisbenzylisoquinoline alkaloids. Their synthesis is exemplified by the synthesis of o-methyldauricine by Gibson *et al.*[44] (**68**). Other classes of alkaloids



68

O-Methyldauricine

can be synthesized in this manner, but as they are not directly related to this research their synthesis will not be discussed and the reader is referred to the literature.[45-52]

C: Methods of Asymmetric Synthesis

" In general, one can define *"asymmetric synthesis"* as the enantioselective conversion of a prochiral substrate to an optically active product by reaction with a chiral addend."[53]

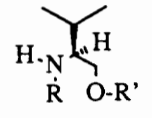
Methodologies for asymmetric synthesis are important, especially in the pharmaceutical industry, since opposite enantiomers of the same compound can have different biological effects. One example of this is Thalidomide. The S enantiomer is a powerful tranquilizer while the R enantiomer causes severe disruption in fetal development.[54] As a consequence of this, the stereochemistry of biologically active compounds is critical in determining their medicinal utility. Thus, practical and inexpensive methods of enantioselective synthesis are invaluable.

Many of the isoquinoline alkaloids have been synthesized as racemates by Reissert chemistry as described above. Many of these alkaloids have phamacological activity. The advantage of synthesizing these alkaloids stereospecifically would thus be to investigate the pharmacology of each enantiomer separately.

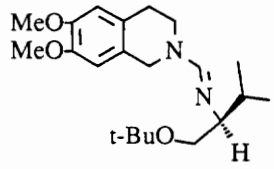
1. Chiral Acyl Auxiliaries

Meyers[55-58] utilizes natural chiral amino acids such as valinol (**69**) as chiral acyl auxiliaries. He has demonstrated an enantioselective alkylation of tetrahydroisoquinolines via the valine

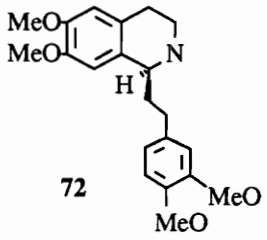
auxiliary **70** to form (S)-(+)-homolaudanosine (**72**) and (-)-salsolidine (**73**). Meyers' synthesis depends on selective formation of a chiral formamidine intermediate such as **71**. The (S)-valinol (**69**) was found to be the best choice among chiral amino acids in forming the chiral formamidine. Meyers' group has also worked with chiral napthylimines. Meyers has been able to demonstrate the synthesis of several of the (S)-isoquinoline alkaloids in over 93 % enantiomeric excess (ee). In recent work Meyers has also used this methodology to form some of the pyrro[2,1-a]isoquinolines in 92 % ee. There are several major disadvantages to the Meyers' approach. The first is that the natural enantiomer of the valinol must be used. Another is that the system is only applicable to 1,3-diamines that can form the chiral formamidine. The reaction also requires the use of strong bases (butyllithium), at low temperature (-78 °C), and allows the introduction of only one alkyl group at C_1.



69 R'=H **70** R'= t-Bu

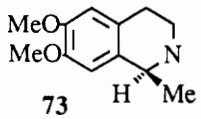


71



72

(S)-(+)-Homolaudanosine
46% overall yield
92-95% ee

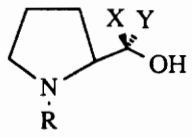


73

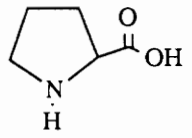
(-)salsolidine
61% chemical yield
95% ee

Kenzo Soai's work[59-60] involves the enantioselective addition of dialkyl zincs to aldehydes. This was done by using chiral pyrrolidinyl methanols (**74**) as the chiral intermediate. The results of this study helped me to select an appropriate aldehyde and chiral acyl auxiliary since the reaction of

Reissert compounds with aldehydes also involves facioselective nucleophilic attack. The enantioselectivity of the system is highly dependent on the structure of the pyrrolidinylmethanol catalyst. Their catalyst was derived from the use of (S)-proline (**75**) as the chiral auxiliary. One of the major disadvantages of this chemistry is the complicated synthesis of the chiral pyrolidinylmethanol (**74**). Primary aminoalcohols afforded no selectivity and tertiary aminoalcohols afforded the greatest selectivity.



74



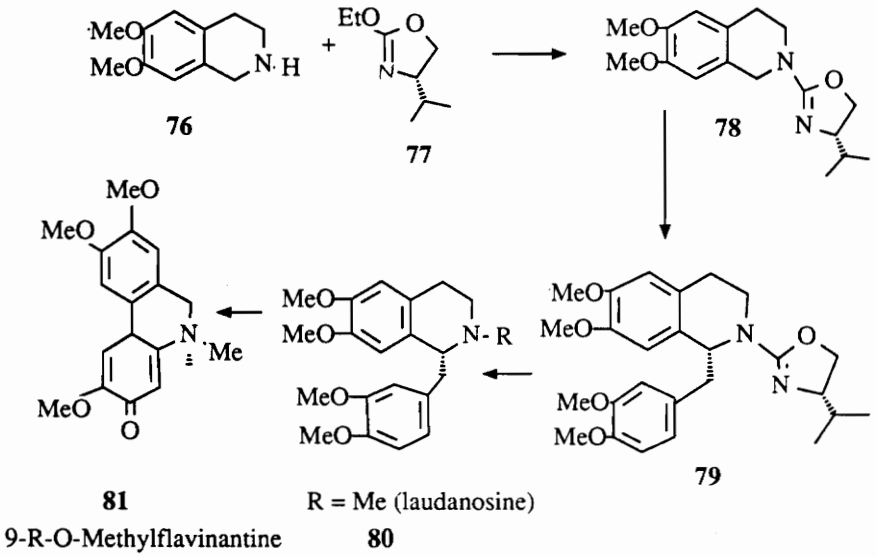
75

A similar approach has also been used by E. J. Corey.[61] He used zinc (II) chelates with tertiary amino phenolic alcohols to catalyze the stereoselective addition of diethylzinc to aromatic aldehydes with predictable absolute stereochemistry.

Recently, Gawley[62-64] accomplished the synthesis of (R)-laudanosine (**80**) and 9-(R)-O-methylflavinantine (**81**) by asymmetric alkylation (Scheme 15). These isoquinoline alkaloids are of biological importance as analgesics. Gawley's methodology hinges on the use of a chiral ethoxyoxazoline **77** as the chiral auxiliary.

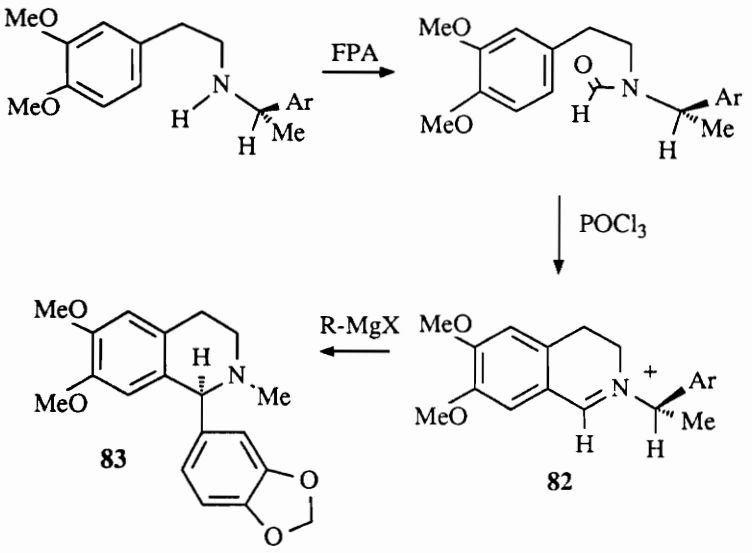
Gawley used 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**76**) prepared by Pictet - Spangler cyclization in 92 % yield. This was then reacted with the chiral ethoxyoxazoline **77** to form the chiral isoquinoyloxazoline **78** in 82 % - 85 % yield. Reaction with t-butyllithium and subsequent alkylation with 3,4-dimethoxybenzoyl chloride yielded **79** in 82 % - 85 % yield. Compound **79** was converted by Kametani's procedure[65] to (R)-laudanosine which was then converted to 9-(R)-methylflavinantine (**81**). Both alkaloids were formed in high (94 %) ee.

Scheme 15



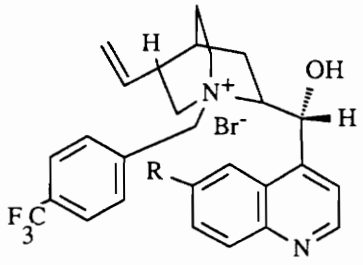
Polniaszek *et al*[66-67] form chiral acyl iminium ions by formylation of substituted 3,4-dimethoxyphenethylamine (his source for formation of the chiral auxiliary) with formyl pivalyl anhydride (FPA) followed by refluxing the resulting formamides in phosphorous oxytrichloride. Addition of Grignard reagents to the chiral formamide **82** was investigated to determine the diastereoselectivity. The average diastereoselectivity of the addition was 87 %. (S)-Cryptostyline (**83**) was formed in 92 % ee by this methodology (Scheme 16).

Scheme 16



2. Chiral Phase Transfer Catalysis

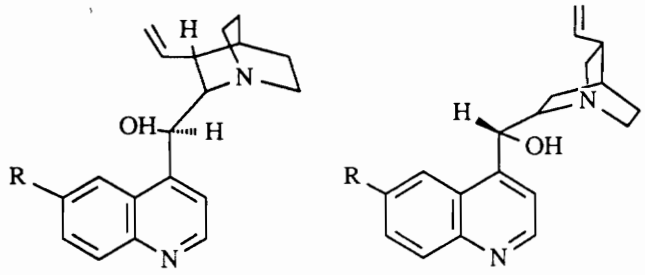
Chiral aminoalcohols, 1,2-aminoalcohols in particular (e. g., quinine, Darvon alcohol, cinchonine, etc.), are effective as asymmetric agents.[68] These 1,2-aminoalcohols are available in nature but are expensive. This calls for the synthesis of inexpensive 1,2-aminoalcohols. Also, recoverability of the catalyst, as well as synthetic tailoring allow optimization of structure for particular systems. Many optically active compounds have been synthesized through formation of asymmetric carbon-carbon bonds in the presence of an optically active catalyst. Wynberg[69-70] and Dolling[71-72] both have done extensive work in this area. A chiral cinchoninium salt is used as the catalyst. For example, p-trifluorobenzyl cinchoninium bromide **84** is used in many cases.



84

The four cinchona alkaloids **85**, **86**, **87**, **88** have been used as asymmetric agents by formation of chiral cinchoninium salts as mentioned above. From this chemistry it is possible to synthesize a series of four cinchona alkaloid based chiral phase transfer catalysts. An advantage of this methodology is that it is possible to form catalysts which exhibit the R configuration or the S configuration. This allows the chiral phase transfer technique to be used in enantiodivergent syntheses.

Selectivity is achieved because the face of the catalyst is planar and the resulting complex allows the substrate to attack at only one face. The transformation is thus mediated by the chiral phase transfer catalyst at the interface between the organic and aqueous phase. Generally benzene is used as the organic phase and 50 % sodium hydroxide solution is used as the aqueous phase. The compound (S)-(+)-6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone has been produced in 95 % yield (94 % ee) from the corresponding indanone using this technique.[75]



85. R = OMe (quinine)
86. R = H (cinchonine)

87. R = OMe (quinidine)
88. R = H (cinchonidine)

We have also been involved in this work by using the chiral phase transfer method to mediate the reaction of the Reissert compound **3** with pivaldehyde to produce the benzoate **27** (R = Ph, R' = t-butyl) in 80% enantiomeric excess (ee).[74]

The reader may consult the literature for further infomation on this subject.[75-84]

D: Mechanisms for Chiral Separation

Pasteur[85] separated the diastereomers of ammonium sodium tartrate and evaluated the physical properties of the diastereomers to determine the differences. Thus methodology was developed to explain and understand the relationship of the two diastereomers of ammonuim sodium tartrate, leading to general knowledge of diastereomers, enantiomers and the subject we now call stereochemistry in general.

Another classic technique is that of Schlenk *et al.*,[86] which utilized urea inclusion complexes to separate enantiomers. Urea forms inclusion compounds with a variety of straight chain aliphatic compounds. The host molecules form a lattice in which channel-like hollow spaces are occupied by long chain organic molecules. The urea molecules exhibit a helix type structure forming two enantiomorphous lattices. This methodology has been utilized to separate diastereomers as well.[86]

A later approach was surface imprinting, which was introduced by Dickey.[87] Silica gel is

produced in the presence of organic molecules. The organic substrate is then removed, leaving "imprints" on the silica. Although not efficient in itself this methodology led to the beginnings of methodologies for the separations of enantiomers and other chiral molecules by chromatography.

High Performance Liquid Chromatography (HPLC) has been the most popular method for the chromatographic separation of chiral compounds. One of the reasons for this is that the HPLC column is a one time investment as opposed to the expense of traditional column chromatography. Another advantage is that many commercial HPLC columns employing chiral stationary phases (CSP's) are available. A last advantage is that mimimal amounts of the compound are needed for analysis, but multigram preparatory separations can also be accomplished.

The direct resolution of enantiomers by chromatography on chiral stationary phases solves a variety of stereochemical problems, accurate determination of enantiomeric excess being the main one. A necessary parameter for the establishment of enantiomeric excess is that there is baseline separation of enantiomers. Consequently, the CSP column should contain efficiently packed small particles. To assign absolute configuration, a consistent pattern of elution should occur for a series of similar compounds. Historically, very few CSP's have been developed that meet these goals. Most of the CSP's reported contain an assemblage of subunits acting in concert to achieve chiral recognition. These are called cooperative CSP's. Examples include derivatized cellulose, cyclodextrin, chiral polymers and CSP's derived from bovine serum albumin. Although these CSP's have demonstrated utility in the separation of a large number of solutes the chiral recognition process is undetermined due to its complexity and the absolute configuration cannot usually be determined.

A second class of CSP's known as independent CSP's do not have these limitations. Baczuk[88], for example, has bonded l-arginine through a cyanuric chloride linkage to Sephadex. As a result, Baczuk was able to separate and assign the absolute configuration to (S)-dopa and (R)-dopa. Other independent CSP's were developed for the resolutions of chiral helicenes and α-amino acids. A three point mechanism has been proposed by Dalgleish.[89]

Pirkle's[90-94] interest in independent CSP's for HPLC began in the 1960's with the

observation that certain diastereomeric complexes exhibited different stability upon HPLC analysis by previously developed stationary phases. Extensions of the observation of differences in the elution of the diastereomeric complexes on chiral CSP's led to the development of the first Pirkle type CSP's. The development of the first Pirkle type CSP's as well as discovery of new chiral recognition mechanisms led to even more sophisticated Pirkle CSP's. One example of which is the phenylglycine column in use today. A systematic approach to CSP design has led to the understanding of the requirements of a good CSP. First, a CSP is designed to utilize a known chiral recognition mechanism. To obtain good chiral recognition, the CSP must be attached to the support in a manner that does not interfere with the essential interactions. Further, the functional groups on the CSP are chosen to maximize chiral recognition. Second, resolutions of a class of racemates are examined systematically to determine the chiral recognition process. This involves studying the effect of variation in analyte structure on chiral efficiency as measured by α (the relative retention of the two solutes, $\alpha = K_2 / K_1$) and using these observations to postulate interactions between CSP and analyte.

The Pirkle CSP utilized in this research was (R)-N-(3,5-dimethoxybenzoyl)phenylglycine covalently bonded to a derivatized silica gel. There is much precedent for this particular column to separate alkyl aryl carbinols.[90] Meyers and Pirkle[91-92] have utilized this column extensively in their work. Chromatography was useful in many cases but failed to solve some of my separation problems. In these cases other methods were utilized.

Chiral reagents have become very useful in the determination of enantiomeric excesses by NMR. Such techniques as chiral lanthanide shift reagents, chiral solvating agents and chiral derivatizing agents have gained in popularity.[95]

The use of chiral solvating agents (CSA's) was proposed by Mislow and Raban[96] and experimentally demonstrated by Pirkle.[90] Since that time, many examples of the use of chiral solvents and other diamagnetic chiral solvating agents have appeared in the literature.[95] The

principal applications reported to date have been the determination of enantiomeric purity and demonstration of chirality, determination of the absolute configuration, and the determination of the kinetics of enantiomerizations.

In a paper on chiral CSA's[97] Pirkle gives an excellent description of how they work.

" *The CSA's work in the following manner. Consider chiral solute enantiomers* S_d *and* S_l *containing corresponding observable nuclei, the latter enantiotopic by external comparison. In an achiral environment, enantiotopic protons are isochronous (i.e., they have the same chemical shift). In the presence of a chiral solvent or CSA the enantiotopic protons become anisochronous (i.e., they have different chemical shifts). This anisochrony is related to the solvation of solute enantiomers by the CSA and is explained by the formation of diastereomeric binary association complexes between the CSA and the solute. Thus an equilibrium is established between complexed and uncomplexed species in solution. The proportions of the two enantiomeric species typically have no influence on the magnitude of the observed anisochrony. Also, the relative areas of the observed resonances are proportional to the ratio of the two enantiomers in the solution. A direct implication of this is that enantiomeric purity determinations are generally possible and feasible.* "

Rosini *et al.*[98] studied the use of quinine as a CSA for the determination of enantiomeric purity of binapthyl derivatives and alkyl aryl carbinols by proton NMR. They were able to obtain signal separations large enough to make the determination of the enantiomeric excess possible in all cases reported. Better resolution was obtained in more concentrated solutions and at lower temperatures, because those conditions would push the equilibrium of the system from the uncomplexed species to the complexed species.

Since the CSA can simply be added to the analyte without a time consuming and possibly incomplete diastereoselective chemical reaction taking place, the technique is simple and attractive. The only posssible drawback is the complexity of the quinine spectrum itself. However, it did not interfere in the determination of enantiomeric excesses in any of the cases reported.[98]

RESULTS AND DISCUSSION

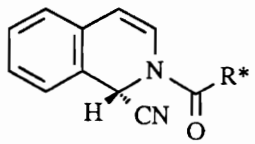
A. Goals and Rationale

In spite of their well developed chemistry, Reissert compounds have not until now been used as chiral reagents. The stereochemistry of Reissert compounds has not been thoroughly studied and reported. It was decided to study the stereochemistry of some isoquinoline Reissert compounds **3** and quinoline Reissert compounds **4** and **5** to develop a rationale for their utility in asymmetric synthesis.

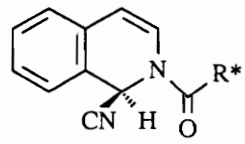
Two approaches to the utilization of Reissert compounds in asymmetric synthesis have been investigated by our group. These approaches take advantage of the fact that the carbon alpha to the cyano group at the one position of the heterocyclic ring is a stereogenic center.

The first approach to asymmetric induction in Reissert compounds is to utilize a chiral phase transfer catalyst (CPTC). This methodology was initially developed by Dolling[71-72] and Wynberg.[69-70] Gibson *et al.*[31] have utilized this technique in Reissert chemistry.

The second approach to asymmetric induction is the present investigation which involves the use of a chiral acyl auxiliary, specifically a chiral acid chloride or chloroformate, to form diastereomeric Reissert compounds of the type **89**, **90**.



89

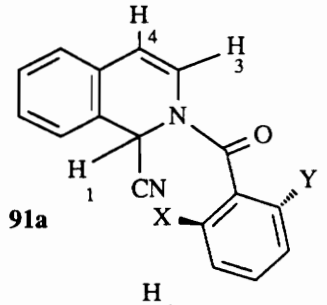


90

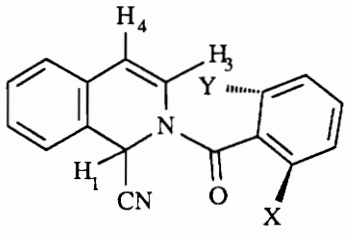
B. Stereochemistry of Isoquinoline Reissert Compounds

Two criteria were used to select the acid chlorides. The first criterion was the selection of acyl chlorides with ortho substituents on the phenyl ring. The other criterion was that the substituents have distinct chemical shifts in the proton NMR. These criteria were chosen since it

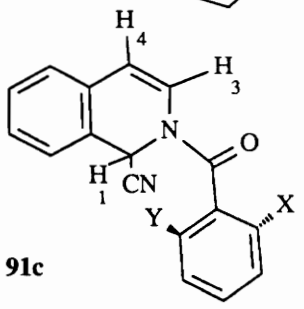
was thought that the ortho substituents would increase the chances of seeing amide isomerism and restricted aryl / carbonyl rotation within the time frame of the NMR. The distinct chemical shifts of the substituents also lead to a simpler interpretation of results.



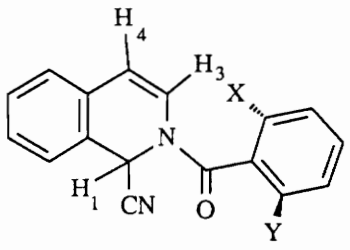
91a



91b



91c



91d

Amide isomerism and restricted aryl / carbonyl rotamers could lead to four total possible conformations of the Reissert compound **91**. Since the H_1, H_3, and H_4 protons on the isoquinoline ring as well as the X and Y protons on the aroyl moiety are placed in different stereochemical environments by this isomerism, they should be anisochronous (i. e., they should have different chemical shifts). If amide isomerism and restricted acyl / carbonyl rotation are fast and not observable on the NMR time scale one would expect to see only one signal for X, Y, H_1, and one doublet ($J_{3,4}$ = 7 - 9 Hz) each for H_3 and H_4. If the amide isomers are slowly rotating and observable on the NMR time scale but aryl / carbonyl rotation is fast and not observable on the NMR time scale one would expect to see two signals each for the protons X, Y, and H_1 and two doublets each for H_3 and H_4 corresponding to the s-trans and s-cis amide populations. If both amide isomers and both

rotamers are observable then one would expect to see four signals each for X, Y and H_1 and four doublets each for H_3 and H_4.

Two isoquinoline Reissert compounds were studied. The isoquinoline Reissert compounds were studied first because (a) their use could lead to the enantioselective synthesis of isoquinoline based alkaloids and design of synthetic analogs with biological activity and (b) proton NMR spectra of the isoquinoline Reissert compounds are simple in comparison to the quinoline case.

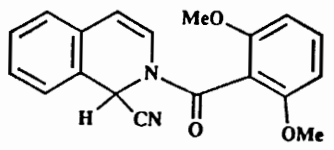
The first compound studied was 2-(2,6-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile (**92**). This new compound was prepared by the two phase method (CH_2Cl_2 / water) from isoquinoline and 2,6-dimethoxybenzoyl chloride with KCN as the cyanide source. The 270 mHz proton NMR spectrum at 25 °C of the analytically pure compound (Figure 1) showed four distinct signals for the methoxy protons at 3.91, 3.89, 3.71 and 3.69 ppm. The ratio of the signal at 3.89 to the signal at 3.91 was 4:1. The ratio of the signal at 3.69 to the signal at 3.71 was also 4:1. Two signals for the H_1 proton of the isoquinoline ring were present, one at 6.84 ppm and the other at 5.70 ppm. The ratio of these signals was 4:1 and the total area of both peaks integrated to one proton. By analysis of the integration and coupling constant ($J_{3,4}$ = 7 Hz) it was determined that two doublets ($J_{3,4}$ = 7 Hz) were present for H_4 at 6.40, and 6.36 ppm in a 4:1 ratio. The H_3 proton was analyzed in the same manner and two doublets ($J_{3,4}$ = 7 Hz) were found at 6.70 and 6.59 ppm in a ratio of 4:1. Thus in the case of compound **92** both amide isomerism and restricted rotation of the acyl / carbonyl bond were observable for the methoxy protons and amide isomerism was observed in the signals for the protons H_1, H_3 and H_4. The two amide isomers were present at 25 °C in a 4:1 ratio.

The other isoquinoline Reissert compound studied was 2-(α-napthoyl)-1,2-dihydroisoquinaldonitrile (**93**). The compound was prepared by the two phase method (CH_2Cl_2 / water) from isoquinoline and 1-napthoyl chloride with KCN as the cyanide source. The 270 mHz proton NMR spectrum at 25 °C (Figure 2) showed only one peak for the H_1 proton at 6.90 ppm. There was one doublet present for the H_3 proton at 6.30 ppm and one doublet for the H_4 proton at 5.99 ppm. These results indicated that the amide bond was rotating too rapidly

270 mHz 1H NMR Spectrum of 2-(2,6-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile

4 : 1 Ratio of amide isomers

$CDCl_3$, 25 °C



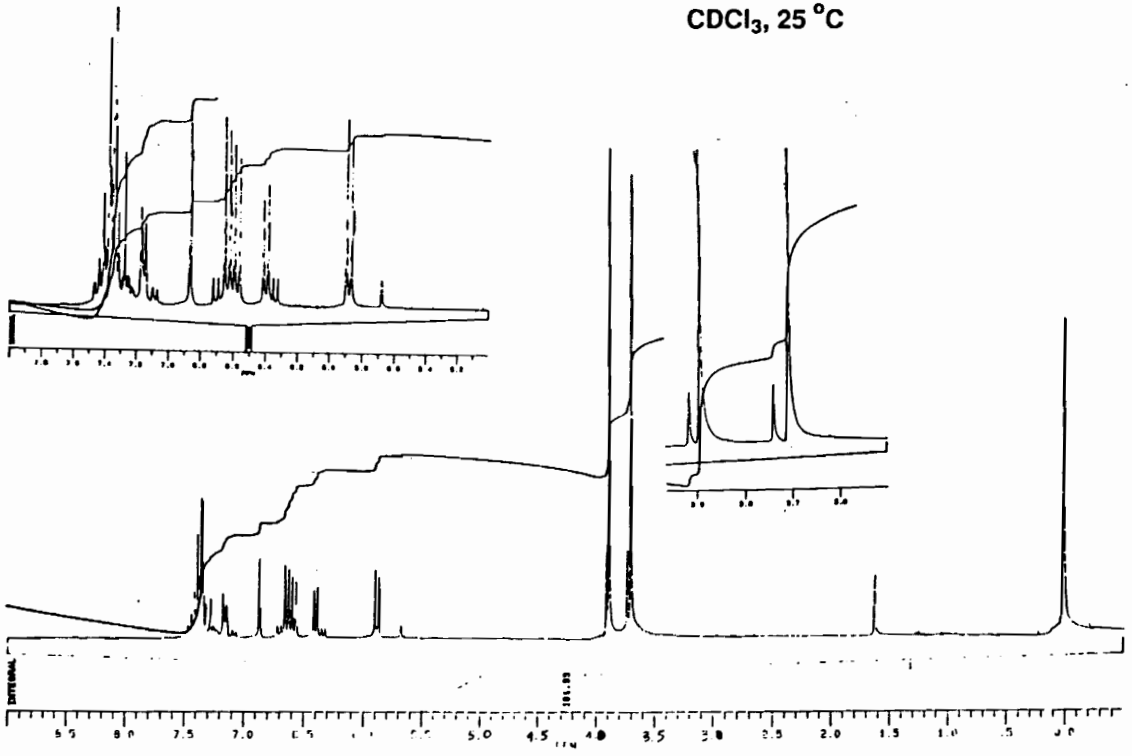


Figure 1

270 mHz 1H NMR Spectrum of 2-(1-Napthoyl)-1,2-dihydroisoquinaldonitrile

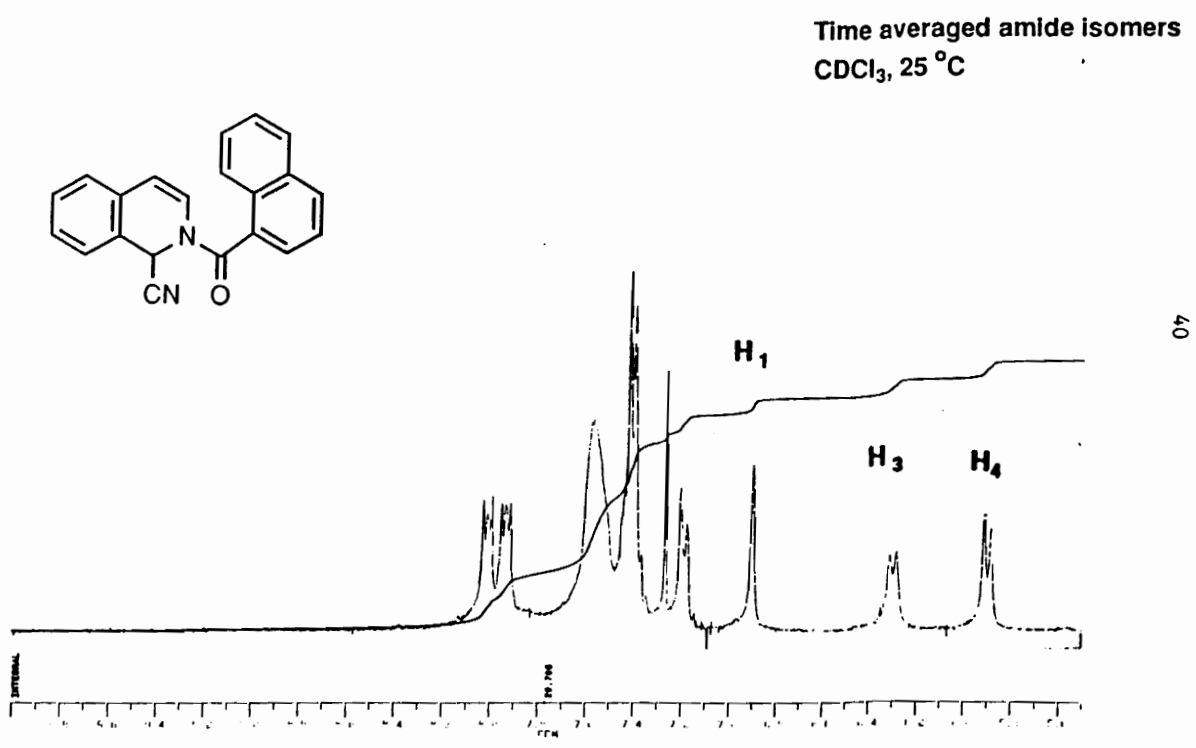
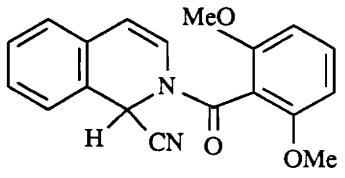
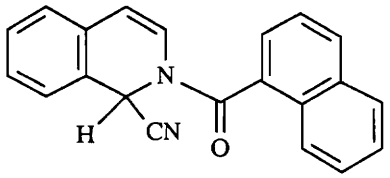


Figure 2

to be observed on the NMR time scale at room temperature or that one amide isomer vastly predominated over the other.



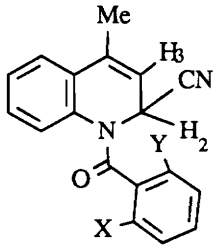
92



93

C. Stereochemistry of Lepidine Reissert Compounds

Two compounds of the lepidine Reissert compound series, 2-(2,6-dimethoxybenzoyl)-1,2-dihydro-4-methylquinaldonitrile (**94**) and 2-(2,6-difluorobenzoyl)-1,2-dihydro-4-methylquinaldonitrile (**95**), were studied next. The lepidine Reissert compounds were chosen because the 4-methyl group simplifies the aromatic region of the proton NMR spectrum for analysis. A second reason for the choice was that many of the natural 1,2-aminoalcohols (e. g. quinine) are 4-substituted quinolines.



94 X = Y = OCH_3
95 X = Y = F

The new compound **94** was prepared by the two phase method (CH_2Cl_2 / water) from lepidine and 2,6-dimethoxybenzoyl chloride with KCN as the cyanide source. It was found that in an analytically pure sample of **94** there were four methoxy signals present in the 270 mHz proton NMR spectrum (Figure 3). They occurred at 4.00, 3.90, 3.70, and 3.17 ppm. The ratio of the peaks at 4.00 and 3.17 ppm to the peaks at 3.90 and 3.70 ppm was 3:1 and the signals integrated to a total

of six protons. The 4-methyl group of the lepidine also showed two peaks, one at 2.23 ppm and the other at 2.17 ppm. The ratio of the peak at 2.23 to the peak at 2.17 was also 3:1. By coupling constant analysis and integrations, H_2 and H_3 were assigned. The H_2 proton was visible as two doublets ($J_{2,3}$ = 8.0 Hz) at 6.20 and 5.30 in a 3:1 ratio. The total integration of the four peaks was one proton. The H_3 proton was found to be present as two doublets ($J_{2,3}$ = 8.0 Hz) at 5.91 and 5.71 ppm in a 3:1 ratio. The total integration of the four peaks was one proton. This result indicates that both amide isomerism and restricted aryl / carboyl rotation are observable for the methoxy protons and that amide isomerism is observable for H_2, H_3, and the 4-methyl protons and furthermore that the amide isomers were present in a 3:1 ratio.

The new Reissert compound **95** was formed by the two phase method from lepidine, 2,6-difluorobenzoyl chloride and KCN. The sample was then purified to analytical purity. Analysis of the 270 mHz proton NMR spectrum (Figure 4) gave the following results. Only one peak was visible for the 4-methyl group at 2.20 ppm. H_2 and H_3 were identified by coupling constant analysis ($J_{2,3}$ = 7.5 Hz). The H_3 proton was found to be present as one doublet at 5.94 ppm. The H_2 proton was found to occur as one doublet at 6.44 ppm. The ^{19}F-NMR ($CDCl_3$, 400 mHz) was then studied (Figure 5). Since the nitrogen containing ring of the heterocycle is not planar, the two fluorines are in different environments and they exhibit two different chemical shifts. Two fluorine signals were found to occur in the spectrum at -113.25 ppm and -113.45 relative to triflurotoluene as internal standard. Each fluorine showed a pair of overlapping doublets. The pattern of each fluorine is the result of coupling to the adjacent hydrogen (J_{HF} = 7 Hz) as well as to the other fluorine (J_{FF} = 2.5 Hz). The two fluorines show an identical splitting pattern. Since as shown with **94** H_2 and H_3 are very sensitive to amide isomerism, we attribute the fluorine signal doubling to restricted aryl / carbonyl rotation. Since the pattern was complicated, the resolved 400 mHz spectrum (Figure 6) was analyzed by calculation and subsequent simulation for a degenerate AA'XX' system (J_{AX} and $J_{A'X'}$ = 7.56 Hz, $J_{AA'}$ = 2.5 Hz and $J_{XX'}$ = 0; where A and A' are F; X and X' are H).

Synthesis of 1-(9-anthroyl)-1,2-dihydro-4-methylquinaldonitrile (**96**) was attempted

270 mHz 1H NMR Spectrum of 1-(2,6-Dimethoxybenzoyl)-1,2-dihydro-4-methylquinaldonitrile

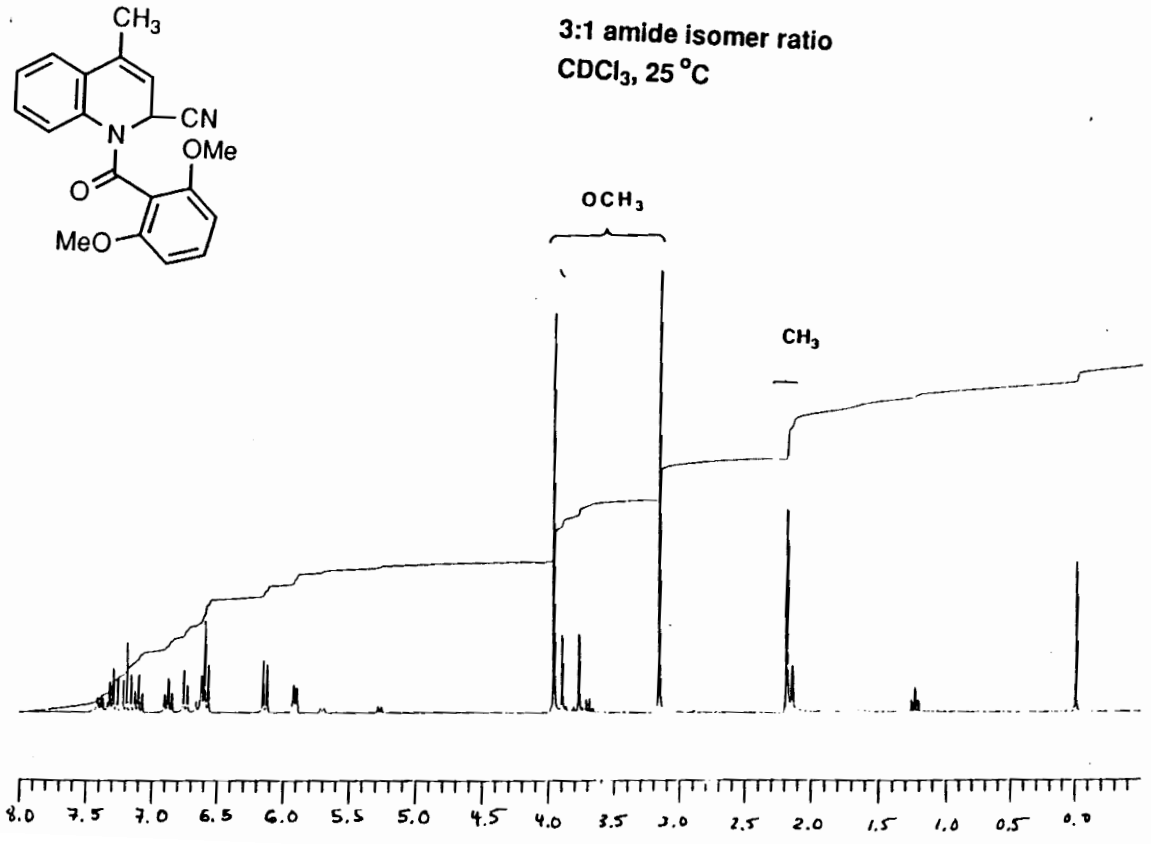


Figure 3

270 mHz 1H NMR Spectrum of 1-(2,6-Difluorobenzoyl)-1,2-dihydro-4-methylquinaldonitrile

time averaged amide isomers

$CDCl_3$, 25 °C

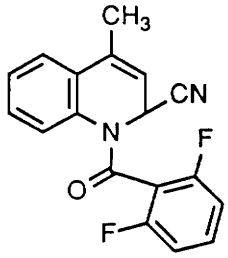


Figure 4

400 mHz 19 F NMR Spectrum of 1-(2,6-Difluorobenzoyl)-1,2-dihydro-4-methylquinaldonitrile

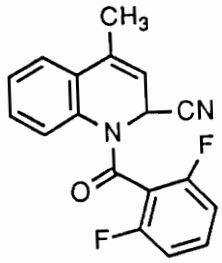


Figure 5

Resolved 400 mHz 19 F NMR Spectrum of 1-(2,6-Difluorobenzoyl)-1,2-dihydro-4-methylquinaldonitrile

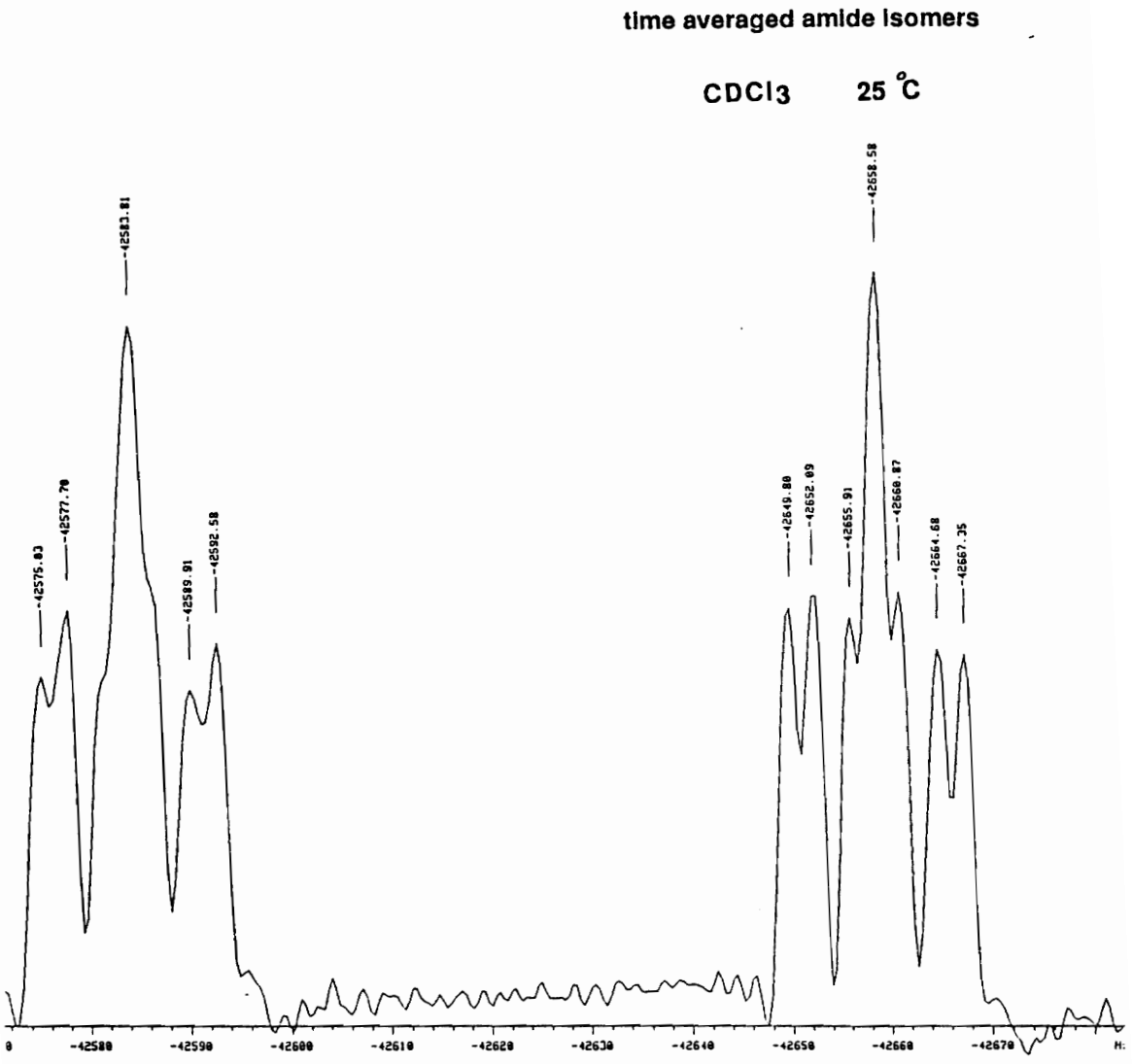
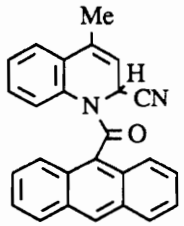
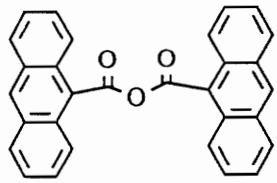


Figure 6

by the two phase method (CH_2Cl_2 / water) from lepidine and 9-anthroyl chloride with KCN as the cyanide source. Upon isolation and purification by recrystalization from toluene, an unusual product was obtained (60 % yield). Characterization of the product by FTIR showed a small carbonyl at 1730 cm^{-1} and a large carbonyl at 1790 cm^{-1}. Typically the amide carbonyl occurs at 1630 - 1680 cm^{-1}. Proton NMR also showed the absence of the 4-methyl group of lepidine. Mass spectrometry resulted in a molecular ion peak of 426 rather than 374 (the molecular mass calculated for the Reissert compound) as well as fragments of 205 and 177 m / e. Fragmentation at 205 m / e was loss of the anthroyl moiety and fragmentation at 177 m / e was due to loss of anthracene. These results led me to believe that the product was anthroic anhydride (mw 426) (**97**). Due to a hydrolysis problem, the acid chloride preferentially attacked the acid and the result was that an anhydride **97** was formed. This result is due to a retro Reissert reaction as described by Popp *et al.*[11] Further study of the compound was not undertaken.



96

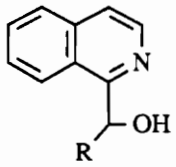


97

D. Development of Methodology for Determination of the Enantiomeric Excess of a 1,2-Aminoalcohol

1. Synthesis of Racemic 1-Isoquinolyl Phenyl Carbinol and 1-Isoqunolyl t-Butyl Carbinol

The next study undertaken was the racemic synthesis of two isoquinoline based 1,2-aminoalcohols. The compounds targeted in the study were 1-isoquinolyl phenyl carbinol (**98**) and 1-isoquinoyl t-butyl carbinol (**99**).



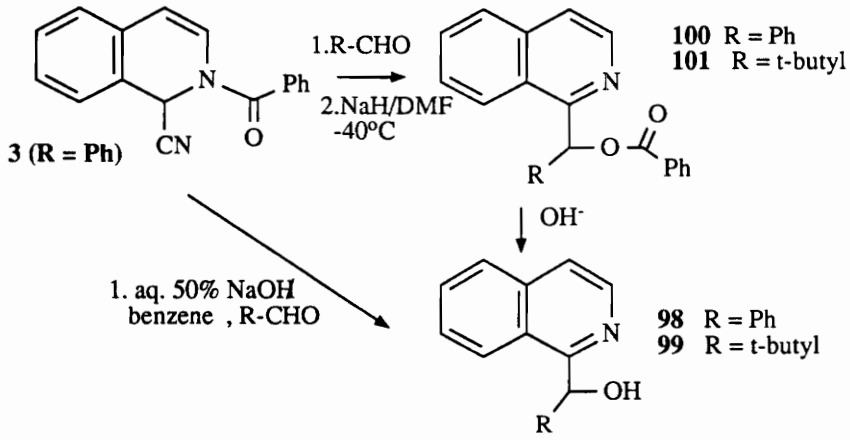
98 R = Phenyl
99 R = t-butyl

Two different conditions were employed for the synthesis of the racemic 1,2-aminoalcohol **98**. The first conditions employed were achiral phase transfer conditions, which involved using 50 % NaOH as the aqueous phase and benzene as the organic phase. Benzyltrimethylammonium chloride was used as the phase transfer catalyst. The condensation of isoquinoline Reissert compound **100** with benzaldehyde was also tried in the presence of a base (like NaH) in DMF at -40 ^{O}C, followed by base hydrolysis of the benzoate ester **101** led to the formation of 1,2-aminoalcohol **98**.

The condensation of the isoquinoline Reissert compound **100** with benzaldehyde by the phase transfer method resulted in the conversion of a substantial amount of the aldehyde to the Cannizzaro product. The Cannizzaro reaction occurs when aromatic aldehydes and aldehydes with no α-proton are treated with a strong base. "*The reaction is an oxidation - reduction process with one molecule of the aldehyde oxidizing another to the acid and is itself reduced to the primary alcohol.*"[99] If the aliphatic aldehyde contains alpha hydrogens, then the aldol condensation is much faster than the Cannizzaro process. It was found in our laboratory that the aldol condensation occured for the reaction of the Reissert compound **3** with acetaldehyde under phase transfer conditions. Condensation of the Reissert compound **3** with pivaldehyde under phase transfer conditions as mentioned above to form the 1,2-aminoalcohol **99** gave a high yield (> 80 %) of product and no Cannizzaro product. Condensation of the Reissert compound **3** with pivaldehyde under NaH / DMF conditions gave the benzoate ester **101** in high yield (> 96 %). Hydrolysis of the benzoate gave the 1,2-aminoalcohol **99** (Scheme 17). Chemical purification of the benzoates **100**, **101** (recrystalization from hexane) and the 1,2-aminoalcohols **98**, **99** (recrystalization from hexane / EtOAc) was easily achieved.

It is necessary to describe the behavior of the methine and hydroxyl protons in the ^1H NMR since their behavior plays a crucial role in the determination of the enantiomeric purity of the compounds. In the compound **98** two singlets for the methine and hydroxyl protons occur at 6.40 and 6.38 ppm respectively. In the case of the 1-isoquinolyl t-butyl carbinol **99** one doublet each (J = 6.75) for the methine and hydroxyl signals were identifiable by exchanging the compound with D_2O, resulting in two singlets. For the compound **99** the methine doublet occurs at 5.20 ppm and the hydroxyl proton appears as a doublet at 4.50 ppm. Assignment of the hydroxyl proton was made based on the fact that the singlet at 4.50 ppm became broad after D_2O exchange while the singlet at 5.20 ppm stayed sharp. The H_8 proton of **99** occurs as a doublet at 8.13 ppm.

Scheme 17



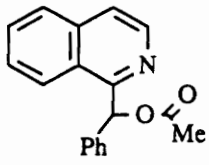
2. Methods of Optical Purity Analysis for 1,2-Aminoalcohols 98 and 99.

Several techniques were attempted to study the optical purity of compounds **98, 99**. These techniques are discussed in the following section.

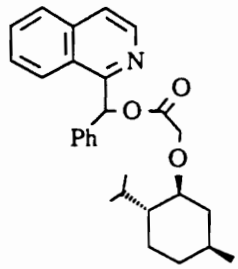
a. Attempts at Formation of a Diastereomeric Ester

The first technique tried was the esterification of the 1,2-aminoalcohol **98** by reaction with an optically active acid chloride to form diastereomeric esters. Analogously, optically active chloroformates were also utilized to form diastereomeric carbonates. Physical separation of the diastereomers could then be undertaken.

The first step in this direction was to do a set of model reactions of **98** with acetyl chloride to form the acetate **102** to find the best conditions for the esterification. Four conditions were tried in the model study and the results are tabulated in Table 4. The best conditions from the model study were found to be the reaction of the 1,2-aminoalcohol with acetyl chloride in toluene with pyridine as the base to give an ester in 96 % yield.



102



103

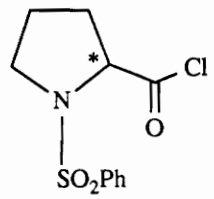
l-(-)-Menthyl chloroformate and cholesteryl chlorofomate were tried first as chiral reagents. These reactions did not to go to high conversion under any of the conditions used in the model study. The chloroformates were found not to be reactive enough toward the tertiary alcohol. The reaction of isoquinolyl phenyl carbinol (**98**) was tried with l-menthoxyacetyl chloride using pyridine as the counter base to form the diastereomeric ester **103**. It was found that the yield was 75% instead of the expected 95 %. The acid chloride **104** was also tried, but not with much success. Complications with quantitation of the reactions as well as complicated NMR spectra made this approach unusable.

Table 4

Model Reaction of the Carbinol **98** to Form the Acetate **102**

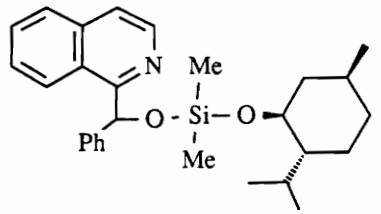
Conditions	Time (hrs)	Solvent (reflux)	Yield (%)
acetic acid / p-TSA	8	benzene	32
acetyl chloride / pyridine	12	toluene	96
acetic acid / H_2SO_4	3	toluene	93
acetyl chloride / TEA	12	toluene	92

104



b. Attempted Formation of a Diastereomeric Silyl Acetal

Next the synthesis of a diastereomeric silyl acetal **105** was tried.[100] Dimethyldichlorosilane was added to toluene under nitrogen. One equivalent of (-)-menthol was then added and the reaction allowed to stir at room temperature for several hours until the silyl ether had been formed. Then 1 equivalent of the racemic **98** was added and the reaction mixture was allowed to stir at 65 °C for two hours. However, this technique also proved problematic. The first problem arises from the difficulty in forming the silyl acetals quantitatively. The other problem involved isolation of the pure product. The Si-CH_3 peaks from side products resulted in difficult NMR analysis.



105

c. Use of Chiral Shift Reagents and Chiral Solvents

Several chiral lanthanide shift reagents and chiral amines were tried next. The chiral lanthanide shift reagents tried were tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) {$Eu(hfc)_3$} and tris[3-(hexafluoropropylhydroxymethylene)-(+)-camphorato]- praseodynium (III) {$Pr(hfc)_3$}. The chiral amines tried were (R)-(+)-1-(1-napthyl)ethyl amine and (S)-(-)-α-methylbenzylamine. Chiral lanthanide shift reagents were used in a 1 : 5 mole ratio of the 1,2-aminoalcohol to shift reagent and chiral amines were used in a 1 : 3 mole ratio of the

1,2-aminoalcohol to chiral amine. These techniques proved unsuccessful due to problems with line broadening in the proton NMR which made the results uninterpretable. The severe line broadening occurs because of the nature of the intermolecular hydrogen bonding in the 1,2-aminoalcohols (like **98**) which takes place in formation of the diastereomeric association complexes. Therefore, these techniques were also deemed unusable.

d. Use of Quinine as a Chiral Solvating Agent

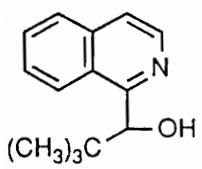
Quinine (**85**) was then investigated as a chiral solvating agent (CSA) based on a paper by Rosini *et al.*[98] This technique was applied to the compounds **98** and **99**. The individual 270 mHz proton NMR spectra of quinine, compound **98**, and compound **99** were taken first to insure that the spectrum of the quinine would not interfere with the interpretation of the results. A sample of the isoquinolyl phenyl carbinol (**98**) (1 mole equivalent) was mixed with quinine (3 mole eqivalents) and the 270 mHz NMR spectrum was taken. Upon complexation the signal for the methine proton was shifted into a complex splitting pattern in the aromatic region making interpretation extremely difficult in the case of the compound **98**.

In the case of the compound t-butyl isoquinolyl carbinol (**99**) this technique proved to be quite satisfactory. A one to three molar ratio of the alcohol **99** to quinine was utilized. Analysis of the proton NMR spectrum of the resulting diastereomeric complex showed doubling of the methine proton and the H_8 proton (Figure 7). The hydroxyl proton also doubled, but broadening made it unusable for analysis. The pair of doublets formed for the methine proton were not quantitatively integratable. This problem was solved by collapsing the pair of doublets to a pair of singlets at 5.19 and 5.21 ppm by exchanging with D_2O (Figure 7). This technique was then investigated for reliability by taking five different samples of the racemic 1,2-aminoalcohol **98** complexed with quinine and performing five integrations of the two singlets for each sample. The reliability of the method was found to be within two percent (Table 5).

The doublet for the proton H_8 at 8.13 ppm also became an overlapping pair of doublets and

Figure 7

270 mHz 1H NMR Spectrum of Racemic 1-Isoquinolyl t-Butyl Carbinol with quinine as CSA



1: 3 mole ratio of carbinol to quinine, $CDCl_3$, 25 °C

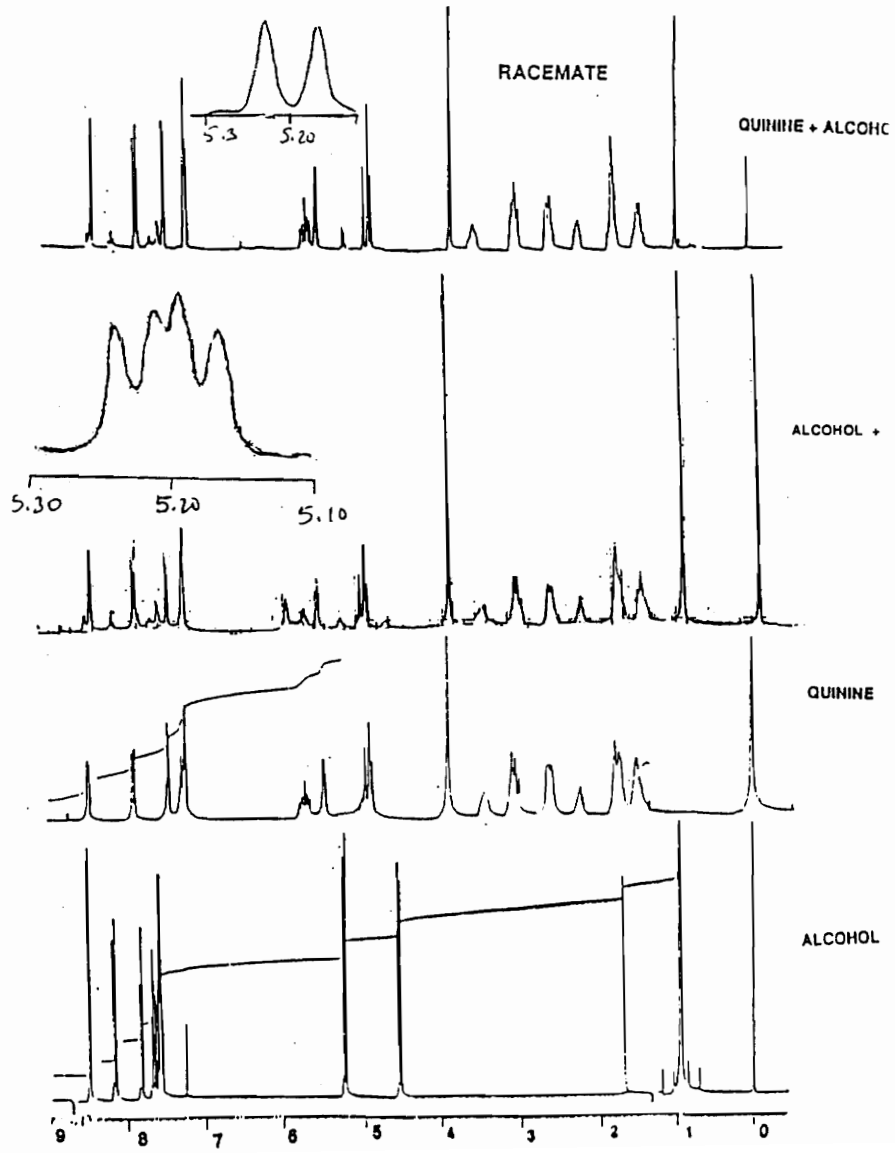


Table 5

Standardization of the Quinine Method

Sample Number	Area % of Peak A[a] (5.21 ppm)	Area % of Peak B[a] (5.19 ppm)
1	49	51
2	45	55
3	52	48
4	44	56
5	52	48

Overall Average Area % of Peak A: 48 +/- 3 %

Overall Average Area % of Peak B: 52 +/- 3 %

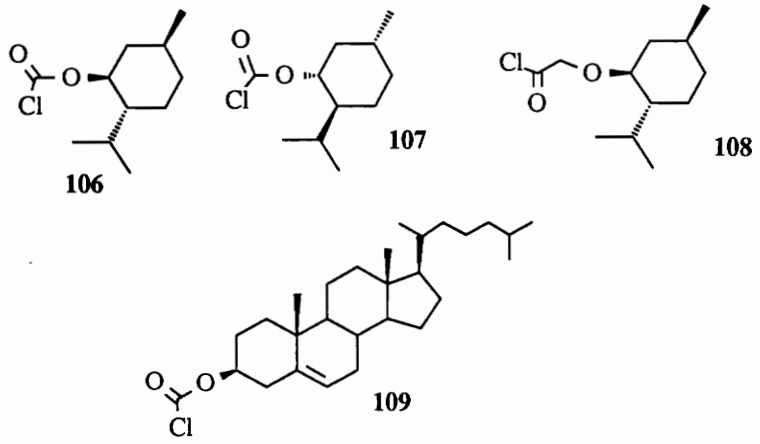
a. Average of the four full page integrations for each sample

integration of the outer peaks was used as a verification of the enantiomeric ratio (Figure 7).

This technique does require special attention to sample preparation. The samples were prepared by dissolving the alcohol and quinine in the proper molar ratios into a minimal amount of $CDCl_3$ followed by the addition of an excess of D_2O. The exchanged D_2O was then removed by Pasteur pipet. The sample was then subjected to another D_2O exchange and again the exchanged D_2O was removed. The sample was finally dried over molecular sieves and filtered into an NMR tube. $CDCl_3$ was then added such that the minimum amount of solvent necessary for the NMR determination was used. Since quinine is a CSA it works by forming a diastereomeric association complex with the 1,2-aminoalcohol. The complexation probably involves hydrogen bonding (H-OH and N-OH) and π-π complexation. Three separate interactions are necessary in order for the complex to be diastereomeric.[97]

E. Synthesis of Optically Pure 1-Isoquinolyl t-Butyl Carbinols (121 and 123)

1. Diastereomeric Reissert Compounds

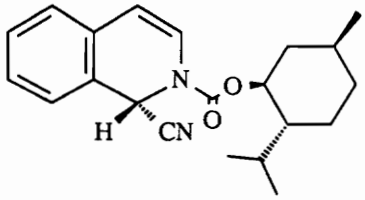


The chiral acyl auxiliaries selected for the study were l-(-)-menthyl chloroformate (**106**),

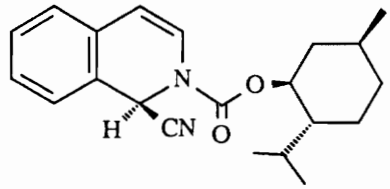
d-(+)-menthyl chloroformate (**107**), l-(-)-menthoxyacetyl chloride (**108**), and cholesteryl chloroformate (**109**).

Pierre Lecavalier of our lab investigated the use of cholesteryl chloroformate (**109**) as the acyl auxiliary. Since cholesterol is such a large group it was thought that there was a better chance for diastereoselective formation of the Reissert compound in this case. The Reissert compound in this case was formed in a 1:1 ratio. The Reissert compound was not formed diastereoselectively in this case, but physical separation of the diastereomers of the Reissert compound was accomplished.

a. Synthesis of the Diastereomeric Reissert Compound 110



110a



110b

We used l-menthyl chloroformate as the chiral auxiliary to form the diastereomeric Reissert compounds **110a** and **110b**. The synthesis of compound **110** (96 % yield) was quite straightforward. The product was then purified by recrystalization from hexane. It was originally believed that the Reissert compound was one diasteromer because the melting point (mp 96 - 97 °C) was constant and occurred over a narrow temperature range and the optical rotation was found to be constant over repeated recrystalizations from hexane ($[\alpha]$= -63.4, c= 1.53, CH_2Cl_2). HPLC results on a Pirkle covalent phenylglycine column as well as a Chiralcel OD column afforded one peak.

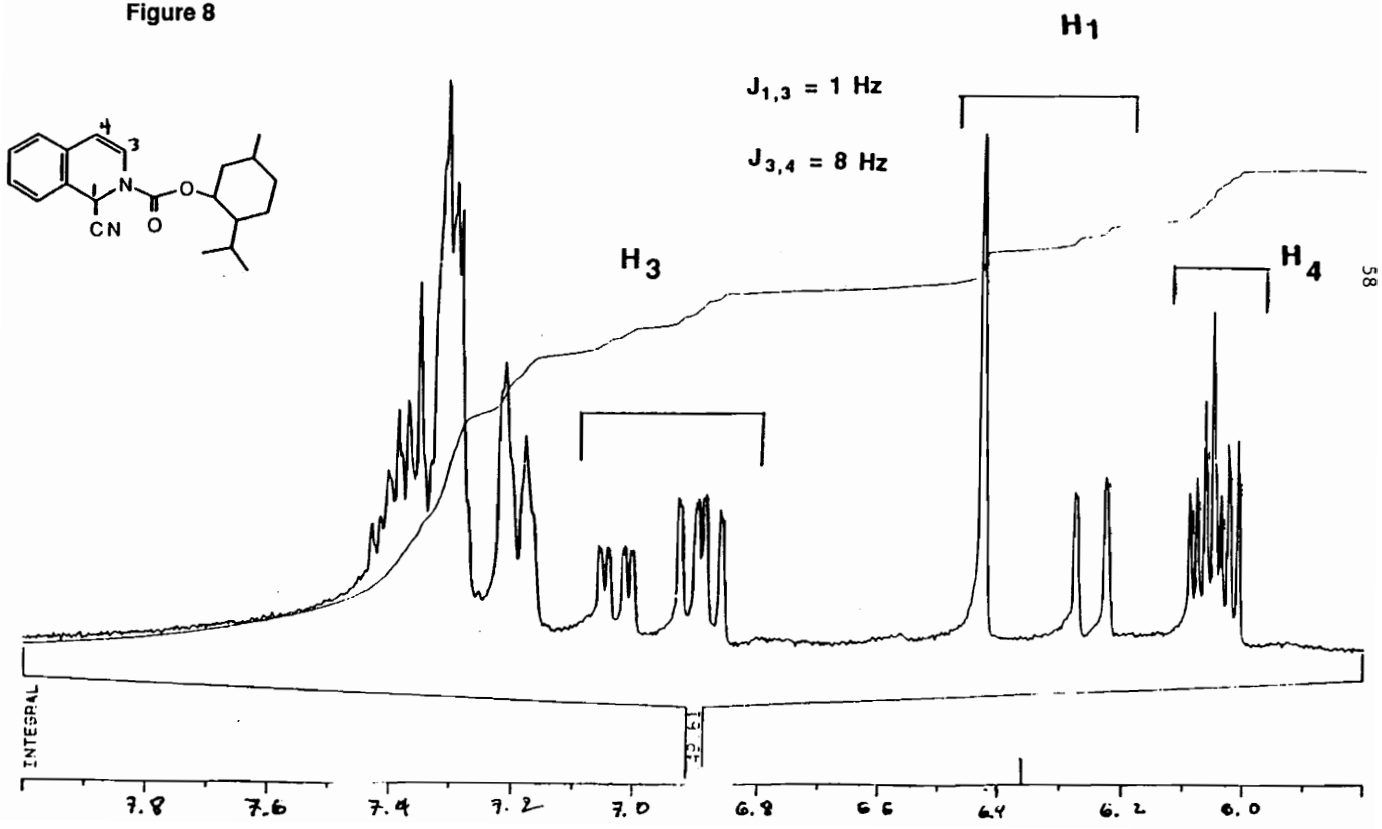
However, by a low temperature (253 °K) 200 mHz proton NMR study (Figure 8) it was determined that both diastereomers and both amide isomers of the Reissert compound **110** were present. The four possible isomers of 2-[(l)-menthoxycarbonyl]-1,2-dihydroisoquinaldonitrile (**110**)

2- l-MENTHOXYCARBONYL-1,2-DIHYDROISOQUINALDONITRILE

Partial 200 MHz Specirum at 253 K (-20 C)

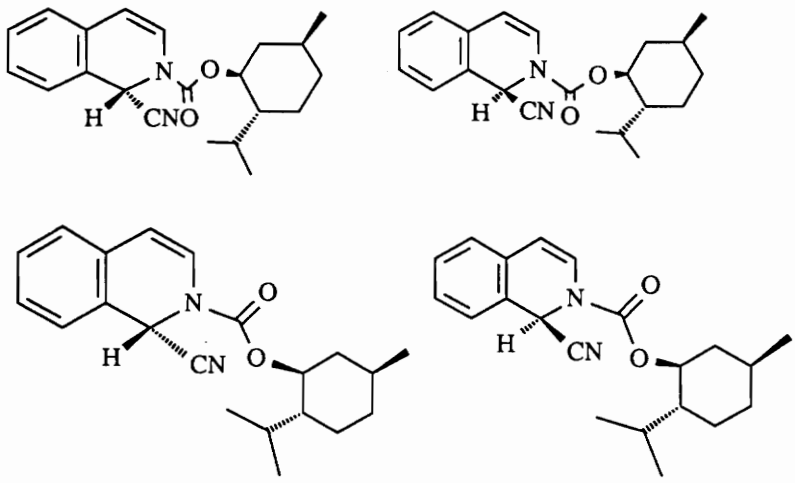
$CDCl_3$

Figure 8



are shown below:

Stereoisomers of Reissert Compound **110**



The analysis of the proton NMR spectrum (Figure 8) of **110** is interpreted in the following manner. There are three signals for the H_1 proton at 6.43 (presumably two peaks superimposed), 6.28, and 6.22 ppm. The proton H_3 appears as a doublet of doublets at 6.90 ppm and a doublet of doublets at 7.05 ppm ($J_{3,4}$ = 6 Hz). The signal for the proton H_4 consists of four doublets at 6.05 - 6.10 ppm. In the case of one diastereomer and one amide isomer there would only be one signal for the H_1 proton, and one doublet each for the H_3 and H_4 protons. In the case of two diastereomers and one amide isomer or two amide isomers and one diastereomer there would be two doublets (four peaks) for the protons H_3 and H_4. For the case of two amide isomers and two diastereomers there would be four doublets for the protons H_3 and H_4 (eight peaks); seven distinct peaks are observed wherein two peaks are overlapping. From analysis of the integrations for the protons H_3 and H_4 with respect to H_1 the ratio of the two diastereomers was determined to be 6:4 and the ratio of the amide isomers was found to be approximately 1:1.

b. Attempts at Separation of the Diastereomers of 110

Several chromatographic techniques were applied. TLC studies were done to determine the best separation using alumina, silica gel or cellulose as the stationary phase and various solvents as the mobile phase. The best separation appeared to be CCl_4 on silica gel. However, column chromatogrphy as well as prep TLC techniuqes afforded very little separation. Separation of the diastereomers was also attempted by chiral HPLC columns. Neither the Pirkle covalent phenylglycine column nor the Chiralcel OD column separated the two diastereomers, in different solvent systems. Typical conditions on the Pirkle column for the HPLC study of **110** were 99% hexane / 1% isopropanol with a flow rate of 1 ml / min. On the Chiralcel OD 95 % hexane and 5 % isopropanol was tried at a flow rate of 0.25 ml / min. The Chiralcel OD column is a cellulose carbamate coated on silica gel. It separated the diastereomers of 2-menthoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile **114** as well as the isomers of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**3**).[101]

It was decided at this point to look at kinetic resolution as a way to separate the diastereomers of **110**. The idea was to look at the diastereomeric excess as a function of time or as a function of degree of conversion.[102] It was hoped that one of the diastereomers of **110** was more reactive than the other such that one of the diastereomers would react and leave the other diastereomer unreacted. The reaction of 2-[(l)-menthoxycarbonyl]-1,2-dihydroisoquinaldonitrile (**110**) with pivaldehyde was thus taken to 45 %, 50 % and 60 % conversion. It was found that the diastereomeric ratio of the unreacted starting material did not change upon partial conversion (Table 6). This result indicated that the combination of acidity of the diastereomeric Reissert compounds **111a** and **111b** and reactivity of the resultant anions was not sufficiently different to separate them by kinetic resolution.

Next, we investigated the possibility of equilibration of the Reissert anions. We chose to use the reaction of the Reissert anion with CS_2 to accomplish this. A solution of the Reissert compound **110** in DMF was cooled to 0 °C and NaH (0.5 eq) was added. The solution immediately turned a

dark red color indicating the formation of the Reissert anion **111**. This was followed by the addition of CS_2 (10 eq) and the solution was allowed to stir for 1 hour. The solution became orange upon addition of the CS_2. The anion **112** was thus formed. The reaction was quenched after one hour with D_2O to give 45 % of the compound **113** (diastereomeric ratio 6:4) and 55 % unreacted **110** (diastereomeric ratio 6:4). The NaH was used as a limiting reagent in the first trial and in the second trial the 45 : 55 mixture of the compounds **113** and **110** was reacted with CS_2 (10 eq), limiting amount of base (0.4 eq) and quenched with D_2O (85 % conversion) to give 85 % of the compound **113** (diastereomeric ratio 6:4) and 15 % **110** (diasteromeric ratio 6:4). To assure control a sample of the anion **111** was reacted with CS_2 under the same conditions and quenched with H_2O (diastereomeric ratio 6:4). The results show that for different degrees of conversion to the compound **113** as well as for the water quenched control that the diastereomeric ratio (**110a** : **110b**) did not change. Analysis of the NMR spectra of the deuterium oxide quenched samples also confirmed the earlier assignment of the H_1 proton. The diastereomeric ratios for the samples of the compound **113** were determined by analyses of the proton H_3. This result indicated to us that the anion equilibrates.

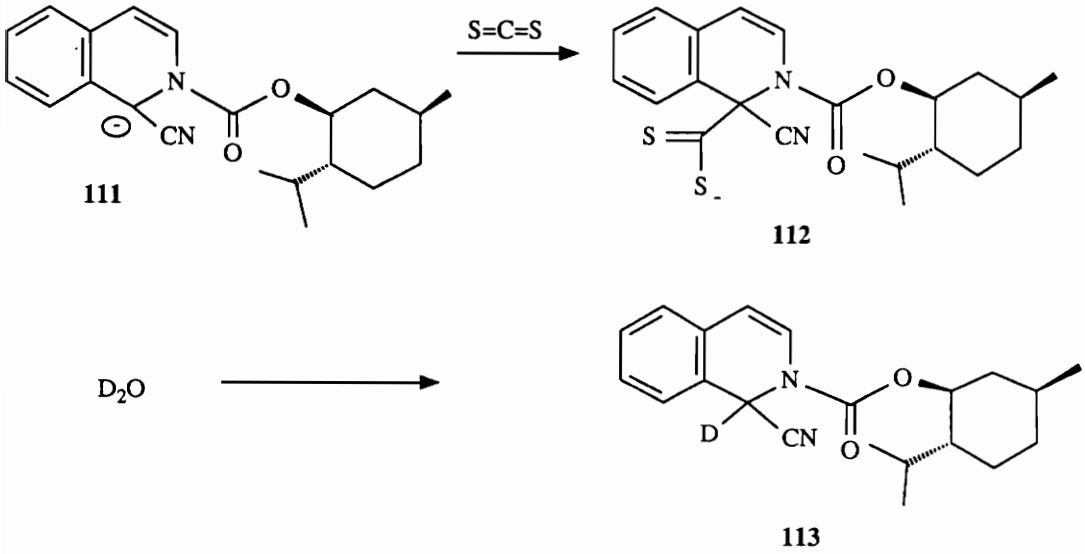
Table 6

Reaction of **110** With Pivaldehyde to Partial Conversion

Aldehyde (eq.)	Base (eq.)	% Conversion	DR[a] of **110**	de[b] of **120**
1.0 eq.	NaH (0.5 eq.)	50 %	60:40	50 %
0.5 eq.	NaH (1.0 eq.)	45 %	60:40	50 %
0.6 eq.	NaH (1.5 eq.)	60 %	65:35	40 %

a. diastereomeric ratio

b. diastereomeric excess



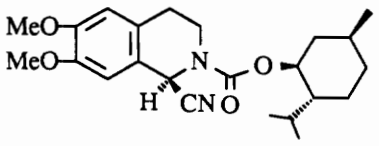
My research efforts were then directed toward using the thermodynamic equilibrium in solution to separate the two diastereomers. Jacques[103] has used thermodynamics to selectively crystalize out one enantiomer. The theoretical basis for separation of the enantiomers was based on the assumption that the enantiomeric mixture was a conglomerate and not a true racemate, the result being that one of the enantiomers was more supersaturated than the other one and that the more supersaturated enantiomer was induced to crystalize selectively by seeding with the pure enantiomer.

The first technique of interest was that of differentiated crystalization, wherein the seed of the pure enantiomer (or diastereomer) was a large crystal and would therefore induce one isomer to form much larger crystals than the other isomer. The large crystals were then separated from the small ones by sifting the sample through a sieve of the appropriate mesh size. The second technique was resolution by entrainment, which involved seeding a solution of the racemate with a known weight of the pure enantiomer of the compound. The solution was then allowed to crystalize for a specific time period and crystals were allowed to form during that period of time. The weight of the

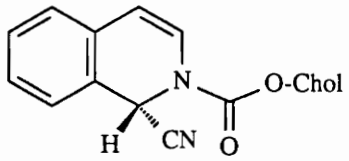
enantiomerically pure isolated compound was then noted and a sample of the other pure enantiomer of the same weight was added to the solution. This process was repeated many times until all of the compound had been recovered in enantiomerically pure form. The method has been reported to give enantiomeric purities of 98% ee or greater.

Since a pure diastereomer of **110** was not available it was decided to try a variation of this technique. A 500 mg sample of the Reissert compound **110** was dissolved in 20 ml of hexane by heating and then allowed to slowly cool to room temperature. The supersaturated solution was then seeded with several large crystals of 2-[(S)-cholesterylcarbonyl]-1,2-dihydroisoquinaldonitrile (**115**) obtained from Pierre Lecavalier of our laboratory. It was hoped that this would result in one of the diastereomers exhibiting a different crystal habit from the other diastereomer. Prior to this point this compound was only obtained in powdered form. This experiment did result in crystals. These crystals were examined under the optical microscope. It was found that there were crystals of rectangular shape, needles and powder. The needles were isolated under the optical microscope. The rotation of the needles was $[\alpha]^{25} = -50.1$ ($CHCl_3$). Proton NMR showed the same ratio of diastereomers as had been found before the experiment (6:4) for the rectangular crystals, the needles and the powder.

A separate 500 mg sample was also heated in hexane and allowed to slowly come to room temperature. This sample was seeded with 2-[(l)-menthoxycarbonyl]-6,7-dimethoxy-1,2,3,4-dihydro-isoquinaldonitrile (**114**) obtained from Mike Berg of our laboratory. The results were similar to those obtained with the cholesteryl compound **115**. The optical rotation and the diastereomeric ratio were unchanged.



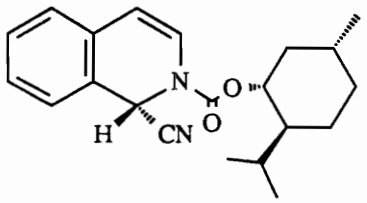
114



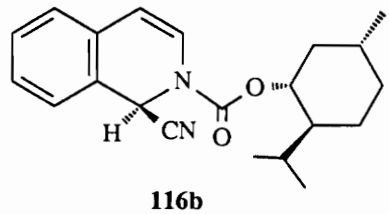
115

Upon completion of the study of 2-l-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**110**) it was decided to synthesize 2-d-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**116a, 116b**).

A sample of d-menthyl chloroformate **93** was prepared from phosgene and (+)-menthol using pyridine as the base. Thus, 2-[(d)-menthoxycarbonyl]-1,2-dihydroisoquinaldonitrile (**116**) was produced which had an optical rotation of [α]= +63.4 (c = 2, CH_2Cl_2). The result of this experiment was that the Reissert compound 116 has an optical rotation equal and opposite in sign to that of 2-[(l)-menthoxycarbonyl]-1,2-dihydroisoquinaldonitrile 110a, 110b. Therefore, this diastereomeric mixture of **116a** and **116b** is also of 60:40 composition.



116a



116b

c. Interpretation of NMR Results of 110

The MM2 calculations gave the following results (CN psudoaxial in all cases):

S-diastereomer with CN trans to isopropyl; MMXE = 26.1 kcal / mol

S-diastereomer with CN cis to isopropyl; MMXE = 25.6 kcal / mol

R-diastereomer with CN trans to isopropyl; MMXE = 26.2 kcal / mol

R-diastereomer with CN cis to isopropyl; MMXE = 27.6 kcal / mol

First we must assume that the MM2 calculations are correct; thus the S diastereomer is lower in energy (more stable) than the R diastereomer of **110.** CPK models of **110** were built to aid in the correlation of these results with the NMR spectra. The H_1 proton was interpreted first. We assumed the singlet at 6.42 (presumably an overlapping doublet) to be the S diastereomer (the major diastereomer, 60 %) and the doublet at 6.25 to be the R diastereomer (minor diastereomer, 40 %), because the hydrogens in the menthyl moiety are closer to H_1 in the case of the R diastereomer than in the case of the S diastereomer. The menthyl moiety of the S diastereomer was much freer in rotation than the R diastereomer, which may account for the fact that the doublet is not resolved in the case of the S diastereomer.

For both amide isomers H_3 of the S diastereomer was found to be deshielded by neighboring hydrogens which are closer than in the case of the R diastereomer. The protons for the S diastereomer should thus be found upfield and in a 60 % ratio, which is indeed the case.

Thus analysis of the MM2 results by CPK models and NMR spectra is consistent with the S diastereomer being the major diastereomer. The MM2 calculations were performed on Serena Software, PC model.

2. Reaction of 2-[(l)-Menthoxycarbonyl]-1,2-dihydroisoquinaldonitrile with Aldehydes

The 60:40 mixture of diastereomeric Reissert compounds **110a** and **110b** was treated with base to form the Reissert anions and subsequently reacted with different aldehydes; the product carbonates **118** were examined for diastereoselectivity (Table 7). The reactions with aldehydes were run at -40 °C to avoid the formation of the cyclic urethane and to promote the quantitative formation of the carbonate. This reaction was also tried at -78 °C in an attempt to increase diastereoselectivity; however, the reaction was found not to occur at this low temperature. Other bases [like KH and potassium hexamethyldisilazane (KHMDS)] were also tried to increase the diastereomeric ratio, but

Table 7

Reaction of 60 : 40 Mixture of Reissrt Compounds **110a** and **110b** with Aldehydes

Aldehyde	Base	Reaction Conditions	Solvent	de(LC)[yield]
pivaldehyde	NaH	5 h / -40 °C	DMF	56 % [> 95 %]
pivaldehyde	KH	4 h / -40 °C	DMF	54 % [> 95 %]
o-tolualdehyde	NaH	5 h / -40 °C	DMF	> 40 % [> 95 %]
o-anisaldehyde	NaH	5 h / -40 °C	DMF	> 30 % [> 95 %]
pivaldehyde	KHMDS[a]	4 h / -40 °C	THF	30 % [12 %]
pivaldehyde	NaH	5 h / -40 °C	toluene	[0 %]
pivaldehyde	NaH	18 h / -40°C	ether	[0 %]
veratraldehyde	NaH	3 h / -40 °C	DMF	0 % [> 95 %]

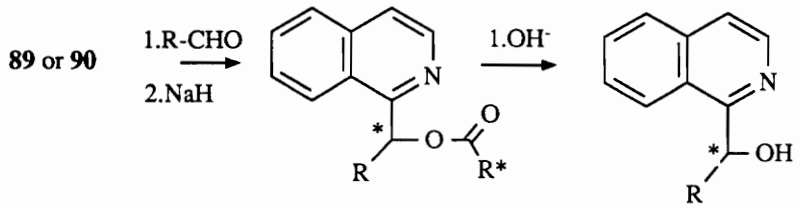
a. KHMDS = potassium hexamethyldisilazane

b. diastereomeric excess determined by HPLC on a Pirkle phenylgylcine column, 99 : 1 :: hexane : isopropanol

were unsuccessful.

The goal was to produce a pure diastereomer of **118** by stereoselective condensation with pivaldehyde and recrystalization of the diastereomeric carbonates and then use basic hydrolysis to form the enantiomerically pure 1,2-aminoalcohol **119** (Scheme 18).

Scheme 18



117 R* = alkyl
118 R* = O-alkyl

119

It was concluded that NaH / DMF at -40 °C was the optimum reaction condition. Pivaldehyde was found to give the highest diastereomeric excess (de) and hence the aldehyde of choice. Thus the most encouaging result obtained was the reaction of **110** with pivaldehyde at -40 °C to form 1-isoquinolyl t-butyl methyl menthyl carbonate (**120**). It was discovered that the major diastereomer of the t-butyl-(1-isoquinoyl) methyl menthyl carbonate (**120**) was easily purified by a single recrystalization from hexane. The diastereomeric purity was established by HPLC on the Pirkle column (Figure 10) and by examination of the methine proton in the NMR (Figure 9). The proton NMR spectrum of the crude product **120** gave two peaks for the methine proton at the newly formed carbinyl center at 6.18 and 6.24 ppm. The ratio of the two peaks was 77 % to 23 %. HPLC on the Pirkle column of the crude product **120** gave two peaks as well which were present at 390 (82 %) and 424 (18 %) sec (Table 8). Upon recrystalization of the crude from hexane the proton NMR exhibited only one peak for the methine proton (6.18 ppm), and the proton NMR spectrum was otherwise unchanged. The HPLC of the pure diastereomer (Figure 10) exhibited only the peak at

Table 8

Determination of the Diastereomeric Excess of **120** by NMR

Sample Number	Area of Peak A[a] (6.24 ppm)	Area of Peak B[a] (6.18 ppm)
1	23.26	76.74
2	22.22	77.78
3	23.14	76.86
Averages :	22.87 +/- 0.5	77.13 +/- 0.5

Average Diastereomeric Excess: 54.26% +/- 0.5

a. full page integrations of two peaks, 2 integrations per sample

Determination of the Diastereomeric Excess of **120** by HPLC[b]

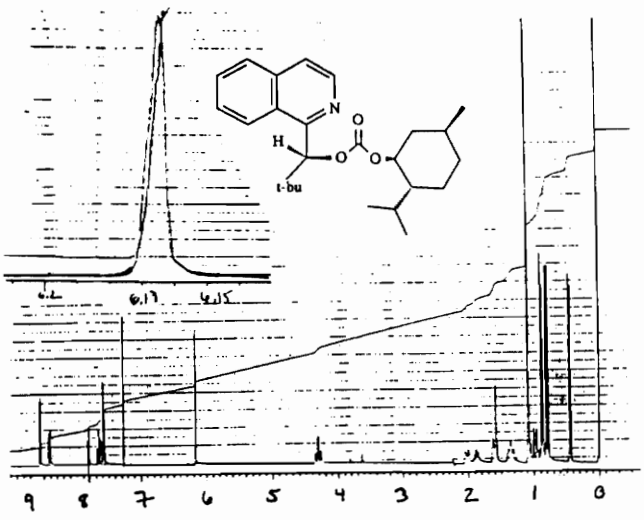
Area of Peak A: 82 %

Area of Peak B: 18 %

Diastereomeric Excess: 64 %

b. HPLC was performed on a Pirkle covalent phenylglycine column with solvent system 99 : 1 :: hexane isopropanol and a flow rate of 1 ml / min. (See Figure 10 for trace)

270 mHz 1H NMR Spectrum of S-(-)-1-Isoquinolyl-t-butyl methyl menthyl carbonate



Pure diastereomer

77 : 23 Diastereomeric mixture

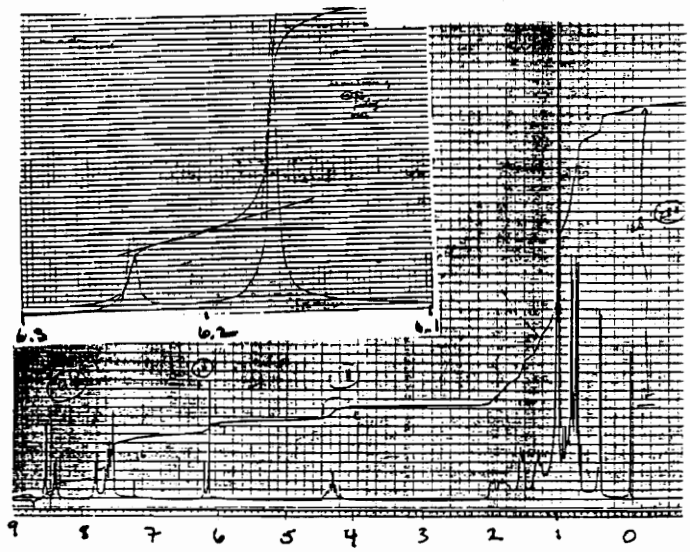


Figure 9

HPLC Results

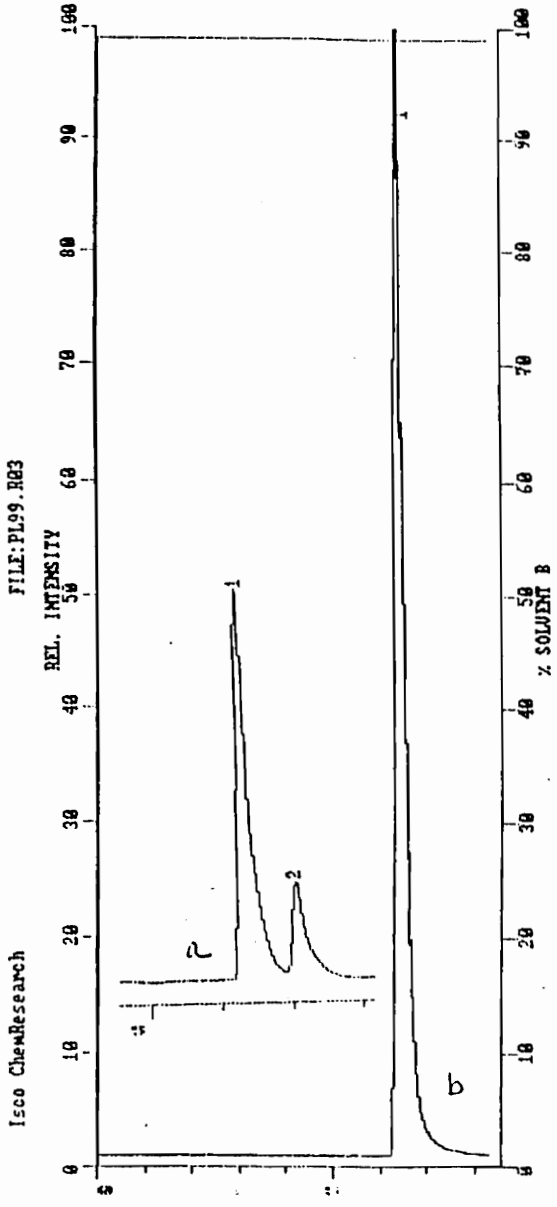
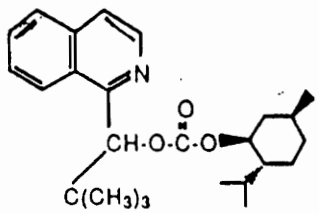


Figure 10

Pirkle phenylglycine column
99% hexane/ 1% isopropanol

flow rate = 1 ml/min



a. 82%-18% RATIO OF DIASTEREOMERS

b. pure diastereomer
(1 recrystalization from hexan

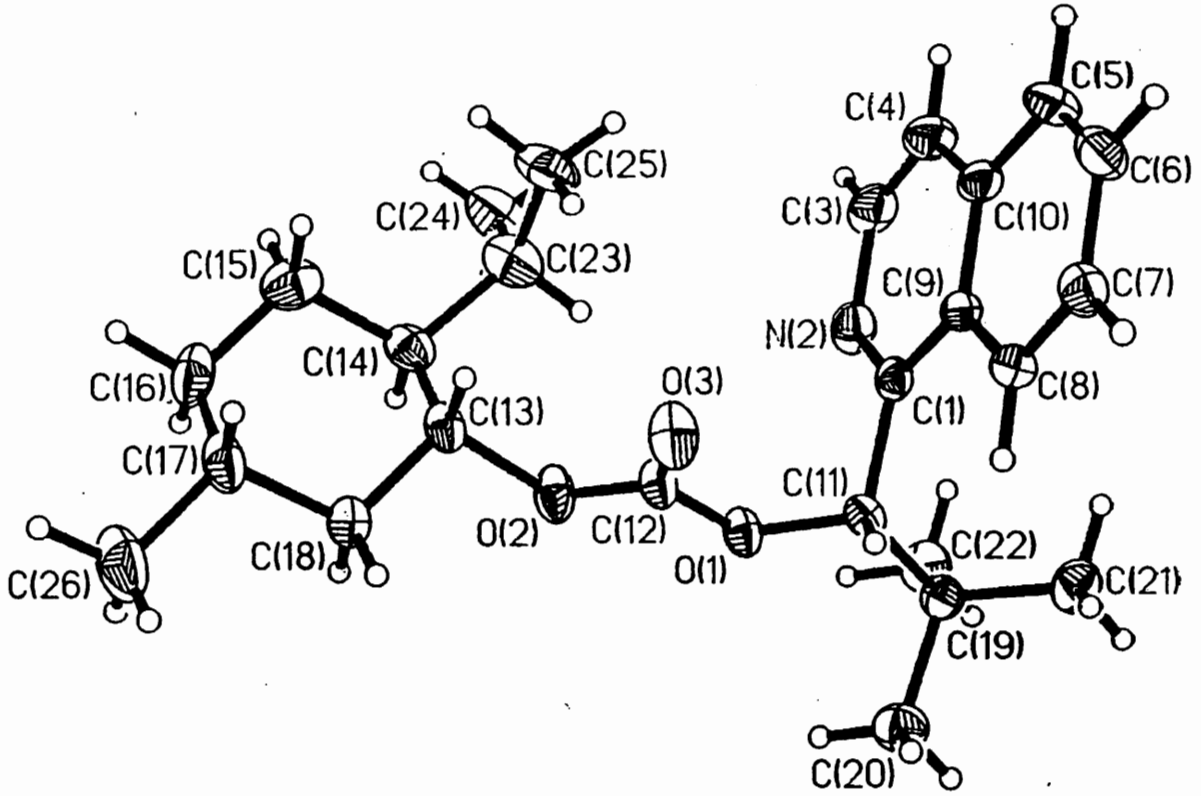
390 sec.

The x-ray structure of the pure major diastereomer of **120** was also obtained (Figure 11). The structural data is tabulated in Tables 9, 10 and 11. The S configuration of the carbonate was observed at the newly formed stereocenter by reference to the known configurations of the l-menthyl stereocenters.

3. Synthesis of the Optically Pure 1,2-Aminoalcohol

A sample of the pure diastereomer of the compound **120** was then subjected to a number of hydrolysis conditions. It was found that a large excess of base and a short reaction period allowed hydrolysis with no loss of stereochemistry to produce the optically pure S-(-)-1-isoquinolyl t-butyl carbinol (**121**). Long reaction times produced racemic product. The optical purity of the 1,2-aminoalcohol was determined by using quinine as a CSA (Figure 12). The optical rotation of optically pure compound **121** was found to be $[\alpha] = -70.1^{\circ}$ (c = 1.17, CH_2Cl_2).

t-BUTYL-(1-ISOQUINOLYL)METHYL (-)-MENTHYL CARBONATE
PURE DIASTEREOMER (JC-1-84)



MP 122.5 - 123.4, [α] = -35.4 (c = 2.04, CH2Cl2)

Table 9

X-Ray Structure Crystal Data

Emperical Formula	$C_{25}H_{35}NO_3$
Color; Crystal Habit	White rectangular prism
Crystal size (mm)	0.4 x 0.4 x 0.8
Crystal System	Orthorombic
Space Group	$P2_12_12_1$
Unit Cell Dimensions	$\underline{a}$ = 9.567 A
	$\underline{b}$ = 10.794 A
	$\underline{c}$ = 23.003 A
Volume	2375.3 A^3
Z	4
Formula Weight	397.5 g / mol
Density (calc.)	1.112 Mg / m^3
Absorption Coefficient	0.067 mm^{-1}
F(OOO)	864

Table 10

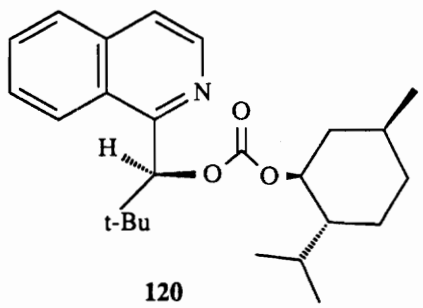
Bond Lengths

C(15)-O(1)	1.320	(5)	C(15)-O(2)	1.32	
C(15)-O(3)	1.200	(5)	C(2)-C(3)	1.41	
C(2)-C(7)	1.412	(6)	C(10)-O(2)	1.45	
C(10)-C(11)	1.526	(5)	C(3)-C(4)	1.35	
C(16)-O(1)	1.491	(5)	C(16)-C(17)	1.49	
C(16)-C(21)	1.495	(6)	C(11)-C(12)	1.54	
C(11)-C(13)	1.517	(7)	C(11)-C(14)	1.52	
C(17)-C(22)	1.588	(7)	C(17)-C(18)	1.53	
C(4)-C(5)	1.396	(7)	C(7)-C(8)	1.40	
C(1)-N(1)	1.316	(5)	C(1)-C(2)	1.43	
C(1)-C(10)	1.540	(5)	C(8)-C(9)	1.33	
C(5)-C(6)	1.331	(8)	C(19)-C(20)	1.51	
C(20)-C(21)	1.528	(7)	C(20)-C(25)	1.52	
C(22)-C(23)	1.495	(8)	C(22)-C(24)	1.42	
C(6)-C(7)	1.425	(7)	C(9)-N(1)	1.37	
C(18)-C(19)	1.521	(8)			

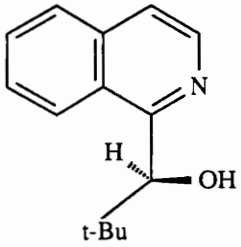
Table 11

Bond Angles

C(15)-O(1)-C(16)	117.8(3)	C(15)-O(2)-C(10)
C(1)-N(1)-C(9)	116.8(4)	O(1)-C(15)-O(2)
O(1)-C(15)-O(3)	126.5(4)	O(2)-C(15)-O(3)
C(3)-C(2)-C(7)	117.6(4)	C(3)-C(2)-C(1)
C(7)-C(2)-C(1)	118.1(4)	O(2)-C(10)-C(11)
O(2)-C(10)-C(1)	108.4(3)	C(11)-C(10)-C(1)
C(2)-C(3)-C(4)	121.0(4)	O(1)-C(16)-C(17)
O(1)-C(16)-C(21)	106.8(3)	C(17)-C(16)-C(21)
C(10)-C(11)-C(12)	107.8(3)	C(10)-C(11)-C(13)
C(12)-C(11)-C(13)	109.6(4)	C(10)-C(11)-C(14)
C(12)-C(11)-C(14)	108.7(4)	C(13)-C(11)-C(14)
C(16)-C(17)-C(22)	111.1(4)	C(16)-C(17)-C(18)
C(22)-C(17)-C(18)	114.7(4)	C(3)-C(4)-C(5)
C(2)-C(7)-C(8)	117.1(4)	C(2)-C(7)-C(6)
C(8)-C(7)-C(6)	123.3(4)	N(1)-C(1)-C(2)
N(1)-C(1)-C(10)	114.9(4)	C(2)-C(1)-C(10)
C(16)-C(21)-C(20)	111.8(4)	C(7)-C(8)-C(9)
C(4)-C(5)-C(6)	120.6(5)	C(20)-C(19)-C(18)
C(21)-C(20)-C(19)	108.9(4)	C(21)-C(20)-C(25)
C(19)-C(20)-C(25)	113.4(5)	C(17)-C(22)-C(23)
C(17)-C(22)-C(24)	113.7(5)	C(23)-C(22)-C(24)
C(7)-C(6)-C(5)	120.4(5)	N(1)-C(9)-C(8)
C(17)-C(18)-C(19)	111.7(4)	



120



121

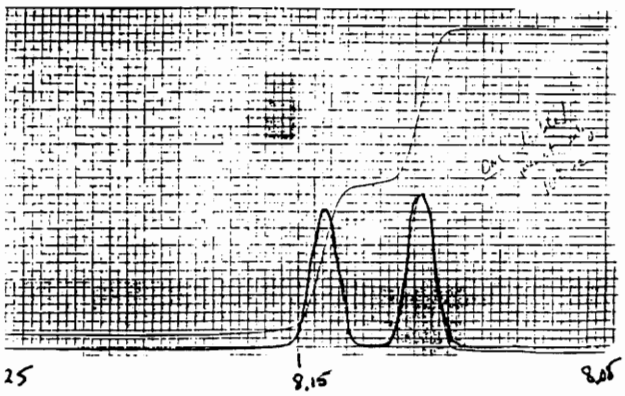
Analogously a sample of the Reissert compound **116** (with the d-menthyl auxilliary) was reacted with pivaldehyde under the NaH / DMF conditions to form R-(+)-1-isoquinolyl-t-butyl methyl menthyl carbonate (**122**) which was then hydrolyzed to form R-(+)-1-isoquinolyl t-butyl carbinol (**123**) [α]= +68.9° of 98 % optical purity as determined by use of quinine as a CSA.

The ee of the compounds **121** and **123** was evaluated by the use of quinine as a CSA for proton NMR on a 270 mHz instrument. The results of the quinine analysis gave a singlet for the methine proton at 5.22 ppm and one doublet (J = 6 Hz) for the proton H_8 at 8.12 ppm, representative of the pure S enantiomer **121**. The quinine study gave an optical purity of 100 % in the case of the S enantiomer. The R enantiomer **123** was also investigated by the use of quinine as a CSA in the same manner (Figure 13). The analysis of the quinine spectrum of the R enantiomer gave the singlet for the methine proton at 5.34 ppm and the major doublet (J = 6 Hz) for H_8 was present at 8.16 ppm. The optical purity was found to be 98 % in the case of the R enantiomer.

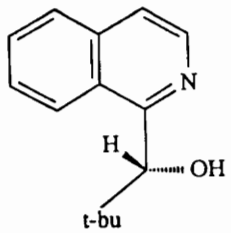
Since the absolute configuration of the compound **120** had been previously determined by x-ray analysis, examination of the proton NMR spectra allowed us to correlate the results of the quinine study (i. e., evaluation of chemical shifts for H_8 and the methine proton) with the absolute configuration of the optical isomers of 1-isoquinolyl t-butyl carbinol (**99**).

270 mHz 1H NMR Spectrum of S-(-)-Isoquinolyl t-Butyl Carbinol

$CDCl_3$, 25 °C



Pure enantiomer



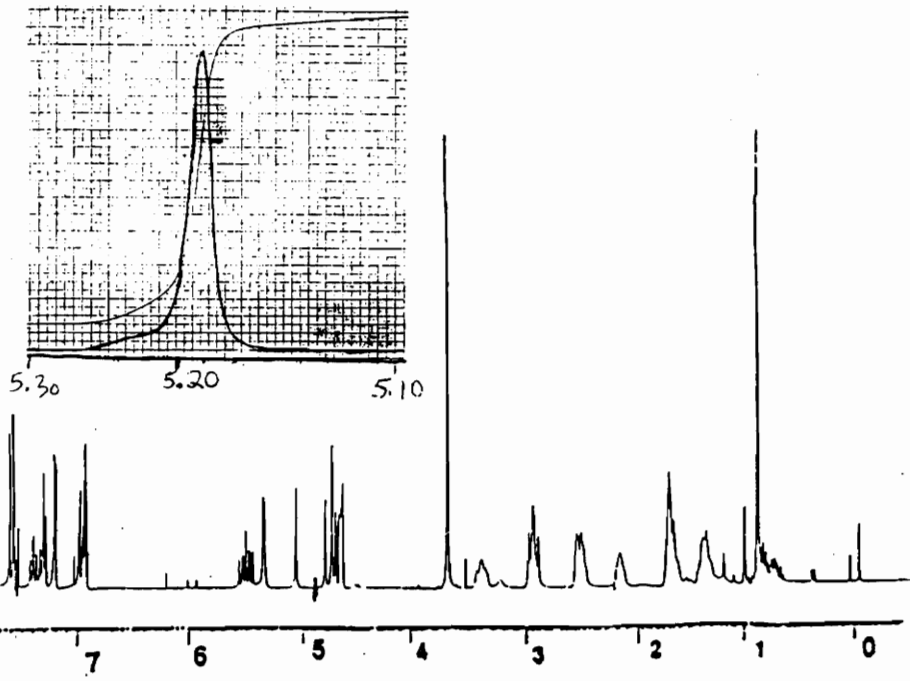


Figure 12

270 mHz 1H NMR Spectrum of R-(+)-1-Isoquinolyl t-Butyl Carbinol with Quinine as CSA after D_2O Treatment ($CDCl_3$, 25 °C)

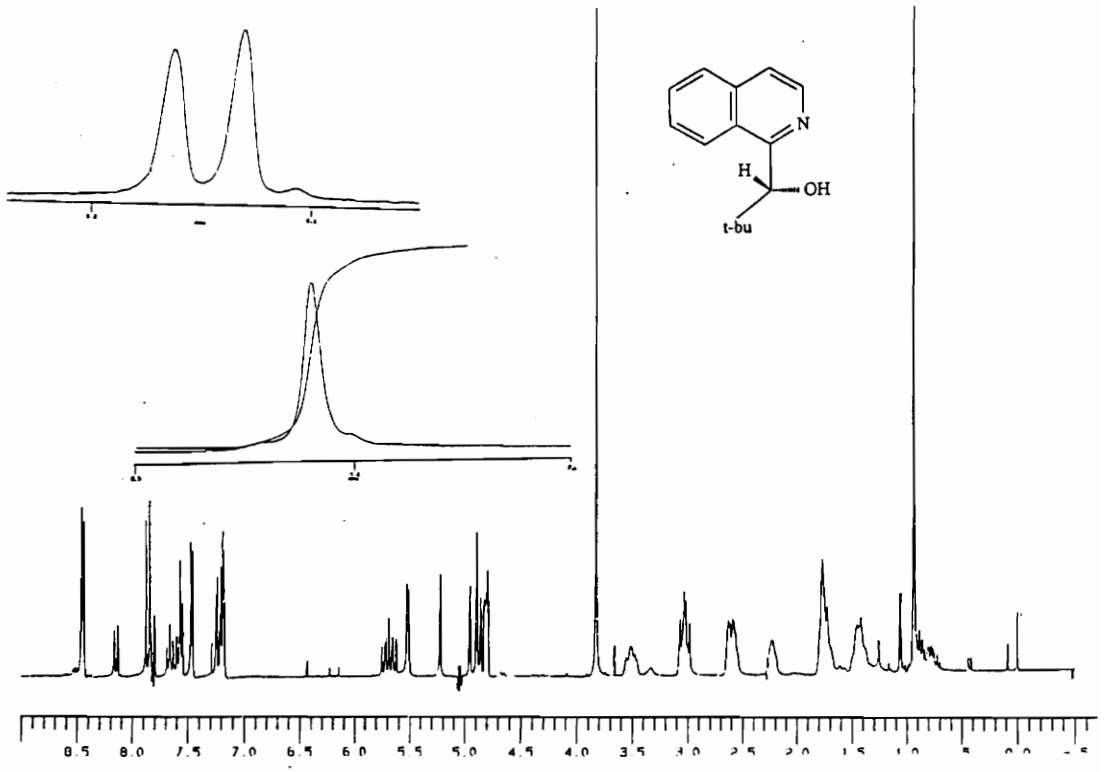
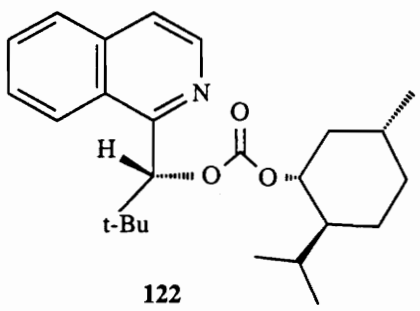
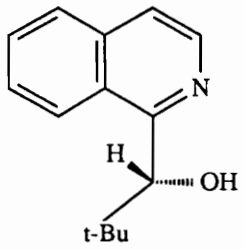


Figure 13



122

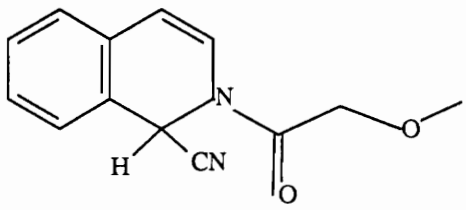


123

F. Attempt at Optimization of the Chiral Acyl Auxiliary

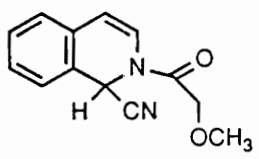
1. Model Study: Formation of 2-Methoxyacetyl-1,2-dihydroisoquinaldonitrile (124)

2-Methoxyacetyl-1,2-dihydroisoquinaldonitrile (**124**) was synthesized by the TMSCN method from isoquinoline, methoxyacetyl chloride, and TMSCN. The 270 mHz Proton NMR spectrum (Figure 14) of the compound (**124**) showed H_1 as a singlet at 6.65 ppm, H_3 as a doublet at 6.90 ppm, and H_4 as a doublet at 6.15 ppm ($J_{3,4} = 7$ Hz). Thus it was concluded that the amide isomers were not detectable within the time frame of the NMR time scale. The compound was purified by a silica gel column and recrystallization from hexane. The yield from the column, however, was low. Therefore, a column was done on a sample of analytically pure **124** to determine its ability to survive the silica gel column. Upon analysis isoquinoline was found to be formed during the column, evidence that the compound degrades on silica gel.



124

270 mHz 1H NMR Spectrum of 2-Methoxyacetyl-1,2-Dihydroisoquinaldonitrile



$CDCl_3$, 25 °C

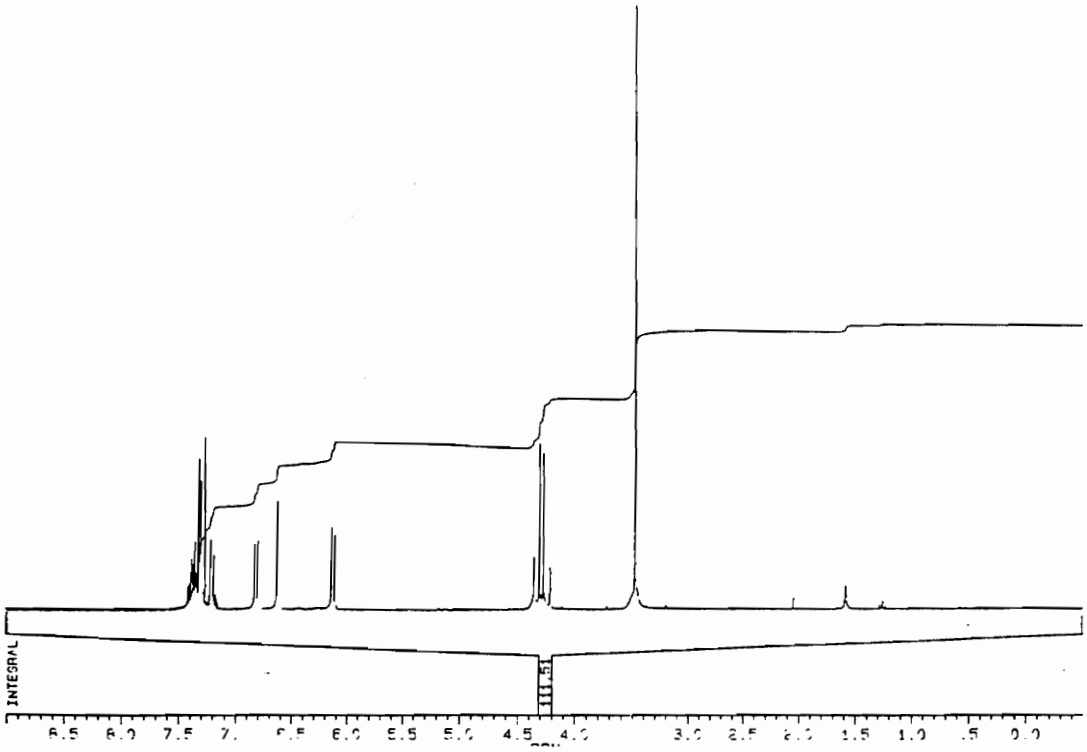
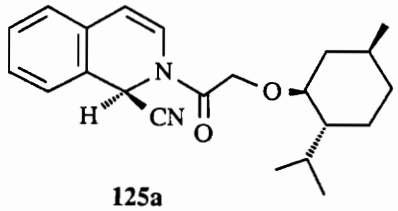
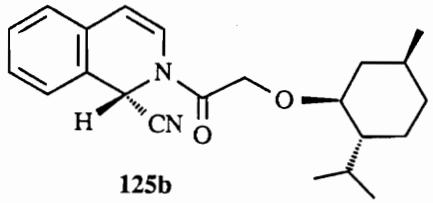


Figure 14

2. Formation of 2-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile (125)



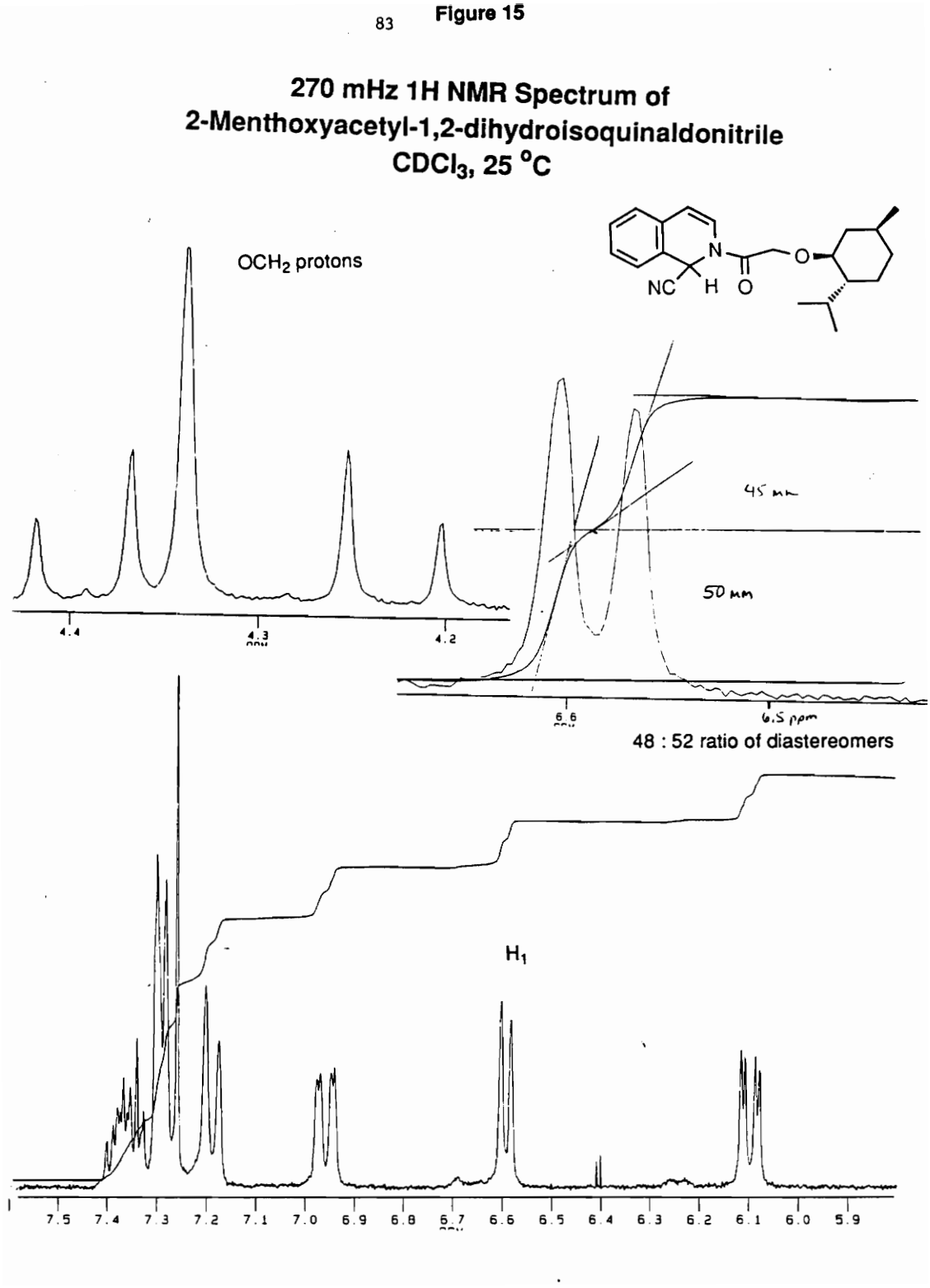
125a



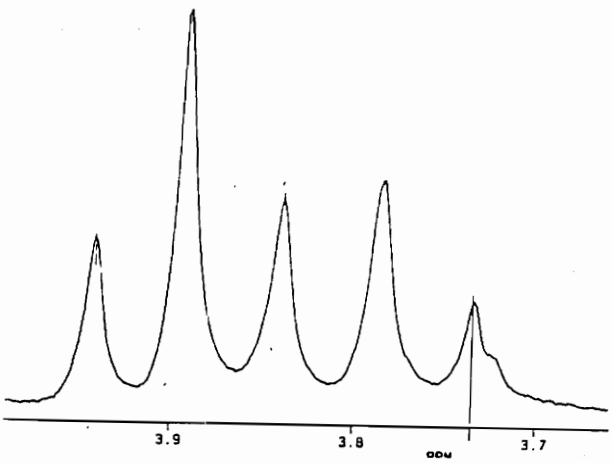
125b

The synthesis of (-)-menthoxyacetyl chloride was carried out following a procedure from Organic Syntheses[104] by reaction of (-)-menthol with sodium to form sodium menthoxide which was then reacted with chloroacetic acid. The resulting (-)-menthoxyacetic acid was then converted to (-)-menthoxyacetyl chloride by reaction with thionyl chloride. The (-)-menthoxyacetyl chloride was then reacted with isoquinoline and TMSCN to form the Reissert compounds (**125a, 125b**). In contrast to the proton NMR spectrum of (-)-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**110**) which showed three peaks (presumably four peaks with two accidentally isochronous) for the H_1 proton, the 270 mHz proton NMR spectrum of the Reissert compound **125** (Figure 15) showed two peaks for the H_1 proton at 6.58 and 6.63 ppm. Since two peaks were observed for H_1, either two amide isomers and one diastereomer or one amide isomer and two diastereomers were being detected. For H_4 two doublets ($J_{3,4}$ = 7 Hz) at 6.08 and 6.11 ppm were observed. The proton H_3 appears as two doublets ($J_{3,4}$ = 7 Hz) broadened by coupling to H_1 at 6.95 and 6.98 ppm. The O-CH_2 protons are diastereotopic and thus seen as two AB patterns. One of the diastereomers shows a

Figure 15


270 mHz 1H NMR Spectrum of
2-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile
CDCl3, 25 °C
OCH2 protons
NC
H
O
N
O
45 mm
50 mm
6.5 ppm
48 : 52 ratio of diastereomers
H1
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9

270 mHz 1H NMR Spectrum of 2-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile (toluene, 25 °C)



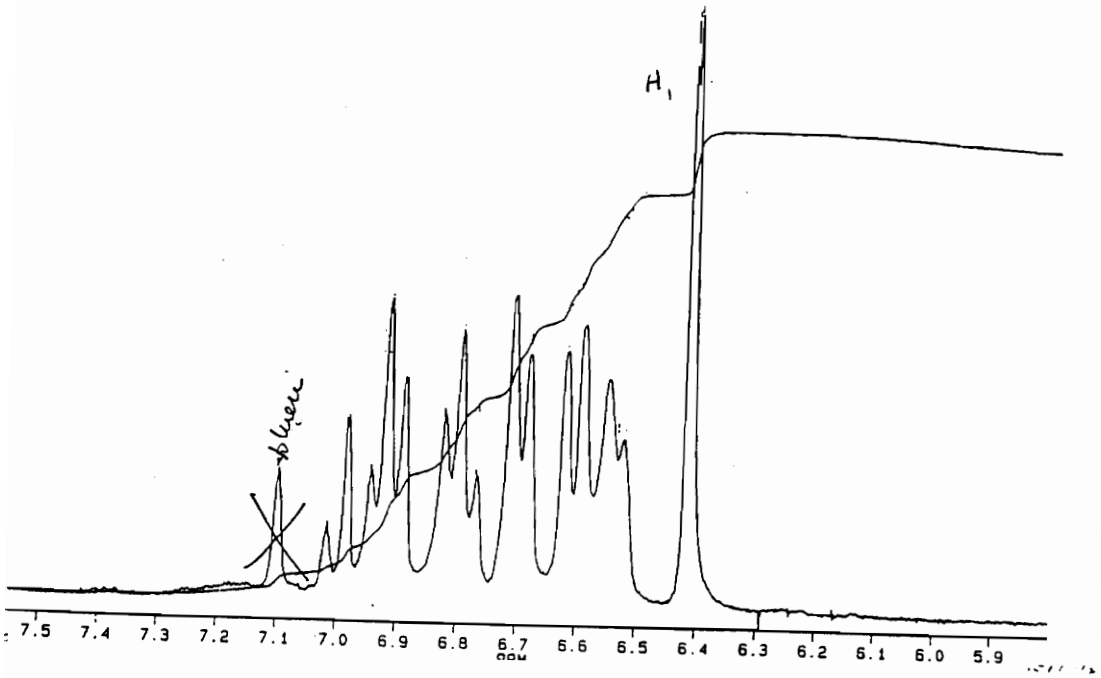


Figure 16

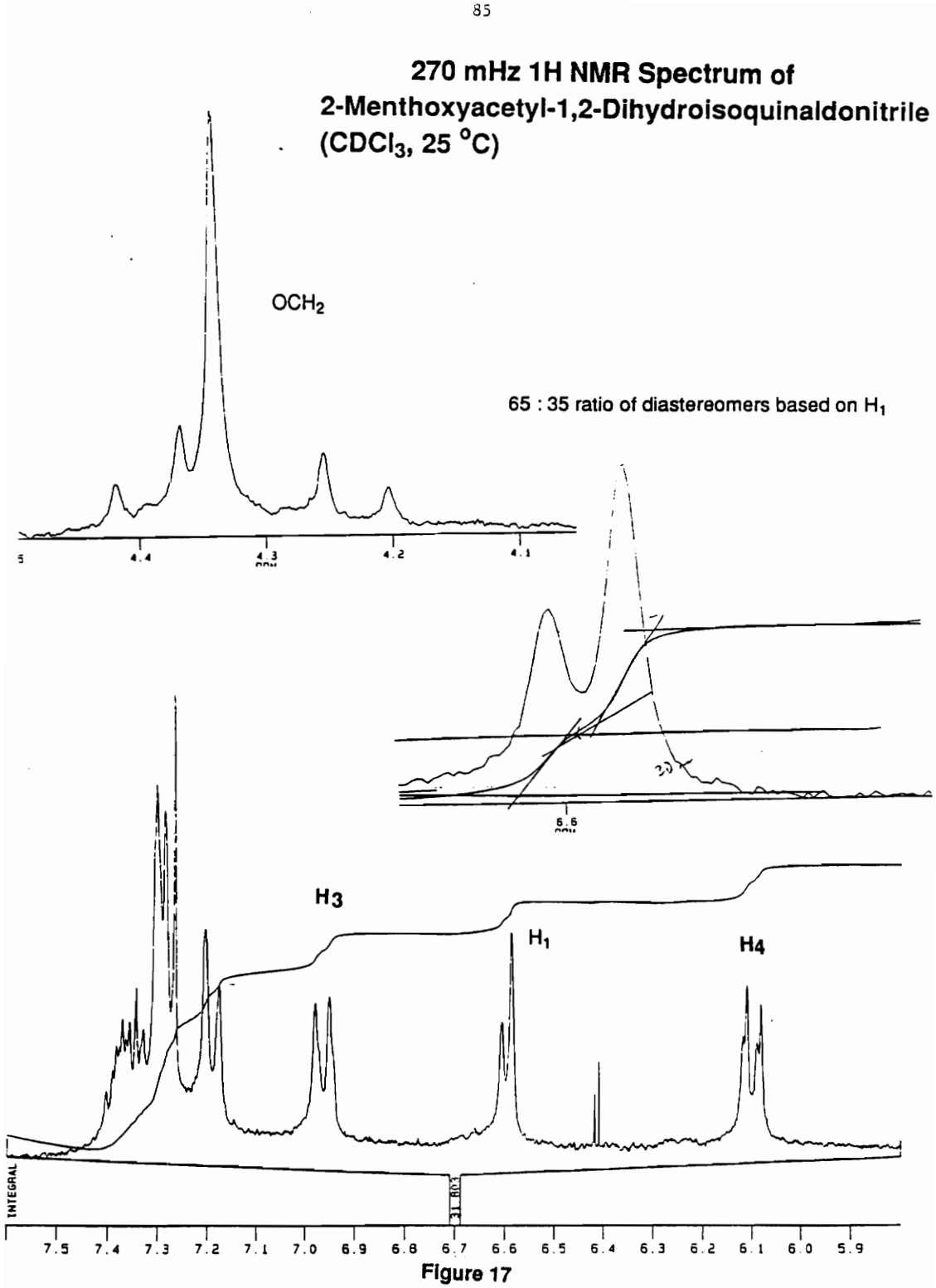

270 mHz 1H NMR Spectrum of
2-Menthoxyacetyl-1,2-Dihydroisoquinaldonitrile
(CDCl3, 25 °C)
OCH2
65 : 35 ratio of diastereomers based on H1
H3
H1
H4
INTEGRAL
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9

Figure 17

doublet at 4.38 ppm and another doublet at 4.23 ppm (J_{AB} = 13.7 Hz). The other diastereomer shows one large signal (presumably a degenerate AB pattern) at 4.30 ppm. Aromatic Solvent Induced Shift (ASIS) studies were performed in deuterated toluene (Figure 16) to determine whether amide isomerism was responsible for this observed signal doubling. Interpretation of the coupling constants and chemical shift differences in the H_1, H_4 and H_3 protons were inconsistent with observability of both amide isomers on the NMR time scale, and showed that the trans amide form predominates. It was thus concluded that both diastereomers were formed in a 1 : 1 ratio.

The mixture of **125a** and **125b** was charged to a silica gel column and eluted with 98 % hexane and 2 % ethyl acetate as eluent. The two peaks in the NMR spectrum for the H_1 proton changed in ratio from 48:52 (Figure 15) to 65:35 (Figure 17). This was qualitatively supported by similar changes in the ratio of doublets for protons H_3 and H_4, and the AB patterns of the O-CH_2 protons. This data confirmed that the amide isomers were present in their time averaged form and that the two diastereomers were responsible for signal doubling, since it is very unlikely that amide isomers would be physically separated while diastereomers can be separated. It was also found that the silica gel caused degradation of the Reissert compound to isoquinoline, analogous to the finding with the methoxyacetyl Reissert compound **124**.

3. Reaction of the Model Compound 124 with Pivaldehyde

The reaction of the compound **124** with pivaldehyde was performed and the product **126** obtained in quantitative yield. The proton NMR spectrum was taken (Figure 18) and the methine proton was found to occur at 6.5 ppm as a singlet. In the aromatic region one doublet each [8.6 ppm (J = 6 Hz), 8.4 ppm (J = 7 Hz)] was found for two of the aromatic protons (H_5, H_8). The diastereotopic O-CH_2 protons were observed as one AB pattern centered at 4.2 ppm.

4. Reaction of (-)-2-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile (125) with Pivaldehyde

A 1 : 1 mixture of the compounds **125a** and **125b** was reacted with pivaldehyde in the presence of

270 mHz 1H NMR Spectrum of 1-Isoquinolyl t-Butyl Carbinyl Methoxyacetate ($CDCl_3$, 25 °C)

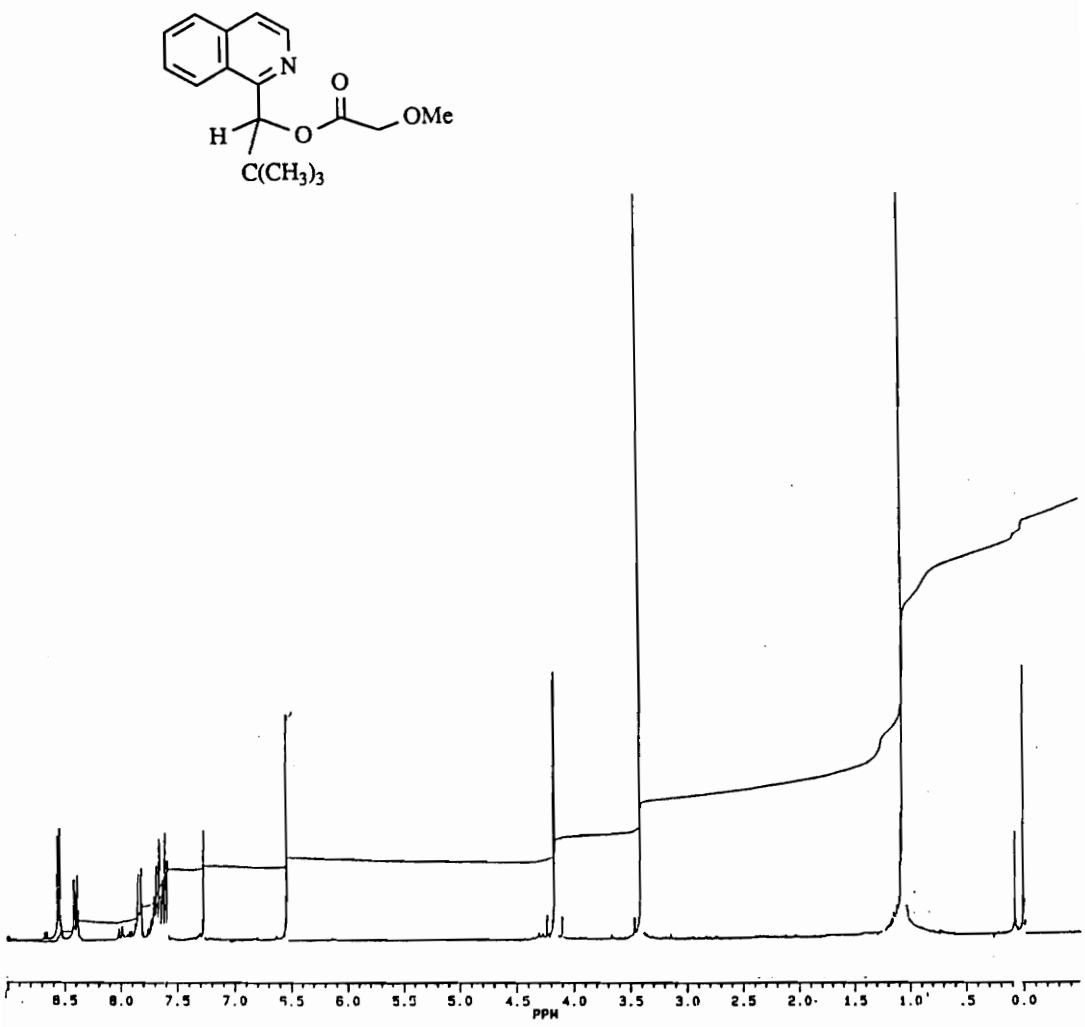
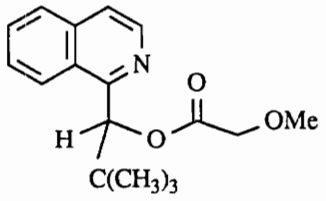


Figure 18

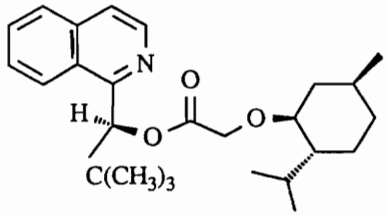
NaH in DMF. The diastereomeric esters **127** were formed in 97 % yield and 0 % de (by NMR analysis) (Figure 19).

The proton NMR spectrum (Figure 19) was obtained after the product was passed through a silica gel column (9 : 1 :: hexane : EtOAc). The methine proton was visible as two peaks at 6.5 ppm in the ratio 70 : 30 (40 % de). Thus separation of the two diastereomers was achieved by the column chromatography. There were also two doublets each for the H_5 and H_8 aromatic protons at 8.6 ppm and 8.4 ppm in the same ratio. The presence of the two diastereomers **127a** and **127b** were presumed to be responsible for signal doubling.

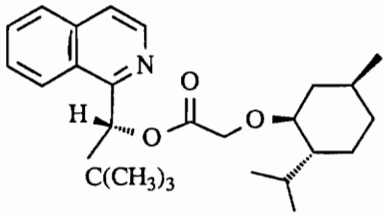
HPLC [Pirkle column, flow rate 1 ml / min, (99 : 1 :: hexane : isopropanol)] of a sample made on a small scale gave 80 % de of the product (Figure 20) after chromatography and subsequent attempts at recrystalization. Thus separation of the diastereomers was easily achieved and the diastereomeric ratios are easily analyzed by NMR and HPLC.



126



127a (S Diastereomer)



127b (R Diastereomer)

270 mHz 1H NMR Spectrum of 1-Isoquinolyl t-Butyl Carbinyl Menthoxyacetates

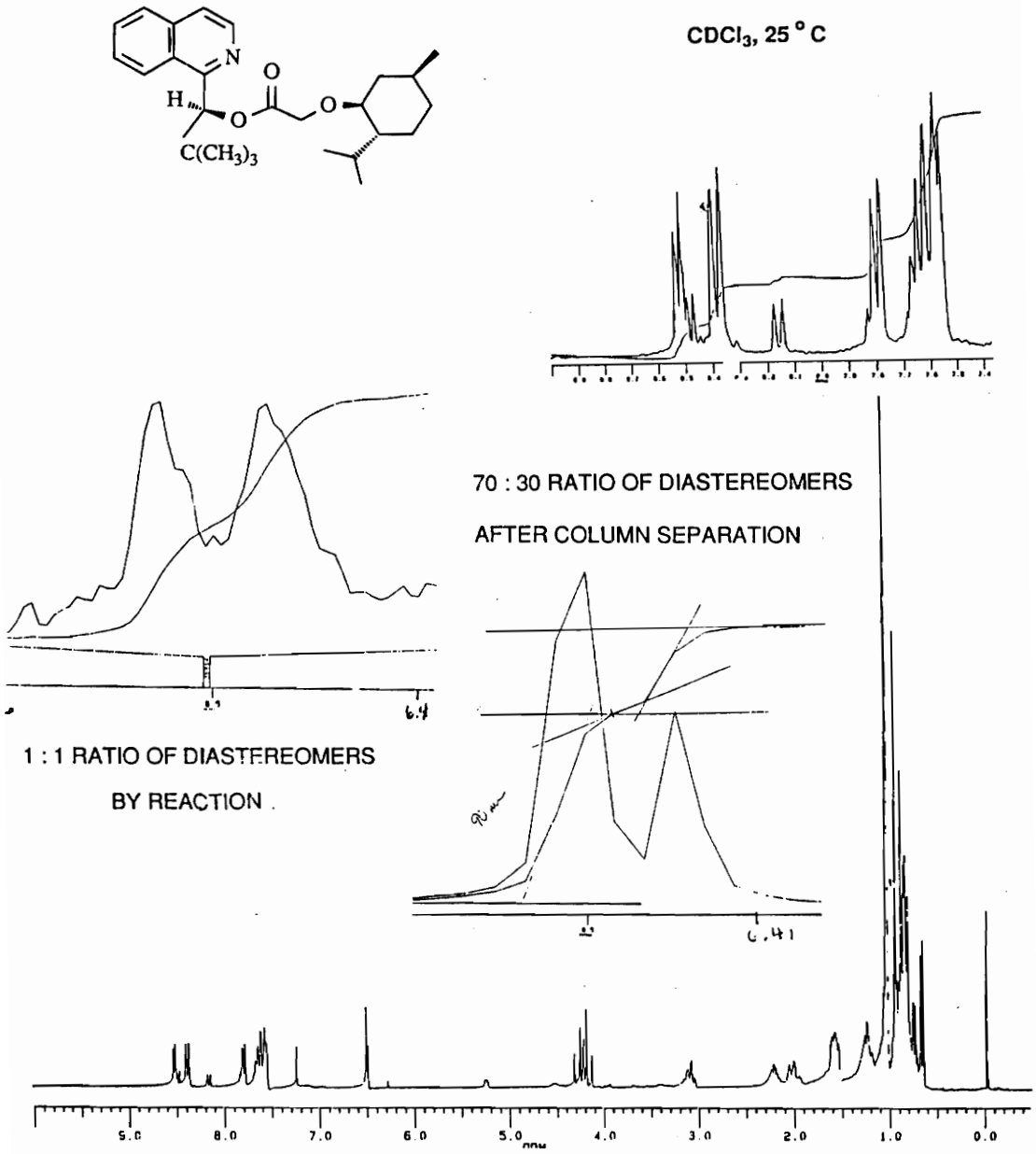
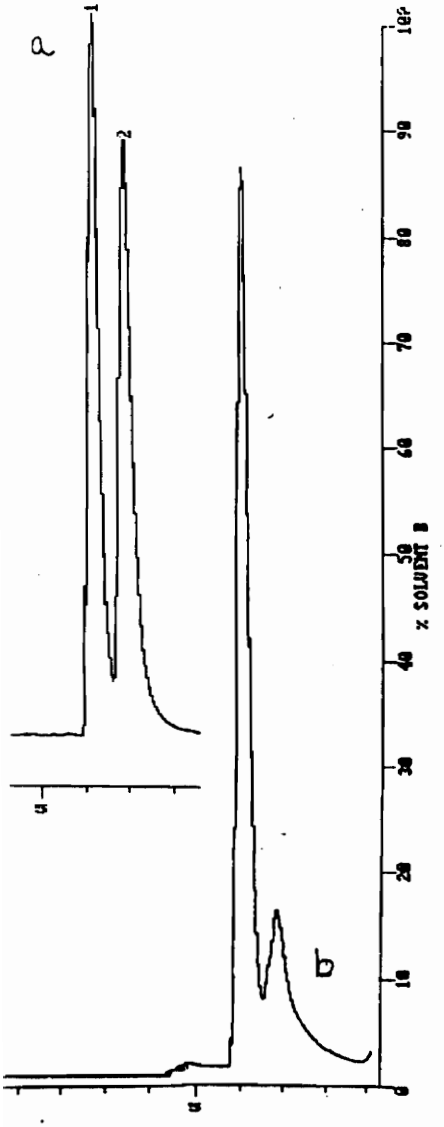


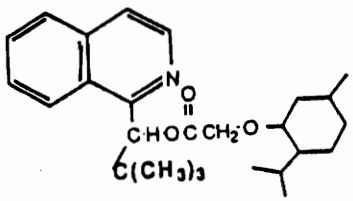
Figure 19

HPLC Results



Pirkle phenylglycine column
99% hexane/ 1% isopropanol

flow rate = 1 ml/min



a. 1: 1 mixture of diastereomers form crude reaction mixture

b. 90 : 10 mixture of diastereomers after selectively solublizing one diastereomer in hexane

Figure 20

An attempt at isolation of the pure diastereomer of the ester **127** can now be made. The compound forms as an oil so it would first necessary to try to obtain a solid. Then the two diastereomers could potentially be separated by recrystalization from hexane.

G. Nature of the Reissert Anion 111

The nature of the Reissert anion **111** was studied by two methods. The first method was the reaction of the Reissert anion with CS_2 and subsequent quenching of the reaction with D_2O to determine if selective deuteration was achievable. The second was to react the Reissert anion with aldehyde to only partial conversion to determine if the diastereomers were different kinetically (See section E1b). From these studies it was found that the Reissert anion is equilibrating. We have also developed a kinetic treatment for the reactivity of the diastereomeric Reissert anion.

1. Possible Anion Geometries

There are three possible geometries for the Reissert anion. In the first case shown in Figure 21 the Reissert anion is planar due to resonance hybridization, resulting in the formation of an sp^2 carbon and consequent loss of stereochemistry at C_1. The second possibility is that the anion is tetrtahedral but equilibrating; this would result in racemization even if the reaction was started with the pure diastereomer. In the third case the Reissert anion would be tetrahedral / pyramidal in nature but not equilibrating. In this case the stereochemistry at C_1 would be retained; use of a diastereomerically pure starting material would yield a diastereomerically pure product.

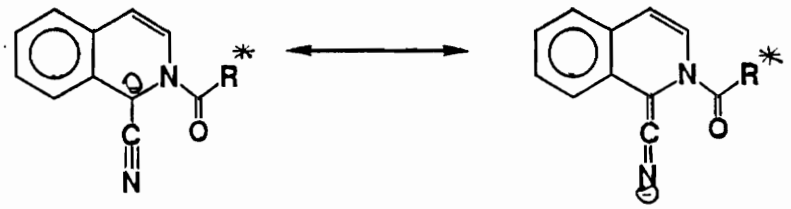
2. Interpretation of Anion Configuration

The results of the reaction of Reissert compounds with aldehydes, CS_2, and the reactions carried out to partial conversion allow us to speculate on the character of the Reissert anion.

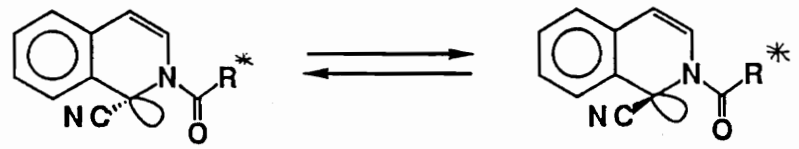
Based on the data from the reaction with CS_2 and the series of reactions taken to partial conversion we began to understand the Reissert anion. The fact that the ratio of the diastereomers of

Nature of the Reissert Anion

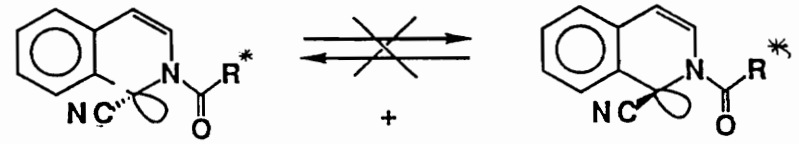
1. Planar



2. Tetrahedral/pyramidal, but equilibrating (racemization)



3. Tetrahedral/pyramidal, no racemization



Current evidence supports (1) or (2)

Figure 21

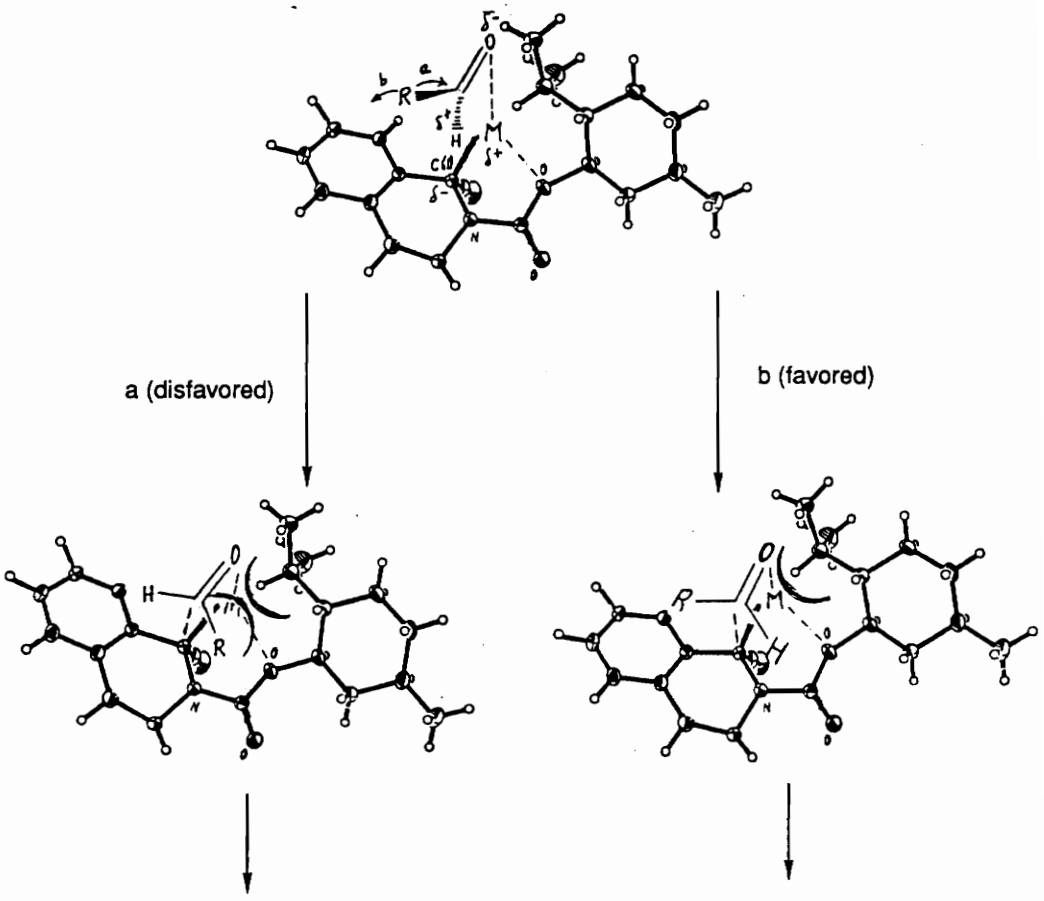
110 was the same before and after deuteration at two different partial conversions (Section E1b) suggests that one can rule out case three (a nonequilibrating anion)(Figure 21). This is consistent with the results obtained from taking the reaction with aldehydes to partial conversion; the ratio of diastereomers did not change.

In the case of the reaction of the diastereomeric Reissert compounds with the aldehydes we assume a tetrahedral but equilibrating anion by the following mechanistic pathway. In examining Figures 22 and 23, the first important point is that the cyano group is trans to the isopropyl group of the menthyl moiety. Metal complexation occurs upon formation of the anion. Reaction of the Reissert anion of **110** in the R configuration with pivaldehyde leads to the formation of the (S)-diastereomer (Figure 22) by the "b" (favored) pathway; there is minimal crowding between the R group of the aldehyde and the isopropyl group of the menthyl moiety. In the case of the "a" (disfavored) pathway there is more steric hindrance between the R group on the aldehyde and the isopropyl group. Reaction of the Reissert anion of **110** in the S configuration leads to the formation of the (R)-diastereomer (not observed) by the "b" (favored) pathway (Figure 23); however, there appears to be more hindrance between the R group on the aldehyde and the isopropyl group in this case than via the "b" pathway from the (S)-diastereomer (Figure 22).

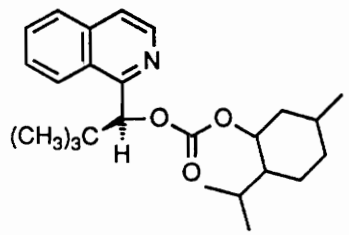
The S diastereomer of the carbonate **120** is the major diastereomer formed from the reaction of the diastereomeric mixture of Reissert compound **110a/110b** with pivaldehyde. **120** may arise from reacton of the R diastereomer of the anion of compound **110** in a stereochemically favorable manner (Figure 22). The formation of the S diastereomer of **120** from the S diastereomer of the anion is an unfavorable pathway (Figure 23). planar. Selectivity of the reaction with aldehydes in the case of the chiral auxiliary would not probably be as high as we have seen if the anion was planar. Thus, with reference to Figure 21 case 2, the tetrahedral / pyramidal Reissert anion, via selective reaction of the R configuration of the anion as shown in Figure 23 is consistent with our observations.

However, facioselective reaction of a planar carbanion (case 1, Figure 21) could also result in

Pathways for Reaction of the R Anion of 111 With Pivaldehyde



R-carbonate **121**



S-carbonate **121** (observed)

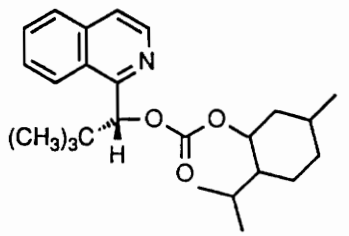
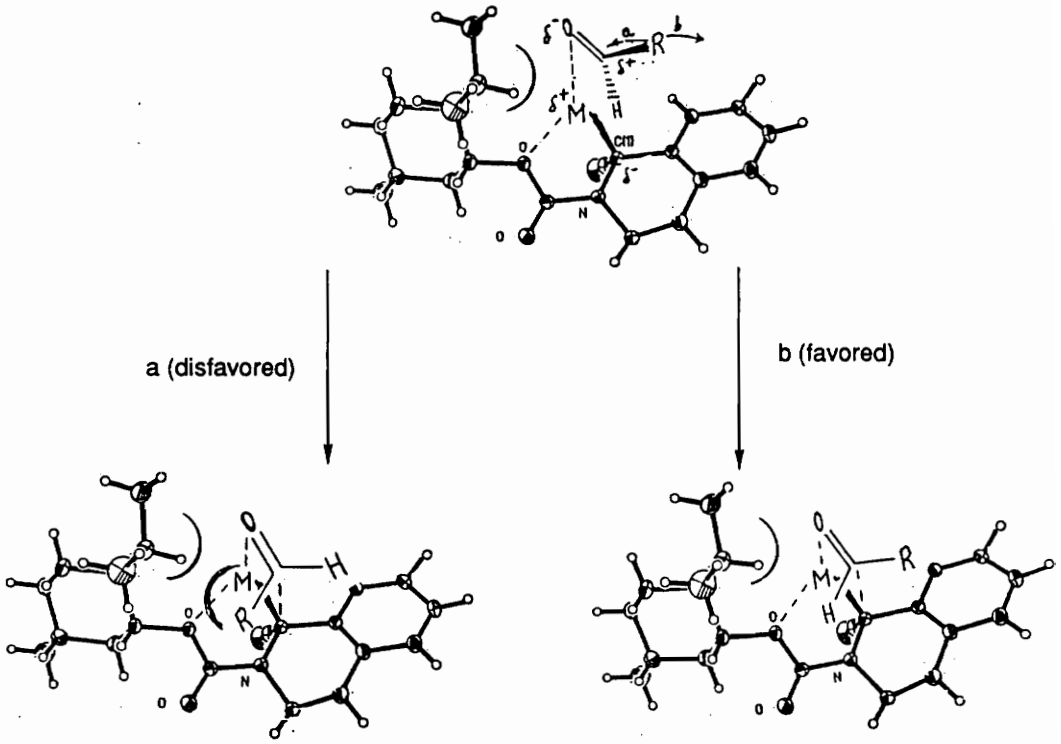
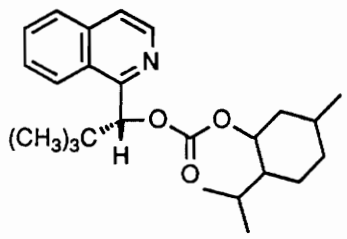


Figure 22

Pathways for Reaction of the S Anion of 111 With Pivaldehyde



S-carbonate **121** (observed)



R-carbonate **121**

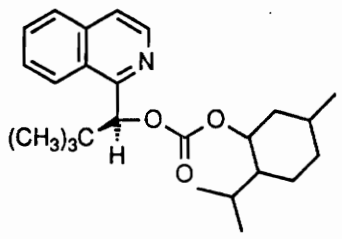


Figure 23

diastereoselective product formation because of the presence of the chiral auxilliary.

3. Kinetic Interpretation

A kinetic interpretation based on this interpretation has also been theorized by Gibson.[105]

$$\frac{d[(S)\text{-prod}]}{dt} = [R\text{-CHO}]\{k_{aS}[(S)\text{-RC}^-] + k_{bR}[(R)\text{-RC}^-]\}$$

and

$$\frac{d[(R)\text{-prod}]}{dt} = [R\text{-CHO}]\{k_{bS}[(S)\text{-RC}^-] + k_{aR}[(R)\text{-RC}^-]\}$$

The subscripts "aS" and "bR" denote reaction of S anion by the a pathway (Figure 23) and reaction of the R anion by the b pathway (Figure 22), respectively, and "bS" and "aR" are analogously defined. Assuming case 2, Figure 21 we can then define an eqilibrium constant.

$$K = \frac{[(R)\text{-RC}^-]}{[(S)\text{-RC}^-] } \quad \text{therefore} \quad [(R)\text{-RC}^-] = K\,[(S)\text{-RC}^-]$$

$$\frac{d[(S)\text{-prod}]}{d[(R)\text{-prod}]} = \frac{k_{aS}[(S)\text{-RC}^-] + k_{bR}K[(S)\text{-RC}^-]}{k_{bS}[(S)\text{-RC}^-] + k_{aR}K[(S)\text{-RC}^-]}$$

Rearranging the Equation gives:

$$\frac{d[(S)\text{-prod}]}{d[(R)\text{-prod}]} = \frac{k_{aS} + k_{bR}K}{k_{bS} + k_{aR}K}$$

Based on the experimentally observed diastereomer ratio for the carbonate 120, [(S)-prod] / [(R)-prod] = 3.4

$$k_{aS} + Kk_{bR} = 3.4(k_{bS} + Kk_{aR})$$

If we infer from mechanistic and steric arguments that $k_{bR} >> k_{aS}$ and $k_{bS} >> k_{aR}$ then:

$$\frac{k_{bR}}{k_{bS}} = \frac{3.4}{K}$$

If the protonation of the diastereomeric anions is assumed to be completely non-selective (Section 1b, Table 6) and therefore reflects the diastereomeric ratio of the anions, then K = 1.5 or 0.67; this in turn would mean that k_{bR}/k_{bS} is 2.3 or 5.1.

An alternative treatment of case 1, Figure 21 involves assignment of two rate constants to the reaction of the planar anion with the aldehyde: k_{si} for attack at the si face of the aldehyde and k_{re} for re facial attack. The product ratio is then a measure of the ratio of these rate constants (i. e., for **110** → **120**) $k_{si} / k_{re} = 3.4$.

Conclusions and Future Work

The results of the study of Reissert compound stereochemistry were two fold. First, the population of the amide isomers for the compounds **92** and **94** were determined to be 4 : 1 and 3 : 1 respectively. Second, the role of the ortho substituents on the aroyl moiety was determined. For the 2,6-dimethoxy compounds **92** and **94** the amide isomers were observable, while for the napthoyl and difluoro compounds **93** and **95** the amide isomers were not observable.

Low temperature proton NMR was used to determine the ratio of diastereomers (6 : 4) of the Reissert compound **110**. This technique also gave the ratio of s-trans to s-cis amide isomers to be 1 : 1. The diastereomeric ratio of the Reissert compound **125** was determined by 270 mHz proton NMR at room temperature to be 1 : 1. Partial separation of the diastereomers of **125** was achieved on silica gel in a solvent system of 99 % hexane and 1 % EtOAc.

The reaction of **110** with pivaldehyde gave the carbonate **120** in 56 % diastereomeric excess. The major diastereomer (S) at C_1 of compound **120** was easily separated from the minor diastereomer by recrystalization from hexane. The diastereomeric purity of the **120** was analyzed by NMR and HPLC. The x-ray crystal structure of the pure diastereomer was also obtained.

The diastereomerically pure compound **120** was then hydrolyzed by treatment with NaOH to form the enantiomerically pure (S)-1,2-aminoalcohol **121**. The enantiomeric excess of the compound was determined by use of quinine as a chiral solvating agent for proton NMR. It was found that a stoichiometric amount of base and long hydrolysis time resulted in the racemization of the compound. However, the use of 10 equivalents of base for a short reaction time gave no racemization, providing the new compound **121** in optically pure form.

Reaction of a 60 : 40 mixture of the diastereomeric Reissert compounds **110** with different aldehydes, with pivaldehyde to partial conversion and with CS_2 / D_2O gave us information on the nature of the Reissert anion. It has been deduced that the Reissert anion equilibrates. However, whether this is due to formation of a planar anion or equilibration of a tetrahedral anion has yet to be

determined.

On the basis of this information and information obtained from the reaction of the compound **110** with aldehydes one could postulate that the diastereoselectivity of the reaction with aldehydes is mediated by a combination of the ratio of the amide isomers in the Reissert compound and the nature of the substituents of the aldehyde. This is because the facioselectivity of the aldehyde attack appears to be crucial and the nature of the aroyl moiety and aldehyde substituent influence how open the re and si faces are to aldehyde attack.

Several avenues of future work on this project could be explored. First, use of other chiral acyl auxilliaries (i. e., (+)-camphorcarboxyl chloride, (-)-myrtanyl chloride, or (-)-mandelyl chloride) to optimize the structure of the acyl moiety for diastereoselectivity could be investigated. Second, the application of this technology to the enantioselective synthesis of biologically active alkaloids could be undertaken. Third, the chemistry could be applied to the synthesis of other 1,2-aminoalcohols for utilization as asymmetric catalysts.

EXPERIMENTAL SECTION

General Experimental

Melting points were determined on a Thomas - Hoover hot stage capillary melting point apparatus and are corrected. Infrared spectra were determined neat, as films cast from hexane, or on KBr pellets on a Nicolet MX-L FTIR. NMR spectra were performed on a Bruker 270 mHz, Bruker 200 mHz with a multinuclear probe, or a Bruker NR 80. The following abbreviations have been used in describing NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). Elemental analyses were determined by Galbraith Lab., Inc., Knoxville, Tenn.; or Atlantic Microlabs, Norcross, Ga. Mass Spectra were determined on a VG Analytical 7070 EMS.

All optical rotations were obtained on a Perkin Elmer 241 polarimeter at the sodium D line at 25 °C. All readings were taken at least 30 min after turning on the polarimeter. The rotations were taken by first washing the polarimeter cell in acetone and drying it under nitrogen. Then a solution of the analyte was made by weighing a sample directly into the volumetric flask on the analytical balance. The solution was then added to the cleaned cell and the optical rotation was taken. The cell was taken out and replaced several times to ensure the precision and accuracy of the polarimeter. The polarimeter sample was then recovered and the polarimeter cell was cleaned with acetone and dried with a nitrogen flow. The polarimeter was calibrated by use of a sample of commercial (-)-menthol available from Aldrich. Reported: $[\alpha] = -50$ (c = 10, EtOH) and $[\alpha] = -48$ (c = 2.5, EtOH) Found: $[\alpha] = - 47.866 +/- 0.185$ (c = 1.25, EtOH).

HPLC was performed on an Isco dual pump model 2350 with UV detection set at a wavelentgth of 254 nm. The columns used were a Pirkle covalent phenylglycine column and a Bakerbond Chiralcel OD column.

X-Ray crystallography was performed by Dr. J. S. Merola on a Nicolet R3m / V with M_oK_α

(λ = 0.71073 A) radiation source at 298 °K. Solution was achieved by direct methods using the Nicolet SHELXTL PLUS (Microvax II) system. Refinement was by Full - Matrix Least Squares riding model, fixed isotropic U was used to place the hydrogen atoms.

Synthesis of 2-(2,6-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile (92)

To a well stirring solution of isoquinoline (12.9 g, 0.10 moles) in CH_2Cl_2 (75 ml) and water (75 ml), KCN (19.6 g, 0.30 moles) was added. This was followed by the addition of 2,6-dimethoxybenzoyl chloride (40.0 g, 0 .20 moles) over a 2 h period. The reaction was continued for 12 h and then the reaction was terminated by dilution with 100 ml of water [Reaction completion was monitored by TLC (EtOAc : hexane :: 2 : 8)]. The CH_2Cl_2 layer was separated and washed with water (2 x 50 ml), 10 % HCl (2x30 ml), water (3 x 30 ml) and aq. sat'd $NaHCO_3$ (2 x 50 ml). It was then dried over magnesium sulfate and concentrated by rotary evaporation to yield the crude product (28.20 g, 88 % yield, mp 155 - 159°C). Pure product was obtained by three recrystalizations from EtOH, mp 160.5 - 161.5 °C (18.6 g, 56 % yield).

FTIR (KBr) 2985 (C-H), 1679 (C=O), 1440, 1170 (C-O), and 1030 cm^{-1}. ^{1}H-NMR (270 mHz, $CDCl_3$): δ 3.70 (O-CH_3, d, 3H), 3.90 (O-CH_3, d, 3H), 5.70 and 6.85 (H_1, 2s, 1H), 5.9 (H_4, d, 1H), 6.35 (H_3, dd, 1H), 6.5 - 6.80 (Ar C-H, m, 2H), 7.05 - 7.50 (Ar C-H, m, 5H) (Figure 1). Anal. Calcd. for $C_{19}H_{15}N_2O_3$: C 71.24, H 5.03, N 8.74. Found: C 71.43, H 5.00, N 8.66.

Synthesis of 2-(α-Napthoyl)-1,2-dihydroisoquinaldonitrile (93)

To a well stirring solution of isoquinoline (3.15 g, 24.4 mmoles) in CH_2Cl_2 (50 ml) and water (50 ml), KCN (4.88 g, 72.7 mmoles) was added. This was followed by the addition of α-napthoyl chloride (9.52 g, 50.0 mmoles) over a period of 45 min. The reaction was continued for 48 h. and then terminated by the addition of water (100 ml) [Reaction completion was monitored by TLC (EtOAc : hexane :: 2 : 8)]. The CH_2Cl_2 layer was then separated and washed consecutively with

water (2 x 30 ml), 10 % HCl (2 x 30 ml), water (3 x 30 ml), aq. sat'd $NaHCO_3$ (2 x 30 ml). It was then dried over magnesium sulfate concentrated by rotary evaporation to give the crude product (2.5 g, 35 % yield). Pure compound was obtained by three recrystalizations from ethanol, mp 210 - 211 °C.

FTIR (KBr): 2900 (C-H), 1640 (C=O), 1452, 1399, 1378, and 1254 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 mHz): δ 5.93 (H_4, d, 1H), 6.32 (H_3, d, 1H), 6.90 (H_1, s, 1H) 7.20 (Ar C-H, d, 1H), 7.40 - 7.70 (Ar C-H, m, 8H), 7.90 - 8.10 (Ar C-H, m, 2H) (Figure 2). Anal Calcd for $C_{21}H_{14}N_2O$: C 81.42, H 4.66, N 8.98. Found: C 81.27, H 4.55, N 9.03.

Synthesis of 1-(2,6-Dimethoxybenzoyl)-1,2-dihydro-4-methylquinaldonitrile (94)

To a well stirring solution of lepidine (3.75 g, 26.2 mmoles) in CH_2Cl_2 (40 ml) and water (40 ml), KCN (4.88 g, 72.7 mmoles) was added. This was followed by the addition of 2,6-dimethoxybenzoyl chloride (10.03 g, 50.0 mmoles) over a 45 min period. The reaction was continued for 24 h and then terminated by the addition of water (100 ml). [Reaction completion was monitored by TLC (EtOAc : hexane :: 2 : 8)]. The methylene chloride layer was then separated and washed consecutively with water (2 x 20 ml), HCl (2 x 20 ml), water (2 x 20 ml), aq. sat'd $NaHCO_3$ (2 x 20 ml) and water (2 x 20 ml). It was then dried over Na_2SO_4 and concentrated by rotary evaporation to yield the crude product (0.65 g, 12 % yield). Pure product was obtained by twice recrystalizing from ethanol (0.50 g, 10% yield), mp 191 - 193.

FTIR (KBr); 2980(C-H), 1636 (C=O),1605 (Ar C-H), 1465, 1350, 1120 (C-O), and 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 2.20 (CH_3 at C_4, s, 3H), 3.15 - 4.1 (O-CH_3, 4s, 6H), 5.95 (H_4, d, 1H), 6.20 (H_3, d, 1H), 6.60 (Ar C-H, t, 1H), 6.76 (Ar C-H, d, 1H), 6.95 (Ar C-H, t, 1H), 7.10 - 7.60 (Ar C-H, m, 3H) (Figure 3). Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C 70.86, H 5.62, N 8.29. Found: C 70.94, H 5.39, N 8.37.

Synthesis of 1-(2,6-Difluorobenzoyl)-1,2-dihydro-4-methylquinaldonitrile (95)

To a well stirring solution of lepidine (3.56 g, 24.9 mmoles) in CH_2Cl_2 (40 ml) and water (40 ml), KCN (5.00 g, 74.6 mmoles) was added. This was followed by the addition of 2,6-difluorobenzoyl chloride (8.2 g, 50.0 mmoles) over a period of 45 min. The reaction was continued for 10 h and then the reaction was terminated by diluting with water (100 ml) [completion of the reaction was monitored by TLC (EtOAc : hexane :: 2 : 8)]. The methylene chloride layer was then separated and washed consecutively with water (2 x 20 ml), 10 % HCl (2 x 20 ml), water (2 x 20 ml), aq. sat'd $NaHCO_3$ (2 x 20 ml), and water (2 x 20 ml). It was then dried over Na_2SO_4 and concentrated by rotary evaporation to give the crude product (2.3 g, 50 % yield). The pure product was obtained by twice recrystalizing from EtOH (1.3 g, 30 % yield), mp 203 - 204 °C.

FTIR (KBr): 2980 (C-H), 1653 (C=O),1370, 1030, and 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 mHz): δ 2.31 (CH_3 at C_4, s, 3H), 6.08 - 7.50 (Ar C-H, m, 8H) (Figure 4); ^{19}F-NMR ($CDCl_3$, CF_3CH_2OH as an internal standard, 188 mHz): δ -113.25 (dd, 1F), -113.45 (dd, 1F) (Figure 5). Anal. Calcd. for $C_{18}H_{12}N_2OF_2$: C 69.68, H 3.89, N 9.02. Found: C 69.47, H 3.92, N 9.00.

General Procedure for the Synthesis of 1-Isoquinolyl Alkyl Carbinols (98, 99)

A. PTC Method

The Reissert compound was dissolved in benzene. Then an equal volume of 50% NaOH solution was added. The reaction was then cooled to 0 °C. One equivalent of the aldehyde was added. The reaction was allowed to stir mechanically for several days. The benzene layer was evaporated. The aqueous layer was extracted into ether. The ether layer was washed with 1.0 % HCl and several times with water. The ether layer was combined, dried over sodium sulfate, filtered and rotary evaporated to dryness. The isolated crude 1,2-aminoalcohol was isolated and purified by recrystalization from ethyl acetate / hexane.

B. NaH / DMF Method

The Reissert compound was dissolved in DMF; aldehyde was added (1.0 eq.). The reaction mixture was cooled to -40 °C. This was followed by addition of NaH (1.1 eq.). The reaction mixture was generally allowed to stir at -40 °C for 5 hours. The reaction mixture was quenched by pouring into water. The aqueous slurry was extracted into ether. The ether layer was washed with water several times to remove DMF, dried over Na_2SO_4 and concentrated to get the crude ester.

The next step involved the hydrolysis of the ester to the 1,2-aminoalcohol. The ester was dissolved in a mixture of ethanol, water and THF (equal volumes of each). Addition of NaOH (10 eq.) then followed. The mixture was allowed to reflux until the hydrolysis was complete (as shown by TLC in 20 % ethyl acetate / 80 % hexane). The reaction mixture was then cooled to room temperature, evaporated and extracted with ether. The ether layer was extracted with 10 % HCl. The HCl layer was made basic to pH 10 by the addition of NaOH. The aqueous layer was extracted with ether. The ether layer was washed with water and brine, dried over sodiun sulfate, and rotary evaporated to dryness. The product 1,2-aminoalcohol was further purified by recrystalization from ethyl acetate / hexane.

Synthesis of Racemic 1-Isoquinolyl Phenyl Carbinol (98)

A. By the Phase Transfer Method

To a well stirring solution of the Reissert compound **3** (1.0 g, 3.90 mmoles) in benzene (35 ml), benzaldehyde (3.9 ml, 39.0 mmoles), and trimethylbenzylammonium chloride (0.0740 g, 3.9 mmoles) were added. 50 % aqueous NaOH (7 ml) was then added and the reaction mixture was allowed to stir mechanically for 24 h [reaction completion was followed by TLC (2 : 8 :: EtOAc : hexane)]. During this period the reaction mixture had become very thick. The reaction was terminated by the addition of water (200 ml). This was followed by separating the benzene layer and washing it with water (2 x 30 ml), aq. sat'd $NaHCO_3$ (3 x 30 ml), and $NaHSO_3$ (10 x 30 ml). The benzene layer was dried over Na_2SO_4, and concentrated by rotary evaporation to yield the crude product (750 mg, 85 % yield). The crude product was purified by recrystalization from ethanol to give the pure product, mp 113 - 115 °C (rep.[32] mp 114 -

116 °C).

FTIR (KBr): 3500 - 2500 (O-H), 2900 (C-H), 1550 cm^{-1}. ^1H NMR (270 mHz, $CDCl_3$): δ 6.20 (s, 1H), 6.23 (s, 1H), 7.20 - 7.40 (m, 5H), 7.42 - 7.52 (m, 1H), 7.60 - 7.80 (m, 2H), 7.80 - 7.85 (m, 1H), 7.85 - 8.00 (m, 1H), 8.50 - 8.60 (m, 1H).

B. By the NaH / DMF Method

To a well stirred solution of the Reissert compound **3** (7.15 g, 26.9 mmoles) in DMF (100 ml) at -40 °C, benzaldehyde (11.4 g, 107.6 mmoles), and after 15 min 80 % NaH (0.71 g, 28.70 mmoles) were added. The reaction was allowed to stir for 3 h at - 40°C [reaction completion was followed by TLC (2 : 8 :: hexane : EtOAc)]. The reaction was terminated by the addition of water (250 ml). The aqueous layer was extracted with ether (4 x 40 ml), and the ether layer was washed with water (2 x 30 ml), and 1.0 % HCl (2 x 20 ml). The ether layer was separated and concentrated to yield the crude benzoate.

To a well stirred solution of the crude benzoate in THF (25 ml), water (25 ml), and EtOH (25 ml), NaOH (2.1 g) was added. The reaction mixture was allowed to reflux overnight. The reaction was terminated by allowing it to reach room temperature, and the product was isolated and purified as in the general procedure above to yield the pure product (5.2 g, 82 % yield). Spectral data were identical to thos of the compound prepared by the phase transfer method.

Synthesis of Racemic 1-Isoquinolyl t-Butyl Carbinol (99)

A. By the NaH / DMF Method

To a well stirred solution of the Reissert compound **3** (10.0 g, 37.6 mmoles) in DMF (100 ml) at -40 °C, pivaldehyde (9.0 ml, 38.0 mmoles) was added. This was followed by the addition of 80 % NaH (1.26 g, 42.0 mmoles). Upon addition of the NaH a blood red color was immediately visible. Stirring was continued at -40 °C for 2 h [Completion of the reaction was followed by TLC (EtOAc : hexane :: 4 : 6)]. The reaction was quenched by the addition of water (200 ml). The aqueous layer

was extracted with ether (3 x 30 ml). The ether layer was washed with water several times. It was dried over sodium sulfate and concentrated by rotary evaporation to yield the crude benzoate (7.76 g, 96 % yield).

To a solution of the crude benzoate in THF, EtOH, and water (25 ml) was added NaOH. The solution was then refluxed for 3 h [completion of the reaction was followed by TLC (EtOAc : hexane :: 4 : 6)]. The crude product was subsequently isolated as indicated in the general procedure above (7.0g, 88 % yield). Pure compound was obtained by several recrystalizations from ethyl acetate / hexane, mp 101 - 102 °C. Spectral data of this sample were identical with those of the sample synthesized by the PTC method (below).

B. By the PTC Method

To a mechanically stirred solution of **3** (7.50 g, 28.3 mmoles) in benzene (100 ml) and 50 % NaOH in water (52.5 ml), triethylbenzylammonium chloride (1.50 g, 8.7 mmoles) was added. This was followed by the addition of pivaldehyde (3.07 ml, 38.3 mmoles). Stirring was contiued for 36 h. and the reaction was terminated by dilution of the aqueous layer with 300 ml of water [completion of the reaction was monitored by TLC (EtOAc : hexane :: 4 : 6)]. The crude product (1.3 g, 25 % yield) was isolated as described in the general procedure above. The pure product was obtained by several recrystalizations from ethyl acetate / hexane. mp 100 - 101 °C.

FTIR (KBr); 3300-3500 (O-H) and 2810-2600 (C-H) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 0.98 (s, 9H), 4.50 - 4.65 (d, 1H), 5.20 - 5.40 (d, 1H), 7.50 - 7.70 (m, 3H), 7.80 - 7.85 (d, 1H), 8.10 - 8.20 (d, 1H), 8.50 (d, 1H). Anal. Calcd. for $C_{14}H_{17}NO$: C 78.10, H 7.98, N 6.51. Found: C 77.97, H 7.98, N 6.34.

Synthesis of (l)-Menthoxyacetic acid[104]

To a mechanically stirred solution of (l)-menthol (40 g, 0.26 moles) in dry toluene (100 ml), sodium metal (7.0 g, 0.30 gram atoms) was added in a nitrogen atmosphere. The reaction mixture

was allowed to reflux overnight with vigorous mechanical stirring and then allowed to reach room temperature. The excess sodium was then filtered from the solution under nitrogen. This was followed by the addition of monochloroacetic acid (9.5 g, 0.10 moles) to the solution. The solution was reheated and the mixture allowed to reflux for 48 h with mechanical stirring. The sodium salt of chloroacetic acid formed an insoluble white precipitate. The reaction was brought to room temperature and then terminated by the extraction of the toluene layer with water (4 x 50 ml). The aqueous layer was then separated and acidified to pH 5 by the addition of 20 % HCl (5 ml). The crude product so formed, an insoluble brown oil, was extracted into toluene (3 x 30 ml). The toluene layer was then washed with water (2x30 ml), dried over sodium sulfate and concentrated by rotary evaporation to give the crude product. Pure (-)-menthoxyacetic acid was obtained by vacumn distillation, bp = 112-115°C at 0.3 torr. FTIR (neat): 3600 - 2600 (O-H), 2870 (C-H), 1762(C=O), 1732 (C=O), 1455, 1237, 1127 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 mHz): δ 0.80 - 1.10 (CH_3's and cyclic CH_2, m, 12H), 1.40 - 2.20 (cyclic CH_2, m, 5H), 3.21 (proton α to C_1 of isoquinoline ring d of t, 1H), 4.15 (acyclic CH_2's, q, 2H), 10.01 (acidic proton, s, 1H). [α] = -92.4° (neat).

Synthesis of (-)-Menthoxyacetyl chloride (108)[104]

A solution of pure (-)-menthoxyacetic acid in thionyl chloride was allowed to reflux for 24 h and then cooled to room temperature [reaction completion was monitored by disappearance of the OH absorption in the FTIR]. The excess thionyl chloride was then distilled from the product (1 atm., 70 °C) and the product, (-)-menthoxyacetyl chloride, was purified by distillation under reduced pressure (bp 80 - 82°C, 0.3 torr). FTIR (neat): 2800 (C-H), 1798 (C=O), 1455, 1237, 1127 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 mHz): δ 0.80 - 1.10 (CH_3's and some cyclic CH_2, m, 12H), 1.40 - 2.20 (cyclic CH_2, m, 5H), 3.21 (proton α to C_1 of isoquinoline ring, d of t, 1H), 4.45 (acyclic CH_2, s, 2H), [α] = -92.1 (neat).

Synthesis of 2-[(l)-Menthoxycarbonyl]-1,2-dihydroisoquinaldonitrile (110)

To a stirred solution of isoquinoline (9.68g, 75.0 mmoles) in CH_2Cl_2 (150 ml), (-)-menthyl chloroformate (18.04g, 82.5 mmoles) was added (0 °C, N_2). After 15 min this was followed by the addition of TMSCN (7.82g, 76.0 mmoles). Stirring was continued for 48 h at room temperature and the reaction was terminated by the addition of water (150 ml) and subsequent stirring overnight [completion of the reaction was monitored by TLC (EtOAc : hexane :: 2 : 8)]. The methylene chloride layer was then separated and washed with water (2 x 30 ml), 10 % HCl (2 x 20 ml), water (2 x 30 ml), aq. sat'd $NaHCO_3$ (2 x 30 ml), and water (2 x 30 ml). It was dried over sodium sulfate and concentrated by rotary evaporation to give the crude product (24.3 g, 96 % yield). Pure product was obtained by three recrystalizations form hexane, mp 93 - 94 °C, [α]= -63.4° (1.53, CH_2Cl_2) (ref HWG-3-21 mp 96.1 - 97.1)

FTIR: 2950 (C-H) and 1713 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 0.50 - 2.20 (m, 18H), 4.60 - 4.90 (m, 1H), 5.93 - 6.60 (m, 1H), 6.20(1d) and 6.38(1d) (dd, 1H), 6.87(1dd) - 7.05(1dd) (m, 1H), 7.15 (d, 1H), 7.20 - 7.38 (m, 3H) (Figure 8). Elemental analysis of HWG-3-21 calc'd for $C_{21}H_{26}N_2O_2$: C 74.52; H 7.74, N 8.28. Found : C 74.51, H 7.74, N 8.30.)

Synthesis of S-(-)-1-Isoquinolyl-t-Butyl-Carbinyl Menthyl Carbonate (120)

To a well stirred solution of a 6 : 4 ratio of the diastereomeric the Reissert compounds **110a** and **110b** (500 mg, 3.0 mmoles) in DMF (50 ml), pivaldehyde was added (0.17 ml, 3.0 mmoles). The reaction mixture was placed under nitrogen and then cooled to -40°C. This was followed by the addition of 80 % NaH (80.0 mg, 3.3 mmoles). The reaction was then allowed to stir for an additional 5 h and then quenched by the addition of water (300 ml) [completion of the reaction was monitored by TLC (EtOAc : hexane :: 1 : 9)]. The crude product was isolated as mentioned in the general procedure. The m.p. of the crude was 90 - 100 °C and the optical rotation was [α]= -42.5° (c=2, CH_2Cl_2). HPLC on a Pirkle covalent phenylglycine column (solvent: 99 % hexane / 1 % isopropanol, flow rate: 1 ml/min) showed two peaks, one at 390 - 400 sec and another at 420-430 sec, ratio 82 : 18 (Figure 10). The crude product was then recrystalized from hexane. Upon

recrystalization three times to constant mp and optical rotation the mp increased to 122 - 123 °C. The HPLC results also showed the disappearance of the peak at 420 - 430 sec (Figure 10). The optical rotation of the major diastereomer was [α]= -35.4° (c = 1.78, CH_2Cl_2). X-ray crystallography (Figure 11) showed the configuration of the major diastereomer to be S. FTIR: 2887 - 2964 (C-H), 1779 (C=O), 1170 (C-O), 1166, and 1128 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 mHz): δ 0.50 (d, 1H),0.70 - 2.03 (m, 26), 4.1 - 4.6 (m, 1H), 6.10 - 6.30 (77 : 23 mixture of diastereomers) (d, 1H) [pure diastereomers (s, 1H)], 7.50 - 7.90 (m, 4H), 8.30 - 8.60 (m, 2H) (Figure 9). Anal. Calcd. for $C_{25}H_{35}NO_3$: C 75.46, H 8.87. N 3.52. Found: C 75.44, H 8.90, N 3.51.

Synthesis of (S)-(-)-1-Isoquinolyl t-Butyl Carbinol (121)

To a stirred solution of S-(-)-1-isoquinolyl-t-butyl methyl menthyl carbonate (318 mg, 0.80 mmoles) in THF (25 ml), EtOH (25 ml), and water (25 ml), solid NaOH (324 mg, 8.0 mmoles) was added and the solution was heated to reflux. The solution was allowed to reflux for 2.5 h and was then terminated by cooling the reaction to room temperature [reaction completion was monitored by TLC (EtOAc : hexane :: 1 : 1)]. The crude product was isolated as noted in the general procedure (90 mg, 80 % yield). Pure product was obtained by twice recrystalizing from EtOAc / hexane, mp 100 - 101, [α] = - 70.58° (c = 1.17, CH_2Cl_2). Utilization of the CSA (quinine) as described in the general procedure below indicated that the compound was optically pure (100 % ee) (Figure 12). FTIR: (identical to that of the racemate). ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 0.90 (s, 9H), 4.3 - 4.5 (d, 1H), 5.1 - 5.3 (d, 1H), 7.50 - 7.70 (m, 3H), 7.80 - 7.90 (d, 1H), 8.10 - 8.20 (d, 1H), 8.50 - 8.60 (d, 1H) (Figure 7).

Synthesis of R-(+)-1-Isoquinolyl t-Butyl Carbinol (123)

To a stirring solution of (R)-(+)-1-isoquinolyl-t-butyl methyl menthyl carbonate (165 mg, 0.36 mmoles) in water (5 ml), EtOH (5 ml), and THF (5 ml), NaOH (10 eq) was added and the

mixture heated to reflux. The mixture was allowed to reflux for 2.5 hours and the reaction was terminated by cooling the mixture to room temperature. The crude product (90 mg, 70 % yield) was isolated as described in the general procedure above. The crude product was purified by one recrystalization from EtOAc / hexane, mp 100 - 101 °C, $[\alpha] = + 68.9°$ (c = 2.00, CH_2Cl_2). The optical purity as measured by the use of quinine as a CSA decsribed below was 98 % ee (Figure 13).

Spectral data of the pure (+)-enantiomer were identical to those of the racemate as reported earlier.

Procedure for Determination of the Enantiomeric Excess of 1-Isoquinolyl t-Butyl Carbinol

A sample of the compound was weighed on the analytical balance and mixed with quinine, weighed out such that the molar ratio of the 1,2-aminoalcohol to quinine was 1:3. The mixture was dissolved in a minimal amount of $CDCl_3$ in a vial. Ten drops of D_2O were then added to the vial and the sample was shaken vigorously for one hour. Then molecular sieves were added and the sample was allowed to sit for five minutes. The sample was then filtered into an NMR tube and the minimum amount of $CDCl_3$ was added to allow NMR determination. The ^{1}H-NMR spectrum of this sample was run. Before the addition of quinine the methine proton of the racemate showed a doublet centered at 5.2 ppm. Upon addition of the quinine the doublet became a pair of doublets which overlap slightly. The pair of doublets was then collapsed to the two singlets by the D_2O exchange. See Figure 7. In the case of the pure enantiomer (Figure 12) only one of the singlets was present. The H_8 proton is also a doublet at 8.13 ppm. This doublet became a pair of doublets upon addition of quinine to the racemate (Figure 7). The pure enantiomer showed only one of the doublets (Figure 12).

Synthesis of 2-Methoxyacetyl-1,2-dihydroisoquinaldonitrile (124)

To a well stirring solution of isoquinoline (13.05 ml, 0.1101 mmoles) in CH_2Cl_2 at 0 °C,

methoxyacetyl chloride (10.01 g, 0.1101 mmoles) was added dropwise. The solution was allowed to stir for 15 min and followed by the addition of TMSCN (16.14 ml, 0.1211). The reaction was allowed to stir at 0 °C under N_2 for 24 h. The reaction was monitored by TLC. The reaction was terminated by the addition of water (100 ml) followed by isolation of the organic layer. The organic layer was dried over sodium sulfate and rotoevaporated to dryness to give crude product (30 g, 100 % yield). The product was purified by column chromatography on silica gel (5 : 95 :: EtOAc : hexane) followed by three recrystalizations from EtOAc / hexane, mp 103.2 - 104.0 °C.

FTIR (KBr): 2957 (C-H), 1680 (C=O), 1630 (Ar C-H), 1344 and 1130 cm^{-1}. NMR (270 mHz, $CDCl_3$) δ 3.5 (s, 3H), 4.3 (s, 2H), 6.15 (d, 1H), 6.65 (s, 1H), 6.90 (d, 1H), 7.2 - 7.5 (m, 4H) (Figure 14).

Elemental anal calc'd for $C_{13}H_{12}N_2O_2$: C 68.40, H 5.30, N 12.28. Found: C 68.48, H 5.32, N 12.30.

Synthesis of 2-(-)-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile (125)

To a well stirring solution of isoqinoline (10.6 g, 82.6 mmoles) in CH_2Cl_2 (50 ml), (-)-menthoxyacetyl chloride (20.4 ml, 82.6 mmoles) was added. After stirring for 15 min, TMSCN (11.20 ml, 84.0 mmoles) was added. The reaction was continued for 36 h and the reaction was then terminated by the addition of water (100 ml) and subseqeuntly stirred overnight [Reaction completion was monitored by TLC (EtOAc : hexane :: 1 : 1)]. The methylene chloride layer was separated and washed with water (3 x 20 mL), 10% HCl (2 x 20 ml), water (2 x 20 ml), aq. sat'd $NaHCO_3$ (2 x 20 ml), and water. It was dried over sodium sulfate and concentrated by rotary evaporation to give the crude product (27.91 g, 97 % yield). The pure product was obtained by first dissolving the compound in EtOAc and twice treating it with activated charcoal and finally filtering the solution through Celite. The ratio of the diastereomers in the crude compound was 1 : 1. The compound was then purified by silica gel column chromatography, eluting consecutively with hexane, hexane : EtOAc (99.75 : 0.25), and hexane : EtOAc (99.50 : 0.50) (mp 79 - 81). This column resulted in partial separation of the diastereomers. The first fraction obtained gave a 65 : 35

ratio of diastereomers (Figure 17)and in the middle of the collection the ratio then went to 48 : 52 (Figure 15) within a few fractions. FTIR: 2960 - 2860 (C-H), 1738 (C=O), 1630 (Ar C-H), 1450, 1221, and 1124 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$, 270 mHz): δ 0.60 (m, 1H), 0.80 ppm - 1.00 (m, 11H), 1.23- 1.45 (m, 2H), 1.52 - 1.75 (m, 2H), 2.03 - 2.38 (m, 2H), 3.10 - 3.35 (m, 1H), 4.21 - 4.43 (m, 2H), 6.10 (dd, 1H), 6.61 (d, 1H), 6.98 (d, 1H), 7.2 (d, 1H), 7.26 - 7.42 (m, 3H) (Figures 15, 16, 17). The compound was not analytically pure at this point, but degradation on silica gel and alumina combined with the high solubility of the compound made further purification attempts of this intermediate impractical. Anal. Calc'd for $C_{17}H_{21}NO_3$: C 71.05, H 7.37, N, 3.51 Found: C , H , N .

Synthesis of 1-Isoquinolyl t-Butyl Carbinyl Methoxyacetate (126)

To a solution of the Reissert compound **125** (250 mg, 1.10 mmoles) in DMF (12 ml), pivaldehyde (0.12 ml, 1.10 mmoles) was added. The mixture was allowed to stir (N_2, -40 °C) for 30 min after which 60 % NaH (52.0 mg, 1.30 mmoles) was added. THe reaction was allowed to continue stirring at -40 °C for 5 h. THe reaction was terminated by the addition of water (100 ml). The aqueous layer was then extracted with CH_2Cl_2 (4 x 20 ml) and the organic layer washed several times with water to remove DMF. The organic layer was then dried over Na_2SO_4 and rotoevaporated to dryness to yield crude product (310 mg, 98 % yield), mp 116 - 117 °C. The product was purified by silica gel chromatography (90 : 10 :: hexane : EtOAc).

FTIR (neat): 2960, 2932, 1750, 1627, 1382, 1273 and 1128 cm^{-1}. ^1H NMR ($CDCl_3$, 270 mHz) δ 1.10 (s, 9H), 3.40 (s, 3H), 4.20 (s, 2H), 6.55 (s, 1H), 7.6 - 8.05 (m, 4H), 8.40 (d, 1H), 8.60 (d, 1H) (Figure 18).

Synthesis of (l)-1-Isoquinolyl t-Butyl Carbinyl l-Menthoxyacetate (127)

To a solution of a 1 : 1 diastereomeric mixture of the Reissert compounds **125a** and **125b** (50.0 mg, 0.20 mmoles) in DMF (10 ml), pivaldehyde (0.021 ml, 0.20 mmoles) was added. The solution was placed under nitrogen and then cooled to -40°C . After 15 min of stirring, 80 % NaH

(5.10 mg, 0.21 mmoles) was added and the solution was allowed to stir overnight at -40 °C. The reaction was quenched by the addition of water 150 ml. The sample was then extracted into ether several times and the ether layer washed with water several times. The sample was evaporated and allowed to dry overnight. he solid was then washed with hexane several times. HPLC on Pirkle phenylglycine column (flow rate 1 ml / min; solvent, 99 : 1 :: hexane : isopropanol) indicated separation of diastereomers on the order of 80 % de (Figure 20). Verification of the peaks and retention times was provided by the sample below since the structure of the sample below was verified by NMR.

A separate sample was made by the same method and the crude product, a brown oil, (3.8g, 98.4 % yield) (0 % de) analyzed by NMR. Column chromatography on silica gel was performed (9 : 1 :: hexane : EtOAc) and pure product as well as separation of the diastereomers (40 % de by NMR, Figure 19) was obtained, mp 65 - 75 °C, $[\alpha] = -49.0°$ (c = 3.3, CH_2Cl_2). HPLC results on the Pirkle column with the same conditions listed above gave the major peak at 533 sec (71 %) and the minor peak at 550 sec (29 %)(i. e., 42 % de).

FTIR (neat): 2955, 2924, 1756, 1126 cm^{-1}. ^1H NMR ($CDCl_3$, 270 mHz) δ 0.60 - 2.30 (m, 26H), 3.10 (m, 1H), 4.21 (m, 2H), 6.50 (d, 1H) for diastereomer mixture, 7.60 - 7.90 (m, 4H), 8.20 and 8.40 (2d, 1H), 8.50 and 8.57 (2d, 1H) (Figure 19). Anal. Calc'd for $C_{25}H_{37}NO_3$: C 75.15, H 9.33, N 3.51. Found: C 75.17, H 9.03, N 3.66.

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