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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

Dedicated to the loving memory of my parents * * *

" There is no problem that will stand

the assault of sustained thought."

Voltaire

"Do not follow where the path may lead.

Go instead where there is no path

and leave a trail."

R. Zaphiropoulos

"Deal with the task at hand and

all else will fall into place."

Anon. (RC)

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LIST OF ABBREVIATIONS AND SYMBOLS

Ac	acetyl
Ar	aryl
Bn	benzyl
Bu	butyl
BOC	butyloxycarbonyl
Bz	benzoyl
°C	degrees Celsius
Calc:	calculated
CI	chemical ionization
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
EI	electron impact
eq.	equivalents
h	hours
Hz	Hertz
HRMS	high resolution mass spectrum
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilizane
m	multiplet
M	molar
$M^{+\bullet}$	parent molecular ion
m/z	mass/charge ratio
mCPBA	meta-chloroperbenzoic acid

min	minutes
mmol	millimoles
mp	melting point
MS	mass spectrum
Ms	methanesulfonyl
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
PDC	pyridinium dichromate
Pf	pentafluorophenyl
Ph	phenyl
PMB	para-methoxybenzyl
ppm	parts per million
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl

ABSTRACT

Chapters 3-6 outline attempts to generate a tri-fused sulfone and sultine suitable as an ortho-quinodimethane precursor that could be used in a novel synthesis of lysergic acid. Several penultimate intermediates were prepared and characterized, but in no cases were the final steps successful. A number of approaches centered on the use of a sulfonium salt as an intermediate. Attempted activation 3-thiomethyl-4-hydroxymethyl indole with methanesulfonyl chloride and triethylamine did not result in the formation of a tricyclic sulfide. The planar geometry of the indole and the inability of the sulfur, electrophilic center and leaving group to align with the geometry necessary for an S_N2 pathway was suspected to be responsible. Attempts to prepare 3-thiomethyl-4-hydroxymethyl-2,3-dihydroindole were not successful. 3-Thioalkyl indolines (2,3-dihydroindole) were found to be quite reactive materials, readily loosing the thiomethyl group and forming indoles. A mechanism that involves nitrogen assistance and proceeds through an 1-aza-1,3-diene is proposed to account for this conversion.

Attempted cyclization of 4-hydroxymethyl-3-thiomethyl-2-oxindole under basic conditions did not afford the desired tricycle and resulted in complicated reaction mixtures. Activation under acidic conditions (HI) resulted in dethiomethylation of the oxindole. This reaction led to the development of a mild, non-reductive method for the desulfenylation of 3-thioalkyl-2-oxindoles. Optimium conditions were found when the reagent pair TsOH and PPh_3 were used.

Attempted cyclization of 3-thiobenzyl-4-hydroxymethylindole-S-oxide with NCS and SO_2Cl_2 did not result in the formation of a tricyclic sultine. The new target was expected to be less strained and therefore remove some of the problems associated with the failure to prepare a tricylic sulfone. However, sultine formation also proved to be problematic. All the difficulties were believed to be due to the electron donating ability of the nitrogen, and and aromatic ring system. A mechanism to account for the formation of a bicyclic chloro-sulfone rather than a tricyclic sultine is proposed.

Factors influencing the metal hydride mediated reduction of pendant ester groups of 3-thiomethyl-2-oxindoles were probed by preparing a number of oxindole derivatives. All compounds prepared differed only in the position of the ester group, and the alkyl substitution at the 1 and 3 position. It was found that if the oxindoles

have a proton α to the oxindole carbonyl, then reduction of the pendant ester occurs first. If a proton is available at C3, then deprotonation occurs. If this center is ortho or para to the benzoate, then initial reduction is difficult, and over-reduction is common. For 1,3-dimethyl-3-thiomethyl-2-oxindoles, a different pathway is followed. Initial reduction of the oxindole carbonyl seems to occur first in this case. The intermediate hemi-aminal which results from the first hydride addition to the carbonyl may follow a number of pathways. An unusual rearrangement of the thiomethyl group from the 3 to 2 position was also observed. Mechanism to explain these transformations are proposed.

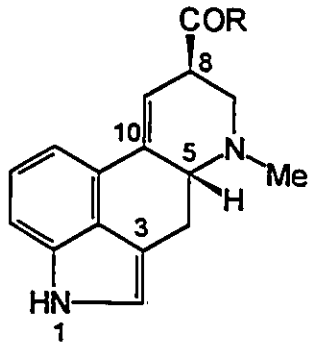
Finally, bicyclic ortho-quinodimethanes were prepared via two routes. New routes to a series of bicyclic carboxaldehydes followed by photo-enolization led to bicylic ortho-quinodimethanes which were trapped with a series of dienophiles. An ionic route was also developed that led to the successful preparation of a 6-6-6 and a 6-6-7 tricyclicsulfone. Chelotropic expulsion of SO_2 led to ortho-quinodimethanes.

Finally, the opportunity of explore the solid state mobility of N-methoxy-N-methyl-1,2,3,4-tetrahydronapthylcarboxamide presented itself. This compound was found to exhibit considerable mobility in the solid state. A cyclohexene-type inversion was found to take place with an apparent activation energy of 12.3 kJ/mol. An analogue which was di-deuterated at the 3 position was also prepared, and broad line ^{2}H-NMR used to study its mobility. The corresponding acid was also found to be mobile, but with only limited mobility at higher temperatures. Although the dipolar dephased spectrum of the acid suggested that it was quite rigid, examination of the change in line shape of the deuterated analogue at higher temperatures suggests that there is some, albeit limited, mobility. An single crystal X-Ray diffraction study also supports the mobility of the amide. The crystal packing of the unit cell is believed to be responsible for this mobility.

Chapter 1 - Introduction

1.1 Isolation, Structure Elucidation and Biological Activity of Lysergic Acid

Lysergic Acid (1) belongs to a large class of natural products known as ergot alkaloids. The term ergot is used to describe the filamentous fungus, *Claviceps purpurea* (Fries) Tulasne, which grows parasitically on the ripening ears of rye in place of the rye grains. Ergot was responsible for outbreaks of epidemics known as St. Anthony's Fire when rye, infested by the fungus, was used to make bread[1,2].

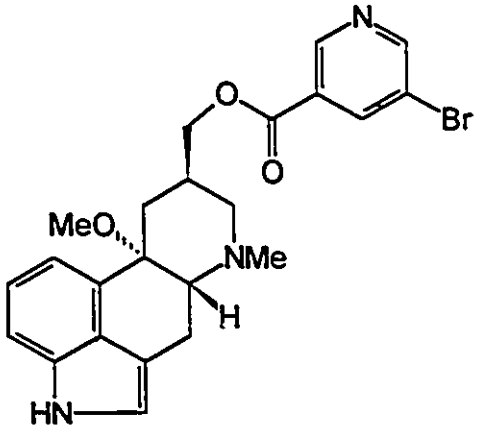


1; R=OH
2; R=NEt2

Lysergic acid (1) was first isolated by basic hydrolysis of ergot alkaloids[3-5]. The structure was established using degradative studies[4,6-8] and physical measurements[9,10]. The relative stereochemistry was assigned by observing that hydrogenation of the Δ^{9-10} double bond of 1 yielded only one stereoisomer, indicating that the carboxylic group at C-8 and the proton at C-5 are on the same side of the molecule, thus screening one side of the double bond[11]. In the case of isolysergic acid, which has the opposite configuration at C-8, two isomers were obtained when it was subjected to similar hydrogenation conditions. The absolute stereochemistry was later deduced by analysis of rotation-dispersion curves[12] and chemical degradation to an amino acid of known configuration[13].

Lysergic acid and some of it derivatives, particularly lysergic acid diethylamide (LSD) 2 have enjoyed rich histories concerning their biological activity. As pointed out by Hofmann in an early review of ergot alkaloids[14], there were more then 1000 reports on the pharmacological effects of LSD in the 20

years following its preparation. All ergot alkaloids display the same biological effects to some degree. The principal effects are: uterotonic action, increase or decrease in blood pressure, induction of hypothermia and emesis, and control of the secretion of pituitary hormones. A number of reviews have appeared dealing with this subject[15-18].



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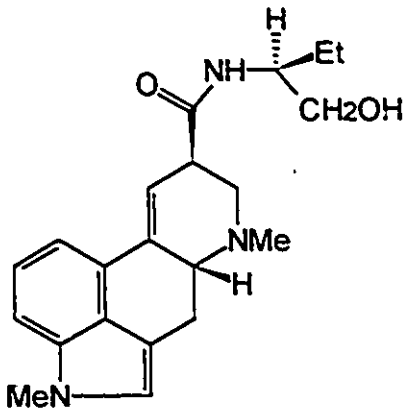

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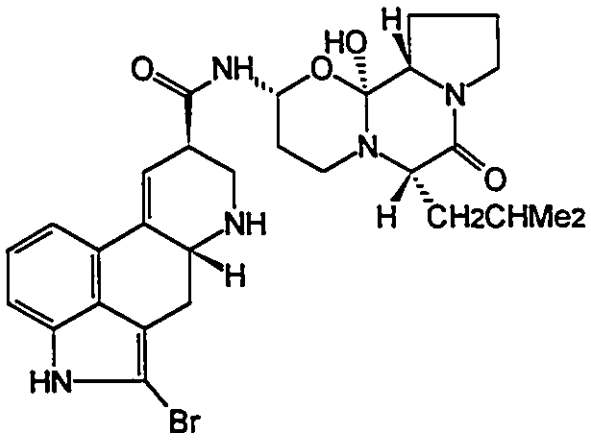


5

A number of ergot alkaloids derivatives have found their way into clinical use for a variety of ailments. These include Nicergoline 3, a vasodilator and antihypertensive, Methysergide 4, a serotonin receptor

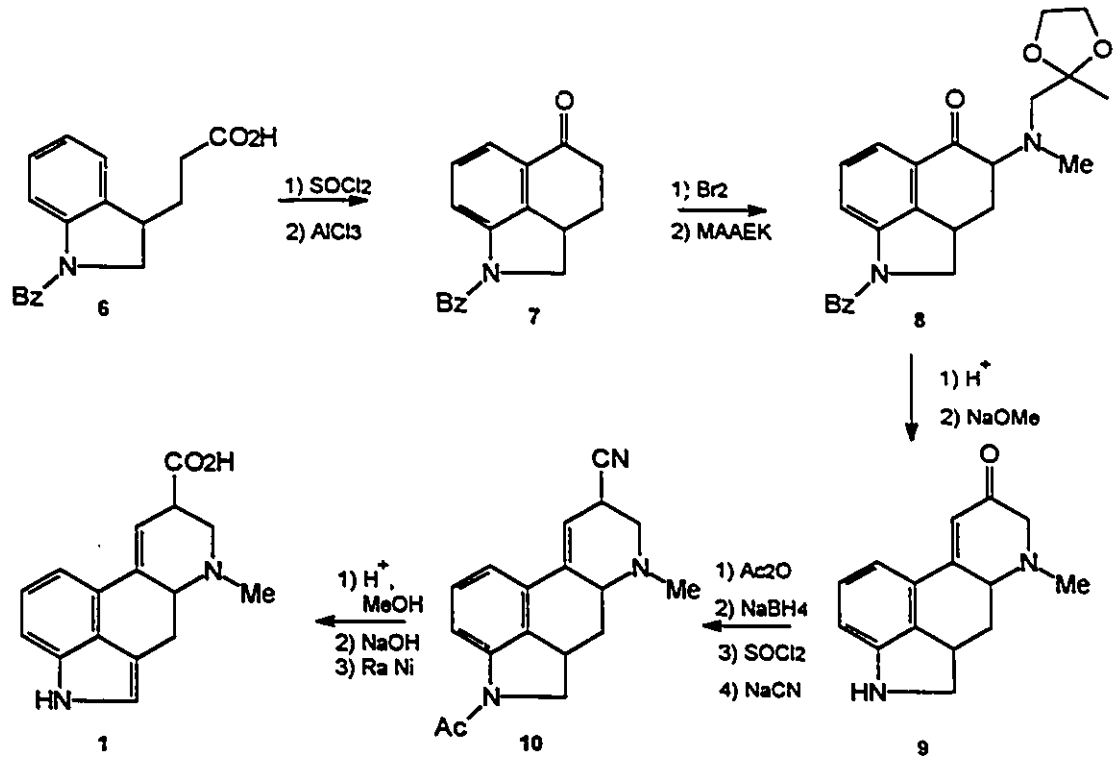
antagonist used in the prevention of migraines, and Bromocriptine 5, a prolactin inhibitor used in Parkinson therapy.

1.2 Previous Synthesis of Lysergic Acid

Owing to the remarkable biological activity of some derivatives of lysergic acid, it has become of central interest not only in medicinal chemistry, but also in synthetic chemistry. Somewhat surprisingly despite the 60 year time span since its isolation, there have been only nine total syntheses published to date[19-27]. This section reviews three of these: Woodward's, since it was the first; Rebek's because it resulted in enantiomerically pure material; and the most recent one published by Vollhardt which illustrates a novel cyclization strategy and is only eight steps from a known compound.

1.2.1 Kornfeld-Woodward Synthesis

The first total synthesis was reported by Kornfeld and Woodward in 1954[19]. Their synthesis started with N-benzoyl-3-(β-carboxyethyl)-dihydroindole (6) which was converted to the tricyclic intermediate 7 by conversion of the acid to the acid chloride, followed by intramolecular Friedel-Crafts acylation. Treatment of 7 with Br_2, followed by addition of methylaminoacetone ethylene ketal (MAAEK) led to formation of the ketal-ketone 8. Treatment of 8 with acid afforded a diketone which was cyclized by treatment with sodium methoxide to afford the tetracyclic intermediate 9. Acetylation of the free amine which had been generated under the cyclization condition with Ac_2O, followed by $NaBH_4$ reduction of the ketone, conversion of the allylic alcohol to the chloride $SOCl_2$, followed by displacement of the allylic chloride with NaCN in liquid HCN gave rise to nitrile 10. Methanolysis of the nitrile to the methyl ester, followed by basic hydrolysis and dehydrogenation with Raney nickel afforded racemic lysergic acid 1.

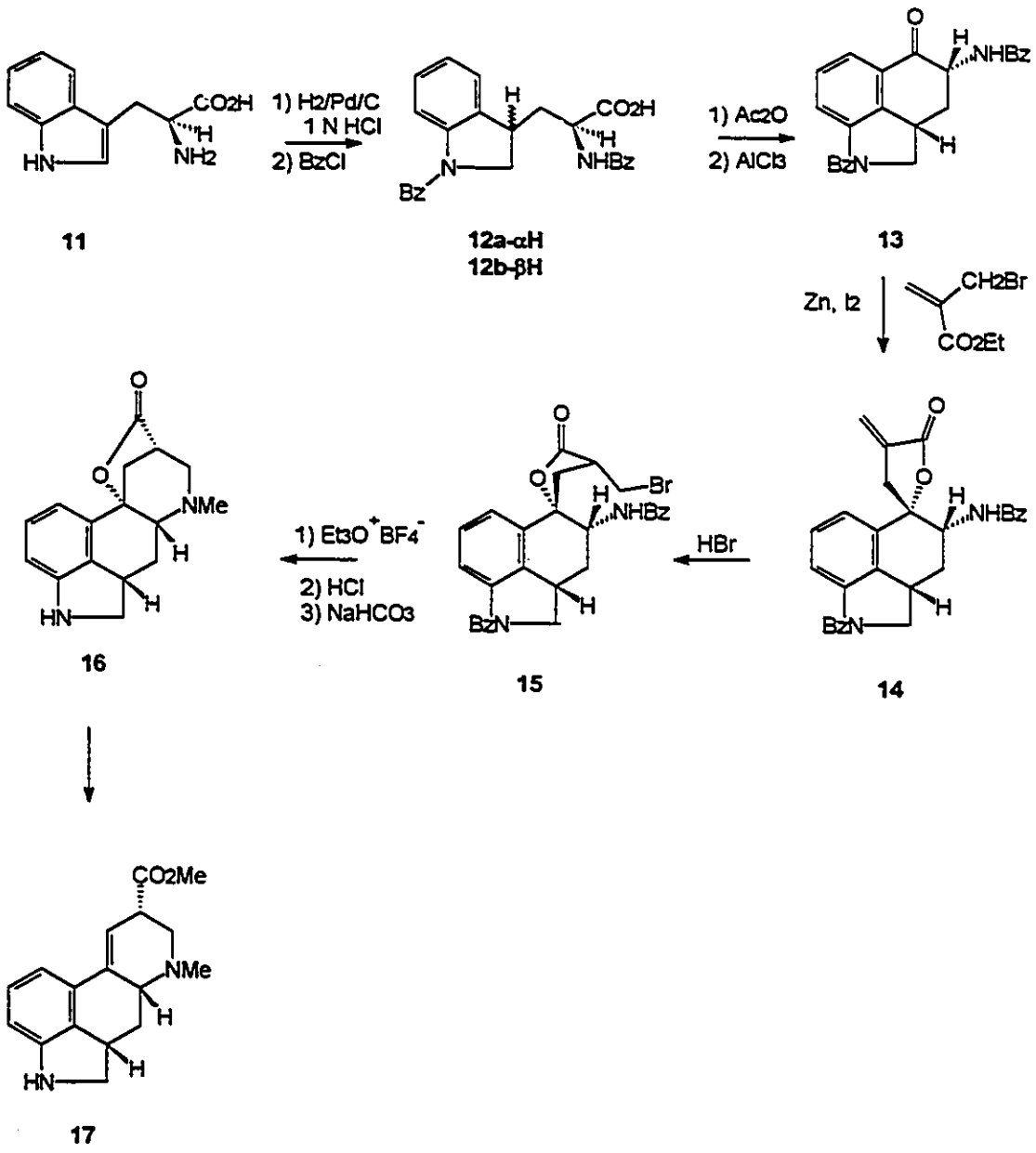


Scheme 1.1 - Kornfeld - Woodward Synthesis of Lysergic Acid

1.2.2 Rebek's Synthesis

Rebek is credited with the only synthesis that can provide enantiomerically pure lysergic acid. His original synthesis started with racemic tryptophan, so racemic material was produced[20a]. However, the synthesis was modified in a way to provide enantiomerically pure material[20b]. Hydrogenation of commercially available L-tryptophan **11** under acidic conditions with Pd/C followed by dibenzoylation provided a mixture of separable diastereomers **12a** and **12b**. Activation of the carboxylic acid as a mixed annhydride, followed by an intramolecular Friedel-Crafts acylation led to a single isomer of the tricyclic ketone **13**. Under these reaction conditions, epimerization of the center α to the carbonyl (i.e., the original asymmetric center in tryptophan) enables each diastereomer to be converted into a single enantiomer. A Reformatsky reaction, followed by intramolecular lactone formation led to **14** which was then converted to bromide derivative **15** by treatment with HBr. Selective debenzoylation led to the

tetracyclic intermediate **16**. Cleavage of the lactone ring with thionyl chloride, followed by dehydration with phosphorous pentoxide afforded dihydroisolysergic acid methyl ester **17**.

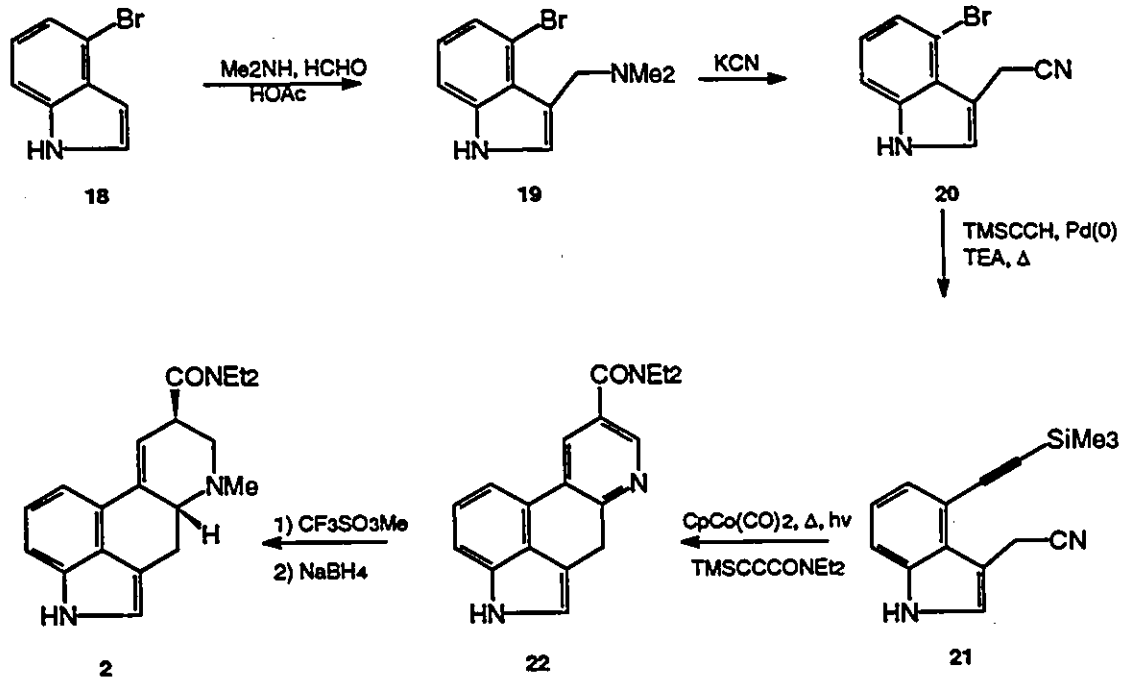


11 **12a-αH** **12b-βH** **13** **14** **15** **16** **17**

Scheme 1.2 - Rebek's Formal Synthesis of iso-Lysergic Acid.

1.2.3 Vollhardt's Synthesis

The most recent synthesis of a member of the lysergic acid family was reported by Vollhardt[21], who synthesized the diethylamide derivative, LSD, 2 in a conceptually different way using the cobalt catalyzed [2+2+2] cycloaddition methodology developed in his laboratory. The synthesis started with 4-bromoindole 18, which was converted to tryptamine derivative 19 via a Mannich reaction followed by conversion to nitrile 20 by displacement with KCN. Pd(0) mediated coupling of the bromoarene with trimethylsilylacetylene in the presence of Cu(I) and base furnished acetylene 21. Use of the author's cobalt catalyzed co-cyclization strategy with the amide partner shown resulted in, after protodesilylation on SiO_2 during chromatography, indolequinoline 22 in a yield of 13%. Methylation followed by reduction with borohydride afforded LSD, along with 10% of the iso-lysergide, as evident by NMR.



Scheme 1.3 - Vollhardt's Synthesis of LSD 2.

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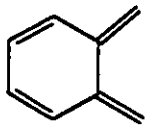
Chapter 2 - Ortho-Quinodimethanes

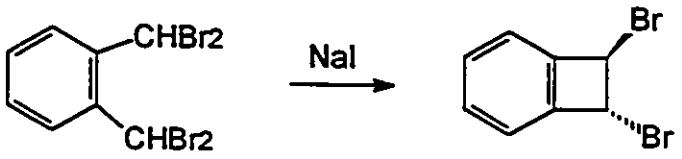
2.1 Introduction

o-Quinodimethane 1 (oQDM) also called o-xylylene, is an extremely reactive intermediate that has been used extensively in organic synthesis[1-5].



1

o-Quinodimethanes are very willing participants in pericyclic reactions, especially in [4+2] cycloadditions, since cycloaddition results in the restoration of aromaticity. First postulated as an intermediate in 1956 by Cava[6] to explain the formation of dibromobenzocyclobutene 2 from α,α',β, β'-tetrabromoxylene, it was not until Errede[7] reported the isolation of the dimer of oQDM 3 and the eventual isolation of o-QDM in a glassy matrix at low temperature[8] that o-QDMs were accepted as being discrete intermediates.



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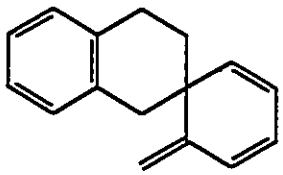

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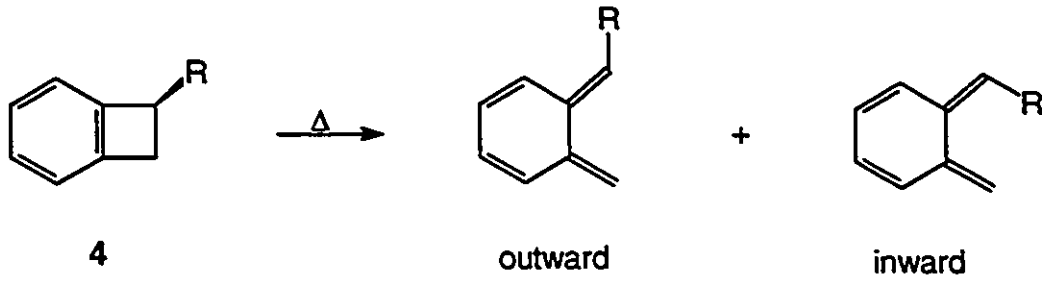
Due to the utility of these intermediates in organic synthesis, considerable effort has been dedicated to finding new ways to generate these reactive intermediates. In general, these methods may be categorized into four headings: electrocyclic ring opening of benzocyclobutenes, 1,4-elimination of α,α'-substituted

o-xylenes, extrusion reactions, and photochemical generation. Each of these methods is briefly reviewed below.

2.2 Electrocyclic Ring Opening of Benzocyclobutenes

One of the most common methods of generating o-QDMs is through the thermolysis of benzocyclobutenes which proceeds via a thermally allowed conrotatory electrocyclic ring opening. Although there are two possible modes of rotation for substituted benzocyclobutenes, one is generally preferred. This preference for inward or outward rotation has been termed torquoselectivity and numerous studies, most notably by the Houk group[9-15] have shown that this effect is mainly electronic, not steric in nature. In general, electron donating groups like alkyl, alcohols, halogens and amines favor outward rotation, whereas electron accepting groups like formyl and boranes prefer inward rotation.

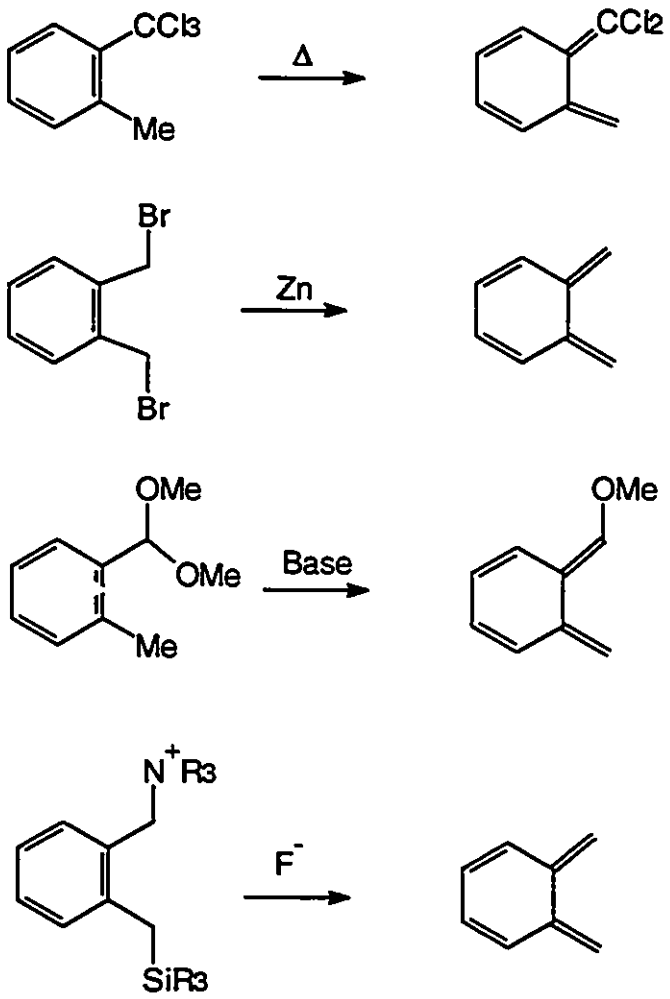


Scheme 2.1 - Conrotatory Ring Opening of Substituted Benzocyclobutene

The nature of the substituent also has a profound effect on the temperature at which the benzocyclobutene undergoes ring opening. Some examples are given for **4**, where the thermolysis temperature follows the nature of the substituent in brackets: R=NH_2 (25 °C), OH (80 °C), OCOR (150 °C), H (200 °C). Although all of these temperatures are attainable under normal laboratory conditions, the biggest drawback of this method for the generation of o-QDMs is the difficulty associated with the synthesis of the appropriately substituted benzocyclobutene.

2.3 1,4-Eliminations of α,α′ - Disubstituted o-Xylenes

As mentioned previously, this method was the first method used to generate o-QDMs. Since the original observation, a number of methods have been developed to carry out the 1,4-elimination. The reaction may be done thermally[16-18], base induced[19-21], fluoride induced[22-25] or a reductive elimination (dehalogenation) the most notable being the recent advances by Sonoda[26] using sodium benzenetellurolate and Rieke[27], using activated nickel[1]. Some examples are shown in the scheme below.

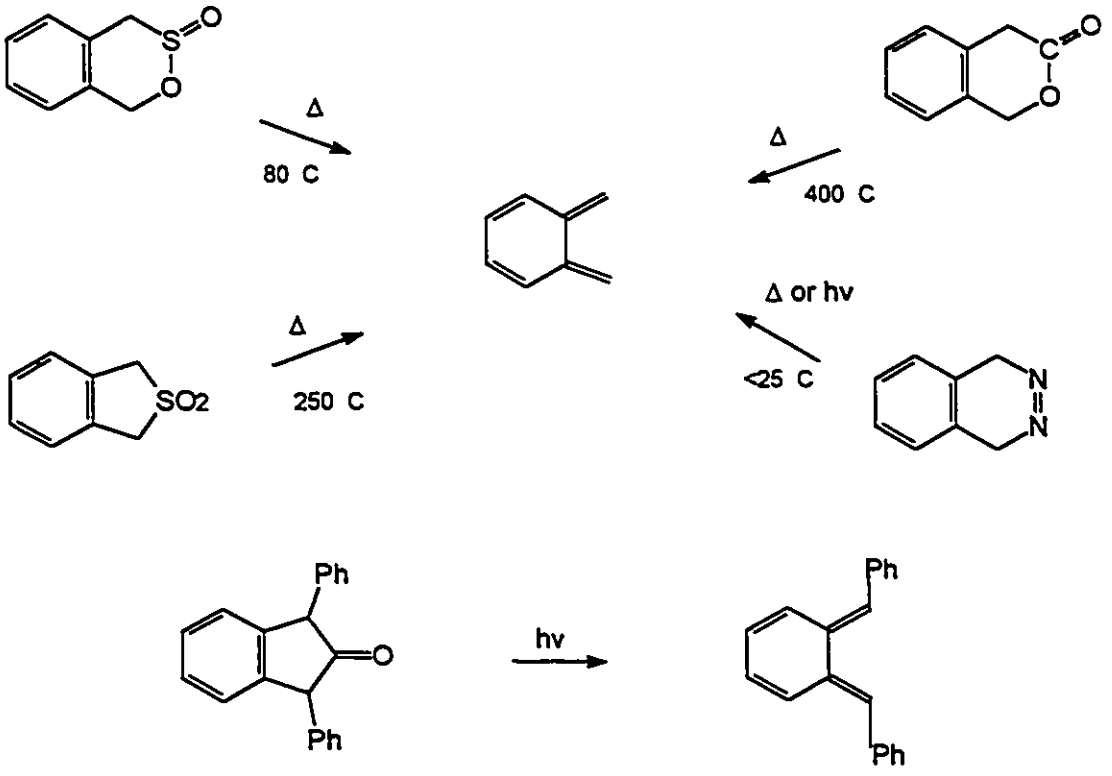


Scheme 2.2 - 1,4-Elimination Route to o-Quinodimethanes

[1] These examples are pointed out only because the 1,4-elimination of dihalides is usually restricted to activated aromatic rings (bearing an alkoxy group). However, in both of the cited references, the reactions may be done on non-activated, and even de-activated (bearing halogen and cyano substituents) substrates.

2.4 Extrusion Reactions

Another popular method for the generation of o-quinodimethanes is the thermal or photochemical expulsion of gaseous molecules such as N_2[28], CO_2[29-30], SO_2[29, 31-38], CO[39] from suitable precursors. An example of each reaction is shown below.

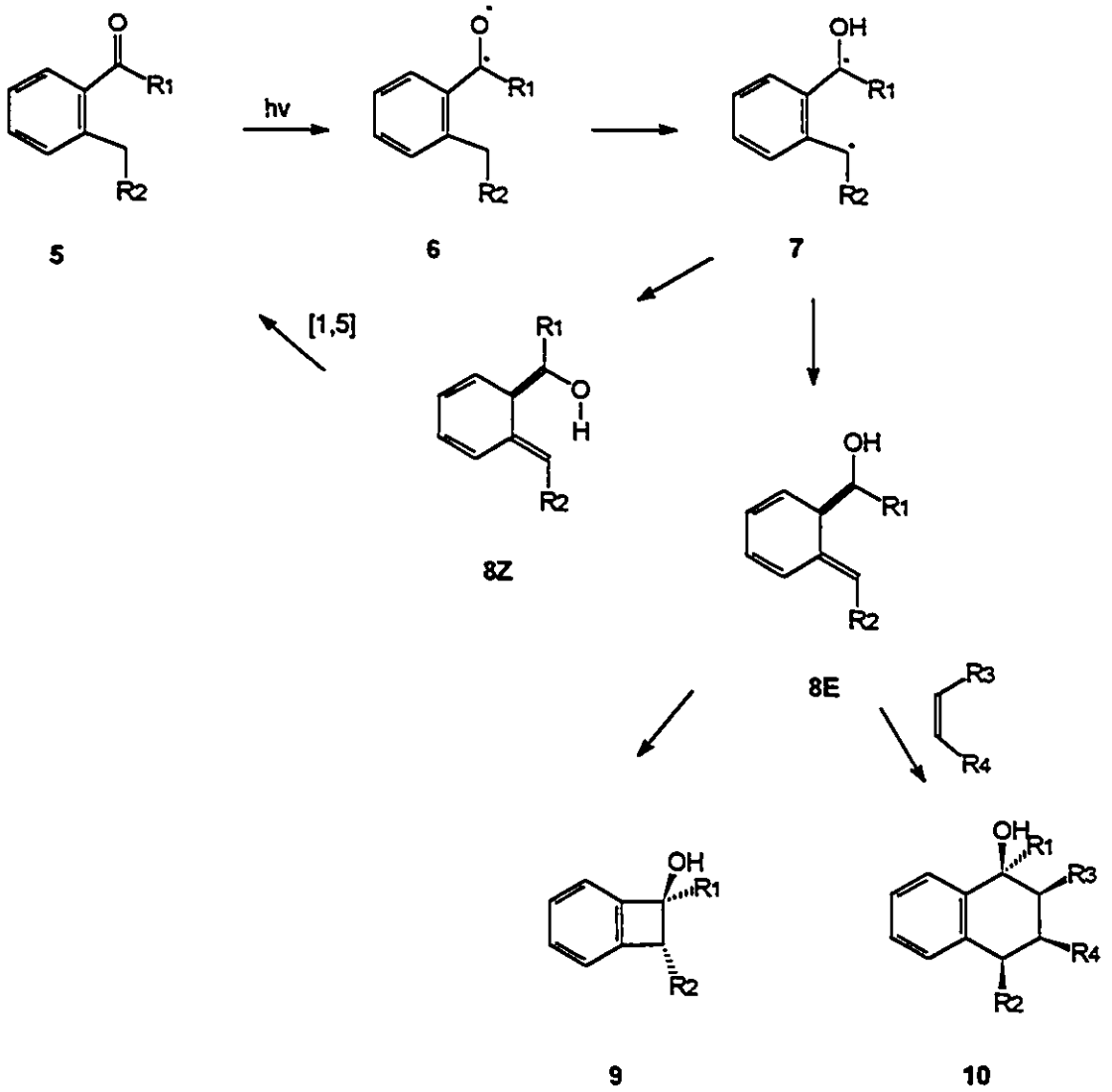


Scheme 2.3 - Extrusion Routes to o-Quinodimethane

2.5 Photoenolization and Photorearrangement

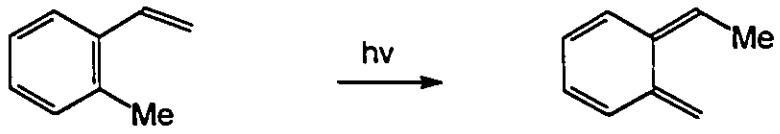
Irradiation of o-alkylated phenyl ketones 5 gives rise to o-quinodimethanes via a mechanism similar to Norrish Type II cleavage[40-42]. Excitation of the carbonyl group results in formation of the singlet excited state, which undergoes rapid intersystem crossing to the triplet 6. γ-Hydrogen abstraction results in the diradical 7, which can then decompose to the Z-dienol 8Z or the E-dienol 8E. The Z-dienol is quite short lived and returns to the starting carbonyl compound via a [1,5] shift. However the E-dienol has a lifetime that is long enough to allow trapping with an external dienophile to form cycloadduct 10. Because of the hydroxy group at the 1-position of the diene, these dienols undergo [4+2] cycloadditions

with a high degree of regioselectivity when reacted with unsymmetrical dienophiles like acrylates. In the absence of an added diene, benzocyclobutenols 9 are sometimes produced, assuming the appropriate precautions are taken during the work-up[40].



Scheme 2.4 - Formation and Reaction of o-Quinodimethanes formed via Photolysis of o-Alkyl Phenyl Ketones

The photoinduced isomerization of o-methyl styrenes has also been reported to give o-quinodimethanes. The reaction is believed to proceed via a [1,5] sigmatropic rearrangement[43], but this reaction has not been studied extensively. Presumably the reverse reaction is also quite facile, limiting this reaction as a suitable method for the generation of o-quinodimethanes.



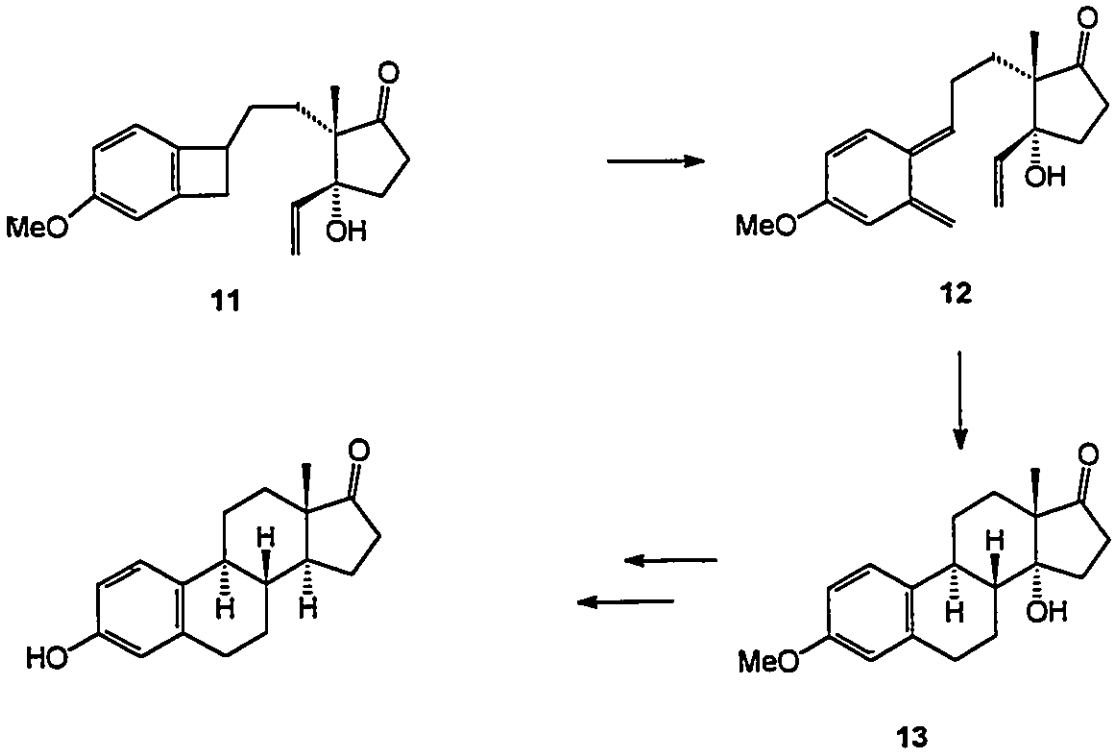
Scheme 2.5 - Photoisomerization of o-Methylstyrenes to o-Quinodimethanes

2.6 Synthetic Applications of o-Quinodimethanes

As mentioned earlier, o-quinodimethanes have been key intermediates in the synthesis of a number of natural products. A few examples are shown below in which the key ring forming reaction utilizes an o-quinodimethane intermediate.

2.6.1 Estrones

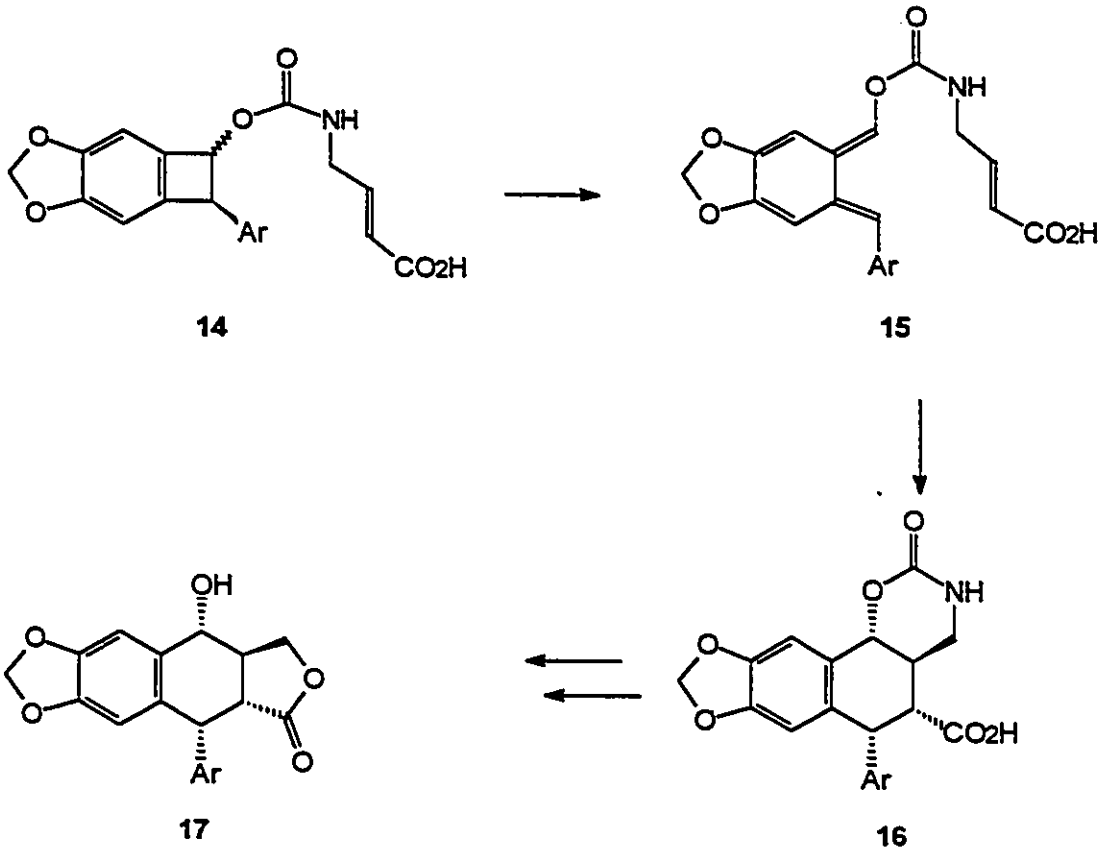
There have been a number of syntheses of the steroid nucleus which utilized an o-quinodimethane to form the B-C ring system[44]. For example, Kametani's[45] synthesis of estrone with the desired stereochemistry proceeded via o-quinodimethane **12** which was generated from the benzocyclobutene **11**.



Scheme 2.6 - Kametani's Synthesis of Estrone

2.6.2 - Podophyllotoxin

The use of o-quinodimethanes in the synthesis of natural products has also been studied in our laboratory. This has culminated in a highly stereoselective synthesis of podophyllotoxin 17[46], in which the key o-quinodimethane 15 was prepared from the benzocyclobutene 14.

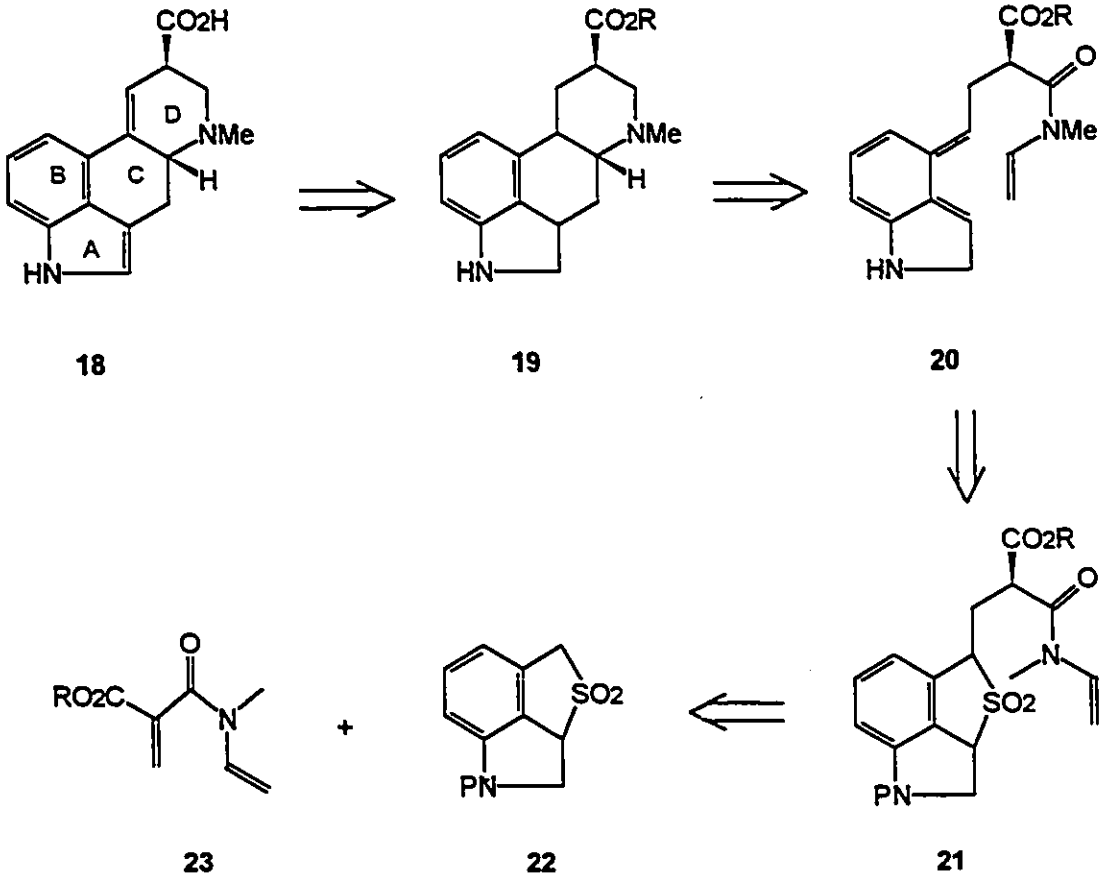


Scheme 2.7 - Durst's Synthesis of Podophyllotoxin

2.7 Retrosynthetic Analysis of Ergot Alkaloids

As pointed out earlier, the ergot alkaloids, such as lysergic acid 18, continue to attract considerable attention from both a medicinal and synthetic viewpoint[47]. The goal of this research program was to study the feasibility of utilizing an ortho-quinodimethane route to provide access to the

ergot alkaloid class of natural products. In the examples shown in the previous section, it is readily apparent that the ortho-quinodimethane disconnection may considered when the target molecule contains an aromatic ring fused to a six membered ring. It should therefore be possible to use this disconnection for the ergot alkaloids. Looking at lysergic acid 18, and removing the two double bonds exocyclic to ring C gives 19. This system should be accessible using the o-QDM strategy.



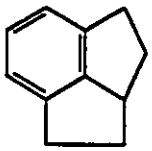
18 19 20

23 22 21

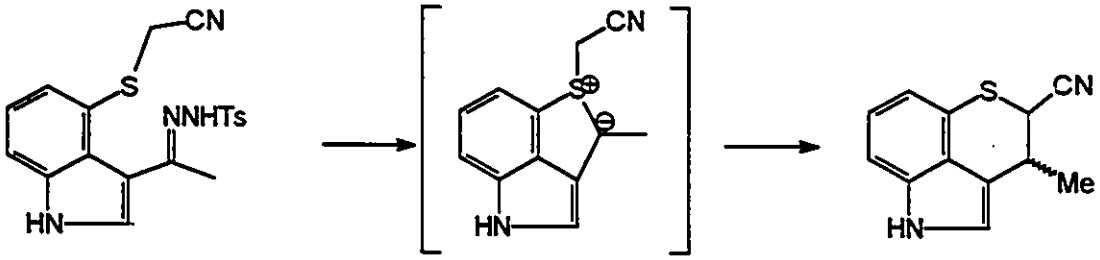
Scheme 2.8 - Retrosynthetic Analysis of Lysergic Acid

This conceptually new approach to lysergic acid had considerable appeal. It would involve a number of innovative steps and if successful, would also be quite short. The synthesis of 22, a new heterocyclic ring system, was chosen as the first synthetic target. It was believed that generation of an anion α to the sulfone group at the less substituted center of 22 would allow rapid access to the ortho-quinodimethane precursor 21 through a Michael addition to receptor 23.

The fact that the literature was devoid of anything structurally related to 22 did cause some concern, however it was believed that 22 was an accessible compound. It was hoped that structure 22 would not be so strained as to make it inaccessible, but that it would possess enough ring strain such that expulsion of SO_2 from 21 would be facile, much below the 250-300 °C usually required for chelotropic expulsion of SO_2 from unactivated sulfones. Also, since the carbon-sulfur bond is longer than a carbon-carbon bond, 22 should resemble the core of the tetahydrolysergic acid series[ii]. In addition, Rapoport[48] has claimed[iii] to have prepared hydrocarbon 24, a structure that would be considerably more strained than sulfone 22 since it contains an all carbon framework. Also, Matsumoto[49] has proposed that the structurally related sulfonium ylide 26 was an intermediate in the transformation from 25 to 27.



24



25 26 27

Using this information as literature precedence, studies began directed towards the synthesis of sulfone 22, with the ultimate goal being the total synthesis of lysergic acid 18. The next few chapters of this thesis outline the approaches that have been investigated to date.

[ii] As a general rule of thumb, having one sulfur in a chain is similar to having 1.5-2 carbons in the chain due to the longer bond length.

[iii] There is no spectroscopic data reported, and the structural assignment is based solely onthe isolation of less then 1% of benzene-1,2-3-tricarboxylic acid when 24 was treated with hot $KMnO_4$ under basic conditions.

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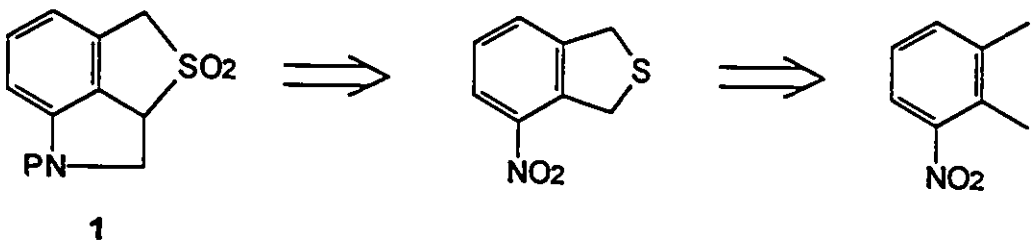
Chapter 3 - Initial Approaches

3.1 Formation of Indole Ring

Initial attempts at preparing the tricyclic sulfone 1 focused on generating the indole ring in the last step. Retrosynthetically, this is represented in Scheme 3.1.



Scheme 3.1 - Retrosynthetic Analysis of Tricyclic Sulfone 1 - Indole Ring Forming Strategy.

It was hoped that a one carbon unit could be built into bicyclic sulfide 2, either at this oxidation state, or at a higher (sulfur) or lower (nitrogen) oxidation state. With this approach in mind, commercially available 3-nitro-o-xylene 2 was subjected to benzylic bromination with two equivalents of NBS in CCl_4 with a catalytic amount of benzoyl peroxide added as an initiator to afford an extremely potent lachrymator as a pale yellow solid (mp 62.8-63.8 °C) in a yield of 51%. Inspection of the ^{1}H-NMR showed two singlets at 4.67 and 4.84 ppm, integrating for two protons, whereas the aromatic region had remained basically unchanged in comparison to the starting material. EI-MS showed a molecular ion at m/z 306, and a pattern consistent with incorporation of two bromine atoms; namely a $M^{\cdot+}$:($M^{\cdot+}$+2):($M^{\cdot+}$+4) in a 1:2:1 ratio. All of this data was consistent with the structure for the dibromide 3. Addition of 3 to a solution of Na_2S in EtOH led to 4 as a pale yellow powder (mp 95.8-96.2 C) which showed a molecular ion at m/z 181. The ^{1}H-NMR of 4 (Fig. 3.1) showed a slight upfield shift of the methylene groups, and HRMS supported a formula of $C_8H_7NO_2S$. The yield in this reaction was quite erratic and depended strongly on the reaction temperature, solvent and addition rate. Optimum results were obtained when the reaction

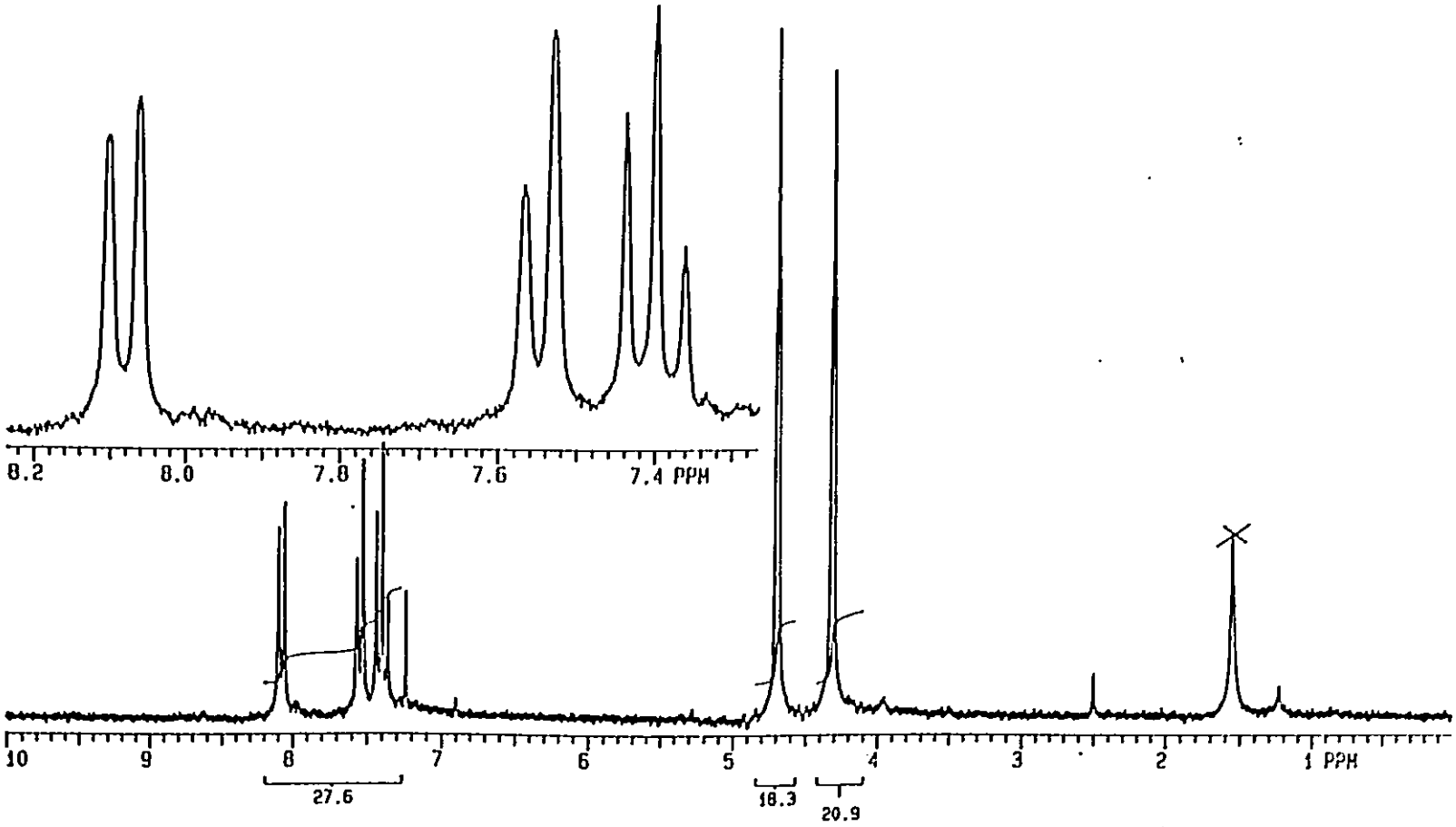
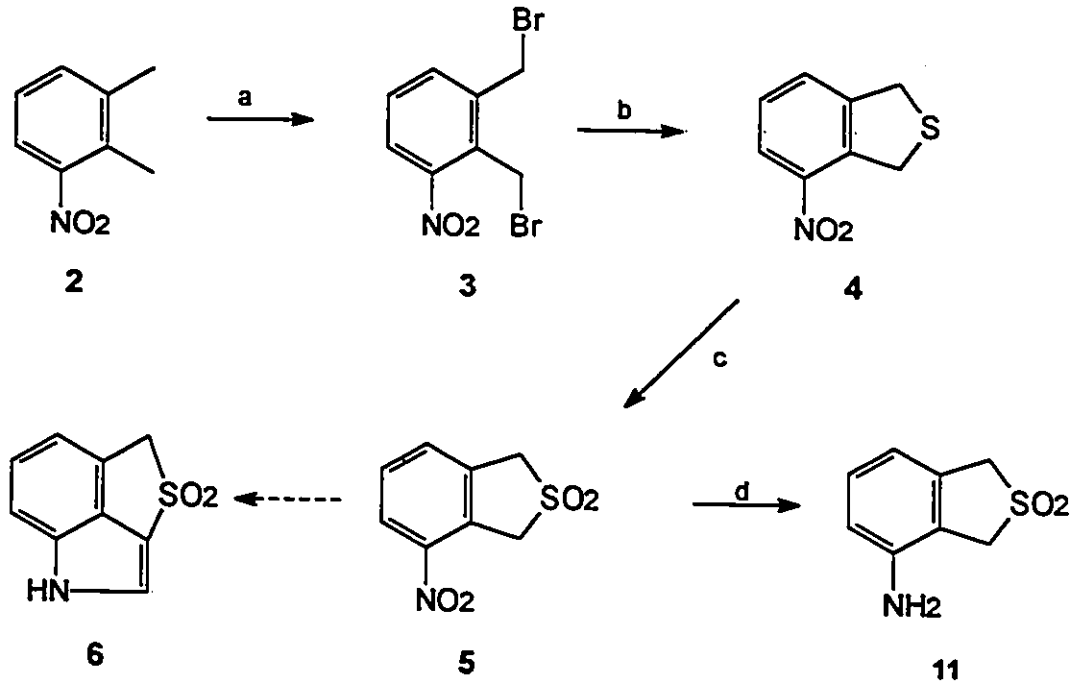


Figure 3.1 200 MHz ^{1}H-NMR Spectrum of Nitro-Sulfide 4 in $CDCl_3$

was carried out at 0 °C in EtOH, with dibromide 3 being added quickly to a solution of Na_2S in EtOH. Even under these "optimized" reaction condition, the yield was only 25-30%, however it was consistent if the reaction was conducted on a 15-20 mmol scale. Minimal workup was required to produce these results; i.e., evacuation of the solvent at reduced pressure and at room temperature, followed by applying the resulting black, thick oil directly to a column of silica gel. The consistently low yield for the conversion of 3 to 4 was the subject of a brief mechanistic investigation that is presented later in this chapter.



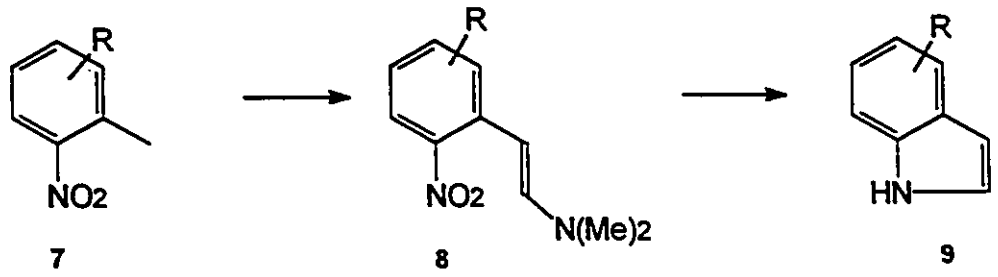
Reagents: a) NBS, Bz_2O, CCl_4, Δ (51%); b) Na_2S, EtOH (28%); c) mCPBA, CH_2Cl_2, -50 °C (85%); d) (i) DMFDA, DMF, Δ; (ii) Fe, HOAc, EtOH

Scheme 3.2 - Attempted Route to Tricyclic Sulfone 6.

Oxidation of 4 with mCPBA proceeded in a straightforward manner to provide 5 as a bright yellow powder in yields of 85-90%. Again, chromatography was not necessary in order to isolate or purify

sulfone 5. After usual workup, the crude product was triturated with diethyl ether. Filtration provided a bright yellow powder (mp 195.4 - 196.0 °C) whose ^{1}H-NMR (Fig. 3.2) displayed two singlets in the aliphatic region that had shifted downfield by about 0.1 ppm. In addition, the aromatic region was not as clearly defined as it had been in the two precursors, with significant overlap occurring. Although 5 did not exhibit a molecular ion in the EI-MS, it did show a parent ion at m/z 149, a peak consistent with the loss of SO_2 from 5. The presence of the sulfone group was confirmed by examining the IR spectrum, which showed the expected two peaks at 1131 and 1352 cm^{-1}.

With sulfone 5 in hand, conversion to 6 was attempted using conventional chemistry. Leimgruber[1] and others[2-5] had shown that o-nitrotoluene derivatives could conveniently be transformed into indole derivatives via a simple two step sequence (Scheme 3.3).



Scheme 3.3 - Leimgruber Indole Synthesis

Simply heating o-nitrotoluene derivatives 7 with dimethylformamide dimethylacetal (DMFDA) in DMF caused condensation to the enamine 8. Reduction of the nitro group of 8 to the amine followed by intramolecular addition-elimination to the enamine resulted in the formation of indoles 9 in high yields.

Attempts to use this methodology on nitro-sulfone 5 failed to give any of the desired indole 6. The only identifiable product isolated after column chromatography of the crude reaction product was the bicyclic sulfone 11. It is unknown if the first step in this reaction failed, or if enamine formation was successful, but cyclization failed, and the enamine was hydrolyzed on work up. The intermediate enamines are sensitive compounds, readily hydrolyzing back to the toluene derivatives. For this

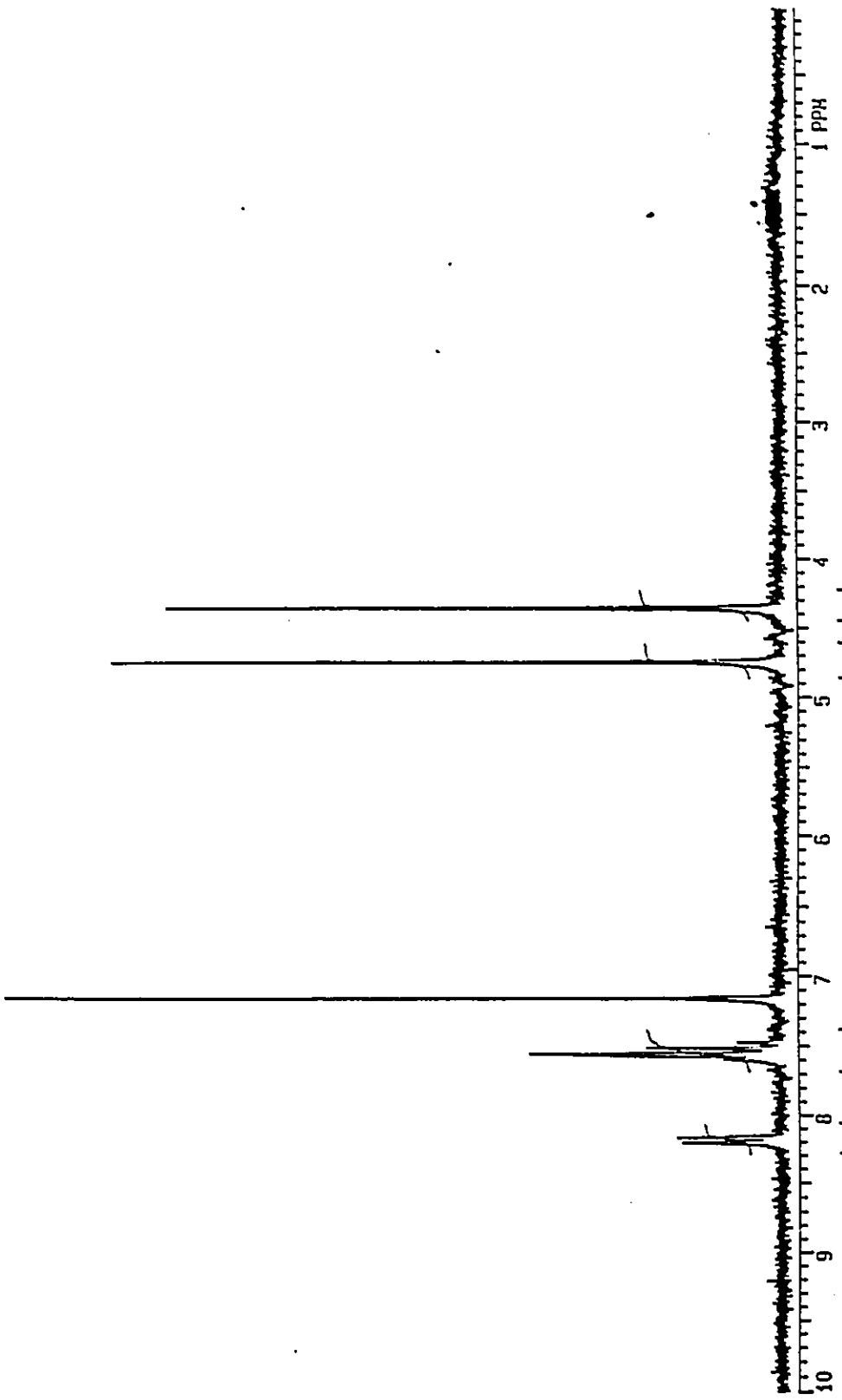
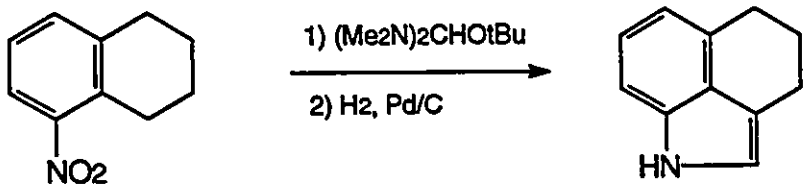


Figure 3.2 200 MHz ^{1}H-NMR Spectrum of Nitro-Sulfone 5 in $CDCl_3$

reason, they are usually not isolated. Instead, the solvent is stripped off at reduced pressures, and the enamine isolated by crystallization in some cases, but in most cases, being subjected to the reduction conditions as a crude material. The use of Gold's reagent (Me_2N-CH=N-CH=NMe_2^+ Cl^-) as described by Gupton[2] was also attempted, but again failed to give any of the desired indole derivative.

Gupton[2b] had reported that the addition of Gold's reagent to o- or p-nitroethylbenzene failed to give any of the desired addition product, which was explained on the basis of a steric argument. However, if the o-methyl group was substituted with an electron withdrawing group (ester) then addition was successful. It was anticipated that the adjacent sulfone would also serve as a sufficient activator for the methylene group, and the longer C-S bond, as compared to a C-C bond, would eliminate steric effects, if present at all. In addition, Haefliger5[b] has described an efficient synthesis of benz[c,d]indoles **10** based on similar methodology. In view of this work, it seems unlikely that condensation of nitro-sulfone 5 with DMFDA failed to give the enamine[1]. Regardless of the reasons for the reaction failing to give the desired product, this approach was abandoned.



10

Scheme 3.4 - Haefliger's Synthesis of Benz[c,d]indoles.

The second approach to tricyclic sulfone 1 involved attempts to form to the indole ring by making the C-C bond in the last step. Nitro-sulfone 5 was converted to amino-sulfone 11 (mp 196.5 °C) using transfer hydrogenation[6] in a 91% yield. The ^{1}H-NMR of this material is shown in Fig. 3.3.

Haefliger had also published an alternative route to tricyclic indoles such as **10** that involved cyclization of benzylic anions onto isonitriles[5a,c]. It was hoped that this same type of methodology could

[1] In connection with another project, (methyl)-2-methyl-3-nitrobenzoate was successfully converted to 4-carbomethoxyindole using identical reaction conditions.

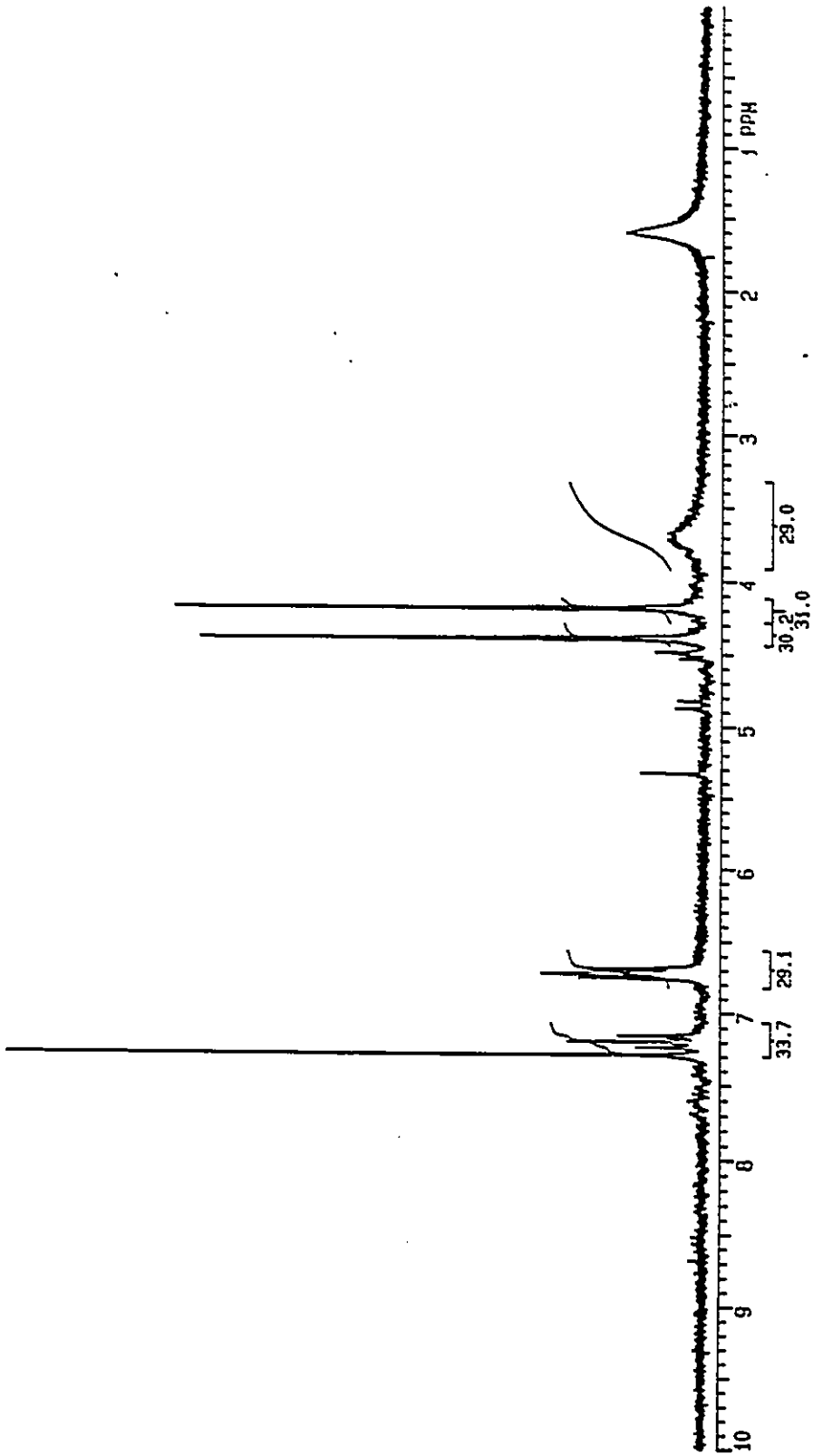
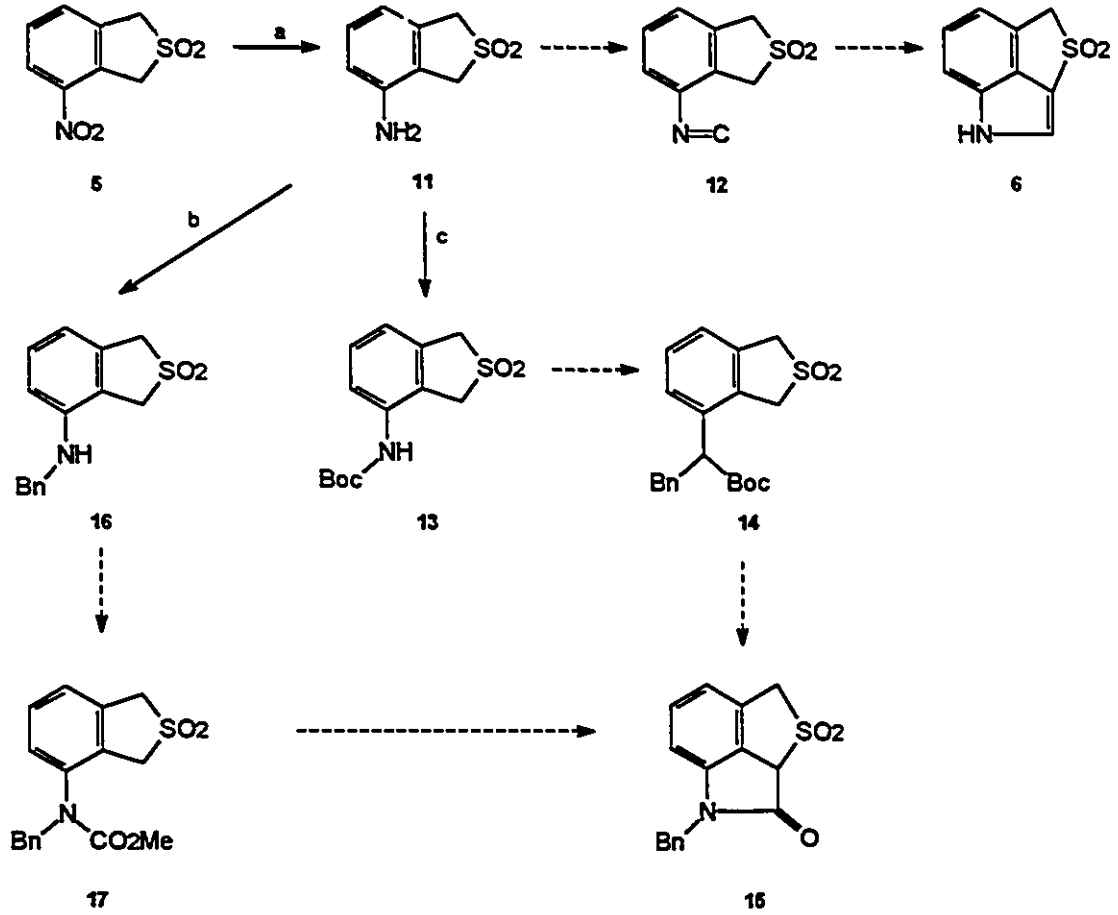


Figure 3.3 200 MHz ^{1}H-NMR Spectrum of Amino-Sulfone 11 in $CDCl_3$

be used in this work by converting amine 11 to isonitrile 12, which, according to Haefliger's work, should cyclize to form tricyclic sulfone 6. When amine 11 was reacted with dichlorocarbene, generated from chloroform under phase transfer conditions[7a], the reaction very quickly became homogenous. Complete destruction of the starting material occurred under the reaction conditions. The reaction was worked up at a variety of pH's, but no product or starting material could be isolated. Using the pyrolysis of sodium trichloroacetate as an alternative source of dichlorocarbene[7b] again led to decomposition. Although both methods of generating dichlorocarbene were successful in converting aniline to benzeneisonitrile, neither method was successful in affecting the desired 11 to 12 transformation. Due to these difficulties, this approach was abandoned.



Reagents: a)$H_2NNH_2{*}xH_2O$, Pd/C, MeOH (91%); b) (i) PhCHO, $MgSO_4$, CH_2Cl_2 (ii) $NaBH_3CN$, H^+, MeOH (92%); c) $(Boc)_2O$, DMAP, CH_3CN (63%).

Scheme 3.5 - Attempted Routes to Tricyclic Sulfone 6 and 15

Again, using materials already on hand, the strategy was modified and 15 was chosen as the next synthetic target. Although both methylenes adjacent to the sulfone group of 14 should be comparable in acidity, only one methylene group is in a position to react with the carbonyl group and cyclize to form 15. With these ideas in mind, a synthesis that was expected to provide 15 was initiated.

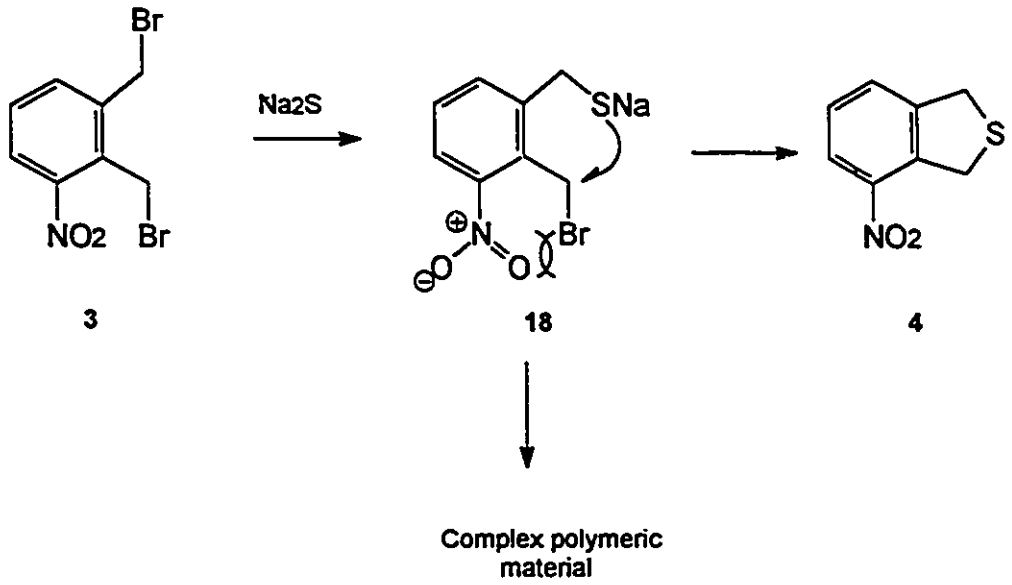
Acylation of the amino group of 11 with $(Boc)_2O$[8] in acetonitrile using a catalytic amount of DMAP gave the Boc-derivitive 13 in a yield of 63%. However, 13 proved to be quite base sensitive. When alkylation was attempted with Na_2CO_3 and benzyl bromide in acetone, no reaction was observed. However, when stronger bases (NaH or KOtBu) were used, complex mixtures were formed, from which no starting material or desired product could be isolated.

It was then decided to reverse the order that these substituents were introduced on the nitrogen, i.e., alkylation then acylation. Accordingly, amine 11 was mono-alkylated using the reductive amination procedure of Borch[9]. Much better yields of the N-benzylated amine 16 were obtained if the reaction was conducted in a two step process rather then the one step sequence suggested by Borch. Condensation of amine 11 with one equivalent of benzaldehyde in dichloromethane in the presence of anhydrous magnesium sulfate, followed by filtration, concentration and then subjecting the crude imine to reductive amination conditions with $NaBH_3CN$ at acidic pH led to N-benzylamine 16 in yields of 92%. The methylene groups adjacent to the sulfonyl group of 16 were shifted from 4.12 and 4.34 ppm to 4.03 and 4.27 ppm. This small upfield shift may be due to anisotropic effects because of the newly introduced benzyl group. The methylene group of the N-benzyl group appeared as a singlet at 4.27 ppm. HRMS also supported a molecular formula of $C_{15}H_{15}NO_2S$. However, when 16 was reacted with methyl or ethyl chloroformate in CH_2Cl_2 in the presence of one equivalent of triethylamine and a catalytic amount of DMAP, only starting material was recovered in quantitative yield. When the more reactive carboxylating reagent methyl cyanoformate was used, starting material was again recovered

in quantitative yield. Higher reaction temperatures and longer reaction times[ii] did not help in affecting the desired transformation of **16** to **17**. Although it is difficult to believe that there would be any significant difference electronically between **16** and N-benzyl aniline, it is even more difficult to understand any steric effect that the addition of the second ring would have on impeding carboxylation on amine **16**. Due to the difficulties associated with this series of reactions, work towards oxindole-sulfone **15** was abandoned.

3.2 Mechanistic Studies on the Formation of Sulfide 4.

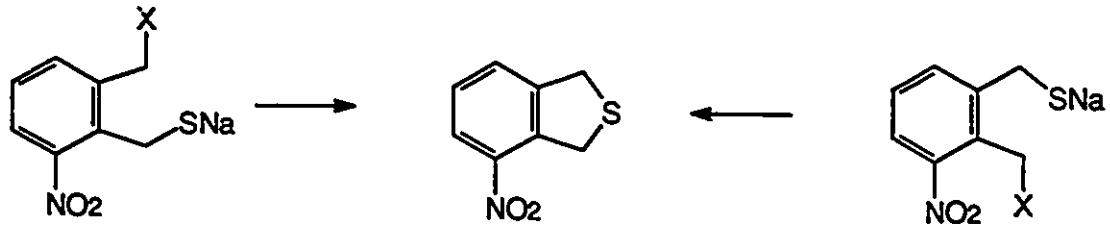
As mentioned earlier, yields for the formation of sulfide **4** from bis-benzylbromide **3** were quite low. Optimized conditions led to the desired product in yields approaching 40% for best runs. One possible mechanistic explanation is shown in Scheme 3.6.



Scheme 3.6 - Speculative Mechanism for Formation of **4** from **3**

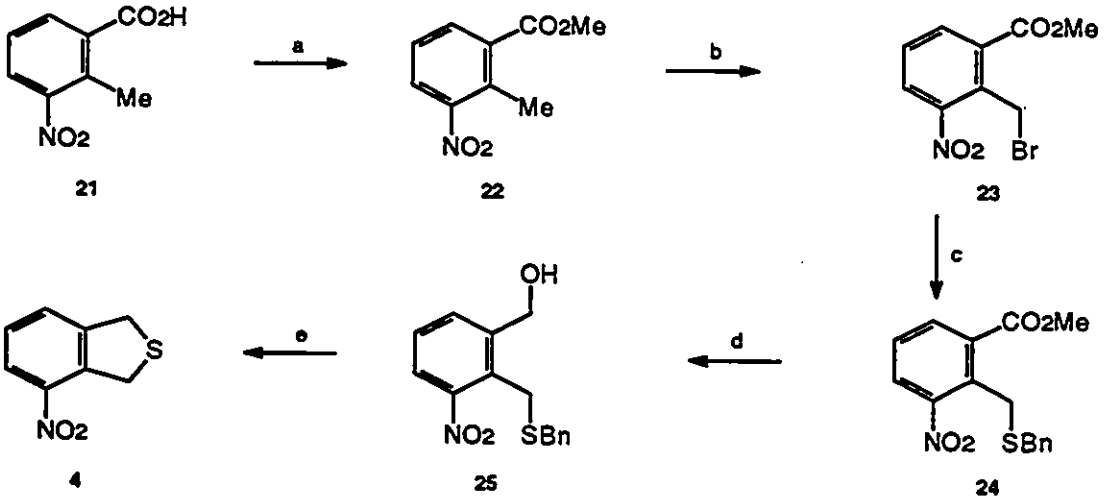
[ii] When these unusual results first surfaced, a model reaction was done using N-benzyl aniline as a substrate and methyl chloroformate as the carboxylating reagent. Although the reaction was somewhat sluggish at room temperature, being only 40% complete after 18 hours, there was no reaction of amine **16** when treated with the same reagents, even after three weeks!

Reaction of sodium sulfide at the more accessible benzylic center would lead to intermediate **18**. It was postulated that intramolecular displacement of the second bromide was impeded by the adjacent nitro group. Because of the resonance interaction with the benzene ring, the nitro group must stay planar and in this arrangement, it may be difficult for the nucleophilic sulfur center and the leaving group to align in an arrangement that would allow displacement. To test this hypothesis it was decided to prepare two compounds, generically represented by **19** and **20**, in which the positions of the nucleophilic sulfur center and the electrophilic carbon center were transposed.



19 **4** **20**

If the above mechanistic explaination were correct, then **19** should form **4** readily, whereas **20** would give a complex mixture due to inter- and intramolecular reactions. The route taken to **19** is shown in Scheme 3.7.



21 **22** **23** **24** **25** **4**

Reagents: a) MeOH, H+, Δ (95%); b) NBS, Bz_2O, CCl_4, Δ (76%); c) BnSH, KOtBu, THF (97%); d) $LiEt_3BH$, THF (50%); e) MsCl, TEA, CH_2Cl_2 (78%).

Scheme 3.7 - Route 1 to Sulfide **4** via Sulfonium Salt Intermediate.

Fisher esterification of commercially available 2-methyl 3-nitrobenzoic acid 21 with methanol afforded methyl ester 22 in greater than 95% yield as a white, highly crystalline solid (mp 65.3-66.2 °C) that had spectroscopic properties identical the literature reported values[10].

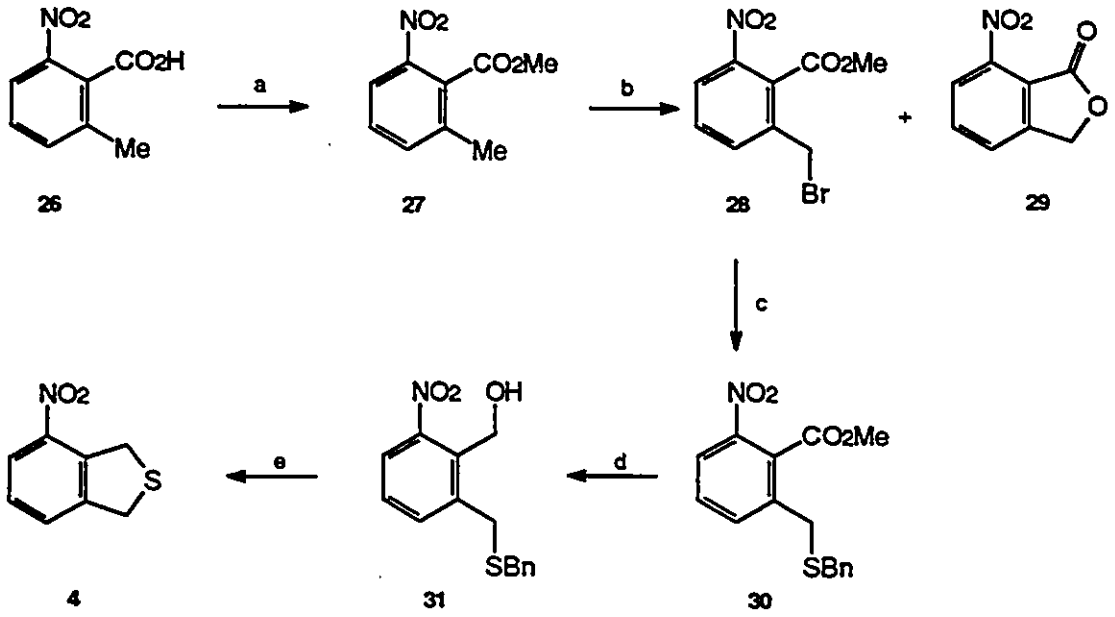
Benzylic bromination with NBS in CCl_4 using benzoyl peroxide as an initiator smoothly converted ester 22 to ester 23, in a crude yield of 90%. Recrystallization from CH_2Cl_2/hexanes provided 23 in 76% yield as pale yellow prisms (mp 67.9-71.8 °C).

Addition of potassium benzylmercaptide, conveniently generated in THF from benzyl mercaptan and KOtBu, gave addition product 24 in an optimized yield of greater than 95% after column chromatography. The pale yellow oil had spectroscopic properties consistent with the proposed structure.

After considerable experimentation, selective reduction of the ester group of 24 to benzylic alcohol 25 was found to proceed best with $LiEt_3B$[11]. Even under these conditions, the yield was still only 50%. Reduction with either $LiAlH_4$ or DIBAL-H, even at low temperatures, led to complex reaction mixtures resulting from competitive partial reduction of both the ester and nitro groups. HRMS of the yellow oil obtained after column chromatography supported a molecular formula of $C_{15}H_{15}NO_3S$. Examination of the ^{1}H-NMR spectra now showed three methylene groups at 3.74, 3.89 and 4.57 ppm. The aromatic region of the spectra still showed two low field doublets at 7.60 and 7.64 ppm with a 8 Hz coupling constant for the protons para and ortho to the nitro group, and a broad overlapping signal at 7.27 ppm representing six protons. A broad signal at 2.75 ppm was assigned to the alcohol proton. The IR spectra showed the absence of a carbonyl group, and the presence of an OH group which showed up as a broad, strong stretch at 3600 cm^{-1}. Stretches at 1356 and 1530 cm^{-1} also indicated that the nitro group was intact.

Finally, reaction of the alcohol with methanesulfonyl chloride in the presence of triethylamine provided sulfide 4 directly. This non-polar compound, isolated as a pale yellow powder after column chromatography in a yield of 78%, displayed spectroscopic properties identical to that prepared as shown in Scheme 3.2.

Having proved the facile displacement representing the transformation **19** to **4**, it remained to prove that **4** would not be formed readily from **20**. A synthesis was envisioned that would use the identical sequence and reagents as shown in Scheme 3.7, except that the starting material would be the isomeric 2-methyl 6-nitrobenzoic acid.



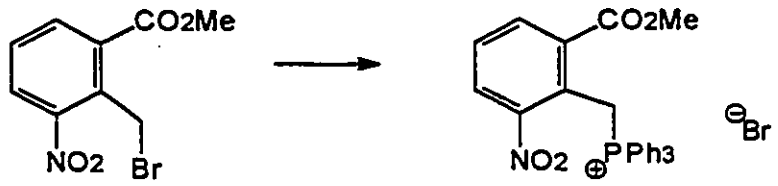
Reagents: a) $NaHCO_3$, MeI, DMF, Δ (85%); b) NBS, Bz_2O, Δ, CCl_4 (64%); c) NaSBn, THF (20%); d) $LiEt_3BH$, THF (11%); e) MsCl, TEA, CH_2Cl_2 (72%).

Scheme 3.8 -Route 2 to Sulfide **4** via Sulfonium Salt

It was immediately obvious from the first step that the reactivity of benzoic acid **26** was very different from its isomeric counterpart **21**. Fisher esterification returned starting benzoic acid **26**. In order to prepare methyl ester **27**, it was necessary to use basic conditions and alkylate the carboxylate salt with MeI in DMF. Aqueous work up and extraction with ether provided ester **27** in a yield of 85% after recrystallization from MeOH. The resulting pale yellow plates (mp 49.8-50.6 °C) exhibited a ^{1}H-NMR consistent with structure **27**. The difficulties associated with esterification of acid **26** were, presumably, a

reflection of the rather crowded steric environment of the acid carbonyl group, the flanking nitro and methyl groups making it very difficult for the nucleophile to approach, or for the carbonyl carbon to go to the necessary tetrahedral intermediate necessary for acid catalyzed esterification. The facile alkylation of the carboxylate anion showed that the problem was associated with the carbonyl carbon, since deprotonation of the acid and subsequent alkylation of the salt proceeded in high yield.

Benzylic bromination of ester 27 gave the desired product 28, but in significantly lower yields than the corresponding reaction of NBS with ester 22, with yields of 40-60% being typical. The ^{1}H-NMR showed the following key resonances: singlet at 3.90 ppm for the methoxy group, singlet at 4.51 ppm for the benzylic methylene group, and two doublets and a triplet in the aromatic region with coupling constants of 8 Hz indicative of a 1,2,3-trisubstituted benzene ring. EI-MS confirmed the presence of bromine by showing fragments of equal intensity at m/z 275 and 273, representing the ($M^{\bullet+}$+2) and ($M^{\bullet+}$) respectively. The IR spectra also confirmed the presence of the ester group (1739 cm^{-1}) and nitro group (1349 and 1538 cm^{-1}). In addition to the desired ester 28, another compound, assigned as lactone 29, was isolated in significant yield (up to 30%). This assignment was based solely on the ^{1}H-NMR, which showed, in addition to the typical pattern for a 1,2,3-trisubstituted benzene, only a single resonance at 4.00 ppm integrating for two protons, and the HRMS which supported a molecular formula of $C_8H_5NO_4$. It was also observed that the isolated ester 28 was slowly converted to lactone 29 if left standing at room temperature for extended periods of time. Contrary to this, ester 23 could be converted to phosphonium salt 32 by refluxing in xylene, and was stable at room temperature indefinitely, at no point was there any indication of lactone formation. This is consistent with the mechanistic speculations outlined earlier in Scheme 3.6.



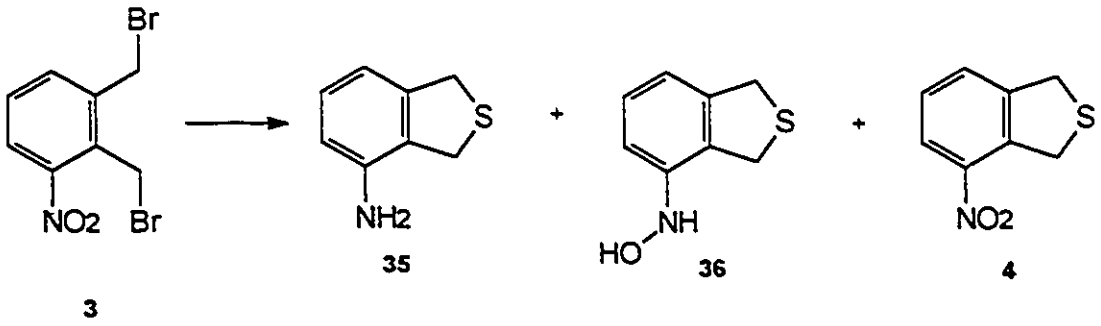
23 32

Reaction of bromide 28 with sodium benzylmercaptide, generated from benzyl mercaptan and sodium hydride, in THF afforded ester 30 as, after column chromatography, a pale yellow oil in a yield of 30%. Nitroaromatics are known to undergo single electron transfer reactions in the presence of mercaptide anions[12], which may help explain the low yield in this step.

The congested steric nature of the ester carbonyl group was made evident once again as reduction of ester 30 with Super-Hydride™ to give the desired benzylic alcohol 31 proceeded in a meager yield of 10%, with reduction of the nitro group being a major side reaction. No attempt was made to optimize this reduction, nor were any alternative reducing agents tried. Benzylic alcohol 31, obtained as a yellow oil after chromatography, was characterized only by a ^{1}H-NMR spectra which showed a singlet at 3.80 Hz, integrating for 4 protons, which was interpreted as being two overlapping methylene group, and a singlet at 4.10 ppm, accounting for the remaining methylene group. Reduction of the ester group was verified by an upfield shift of the two doublets corresponding to the protons that had been ortho and para to the ester group.

Exposure of benzylic alcohol 31 to the same cyclization conditions of 25 led to the isolation of a single product that had a ^{1}H-NMR spectra identical to bicyclic sulfide 4 in a yield of 72%.

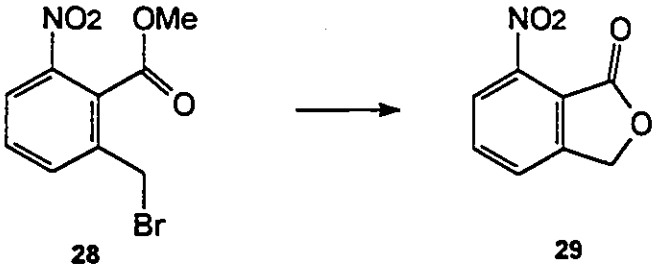
At this point, the mechanistic explanation for the low yield of sulfide 4 from benzyl bromide 3 had to be re-examined and the striking differences in reactivity of the two series of compounds explained. Repeating the reaction of 3 and Na_2S, and performing GC-MS on the crude reaction mixture led to the identification of a two other products, and a major reaction pathway that was previously overlooked. Peaks with molecular ions at m/z of 151 and 168 were assigned as amine 35 and hydroxyl-amine 36.



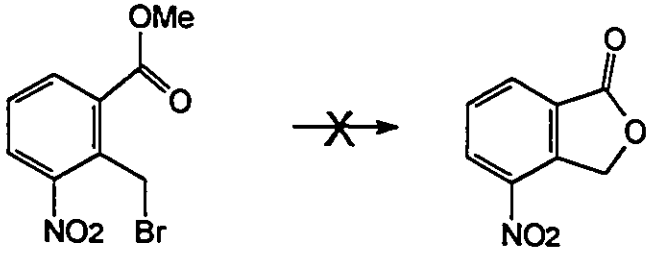
Scheme 3.9 - Products Detected in Reaction of 3 with Na_2S

Complete and partial reduction of the nitro group of 3 by Na_2S[13] to the amine 35 and hydroxylamine 36 may help explain the low yield consistently encountered in this step. A significant amount of insoluble, presumably polymeric material was formed during the reaction, and a large amount of baseline material was left behind during column chromatography. Polymeric material could form by the reaction of amine 35 with starting material 3. Regardless of the nature of the final side products, it was clear that the low yield in this step was associated with reduction of the nitro group, and further reaction of the amine, and not the result of a difficult intramolecular displacement of the 2-benzylic bromide due to a high energy S_N2 trajectory as postulated in Scheme 3.6.

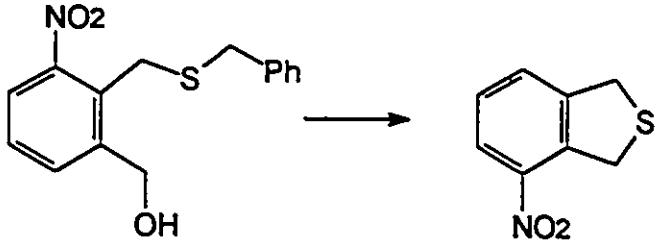
However, intramolecular displacement from ring position 1 to 2 when a nitro group occupies position 3 is not always possible, as evident by the remarkable stability of bromo-ester 23 as compared to the sensitivity of bromo-ester 28. Shown in Scheme 3.10 is a summary of the intramolecular reactions that were observed for the isomeric series of compounds. As can be seen from the transformations of either 25 or 31 to 4, if the center α to nucleophile is sp^3 hybridized, then displacement is facile. This became even more apparent when, in connection with another approach, reduction of ester 23 to alcohol 38 was attempted, but reduction conditions gave rise to ether 39 exclusively in essentially quantitative yield. This proved, inarguably, that the nitro group does not interfere with intramolecular displacement of the benzylic bromide.



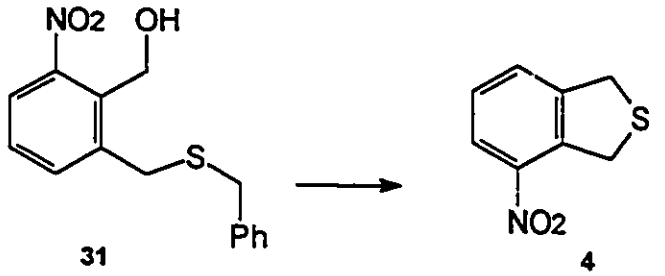
28 29



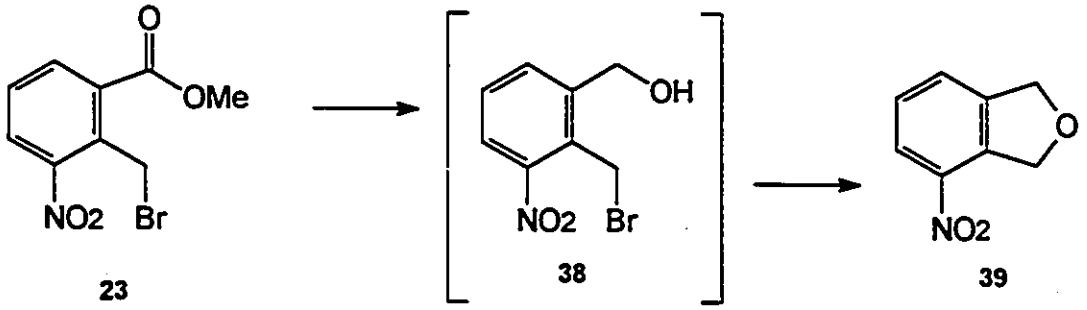
23 37



25 4

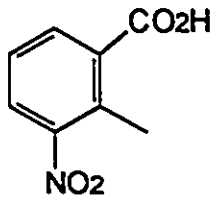


31 4



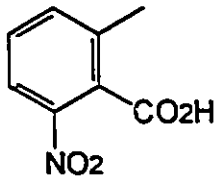
23 38 39

Contrary to this, intramolecular displacement when the carbon center is sp^2 hybridized is impossible, evident from the failure of ester **23** to cyclize to lactone **37**. Presumably in the case of **23**, the ester group remains planar and in conjugation with the aromatic ring. In this planar geometry, intramolecular displacement is impeded by the adjacent nitro group. This was even more obvious by the previously mentioned reaction of ester **23** with PPh_3 to cleanly afford the phosphonium salt. Presumably, the ester functionality in **28** is too sterically crowded to adopt a planar geometry. This notion seemed to be supported by inspection of the IR spectra of esters **23** and **28**, which showed carbonyl stretches at 1729 and 1739 cm^{-1} respectively. Since the positions ortho and meta to the nitro group are not electronically equivalent, it was decided to inspect the spectra of acids **21**, **26**, and **40**[14].



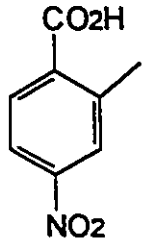
21

1695 cm^{-1}



26

1700 cm^{-1}



40

1685 cm^{-1}

As can be seen from the C=O stretching frequency for these isomers, there was a considerable difference in the energy required to stretch the bond. Although there appeared to be very little difference between **21** and **26**, it is apparent by comparing **26** and **40** which both had the acid function either ortho or para to the nitro group and therefore in similar electronic positions, that the frequency for **26** was high, indicating that the carbonyl group was not in conjugation with the benzene ring.

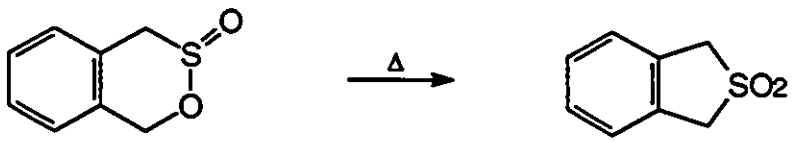
Considering this structural difference of isomers **21** and **26** was critical in understanding the differences in reactivity of the two series of compounds. Reactions for the series in which the methyl group was located between the nitro group and the acid group were as would be predicted; esterification proceeded in high yields under the usual Fisher conditions, the carbonyl group remained flat relative to the ring, and the nitro group impeded displacement of the halogen thereby preventing lactonization, and

accounting for the remarkable stability of the benzylic bromide. However, once the easily accessible carbonyl group was reduced, there was no longer a need for the side chain to remain flat, thereby explaining the ease of formation of ether **39**.

In the case of the isomer series that started with the carboxylic acid group between the nitro and methyl group, both faces of the carbonyl group were blocked by the neighboring substituents since the carbonyl group was likely perpendicular to the ring due to the crowded steric environment, which readily explained why a nucleophile the size of methanol could not get in, and even one as small as hydride had trouble approaching, as evident from the low yield and number of side reactions when ester reduction conditions were employed. In the case of this series, the hybridization of the carbon substituent flanked by the two other substituents was irrelevant, since displacement of an electrophile ortho to it occurred readily from both the Csp^2 hybridized center (ester to lactone) and Csp^3 hybridized centered (acyclic sulfide to cyclic sulfide).

3.3 Probing Regioselectivity of 3-Nitro-o-quinodimethane

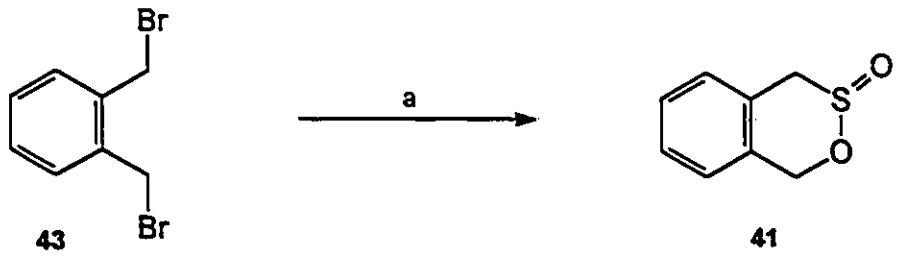
Due to the low yields associated with the synthesis of nitro-sulfone **5** as desribed in the previous section, another route to **5** was desired. Durst et al[15] had previously shown that sultines, such as **41**, could be cleanly and almost quantitatively isomerized to sulfones, in this case **42**, by simply heating at 80 °C in benzene.



41 **42**

Scheme 3.11 - Durst's Route to Sulfones via Isomerization of Sultines.

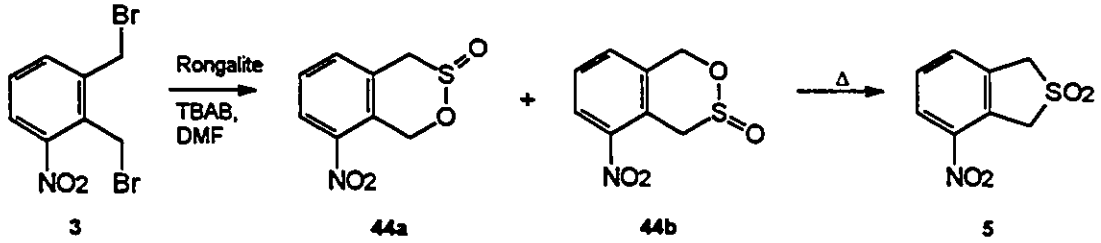
Dittmer[16] had also shown that α,α'-dibromoxylene, 43, could be cleanly converted to sultine 41 with Rongalite™ in DMF in the presence of NaI or a phase transfer catalyst such as tetrabutylammonium bromide.



Reagents: a) $HOCH_2SO_2Na*2\ H_2O$, TBAB, DMF

Scheme 3.12 - Dittmer's Route to Sultines

With these reactions in mind, it was decided to investigate the possibility of combining them as outlined in Scheme 3.13 as an alternative route to sulfone 5.



Scheme 3.13 - Alternative Route to Sulfone 5

Reaction of 3 with Rongalite™ under the conditions specified by Dittmer[16] afforded, after column chromatography, two compounds in essentially identical yields (35-40% of each). Both compounds gave IR spectra that were quite similar, and remarkably devoid of any stretching bands, except for a single stretch at 1120 cm^{-1}, assigned to the S=O bond of a sultine, and peaks at 1350 and 1530 cm^{-1} representing a nitro group. Neither compound showed a molecular ion in the EI-MS, with the highest mass peak at

149, but both showed ($M^{+\cdot}$+1) peaks in the CI-MS, all of which was interpreted as these two compounds being isomeric sultines **44a** and **44b**. The 500 MHz ^{1}H-NMR of the less polar isomer, isolated as pale yellow needles (mp 97.4 - 98.2 °C), showed AB patterns for both methylene groups, one having doublets at 3.83 and 4.70 ppm, with a coupling constant of 16.5 Hz, and the other set of doublets at 5.02 and 5.36 ppm with a coupling constant of 14.2 Hz. Based on the previous work of Durst[15], the signals at 5.02 and 5.36 ppm could be assigned to the methylene group α to the endocyclic oxygen. Inspection of the 500 MHz COSY (Fig. 3.4) showed a correlation between the doublet at 5.02 ppm and an aromatic proton at 7.45 ppm. Since the lowest field resonance at 8.00 ppm was assigned to the proton ortho to the nitro group, and the two remaining aromatic resonances overlapped at 7.45 ppm, this correlation was interpreted as evidence that this isomer had structure **44b**.

Examination of the 500 MHz ^{1}H-NMR spectra of the more polar fraction, also isolated as pale yellow needles (mp 106.4 - 107.0 °C), showed two AB patterns, one having doublets at 3.65 and 4.34 ppm with a coupling constant of 15.7 Hz assigned to the methylene group α to the sulfoxide moiety of the sultine, and one with doublet at 5.43 and 5.46 ppm with a coupling constant of 16.3 Hz assigned to the methylene group adjacent to the endocyclic oxygen. Once again, 500 MHz COSY (Fig. 3.5) showed a correlation between the aromatic proton representing the proton para to the nitro group, and the proton which resonated at 4.34 ppm which had previously been assigned to one of the protons adjacent to sulfur. These spectroscopic data were consistent with a structural assignment corresponding to the other possible regioisomer **44a**.

With these sultines in hand, isomerization to the desired sulfone was attempted. Whereas the parent sultine **41** was smoothly isomerized at 80 °C to sulfone **42** in essentially quantitative yield, no isomerization occurred for either sultines **44a** or **44b** until temperatures of 110 °C were reached. Unfortunately, at this higher temperature, considerable dimerization of the intermediate o-quinodimethane occurred, and although the ^{1}H-NMR of the crude product showed that the desired material was present, the difficulty associated with purification and the yield of the sulfone made this sequence unattractive as an alternative route to sulfone **5**.

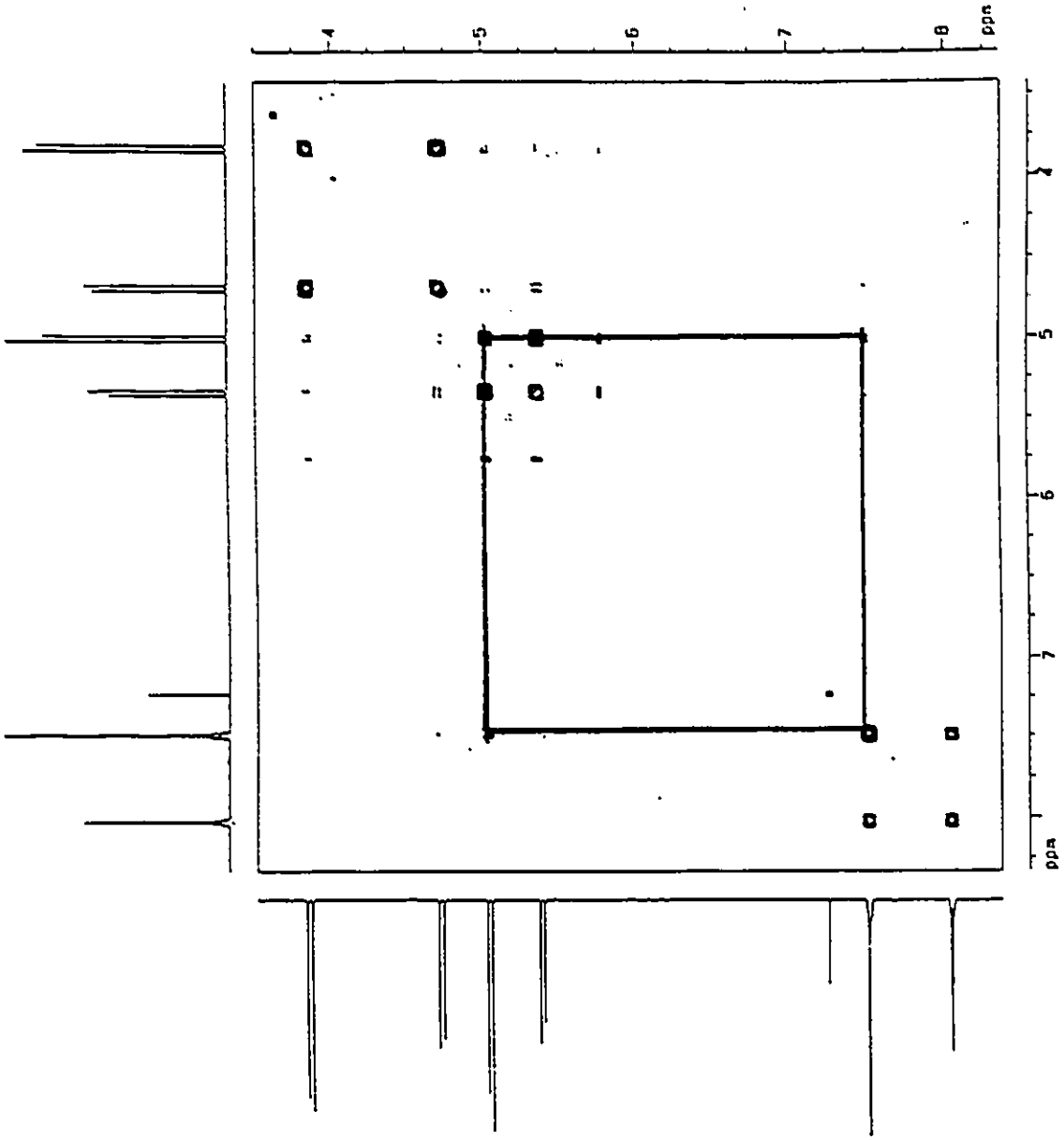


Figure 3.4 500 MHz COSY Spectrum of Suline 44b in $CDCl_3$

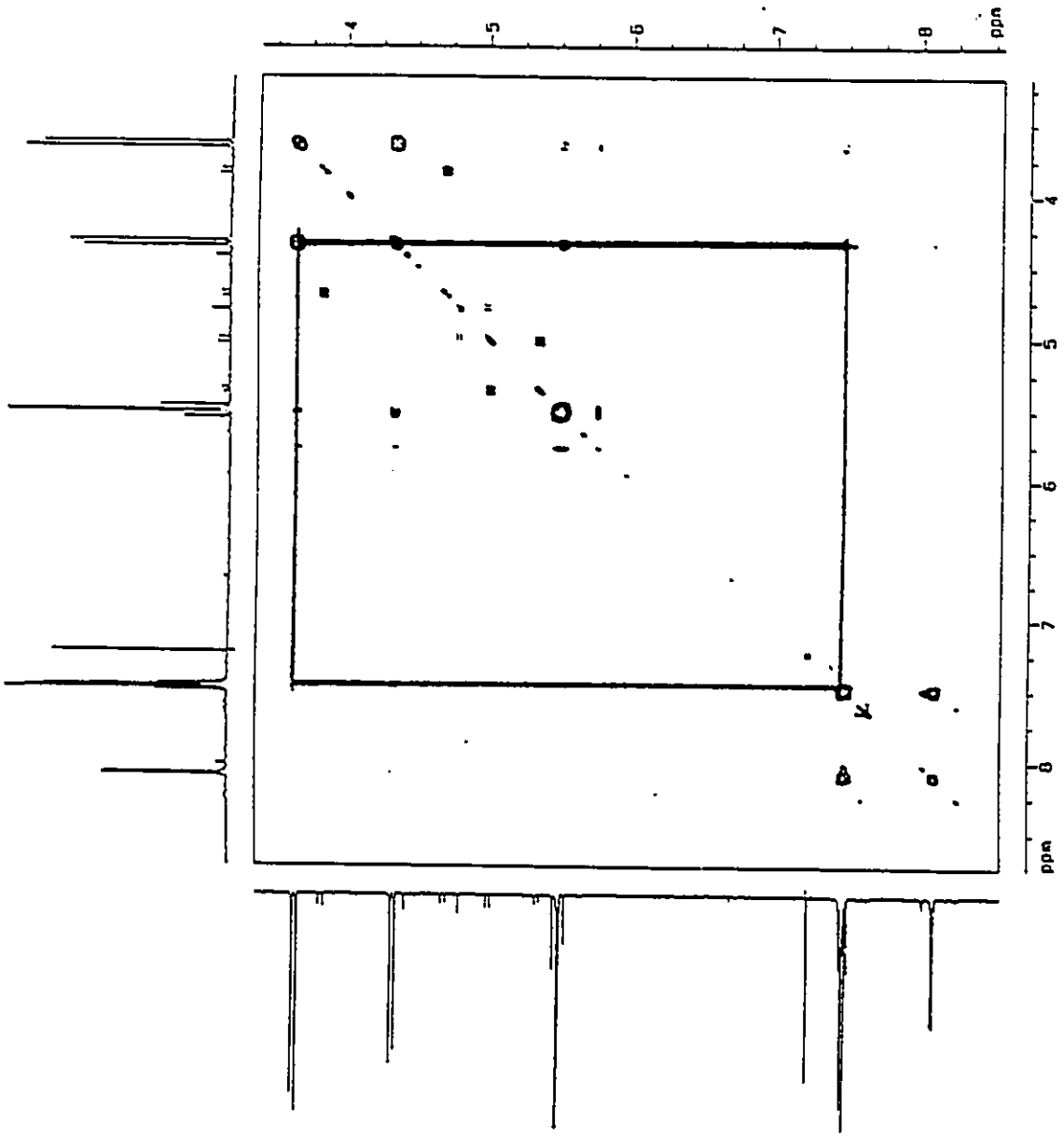
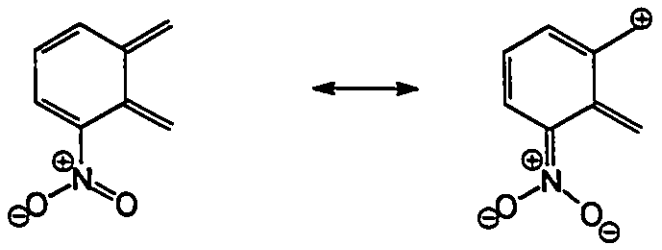


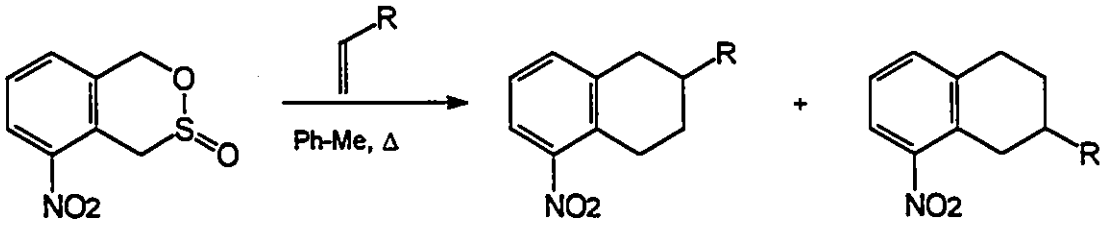
Figure 3.5 500 MHz COSY Spectrum of Sultine 44a in $CDCl_3$

Since the presence of the nitro group on the aromatic ring led to an increase in the thermolysis temperature of the sultine, presumably due to increasing the C-S and C-O bond strengths, it was hoped that its presence may also lead to some modification on the chemistry of the intermediate oQDM. Using a valence-bond approach and examination of the major resonance contributor, **46**, for 3-nitro-o-quinodimethane **45**, it appeared that the electron density of the exocyclic methylene groups should be quite different.



45 **46**

With this notion in mind and a convenient source of **45** in sultines **44a** and **44b**, a study aimed at probing the regioselectivity of reactions of **45** with unsymmetrical dienophiles was initiated. Heating either sultine **44a** or **44b** with methyl acrylate, vinyl acetate or butyl vinyl ether in toluene led smoothly to the expected cycloadducts in chromatographed yields of 93, 85 and 62% respectively. Unfortunately, the regioselectivity was essentially non-existent, with best selectivity being seen for the reaction with methyl acrylate being (6:5). No attempt was made to separate the isomers and determine unambiguously the structures of the major and minor isomers.



44

47; R=CO2Me; 93% (5:2)
48; R=OAc; 85% (2:1)
49; R=OnBu; 62% (1:1)

Scheme 3.14 - [4+2] Cycloadditions of Sultine **44** With Various Dieneophiles

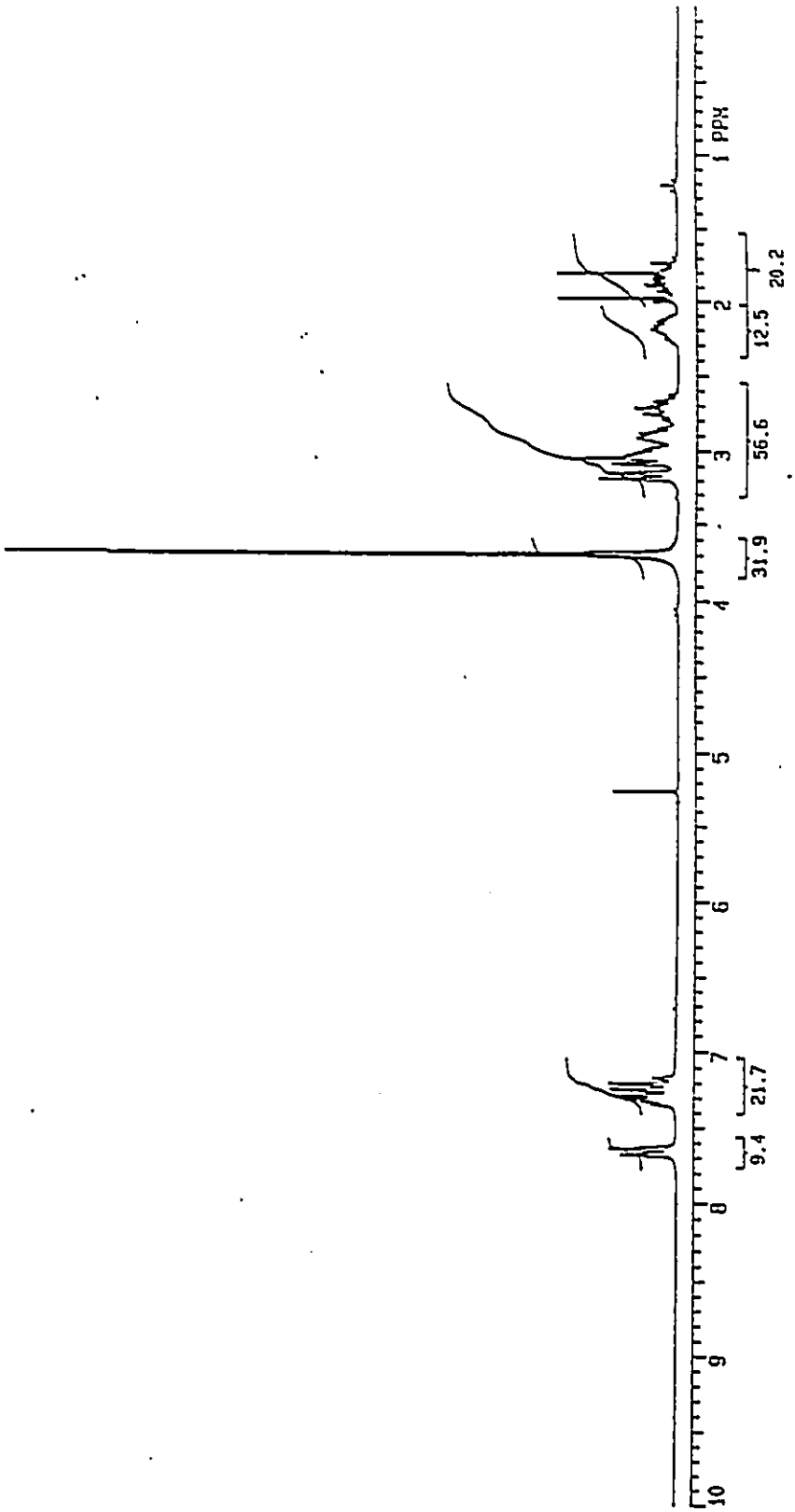
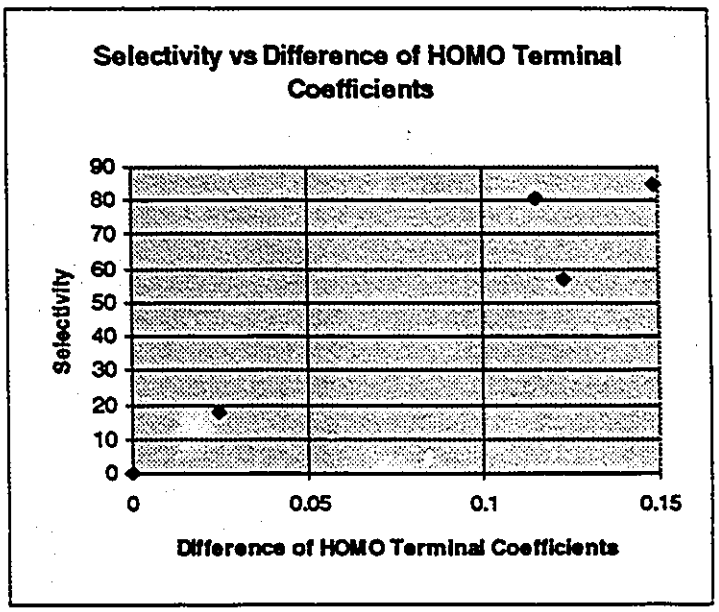


Figure 3.6 200 MHz ^{1}H-NMR Spectrum of Cycloadduct 47 in $CDCl_3$

These results were considered somewhat unusual, since any contribution of resonance form **46** was expected to influence the regiochemistry of the cycloaddition. Since it was not possible to explain the almost negligible effect of the strongly electron withdrawing nitro group on the regioselectivity using a valence-bond approach, a molecular orbital theory based approach[17] was adopted. The ability of frontier molecular orbital (FMO) theory to explain the regiochemistry of Diels-Alder cycloadditions has been well documented[17]. Based on Alston's[19] analysis of the reaction of a series of substituted 1,3-butadienes with methyl acrylate, a somewhat linear relationship can be found between the regioselectivity and the difference of the CNDO/2 calculated C1 and C4 coefficients of the diene HOMO. Using this as precedence, it was hoped that evaluation of the HOMO would explain the apparent lack of regioselectivity.



Inspection of the PM3 calculated HOMO for 3-nitro-ortho-quinodimethane, shown in Figure 3.7, showed that there was little difference in the size of the coefficients on the terminal ends of the diene. With a difference of only 0.0064, there was virtually no way for the dieneophiles to discriminate between the terminal ends of the diene. Once again, FMO theory showed its superior predictability power over the "arrow pushing" valence-bond approach.

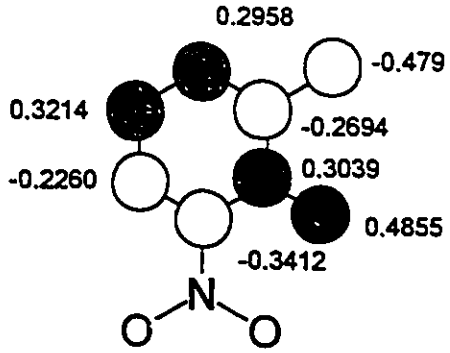


Figure 3.7 - PM3 Calculated HOMO of 3-Nitro-ortho-Quinodimethane

Having completed these mechanistic studies, research was once again focused on the synthesis of tricyclic sulfone 1. The next few chapters discuss alternative routes aimed at this goal.

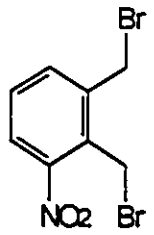
3.4 Experimental

General

All reactions were carried out in flame-dried glassware that had been cooled under a stream of nitrogen. All reactions were carried out under an inert atmosphere with the exclusion of moisture unless otherwise noted. Melting points were determined with a Fisher-Johns Unimelt melting point apparatus and are uncorrected. When no range is given for melting points, the number given is the average of a one to two degree melting point range. Infrared spectra were recorded with a Bomem MB 101 FT-IR spectrometer with solution cells using the highest grade of methylene chloride available unless otherwise noted. Proton and carbon nuclear magnetic resonance spectra were recorded on either a Bruker AMX-500, Varian XL-300 or Varian Gemini 200 operating at frequencies of 500, 300 and 200 MHz for proton, and 125, 75 and 50 MHz for carbon, using the specified solvent. Spectra were referenced to residual protonated solvents, but are reported relative to TMS = 0.00 ppm. Multiplicities are reported as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet, br, broad singlet; and m, multiplet. Low and high resolution mass spectra were recorded on a VG 7070 Mass Spectrometer or a Concept II instrument. MS peak intensities are reported as a percent of the base peak.

The phrase "usual work up" refers to drying the solvent over anhydrous magnesium sulfate, filtering and removing the solvent under reduced pressure using a Buchi Rotovapor. The term chromatography refers to flash column chromatography performed using 230-400 mesh silica gel supplied by Terochem Laboratories in the solvent system specified. All solvents were routinely dried and distilled prior to use. All starting materials were used as received from commercial sources except for the following: triethylamine was distilled from CaH_2 immediately before use, THF was dried over sodium with benzophenone as an indicator, and CH_2Cl_2 was distilled from P_2O_5.

3-Nitro-o-α,α'-dibromoxylene (*3*).



3

To a solution of 3-nitro-o-xylene (10.00 g, 66.2 mmol) in CCl_4 (100 mL) was added NBS (26.00 g, 147.8 mmol) and benzoyl peroxide (cat, 1.0 g). The resulting mixture was heated to reflux for 24 h, cooled to RT, filtered, washed with Na_2CO_3 (4 x 50 mL) and worked up in the usual manner affording a thick yellow oil. The desired product 3 was obtained by crystallization with hexanes from CH_2Cl_2, affording 10.92 g (53%) of pale yellow prisms. CAUTION! The product and reaction mixture are very potent lachrymators and should be handled with extreme care!

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.67 (s, 2H), 4.84 (s, 2H), 7.45 (t, 1H, J=8.0 Hz), 7.64 (d, 1H, J=8.0 Hz), 7.88 (d, 1H, 8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.47, 28.40, 125.33, 129.72, 130.84, 135.38, 139.40, 149.90 ppm.

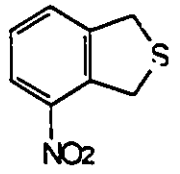
IR (CH_2Cl_2): 1354, 1534 cm^{-1}.

EI-MS (m/z, %): 310 (3.3, M^{++}+4), 308 (7.0, M^{++}+2), 306 (3.1, M^{++}), 230 (59.0), 228 (59.0), 149 (50.0), 91 (100).

HRMS: Calc. for $C_8H_7NO_2Br_2$: 306.88434; Found: 306.88206.

mp: 62.8-63.8 °C.

3-Nitro-dihydroisobenzothiophene (4).



4

A solution of dibromoxylene 2 (5.00 g, 16.2 mmol) in MeOH (50 mL) was added dropwise over 0.5 h to a cooled (0 °C) solution of Na_2S (5.00 g, 8.1 mmol) in MeOH (200 mL). The resulting yellow solution was stirred at 0 °C for 0.5 h, then the solvent was removed under reduced pressure with the water bath at RT. The resulting black residue was suspended in CH_2Cl_2 and applied to a column of SiO_2. Elution with Hex:EtOAc (7:1) afforded the title compound 4 as a yellow powder (1.27g, 43%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.31 (s, 2H), 4.70 (s, 2H), 7.40 (t, 1H, J=7.5 Hz), 7.55 (d, 1H, J=7.5 Hz), 8.08 (d, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 37.18, 38.37, 123.07, 126.10, 128.13, 130.36, 136.73, 144.97 ppm.

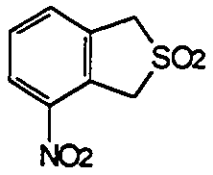
IR (CH_2Cl_2): 1352, 1530 cm^{-1}.

EI-MS (m/z, %): 181 (33.2, $M^{+\cdot}$), 164 (57.7), 134 (100).

HRMS: Calc. for $C_8H_7NO_2S$: 181.01975; Found: 181.02143.

mp: 95.8-96.2 °C.

3-Nitro-dihydroisobenzothiophene-S,S-dioxide (5).



5

A solution of sulfide 4 (5.43 g, 30.0 mmol) in CH_2Cl_2 (300 mL) was cooled (0 °C) as mCPBA (13.03 g, 85%, 61.0 mmol) was added portionwise over 10 min. The solution was allowed to warm to RT over 12 h, washed with $NaHSO_3$ (10%, 2 x 50 mL) and $NaHCO_3$ (5%, 4 x 50 mL), followed by the usual work up. The resulting bright yellow solid was triturated with Et_2O (25 mL) and filtered affording the title compound 5 as a bright yellow powder (5.26 g, 82%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.44 (s, 2H), 4.82 (s, 2H), 7.62 (m, 2H), 8.60 (d, 1H, 8.5 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 55.41, 57.08, 124.98, 127.59, 129.64, 131.81, 134.35, 145.80 ppm.

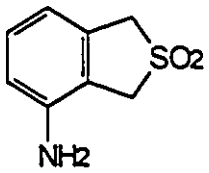
IR (CH_2Cl_2): 1131, 1329, 1352, 1536 cm^{-1}.

EI-MS (m/z, %): 149 (100, $M^{+\bullet}$-SO_2).

HRMS: Calc. for $C_8H_7NO_2$: 149.04768; Found: 149.04784. ($M^{+\bullet}$-SO_2).

mp: 195.4-196.0 °C.

3-Amino-dihydroisobenzothiophene-S,S-dioxide (11).



11

A solution of nitro-sulfone 5 (5.00 g, 23.5 mmol) in MeOH (300 mL) was added dropwise to a cooled (0 °C) solution of Pd on Carbon (10%, 50 mg) in MeOH (10 mL). A solution of hydrazine hydrate (8 mL) was added dropwise over 10 min, and the resulting solution was heated to reflux for 6 h, cooled to RT, filtered through Celite, and the solvent evaporated off. The residue was dissolved in CH_2Cl_2 (75 mL), washed with H_2O (2 x 25 mL) and worked up in the usual fashion affording the title compound 11 as white prisms (3.91 g, 91%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.12 (s, 2H), 4.34 (s, 2H), 6.68 (m, 2H), 7.14 (t, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): 54.03, 57.39, 114.76, 115.56, 115.90, 129.63, 131.78, 143.05 ppm.

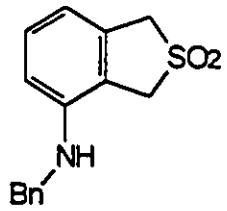
IR (CH_2Cl_2): 1130, 1321, 3400 cm^{-1}.

EI-MS (m/z, %): 183 (20.5%, $M^{+\bullet}$), 119 (100).

HRMS: Calc. for $C_8H_9NO_2S$: 183.03540; Found: 183.03648.

mp: 196.5-197.0 °C.

3-(N-Benzyl-amino)-dihydroisobenzothiophene-S,S-dioxide (16).



16

The pH of a solution of amino-sulfone **11** (300 mg, 1.65 mmol) and benzaldehyde (210 mg, 1.98 mmol) in MeOH (100 mL) was adjusted to pH~6 by the dropwise addition of HCl (10%). $NaBH_3CN$ (750 mg, 9.50 mmol) was then added portionwise and the solution stirred at RT for 1.5 h, after which time concentrated HCl was added to the cloudy solution until pH< 2. The solvent was removed, water was added, and the solution was extracted with Et_2O (2 x 20 mL). The organic phase was discarded, and the pH of the aqueous layer adjusted to pH>10, saturated with NaCl, and extracted with Et_2O (4 x 50 mL). Usual work up, followed by chromatography (3:1 Hex:EtOAc) afforded the title compound **16** as white fluffy needles (410 mg, 92%).

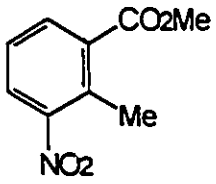
^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.03 (s, 2H), 4.27 (s, 4H), 6.49 (d, 1H, J=8.0 Hz), 6.55 (d, 1H, J=8.0 Hz), 7.12 (t, 1H, J=8.0 Hz), 7.30 (s, 5H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 47.84, 53.75, 57.29, 110.02, 114.22, 115.40, 127.16, 127.34, 128.48, 129.55, 131.19, 137.59, 143.89 ppm.

EI-MS (m/z, %): 273 (3.8, $M^{+\bullet}$), 225 (21.9), 183 (15.5), 161 (36.7), 146 (100).

HRMS: Calc. for $C_{15}H_{15}NO_2S$: 273.08235; Found: 273.08276.

Methyl (2-methyl-3-nitro)benzoate (22).



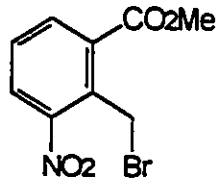
22

A solution of 2-methyl-3-nitro benzoic acid (50.00 g, 0.28 mol) in MeOH (500 mL) containing H_2SO_4 (conc., 1 mL) was heated at reflux for 24 h. The solution was then evaporated, and the solid that resulted was recrystallized from MeOH, affording the title compound **22** as white needles.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.60 (s, 3H), 3.90 (s, 3H), 7.38 (t, 1H, J=8.0 Hz), 7.81 (d, 1H, J=8.0 Hz), 7.98 (d, 1H, J=8.0 Hz) ppm.

mp: 65 °C (lit.[3] 65-66 °C).

Methyl (2-bromomethyl-3-nitro)benzoate (23).



23

A mixture of ester **22** (5.00 g, 25.6 mmol), NBS (5.00 g, 28.4 mmol) and benzoyl peroxide (cat) in CCl_4 (50 mL) was heated to reflux for 24 h, cooled to RT, filtered, washed with Na_2CO_3 (10%, 4 x 20 mL) and worked up in the usual manner. The yellow solid that resulted was recrystallized from MeOH, affording the title compound **23** as pale yellow plates (4.74 g, 68%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 5.13 (s, 2H), 7.82 (t, 1H, J=8.0 Hz), 7.93 (d, 1H, J=8.0 Hz), 8.08 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): 22.72, 53.07, 127.81, 129.09, 132.33, 132.64, 134.70, 151.48, 165.85 ppm.

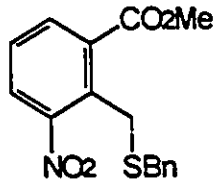
IR (CH_2Cl_2): 1120, 1356, 1535, 1729 cm^{-1}.

EI-MS (m/z, %): 244 (((M$^{+\cdot}$+2)-MeO), 8.2), 242 (((M$^{+\cdot}$)-MeO),8.2), 162 (100).

HRMS: Calc. for $C_8H_5BrNO_3$: 243.04295; Found: 242.94465 (M$^{+\cdot}$-MeO).

mp: 69.7-71.8 °C.

Methyl (2-(thiobenzyl)methyl)-3-nitro-benzoate (24).



24

Benzyl mercaptan (4.76 g, 38.4 mmol) was added dropwise over 15 min to a solution of KOtBu (4.23 g, 38.1 mmol) in THF (150 mL). The resulting bright yellow solution was stirred at RT for 10 min. A solution of benzyl bromide **23** (9.60 g, 34.9 mmol) in THF (50 mL) was added dropwise over 10 min. Stirring was continued at RT for 2 h, after which time the THF was evaporated off, and the residue partitioned between CH_2Cl_2 and H_2O. The organic phase was separated and worked up in the usual fashion to afford the title compound **24** as a yellow oil (13.59 g, 97%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.65 (s, 2H), 3.85 (s, 3H), 4.28 (s, 2H), 7.20 (s, 5H), 7.38 (t, 1H, J=8.0 Hz), 7.78 (d, 1H, J=8.0 Hz), 7.92 (d, 1H, J=8.0 Hz) ppm.

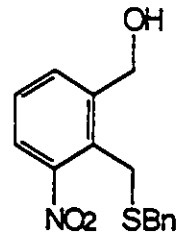
^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.36, 37.13, 52.80, 127.03, 127.13, 127.59, 128.42, 128.74, 133.18, 133.99, 134.68, 137.47, 151.00, 166.70 ppm.

IR (CH_2Cl_2): 1121, 1358, 1534, 1727 cm^{-1}.

EI-MS: 317 (1.8, $M^{+\cdot}$), 226 (2.2), 194 (4.6), 91 (100).

HRMS: Calc. for $C_{16}H_{15}NO_4S$: 317.07218; Found: 317.07484.

1-(Hydroxymethyl)-2-(thiobenzyl)methyl-3-nitro-benzene (25).



25

A solution of $LiEt_3BH$ (2.80 mL, 1.0 M, 2.80 mmol) was added dropwise to a cooled (0 °C) solution of ester 24 (750 mg, 2.37 mmol) in THF (20 mL). The resulting wine-red solution was stirred at 0 °C for 2 h. It was poured into H_2O (50 mL) and neutralized with HCl (10%), at which point the solution turned pale yellow. Extraction with EtOAc (6 x 20 mL) followed by usual work up afforded crude 25 as a reddish oil. Chromatography (3:1 Hex:EtOAc) provided the title compound 25 as a yellow oil (337 mg, 50%).

^{1}H-NMR: (200 MHz, $CDCl_3$): δ 2.75 (br, 1H), 3.74 (s, 2H), 3.89 (s, 2H), 4.57 (s, 2H), 7.27 (m, 6H), 7.60 (d, 1H, J=8.0 Hz), 7.64 (d, 1H, J=8.0 Hz) ppm.

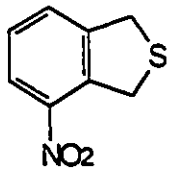
^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.33, 38.17, 62.63, 124.44, 127.95, 128.64, 129.22, 129.50, 130.67, 133.30, 137.95, 142.67, 151.11 ppm.

IR (CH_2Cl_2): 1014, 1356, 1530, 3600 cm^{-1}.

EI-MS (m/z, %): 289 (5.6, $M^{+\cdot}$), 180 (8.7), 148 (8.4), 134 (5.2), 118 (7.8), 91 (100).

HRMS: Calc. for $C_{15}H_{15}NSO_3$: 289.07727; Found: 289.07841.

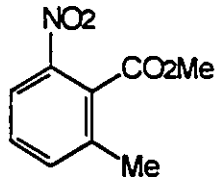
3-Nitro-dihydroisobenzothiophene (4).



4

A solution of methanesulfonyl chloride (43.6 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of hydroxy-sulfide 25 (100 mg, 0.35 mmol) and triethylamine (38.4 mg, 0.38 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred at RT for 1 h. Water (20 mL) was added, the solution was extracted with CH_2Cl_2 (2 x 10 mL) and worked up in the usual fashion to afford, after chromatography (10:1 Hex:EtOAc) sulfide 4 as a bright yellow solid (53.2 mg, 85%). The isolated product was identical to that prepared via a different route and mentioned earlier.

Methyl (2-methyl-6-nitro)benzoate (27).



27

A solution of 2-methyl-6-nitro-benzoic acid (5.00g, 27.6 mmol), MeI (4.70 g, 32.7 mmol) and $NaHCO_3$ (11.50 g, 136.9 mmol) in DMF (75 mL) was heated to 60 °C for 6 h, after which time the solution was poured into H_2O (200 mL) and extracted with Et_2O (6 x 50 mL). Usual work up afforded an orange solid that was recrystallized from MeOH to afford the title compound 27 as pale yellow plates (4.60 g, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.89 (s, 3H), 7.42 (m, 2H), 7.90 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.67, 52.71, 121.35, 128.93, 129.41, 135.64, 137.128, 145.75, 166.54 ppm.

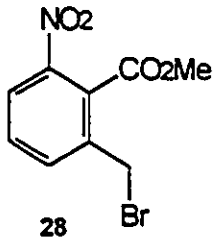
IR (CH_2Cl_2): 1351, 1535, 1740 cm^{-1}.

EI-MS (m/z, %): 195 (17.2, $M^{+\cdot}$), 178 (58.2), 163 (89.5), 133 (79.6), 89 (100).

HRMS: Calc. for $C_9H_9NO_4$: 195.05316; Found: 195.05138.

mp: 49.8-50.6 °C.

Methyl (2-(bromomethyl)-6-nitro)benzoate (28).



28

A solution of ester 27 (3.50 g, 18.0 mmol) and NBS (4.70 g, 26.7 mmol) in CCl_4 (100 mL) containing a catalytic amount of benzoyl peroxide was heated to reflux for 4 h. After this time, the solution was cooled to RT, filtered, washed with Na_2CO_3 (10%, 2 x 25 mL) and worked up in the usual manner to afford an orange solid. Purification via column chromatography (5:1 Hex:EtOAc) afforded the title compound as a white crystalline solid (3.07 g, 63%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.51 (s, 2H), 7.52 (t, 1H, J=8.0 Hz), 7.74 (d, 1H, J=8.0 Hz), 8.00 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.56, 53.10, 123.85, 128.47, 130.39, 135.42, 137.22, 146.73, 165.19 ppm.

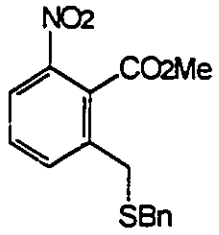
IR (CH_2Cl_2): 1349, 1538, 1740 cm^{-1}.

EI-MS (m/z, %): 275 (6.6, $M^{+\cdot}$ + 2), 273 (6.6, $M^{+\cdot}$), 258 (42.0), 256 (42.0), 194 (100.0).

HRMS: Calc. for $C_9H_8BrNO_4$: 272.96376; Found: 272.97158.

mp: 82.8-83.6 °C.

Methyl (2-(thiobenzyl)methyl-6-nitro)benzoate (30).



30

A solution of benzyl mercaptan (164.0 mg, 2.20 mmol) in THF (5 mL) was added dropwise to a suspension of NaH (110.0 mg, 4.6 mmol) in THF (10 mL). This mixture was stirred at RT until H_2 evolution ceased, at which point a solution of benzyl bromide **28** (600.0 mg, 2.19 mmol) in THF (10 mL) was added dropwise over 20 min. The resulting mixture was stirred at RT for 20 min, then refluxed for 10 h. The resulting orange-brown solution was poured into H_2O (50 mL) and extracted with Et_2O (4 x 25 mL). Usual work up followed by chromatography (10:1 Hex:EtOAc) afforded a pale yellow oil (135.9 mg, 20%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.50 (s, 2H), 3.70 (s, 2H), 3.80 (s, 3H), 7.20 (s, 5H), 7.40 (d, 1H, J=8.0 Hz), 7.50 (t, 1H, J=8.0 Hz), 8.00 (d, 1H, J=8.0 Hz) ppm.

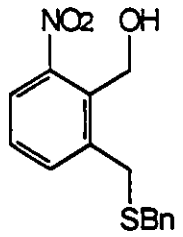
^{13}C-NMR (75 MHz, $CDCl_3$): δ 29.09, 32.73, 48.18, 111.82, 115.46, 116.82, 117.27, 118.18, 123.64, 124.36, 125.00, 126.36, 134.36, 150.91 ppm.

IR (CH_2Cl_2): 1115, 1352, 1535, 1738 cm^{-1}.

EI-MS (m/z, %): 317 (11.8), 300 (8.2), 162 (14.5), 91 (100).

HRMS: Calc. for $C_{16}H_{15}NO_4S$: 317.07218; Found: 317.07270.

1-(Thiobenzyl)methyl-2-(hydroxymethyl)-3-nitro-benzene (31).



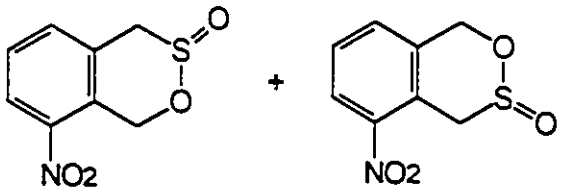
31

A solution of $LiEt_3BH$ (1.01 mL, 1.0 M in THF, 1.01 mmol) was added dropwise to a cooled (0 °C) solution of ester **30** (120 mg, 0.38 mmol) in THF (10 mL). Stirring was continued at 0 °C for 3 h. The solution was warmed to RT and stirring continued for 2 h, after which time the reaction mixture was poured into H_2O (20 mL), neutralized with HCl (10%), and extracted with EtOAc (6 x 10 mL). Usual work up and chromatography (3:1 Hex:EtOAc) afforded the title compound as a yellow oil (12 mg, 11%).

^{1}H-NMR (200 MHz, $CDCl_3$): 3.80 (s, 4H), 4.10 (s, 2H), 6.80 (d, 1H, J=8.0 Hz), 7.10 (d, 1H, J=8.0 Hz), 7.30 (s, 5H), 7.50 (d, 1H, J=8.0 Hz) ppm.

Addition of MsCl and TEA to a solution of **31** in CH_2Cl_2 afforded sulfide **4** in a yield of 72%.

Sultines 44a and 44b



44a **44b**

Sultines **44a** and **44b** were prepared following the general procedure of Dittmer[16].

A suspension of benzyl bromide **3** (3.00 g, 10.0 mmol), Rongalite™ (3.00 g, 20.0 mmol) and tetrabutylammonium bromide (0.70 g, 2.0 mmol) in DMF (20 mL) was stirred at RT for 6 h, poured into H_2O (150 mL), extracted with Et_2O (6 x 20 mL) and worked up in the normal manner, affording a bright yellow solution (1.33g). Elution through a column of SiO_2 afforded two compounds in almost identical yields.

Sultine **44b**, R_f=0.34 (2:1 Hex:EtOAc), pale yellow needles (702.1 mg, 34%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.83 (d, 1H, J=16.5 Hz), 4.70 (d, 1H, J=16.5 Hz), 5.02 (d, 1H, J=14.3 Hz), 5.36 (d, 1H, J=14.3 Hz), 7.45 (m, 2H), 8.00 (m, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 51.38, 60.84, 121.41, 124.96, 128.12, 130.60, 135.34, 149.47 ppm.

IR (CH_2Cl_2): 1119, 1352, 1533 cm^{-1}.

CI-MS (m/z, %): 214 (100, $M^{+\cdot}$+1).

HRMS: Calc. for $C_8H_7NO_2$ ($(M^{+\cdot})$-SO_2): 149.04768; Found: 149.04677.

mp: 97.4-98.2 °C.

Sultine **44a**, R_f=0.20 (2:1 Hex:EtOAc), pale yellow needles (562.7 mg, 27%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.65 (d, 1H, J=15.7 Hz), 4.34 (d, 1H, J=15.7 Hz), 5.48 (d, 1H, J=16.3 Hz), 5.50 (d, 1H, J=16.3 Hz), 7.47 (m, 2H), 8.10 (dd, 1H, J=8.0, 1.5 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 54.58, 58.57, 124.58, 128.40, 128.56, 129.34, 135.94, 146.83 ppm.

IR (CH_2Cl_2): 1118, 1352, 1533 cm^{-1}.

CI-MS (m/z, %): 214 (90.9, $M^{+\bullet}$+1).

HRMS: Calc. for $C_8H_7NO_2$ (($M^{+\bullet}$)-SO_2): 149.04768; Found: 149.04883.

mp:106.4-107.0 °C.

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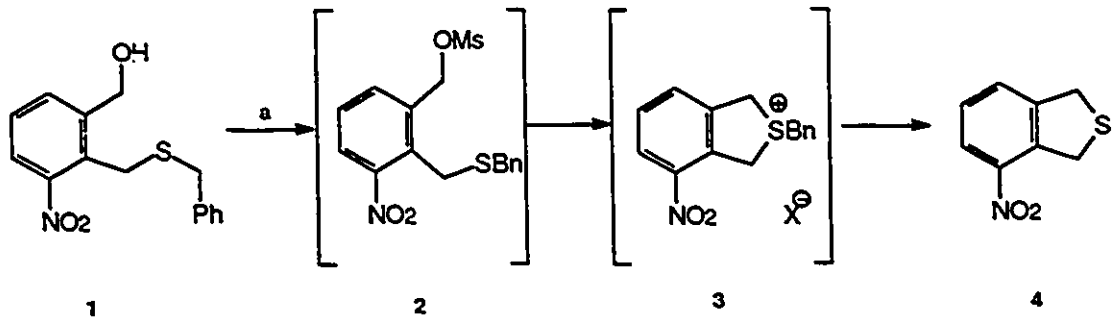
Chapter 4 - Indole Approach

4.1 Introduction

While exploring a mechanistic problem discussed in Chapter 3, it was found that bicyclic sulfides such as 4 could be prepared via activation of alcohol 1, presumably through sulfonium salt 3.

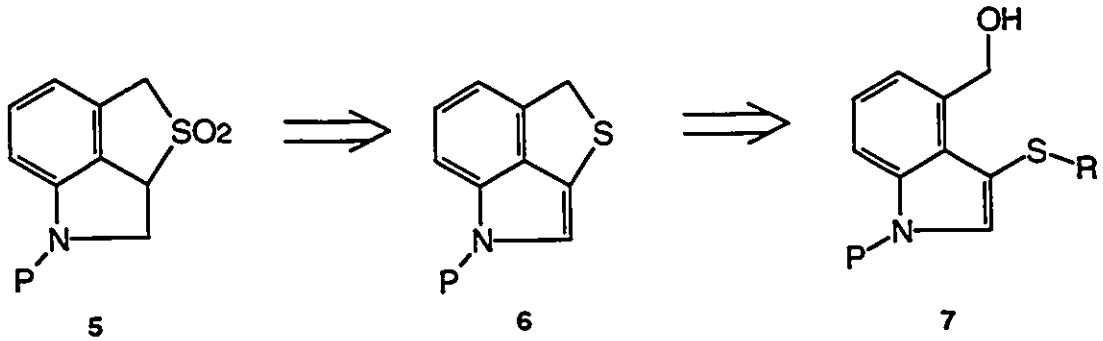


1 2 3 4

Reagents: a) MsCl, TEA, CH_2Cl_2.

Scheme 4.1 - Sulfide Formation via Sulfonium Salt Intermediate.

It was found that by simply activating the alcohol 1 by converting it to a mesylate, the sulfide 4 was formed quickly in near quantitative yields. The possibility of using this methodology to construct desired tricyclic sulfide 5, represented retrosynthetically in Scheme 4.2, was therefore explored.

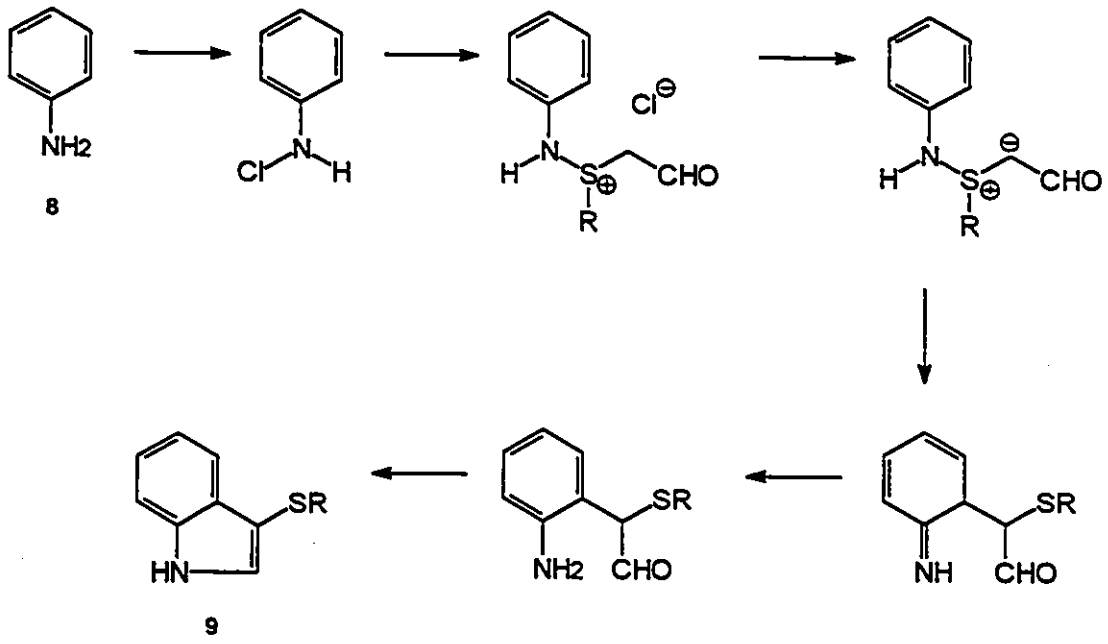


5 6 7

Scheme 4.2 - Retrosynthetic Analysis of 5 using Sulfonium Salt Methodology

4.2 Indole-Sulfonium Salt Approach

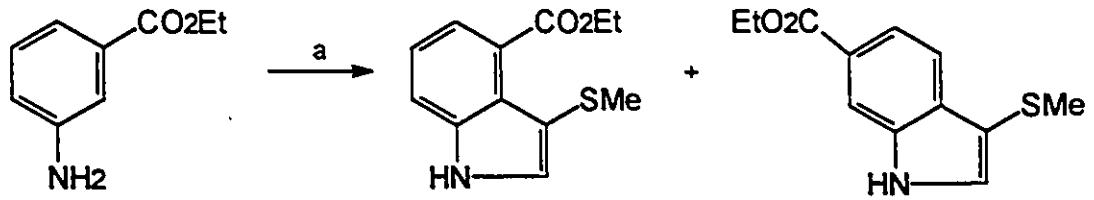
A route to a synthon for 7 was devised that relied on Gassman's aza-sulfonium salt[1] chemistry to construct the desired indole skeleton. Gassman had shown that anilines could be converted into indoles in a one pot procedure. His proposed mechanism is shown in Scheme 4.3. Initial N-chlorination of the aniline, followed by addition of a sulfur nucleophile gives an aza-sulfonium salt as an intermediate. Deprotonation of the methylene group adjacent to the sulfur provides a sulfonium ylide that undergoes a [2,3]-sigmatropic rearrangement. Re-aromatization of the benzene ring, followed by intramolecular condensation of the amine and the carbonyl group, and a final rearrangement affords the 3-thioalkyl indole 9 as a final product.



Scheme 4.3 - Gassman's Aza-sulfonium Salt Route to 3-Thioalkyl Indoles.

Use of this methodology and starting with ethyl 3-aminobenzoate and thiomethylacetaldehyde dimethylacetal as a sulfur nucleophile afforded a mixture of isomeric indoles 10 and 11. As can be seen

in Scheme 4.3, if the starting aniline is not symmetric, then two isomers can result from the sigmatropic rearrangement. In the present case, both isomers were formed in essentially identical yields.



10 (21%) **11** (20%)

Reagents: a) (i) tBuOCl, CH_2Cl_2, -78 °C; (ii) $MeSCH_2CH(OMe)_2$; (iii) TEA, (iv) Δ

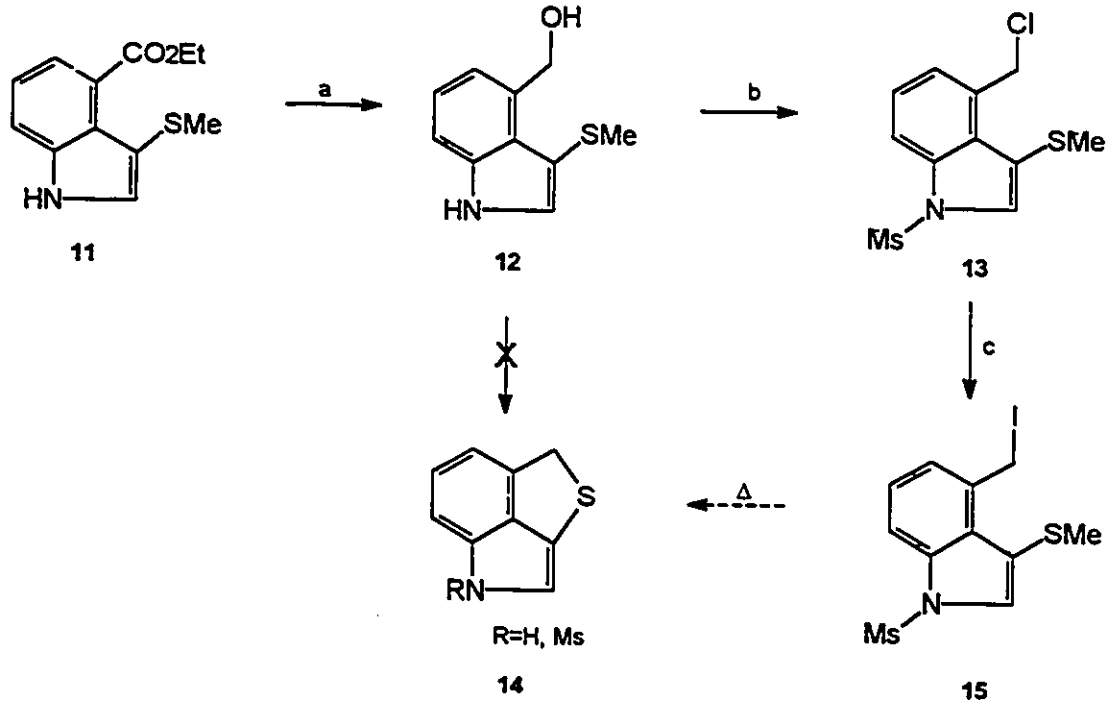
Scheme 4.4 - Synthesis of Indole **10** using Gassman's Aza-sulfonium Salt Methodology

The two isomers were easily separated and readily distinguished by examination of the aromatic region of the ^{1}H-NMR spectra since **10** and **11** are 1,2,3- and 1,2,4-trisubstituted aromatics respectively. Indole **10** displayed two sets of doublets at 7.30 and 7.39 ppm with a coupling constants of 8.0 Hz, and a multiplet pattern centered at 7.05 ppm, the aromatic region of isomer **30** was cleanly separated into three distinct resonances for the benzene ring protons; two doublets at 7.79 and 7.90 ppm with a coupling constant of 8 Hz, and a singlet at 8.15 ppm, representing the remaining, isolated aromatic proton.

Reduction of **10** with $LiAlH_4$ in THF provided 3-thiomethyl-4-hydroxymethyl indole **12** in a yield of 93% as a colorless oil. The ^{1}H-NMR exhibited peaks at 2.00 ppm (s, 3H, SCH_3), 3.80 ppm (bs, 1H, OH), 5.00 ppm (s, 2H, $-CH_2O-$) and 7.0 - 7.3 ppm (m, 4H).

Activation of the benzylic alcohol of indole **12** with MsCl/TEA, conditions that had afforded bicyclic sulfides (cf Chapter 3) gave no trace of the desired tricyclic sulfide **14**. The EI-MS of the product obtained showed two peaks at m/z 289 and 291 in a ratio of 3:1, indicative of a compound containing one chlorine atom. Analysis of the ^{1}H-NMR spectra showed three singlets at 2.55, 3.15 and 5.25 ppm in an integral ratio of 3:3:2, consistent with the presence of a thiomethyl and a methanesulfonyl group and a benzylic chloride. The aromatic region remained complicated due to significant overlap of signals for three protons around 7.45 ppm, but there was a single resonance representing one proton that had moved downfield and now appeared as a doublet of doublets centered at 7.95 ppm with coupling constants of 8

and 1 Hz. These data were consistent with a structure of 13. In an attempt to induce cyclization, 13 was heated in acetone in the presence of excess NaI. Smooth quantitative conversion to the benzylic iodide 15 (yellow solid, mp 95 °C) was observed after short reaction times. The ^{1}H-NMR of 15 is shown in Fig. 4.1. The ^{13}C spectra showed an upfield shift of 50 ppm for the carbon that had been assigned to the benzylic methylene group when compared to the benzylic alcohol or chloride. After prolonged reflux, the mass balance decreased, but no other material could be isolated. Trying to induce an S_N1 pathway by heating 13 or 15 in ionizing solvents like DMF resulted in considerable decomposition. Addition of silver salts, either $AgClO_4$ or $AgBF_4$, also did not lead to the formation of 14. Instead, the CH_2Cl_2 solution turned bright yellow immediately upon addition of the silver salt, but in less then one second, the reaction mixture turned black, and no starting material or product could be isolated from the reaction mixture. These results indicate that intramolecular displacement, via either an S_N1 of S_N2 mechanism, was very difficult for substrates 13 or 15.



Reagents: a) $LiAlH_4$, THF, RT (93%).; b) MsCl, TEA, RT (26%); c) NaI, acetone, Δ (91%).

Scheme 4.5 - Postulated Synthesis of Tricyclic Sulfide 14 via Indole-Sulfonium Salt Approach

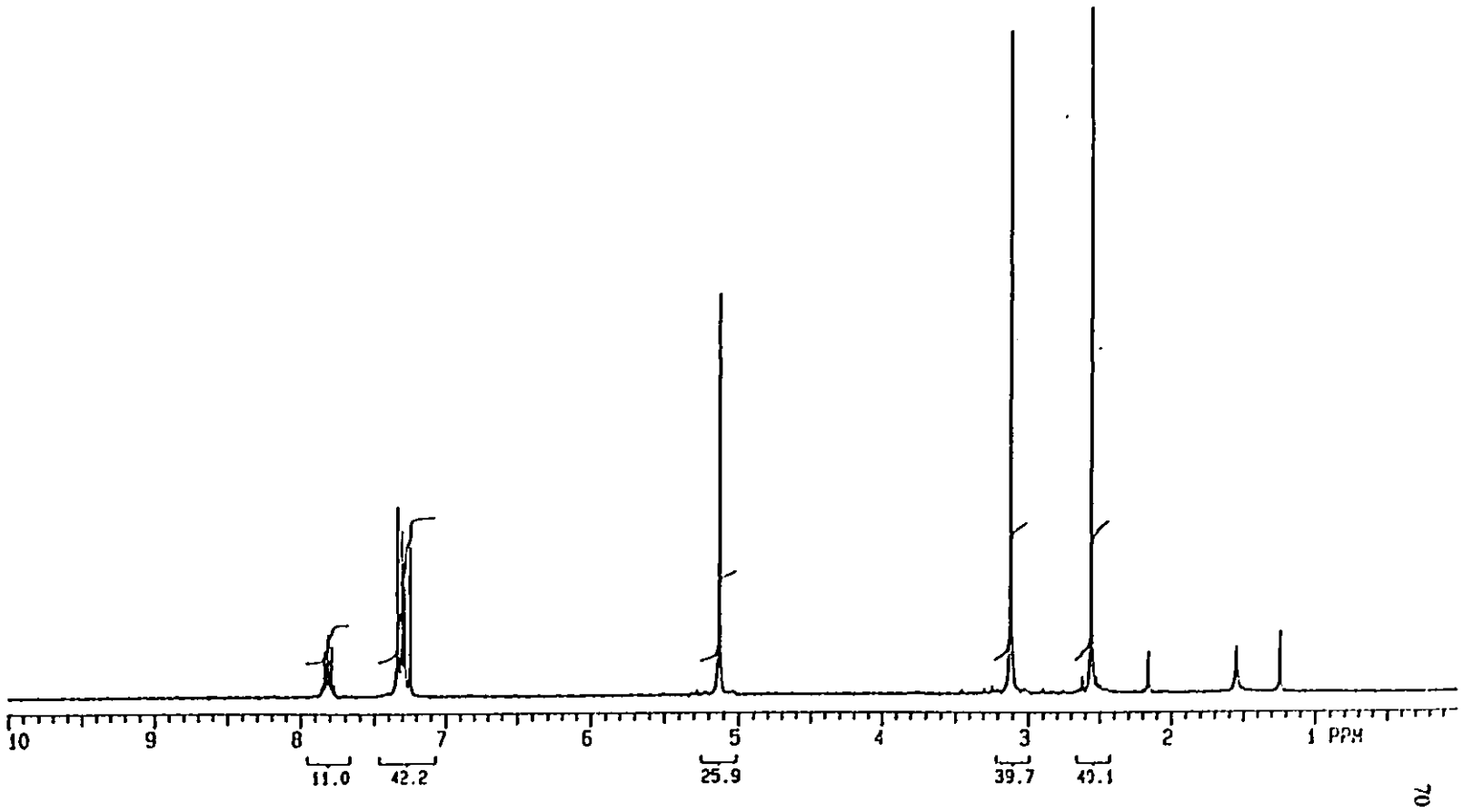
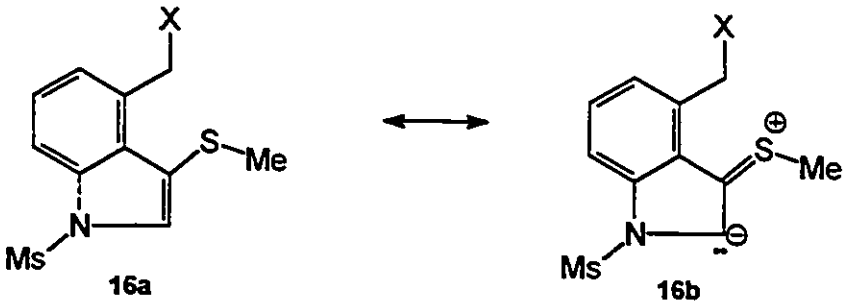


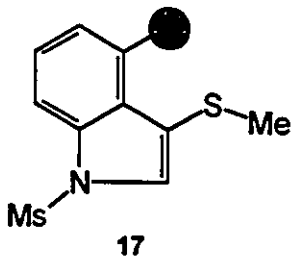
Figure 4.1 200 MHz ^{1}H-NMR of Benzylic Iodide 15 in $CDCl_3$

Although in indoles **13** and **14** the sulfur was in conjugation with the indole ring, a factor which may decrease the nucleophilicity of this center, it was doubtful that this was solely responsible for the failure of forming tricyclic **14**. The resonance forms in which the sulfur electron density is pumped into the aromatic ring were not considered to be major contributors since one resonance form, **16b**, places a lone pair or electrons adjacent to the nitrogen, a factor known to be destabilizing.



16a **16b**

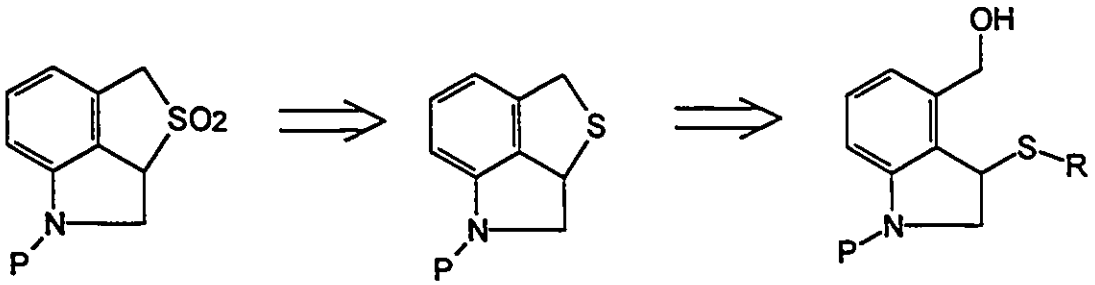
A more reasonable conclusion was that **16a** was too flat to allow for the correct geometry and trajectory necessary for S_N2 displacement, since the nucleophile, electrophilic center and leaving group should ideally align with an angle between them of 180 °. In the case of trying to induce an S_N1 reaction, the intermediate benzylic carbocation **17** may not have been able to get the correct orbital alignment since the sp^2 hybridized carbocation would prefer to stay planar and in conjugation with the benzene ring. It was anticipated that if the ring system was more flexible, then the desired intramolecular displacement may proceed. The strategy was therefore changed, the results of which are presented in the next section.



17

4.3 Indoline-Sulfonium Salt Approach

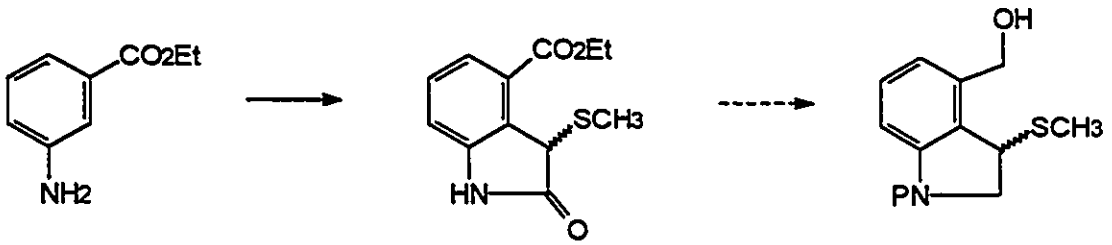
The modified approach, represented retrosynthetically in Scheme 4.6, called for the synthesis of a 3-thioalkyl-4-hydroxymethylindole 19. It was anticipated that with a compound such as 19 in hand, activation of the benzylic alcohol followed by intramolecular ring closure and in situ dealkylation of the sulfonium salt would afford tricyclic sulfide 18. Oxidation of the sulfur would give the target sulfone 5.



5 18 19

Scheme 4.6 - Retrosynthetic Analysis II of Tricyclic Sulfone 5

A route to the 3-thioalkyl indoline 19 was envisaged based on the impressive work done by Gassman on the synthesis of 3-thioalkyl oxindoles[2] This is shown in Scheme 4.7.



8 20 21

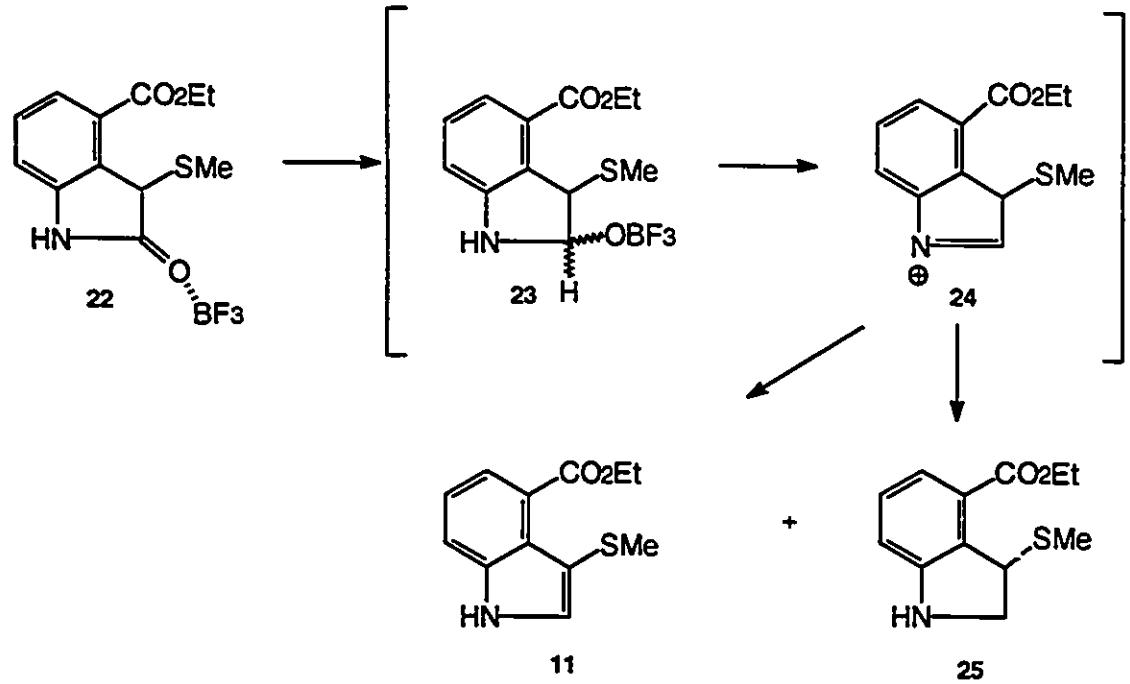
Scheme 4.7 - Approach II to Tricyclic Sulfide Precursor 21

Starting again with ethyl 3-aminobenzoate, oxindole 20 was prepared in one pot by treatment with tBuOCl, followed by addition of methyl (methylthio)acetate, and finally addition of triethylamine. Oxindole 20 (colorless crystals, mp 150.2 - 151.0 °C) was isolated as a single regioisomer by

crystallization from the crude reaction mixture, in a yield of 72%. Its structural assignment was based on its MS and ^{1}H-NMR data. The ^{1}H-NMR showed the expected peaks for the ester, S-methyl and the 1,2,3-trisubstituted aromatic units. The singlet at 4.68 ppm was assigned to the benzylic methine group adjacent to both the carbonyl and thiomethyl groups.

As mentioned in the previous section, the key [2,3]-sigmatropic rearrangement of the intermediate ylide can result in the formation of two regioisomers. However, in this case, only the product arising from reaction at the center ortho to both substituents was isolated; an exhaustive search of the mother liquor was not carried out. Gassman[3] had reported a similar result when the starting aniline derivative contained a nitro group ortho to the amino group.

With a supply of oxindole **20** in hand, conversion to the desired 3-thioalkyl indoline derivative was attempted. After considerable experimentation, conditions were found that would convert oxindole **20** to indoline derivative **25**. When a THF solution of oxindole **20** and 1 equivalent of BF_3•OEt_2 was added dropwise to a solution of $LiAH_4$ in THF at 0 °C, followed by warming to RT, then heating at reflux for one hour, followed by the usual work up and column chromatography, a cloudy oil was obtained. EI-MS showed a molecular ion at m/z 237 and the ^{1}H-NMR was consistent with a structure of **25**.



Scheme 4.8 - Reduction of Oxindole **20** with $LiAlH_4/BF_3$•OEt_2

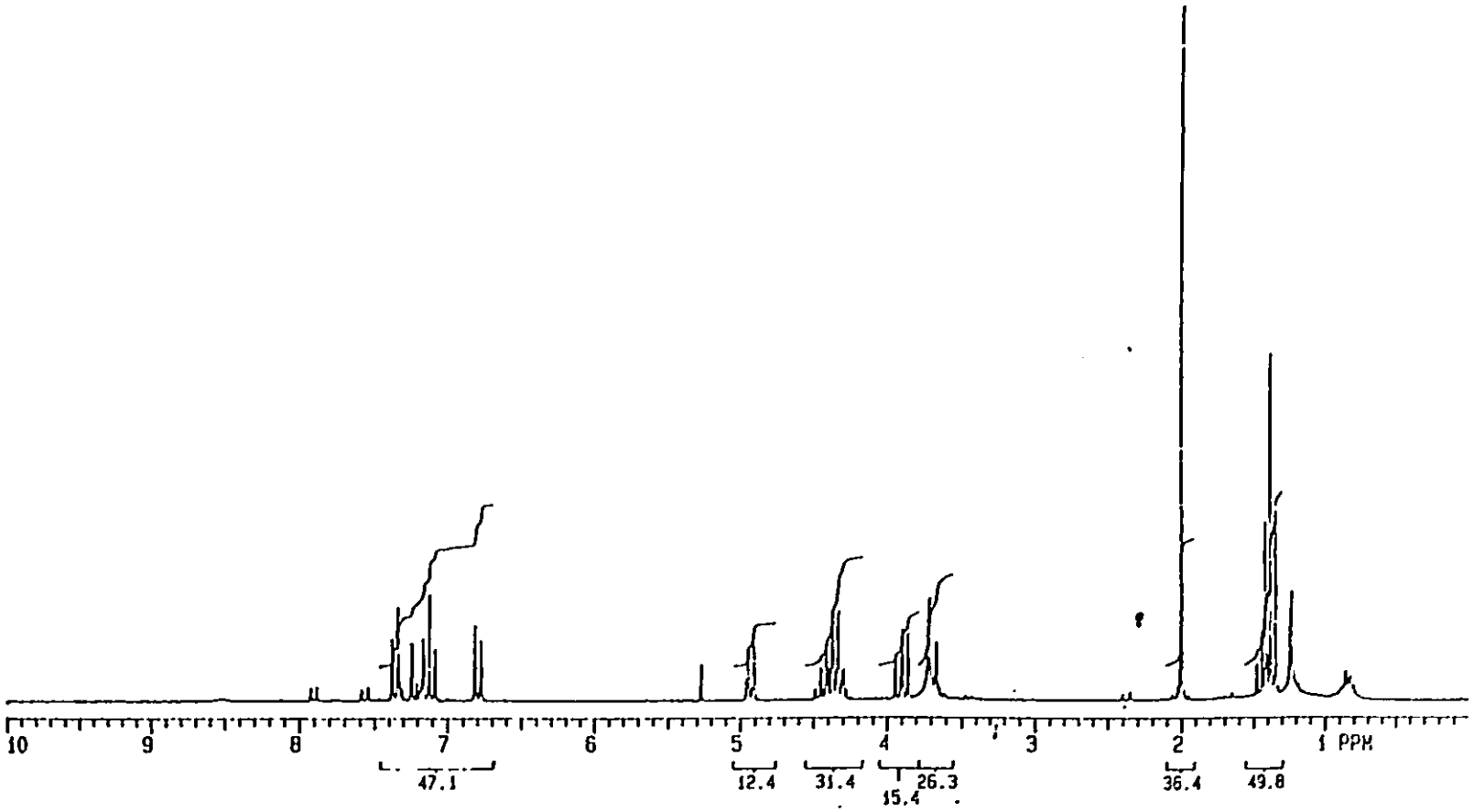
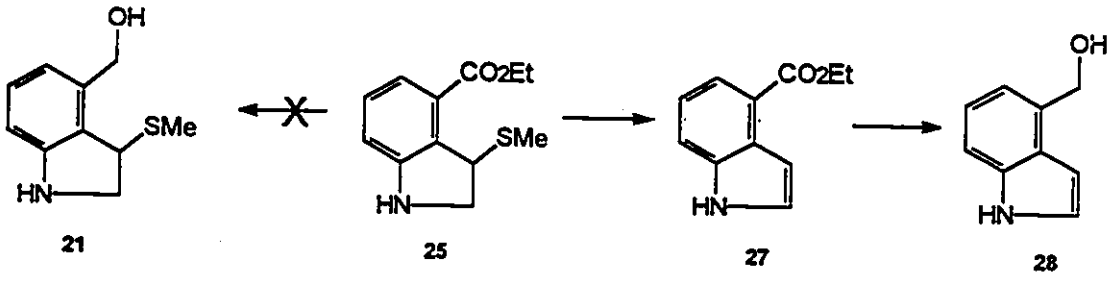


Figure 4.2 200 MHz ^{1}H-NMR Spectrum of Indoline 25 in $CDCl_3$

In addition to indoline 25, another product was isolated by chromatography as a colorless solid. This material was identified as the indole 11 based on its simple ^{1}H-NMR spectra which was identical to the spectra of 11 that had been prepared previously in this chapter via an alternative route. Both compounds were present in almost equal proportions, in a combined overall yield of 73%. This reaction was not studied in any detail so conditions that maximized the formation of either 11 or 25 were not found.

Presumably, complexation of the more Lewis basic amide group with the Lewis acid led to the formation of complex 22 which was converted to hemiaminal 23 by the first equivalent of hydride. Elimination of metal alkoxide in a manner similar to simple amide reduction[4] provided imine 24, which could then undergo further reduction to indoline 25, or isomerize to indole 26.

With reasonable access to indoline 25 (two steps from commercial material), it was assumed that reduction of the 4-carboethoxy group to the hydroxymethyl group would be a trivial transformation. Reduction of ester 25 with a variety of reducing agents, including $LiAH_4$, Dibal-H, $LiEt_3BH$ and $LiBH_4$ under a variety of conditions failed to provide any of the desired benzylic alcohol 21. Instead, ester 27 was isolated along with benzylic alcohol 28. When the reaction was carried out under more controlled conditions, using only one equivalent of hydride at in the form of Super-Hydride™ at -78 °C, 27 was produced in nearly quantitative yield.



Scheme 4.9 - Reduction of Ester 25 with Metal Hydrides

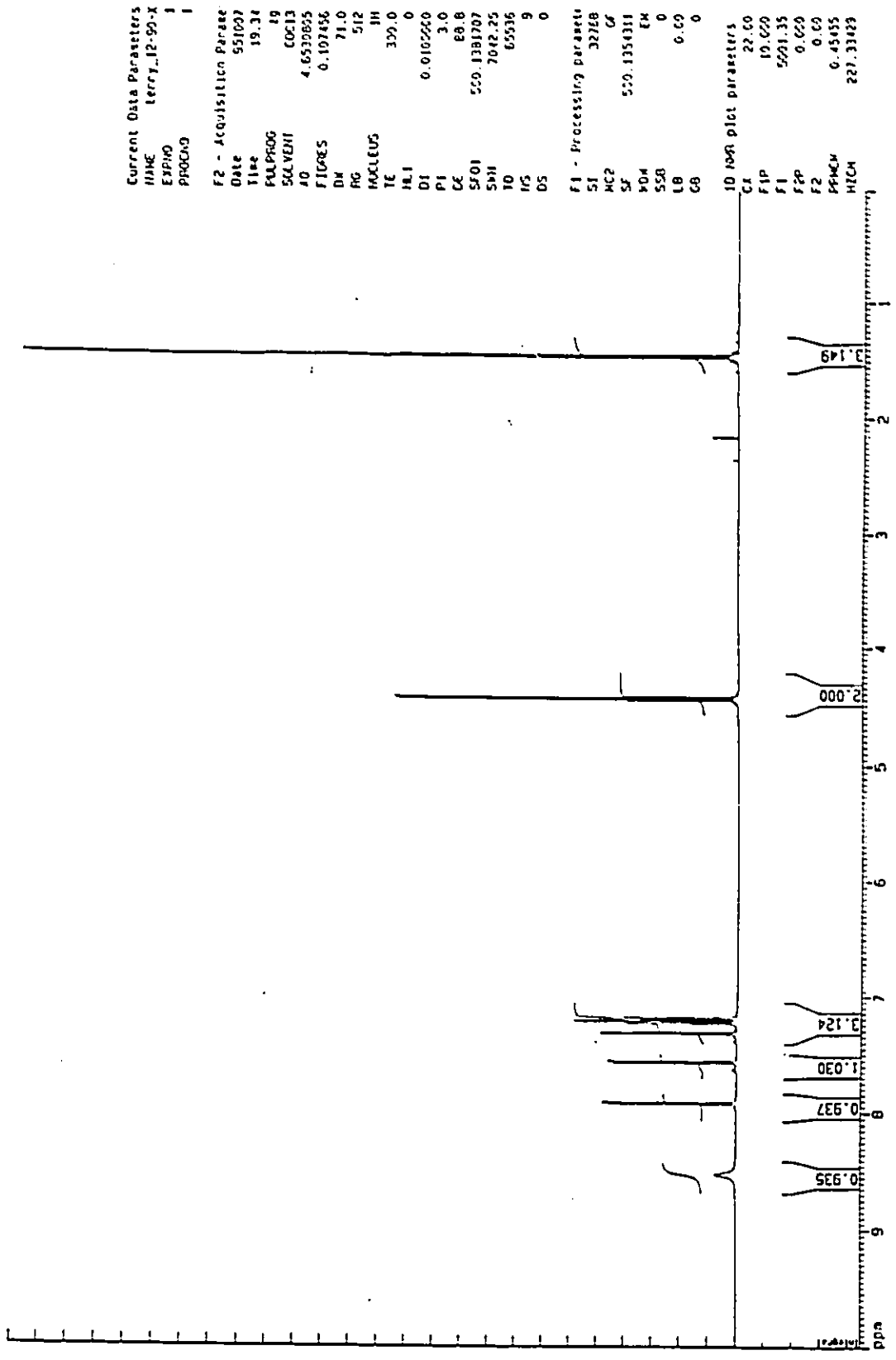
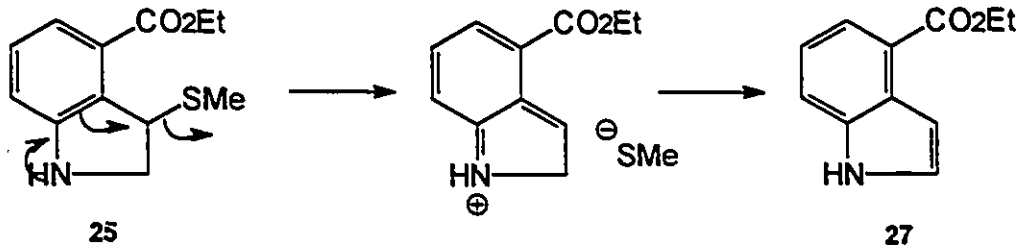


Figure 4.3 500 MHz ^{1}H-NMR Spectrum of Indole 11 in $CDCl_3$

One possible mechanistic explanation is shown in Scheme 4.10. Nitrogen assisted elimination of the thiomethyl group, followed by re-aromatization of the indole nucleus would account for the facile conversion of indoline 25 to indole 27.

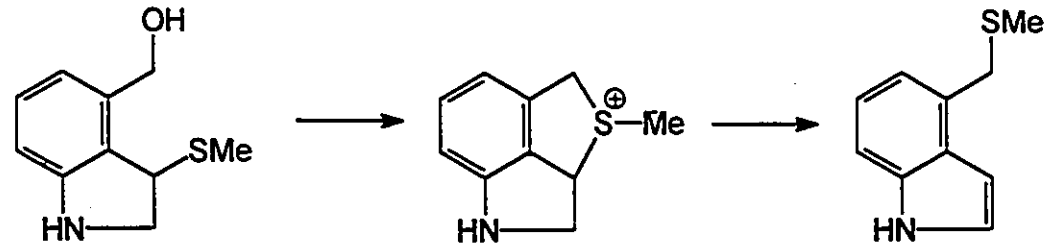


25 27

Scheme 4.10 - Proposed Mechanism for the Formation of 27 from 25.

Further supporting evidence for the mechanism proposed in Scheme 4.10 was the observation that 25 was converted to 27 by standing at room temperature in the absence of any added metal hydride.

With this result, it became apparent that formation of the desired 3-thioalkylindoline derivative 21 would be quite difficult. Additionally, the above transformation pointed out a possible reaction pathway that had not been considered previously, the facile elimination of the thioalkyl group. Such an elimination could conceivably complicate the proposed synthesis of the desired tricyclic sulfide as shown in Scheme 4.11.



21 29 30

Scheme 4.11 - Re-examination of Sulfonium Salt Approach to Tricyclic Sulfide 29.

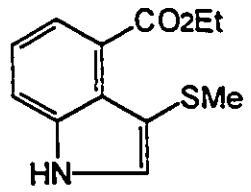
β-elimination from the sulfonium salt 29 could compete with de-alkylation. Even if de-alkylation proved to be the major pathway, the formed tricyclic sulfide could be prone to the same elimination. This possibility coupled with the problems in accessing 21 caused the abandonment of this approach.

4.4 Experimental

General

For general experimental, see chapter 3. In addition to this, tBuOCl was prepared according to the literature method[4].

3-(Thiomethyl)-4-carboethoxy-indole (10).



10

The general procedure of Gassman[1] was used. In this way, a solution of freshly prepared tBuOCl (4.60 g, 42.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a cooled (-78 °C) solution of ethyl 3-aminobenzoate (7.00 g, 42.4 mmol) in CH_2Cl_2 (175 mL). The resulting yellow solution was stirred at -78 °C for 15 min, then a solution of thiomethylacetaldehyde dimethylacetal (5.80 g, 42.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Stirring was continued for 1.5 h, then a solution of triethylamine (4.28 g, 42.5 mmol) in CH_2Cl_2 (10 mL) was added, the cooling bath removed, and the reaction allowed to warm to RT over a period of 12 h. The reaction mixture was heated to reflux for 12 h, cooled to RT, water (100 mL) added, the organic phase separated and the resulting reddish solution evaporated to dryness. The dark residue was dissolved in THF (50 mL), and HCl was added (10%). The reaction mixture was heated at reflux for 4 h, cooled to RT and extracted with Et_2O (4 x 50 mL). Usual work up on the combined organic extracts followed by chromatography (3:1 Hex:EtOAc) afforded the title compound (2.42 g, 24%).

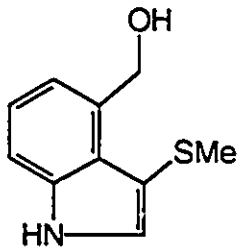
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.0 Hz), 2.21 (s, 3H), 4.40 (q, 2H, J=7.0 Hz), 7.05 (m, 2H), 7.35 (m, 2H), 8.90 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.86, 19.74, 60.90, 108.60, 114.47, 121.05, 121.23, 124.25, 124.68, 127.46, 136.91, 168.93 ppm.

EI-MS (m/z, %): 235 (100, $M^{+\cdot}$), 207 (12.1), 190 (49.7), 176 (42.5), 144 (47.6), 116 (27.4).

HRMS: Calc. for $C_{12}H_{13}NO_2S$: 235.06670; Found: 235.06518.

3-(Thiomethyl)-4-(hydroxymethyl)-indole (12).



12

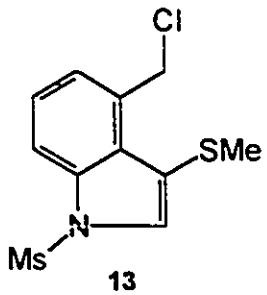
A solution of ester **10** (100 mg, 0.43 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (16 mg, 0.43 mmol) in THF (5 mL). The gray, cloudy mixture was stirred at RT for 1 h, then poured into a saturated solution of potassium sodium tartrate (50 mL) and EtOAc (25 mL) and stirred at RT for 4 h. Separation of the organic phase followed by usual work up and chromatography (2:1 Hex:EtOAc) afforded the title compound **12** as a clear oil (62 mg, 80%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.80 (br, 1H), 5.00 (s, 2H), 7.00-7.20 (m, 4H), 9.00 (br, 1H).

EI-MS (m/z, %): 193 (98.1, $M^{+\bullet}$), 160 (39.1), 117 (100).

HRMS: Calc. for $C_{10}H_{11}NOS$: 193.05614; Found: 193.05628.

1-(methanesulfonyl)-3-(thiomethyl)-4-(chloromethyl)-indole (13).



13

A solution of methanesulfonyl chloride (330 mg, 2.88 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of alcohol **12** (250 mg, 1.30 mmol) and triethylamine (262 mg, 2.60 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred at RT for 3 h, then poured into H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were worked up in the usual manner and chromatographed (2:1 Hex:EtOAc) affording a slightly green solid, which was triturated with Et_2O and filtered, providing the title compound as white needles (95.2 mg, 26%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.15 (s, 3H), 5.25 (s, 2H), 7.45 (m, 3H), 7.95 (dd, 1H, J=8.0, 1.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.19, 39.83, 42.07, 112.77, 116.24, 124.49, 124.73, 125.08, 126.85, 130.64, 134.85 ppm.

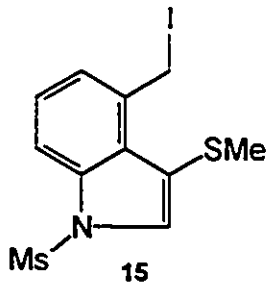
IR (CH_2Cl_2): 1174, 1355 cm^{-1}.

EI-MS (m/z, %): 291 (8.0, $M^{+\cdot}$+ 2), 289 (25.3, $M^{+\cdot}$), 210 (66.1), 164 (26.1), 149 (100).

HRMS: Calc. for $C_{11}H_{12}NO_2S_2Cl$: 288.99980; Found: 288.99981.

mp: 98 °C.

1-(methanesulfonyl)-3-(thiomethyl)-4-(iodomethyl)-indole (15).



15

A mixture of chloride **13** (90mg, 0.43 mmol) and NaI (65 mg, 0.43 mmol) in acetone (5 mL) was heated to reflux for 2 h, cooled to RT, diluted with CH_2Cl_2, filtered, and the resulting bright yellow solution concentrated, affording the title compound **15** as a yellow powder (147 mg, 91%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.11 (s, 3H), 5.13 (s, 2H), 7.30 (m, 3H), 7.80 (dd, 1H, J=8.0 Hz, 1.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 2.89, 19.78, 40.56, 112.87, 117.13, 125.03, 125.54, 125.71, 126.40, 133.63, 135.53 ppm.

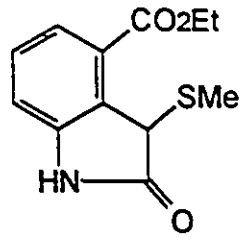
IR (CH_2Cl_2): 1179, 1369 cm^{-1}.

EI-MS (m/z, %): 381 (2.9, $M^{+\cdot}$), 254 (100), 208 (35.5).

HRMS: Calc. for $C_{11}H_{12}NO_2S_2I$: 380.93542; Found: 380.93421.

mp: 95 °C.

3-(Thiomethyl)-4-carbocthoxy-2-oxo-2,3-dihydroindole (20).



20

Oxindole **20** was prepared according to the general procedure of Gassman[2] In this way, a solution of freshly prepared tBuOCl[4] (3.30 g, 30.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a cooled (0°C) solution of ethyl 3-aminobenzoate (5.00 g, 30.3 mmol) in CH_2Cl_2 (100 mL). The resulting bright yellow mixture was stirred at this temperature for 10 min, at which point a solution of methyl (thiomethyl)acetate (3.65 g, 30.4 mmo) in CH_2Cl_2 (15 mL) was added and stirring continued for 2.5 h. A solution of triethylamine (3.10 g, 30.7 mmol) in CH_2Cl_2 (15 mL) was then added, and the initially yellow solution was allowed to warm to RT over 12 h. The reddish solution that resulted was poured into a solution of H_2O (200 mL), the organic phase separated and worked up in the usual manner to provide an orange solid. Recrystallization from CH_2Cl_2 afforded the title compound as colorless plates (5.70 g, 75%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=8.0 Hz), 1.51 (s, 3H), 4.38 (q, 2H, J=8.0 Hz), 4.68 (s, 1H), 7.02 (d, 1H, J=8.0 Hz), 7.31 (t, 1H, J=8.0 Hz), 7.62 (d, 1H, J=8.0 Hz), 8.05 (br, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.15, 14.05, 46.74, 61.33, 113.39, 124.26, 127.89, 128.19, 129.00, 142.04, 165.52, 177.46 ppm.

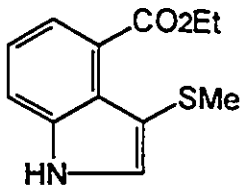
IR (CH_2Cl_2): 1613, 1723, 3424 cm^{-1}.

EI-MS (m/z, %): 251 (2.2, $M^{+\bullet}$), 205 (100), 176 (13.2), 160 (36.6).

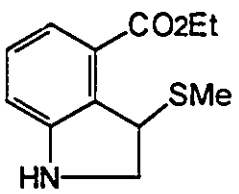
HRMS: Calc. for $C_{12}H_{13}NO_3S$: 251.06162; Found: 251.06118.

mp: 150.2-151.0 °C.

Reduction of Oxindole 20 with $LiAlH_4/BF_3{\cdot}OEt_2$



10



25

A cooled (0 °C) solution of oxindole **20** (500 mg, 1.99 mmol) and $BF_3{\cdot}OEt_2$ (0.50 mL, 3.95 mmol) in THF (10 mL) was added dropwise to a solution of $LiAlH_4$ (75 mg, 1.98 mmol) in THF (10 mL). The resulting solution was stirred at 0 °C for 1h, refluxed for 3.5 h, cooled to RT and quenched with a solution of potassium sodium tartrate (saturated, 50 mL) anf EtOAc (50 mL). Separation of the organic phase, usual work up and purification of the residue by chromatography (4:1 Hex:EtOAc) afforded two compounds.

25: R_f=0.25 (4:1 Hex:EtOAc); cloudy yellow oil (200 mg, 42%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.35 (t, 3H, J=8.0 Hz), 2.00 (s, 3H), 3.65 (d, 1H, 7.0 Hz), 3.70 (br, 1H), 3.89 (dd, 1H, J=7.0, 1.0 Hz), 4.35 (m, 2H), 4.92 (d, 1H, J=7.0 Hz), 6.80 (d, 1H, J=7.5 Hz), 7.11 (t, 1H, J=7.5 Hz), 7.38 (d, 1H, J=7.5 Hz) ppm.

EI-MS (m/z, %): 237 (2.5, $M^{+\cdot}$), 189 (39.7), 144 (100), 116 (49.6).

HRMS: Calc. for $C_{12}H_{15}NO_2S$: 237.08235; Found: 237.08185.

10: R_f=0.10 (4:1 Hex:EtOAc); pale yellow solid (145 mg, 40%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.0 Hz), 2.21 (s, 3H), 4.40 (q, 2H, J=7.0 Hz), 7.05 (m, 2H), 7.35 (m, 2H), 8.90 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.86, 19.74, 60.90, 108.60, 114.47, 121.05, 121.23, 124.25, 124.68, 127.46, 136.91, 168.93 ppm.

EI-MS (m/z, %): 235 (100, $M^{+\cdot}$), 207 (12.1), 190 (49.7), 176 (42.5), 144 (47.6), 116 (27.4).

HRMS: Calc. for $C_{12}H_{13}NO_2S$: 235.06670; Found: 235.06518.

References

1) Gassman, P.G.; van Bergen, T.J.; Gilbert, D.P.; Cue, B.W., Jr. *J. Amer. Chem. Soc.*, 1974, 96, 5495.

2) Gassman, P.G.; van Bergen, T.J. *J. Amer. Chem. Soc.*, 1974, 96, 5508.

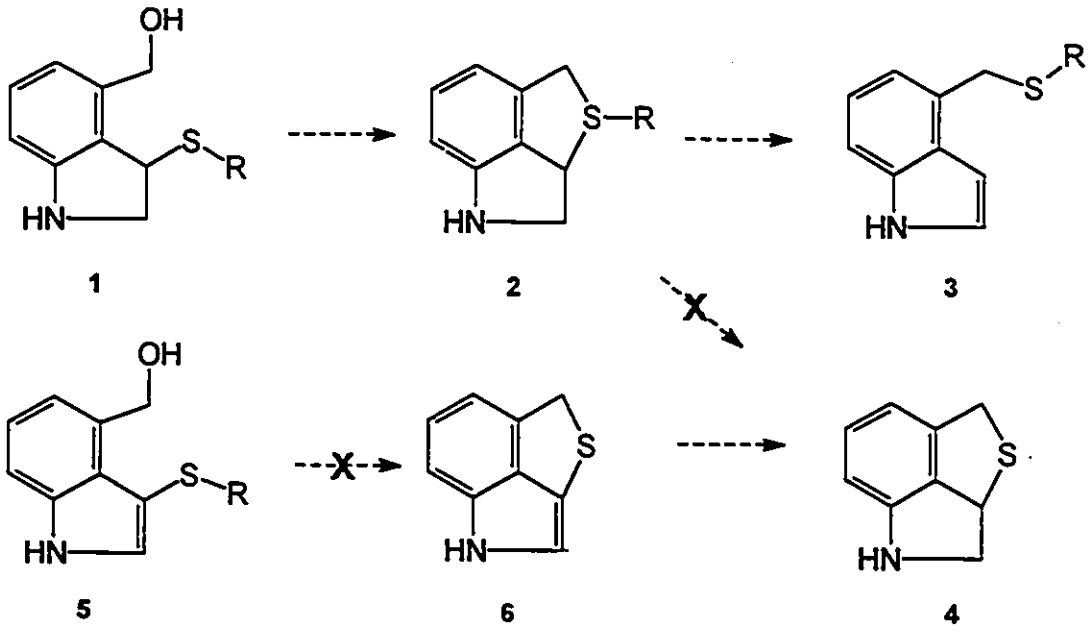
3) Smith, M.B. Organic Synthesis, p. 352, McGraw-Hill, Inc., Toronto (1994).

) Mintz, M.J.; Walling, C. *Organic Synthesis* Coll. Vol. V, 184 (1973).

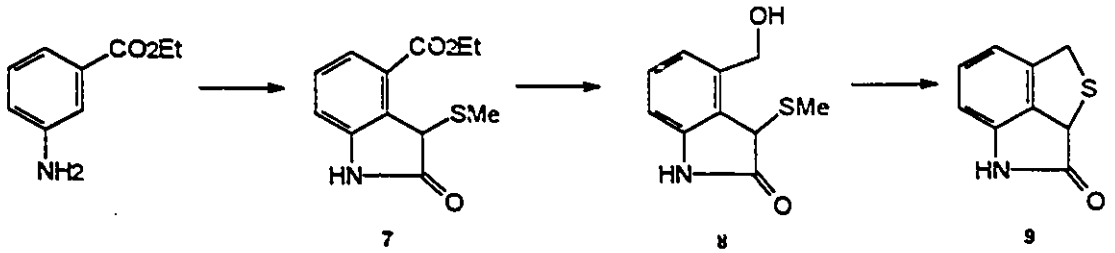
Chapter 5 - Oxindole-Sulfonium Salt Approach

5.1 Introduction

In the first approach to 4 (Ch. 4) based on an indole precursor, the hydroxy-sulfide 5 was synthesized, but cyclization to provide 6 was not successful, possibly due to the rigid nature of the planar intermediate and the inability to achieve the trajectory necessary for displacement. In the second approach, the synthesis of the indoline precursor 1 proved troublesome, and it was believed that the intermediate sulfonium salt 2 would eliminate to form indole 3 rather than dealkylate to form the desired tricyclic sulfide 4. A precursor to 4 which would avoid these problems would have an sp^2 hybridized center at C2, yet have an sp^3 hybridized carbon at position 3 to give enough flexibility to allow the desired displacement; the oxindole 8 appeared to fit these criteria.



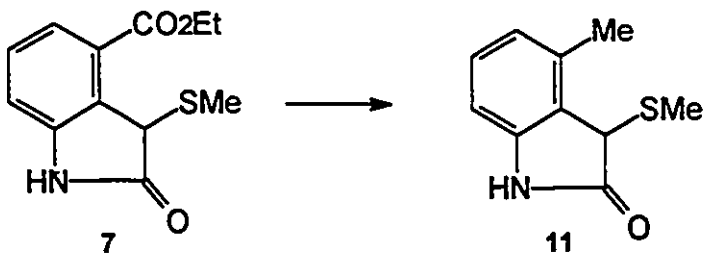
It was expected that 8 could be made rapidly from commercial ethyl 3-aminobenzoate according to Scheme 5.1 using Gassman's oxindole methodology[1].



Scheme 5.1 - Proposed Synthesis of Oxindole-Sulfide 9

5.2 Oxindole-Ester Approach

Based on the vast amount of literature precedence indicating that N-unsubstituted oxindoles are extremely difficult to reduce, the reduction of the pendant ester side chain in 7 to benzylic alcohol 8 was expected to be a trivial transformation. However, exposure of oxindole-ester 7 to typical reduction condition with Dibal-H in THF at 0 °C led to the quantitative recovery of starting material. Use of the Super-Hydride™, a reagent that is usually quite effective for the reduction of esters[2] also led to quantitative recovery of starting material. A number of other reducing agents were screened including the already mentioned Dibal-H and $LiEt_3BH$, $LiBH_4$, $Ti(oiPr)_4$ / $(EtO)_3SiH$[3], Red-Al and $LiAlH_4$ over a temperature range from -78 °C to refluxing THF, with an excess of reducing agent present. In almost all cases, starting material was recovered in near quantitative yield. A hint of a reaction was observed when excess (10 molar equivalents) of $LiAlH_4$ was used and the reaction mixture was refluxed for 18 h in THF, and even then, the only sign of reaction was that the recovery of starting material was only 50% of the original mass balance.



Scheme 5.2 - Reduction of Oxindole-Ester 7

Reduction of oxindole-ester 7 with excess $LiAlH_4$ in refluxing THF for 18 h, followed by cooling to 0 °C and quenching with a saturated solution of Rochelle's salt[5] led to two products; starting material, recovered in almost 50% yield, and another *less polar* compound. This less polar compound, isolated via chromatography, was identified as 4-methyl-3-thiomethyl-2-oxindole **11**. The ^{1}H-NMR of the new compound (Fig. 5.1) showed three singlets at 2.10, 2.50 and 4.25 ppm in a ratio of 3:3:1 ascribed to the aromatic methyl, thiomethyl and benzylic methine respectively. The IR spectrum (carbonyl at 1724 cm^{-1}) and the aromatic portion of the ^{1}H-NMR (doublet-doublet-triplet pattern shifted upfield to 6.70, 6.80 and 7.20 ppm respectively) confirmed that the oxindole nucleus was still intact. Repetition of the reaction at lower temperatures and for longer reaction times did not lead to interception of the desired, presumed benzylic alcohol **8**.

The harsh conditions necessary in order to observe any reduction of ester 7 and the complete lack of control led to an interesting mechanistic speculation. The relative inertness of the ester carbonyl towards addition of hydride, and the subsequent high propensity for over reduction to **11** was consistent with reduction of benzoates having an electron donating group either ortho or para to the ester group[6]. In oxindole 7, the amide N-H could hardly be viewed as a strong electron donating group and, regardless of its electron density, it was situated meta to the ester group. The relative acidity of the benzylic methine proton was then considered. Gassman[7] had found this proton to be quite susceptible to deprotonation. Based on this work, the reduction results of oxindole-ester 7 were explained based on the following mechanism.

Addition of a hydride source to a solution of 7 in THF leads to anion **12**. The high electron density of the ester carbonyl group as illustrated by **12b** makes the carbonyl relatively inert to addition of all hydride sources, except for $LiAlH_4$. The first addition of hydride leads to aldehyde **13**, which is more susceptible to addition of another hydride, giving rise to the benzylic alkoxide **14**. At this point, the extra electron density donated by the anion formed α to sulfide and oxindole carbonyl which initially made the ester carbonyl inert to addition of hydride now makes it very prone to over-reduction, presumably via

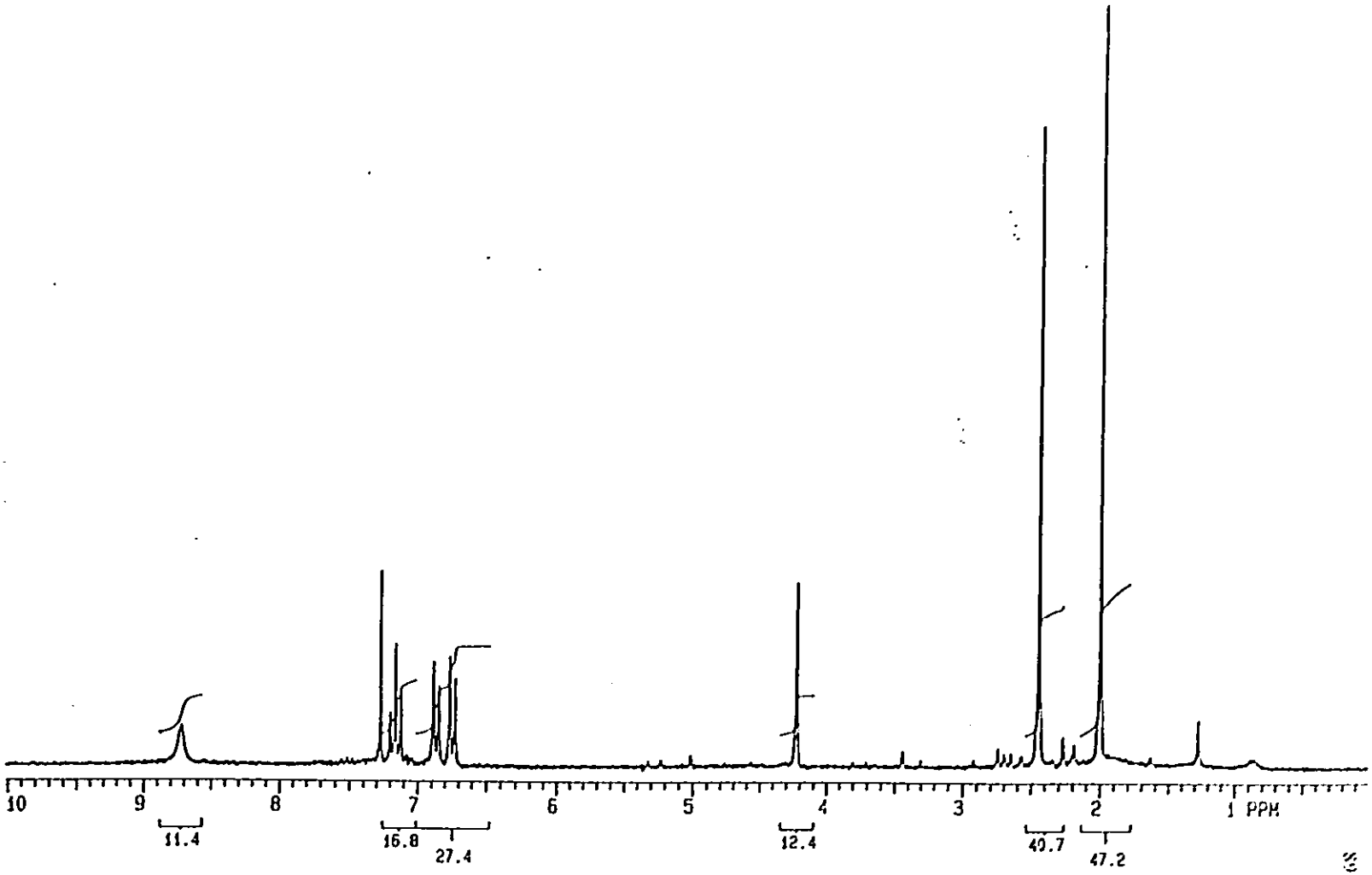
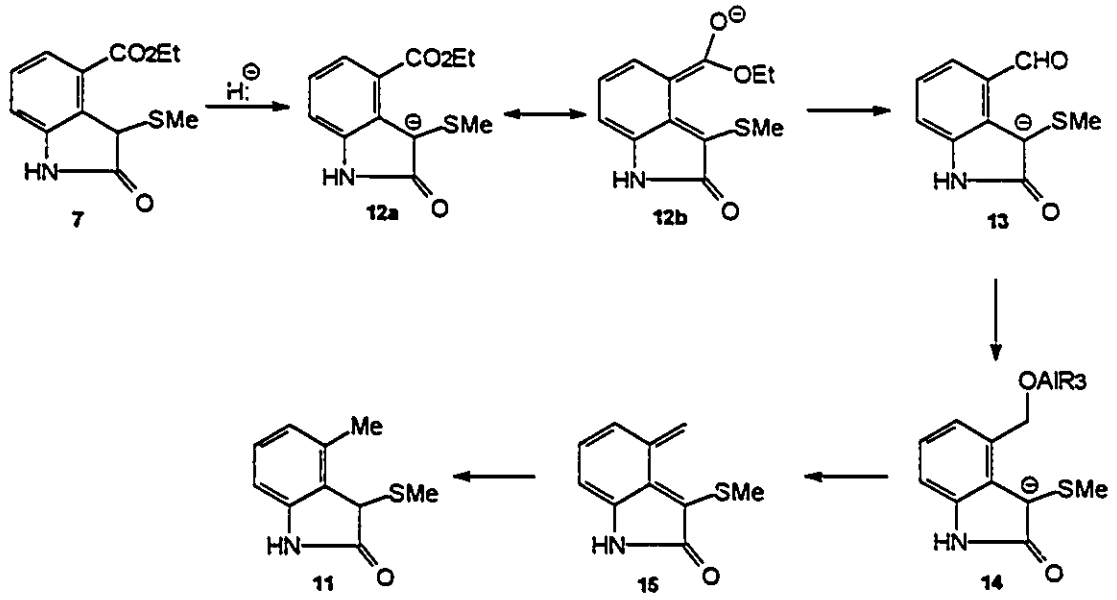


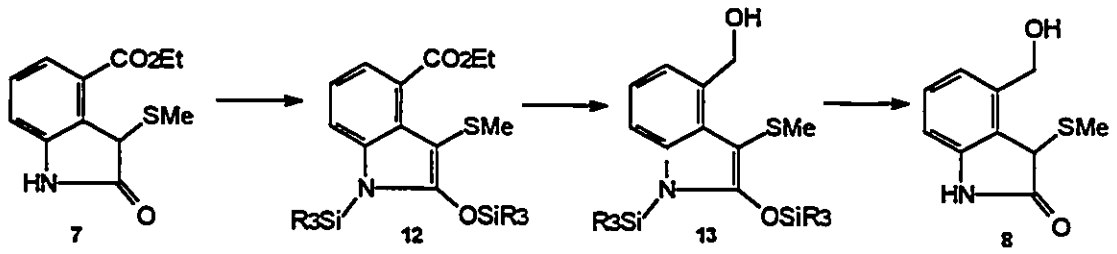
Figure 5.1 200 MHz ^{1}H-NMR Spectrum of Oxindole 11 in $CDCl_3$

elimination of an aluminum alkoxide forming, ironically, ortho-quinodimethane 15. Very rapid addition of hydride to intermediate 15 would result in 11 being formed.



Scheme 5.3 - Proposed Mechanism for Reduction of Oxindole-Ester 7.

An obvious solution to both the difficulty in reducing the ester in 7 and then the subsequent over-reduction was to enolize the oxindole, and trap it as a silyl enol ether. This methodology was chosen for a number of reasons: The reaction is quite simple and high yields are usually reported; it was anticipated that once 12 was formed, reduction of the ester sidechain would proceed without any complications to provide alcohol 13, desilylation of which would generate the desired alcohol 8.



Scheme 5.4 - Proposed Route to 8 via Silyl Enol Ether 12

However, the first step of the sequence outlined in Scheme 5.4 failed. A variety of condition were tried with temperature ranging from -78 °C to 100 °C, bases including Et_3N, $Et(iPr)_2N$, LiHMDS, NaHMDS, KHMDS, LDA, NaH and KOtBu in THF, and no base with heating in DMF. A number of silylating reagents were tried including TMSCl, TBDMSCl, TBDMSOTf, and TBDMSIm in one, two and three molar equivalents. Aqueous work ups were carried out, no work ups were done and the solvent was stripped off under reduced pressure, and a number of deuterated solvents were used to analyze the crude reaction mixtures including $CDCl_3$, benzene-d^6, and acetone-d^6 fearing decomposition of the product due to HCl present in the chloroform. In all cases, no trace of reaction was found. Based on this work and the results of Gassman[7], it is quite clear that deprotonation takes place. There should be no steric restrictions preventing the formation of **12**, assuming O-silyation occurs. It would be quite unusual if the anion or dianion formed was so stable that silylation would not occur. Even considering such a preposterous explanation, in several of the silylations, the reactions were allowed to stir for up to 18 hours before being quenched. Regardless of the reasons for the failure to form **12**, work on this route was abandoned.

It was found that reaction of oxindole **7** with two equivalents of LDA in THF at -78 °C followed by quenching with MeI led to smooth formation of the 1,3-dimethylated oxindole derivative **14**. The permethylated oxindole **14**, which was isolated as a pale yellow oil after chromatography, displayed spectroscopic data consistent with its structure, the key requirements being the appearance of two new singlets in the ^{1}H-NMR (Fig. 5.2) at 1.80 and 3.21 ppm, each integrating for three protons.

With a route to **14**, and having blocked the problematic methine proton thereby simplifying the situation that would occur during reduction, it was anticipated that reduction of **14** would afford alcohol **15**. It was anticipated that alcohol **15** could be transformed to sulfone **16** via the sulfonium salt strategy and subsequent oxidation. Although the expected reduction product **15** would likely be useless from a synthesis point of view owing to the [1,5] snift shown for the transformation **17** to **18**, it was hoped that this study would serve an important purpose. It would address what had become key questions: Can a ring system such as **16** be made using this methodology? and does **16** undergo chelotropic expulsion of SO_2, and if so, at what temperature?

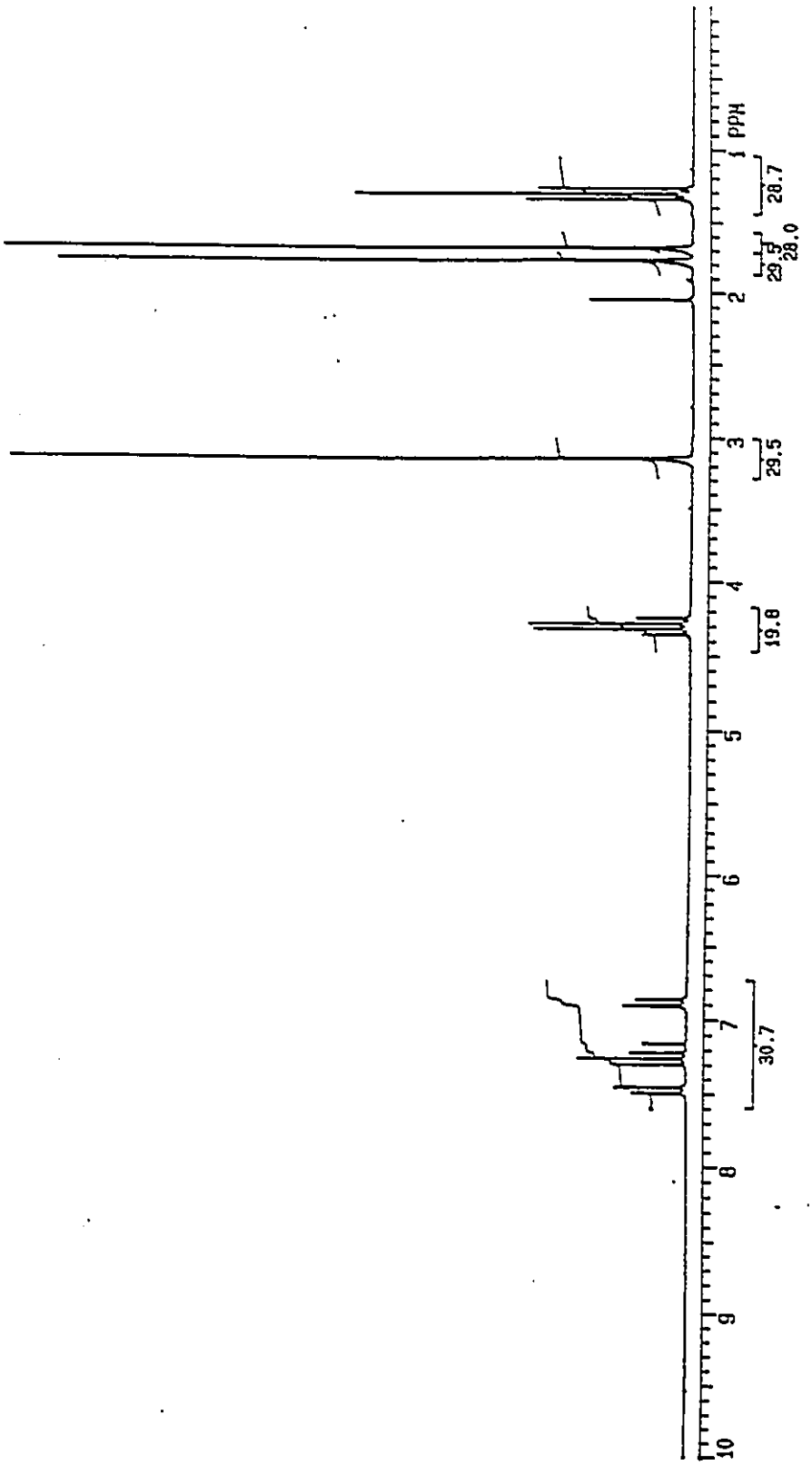
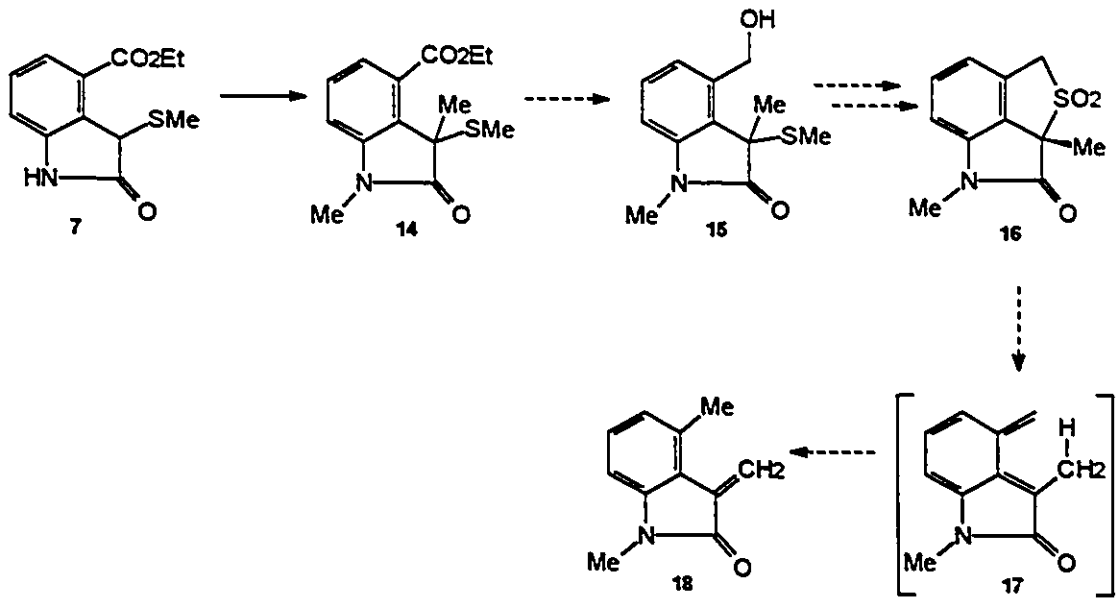


Figure 5.2 200 MHz ^{1}H-NMR Spectrum of Oxindole 14 in $CDCl_3$



Scheme 5.5 - Postulated Route to Tricyclic Sulfone **16**

Reduction of a THF solution of **14** with $LiAlH_4$ led, very quickly, to a new product which was isolated as a pale yellow solid after chromatography and identified as **19**. Inspection of the ^{1}H-NMR spectrum (Fig. 5.3) indicated that the thiomethyl group had been lost. Additionally, it showed a singlet at 3.14 ppm due to the N-methyl group and a set of peaks at 2.70 (s, 1H), 4.65 (d, 1H, J=13 Hz) and 4.73 (d, 1H, J=13 Hz) ppm, consistent with a benzylic alcohol. Since the benzylic methylene group had appeared as an AB pattern rather than a singlet, it was obvious that a chiral center was still present. A quartet at 3.44 ppm (1H), doublet at 1.44 ppm (3H) and the signals consistent with three contiguous aromatic protons were also observed.

Scheme 5.6 - $LiAlH_4$ Reduction of Permethylated Oxindole Ester **14**

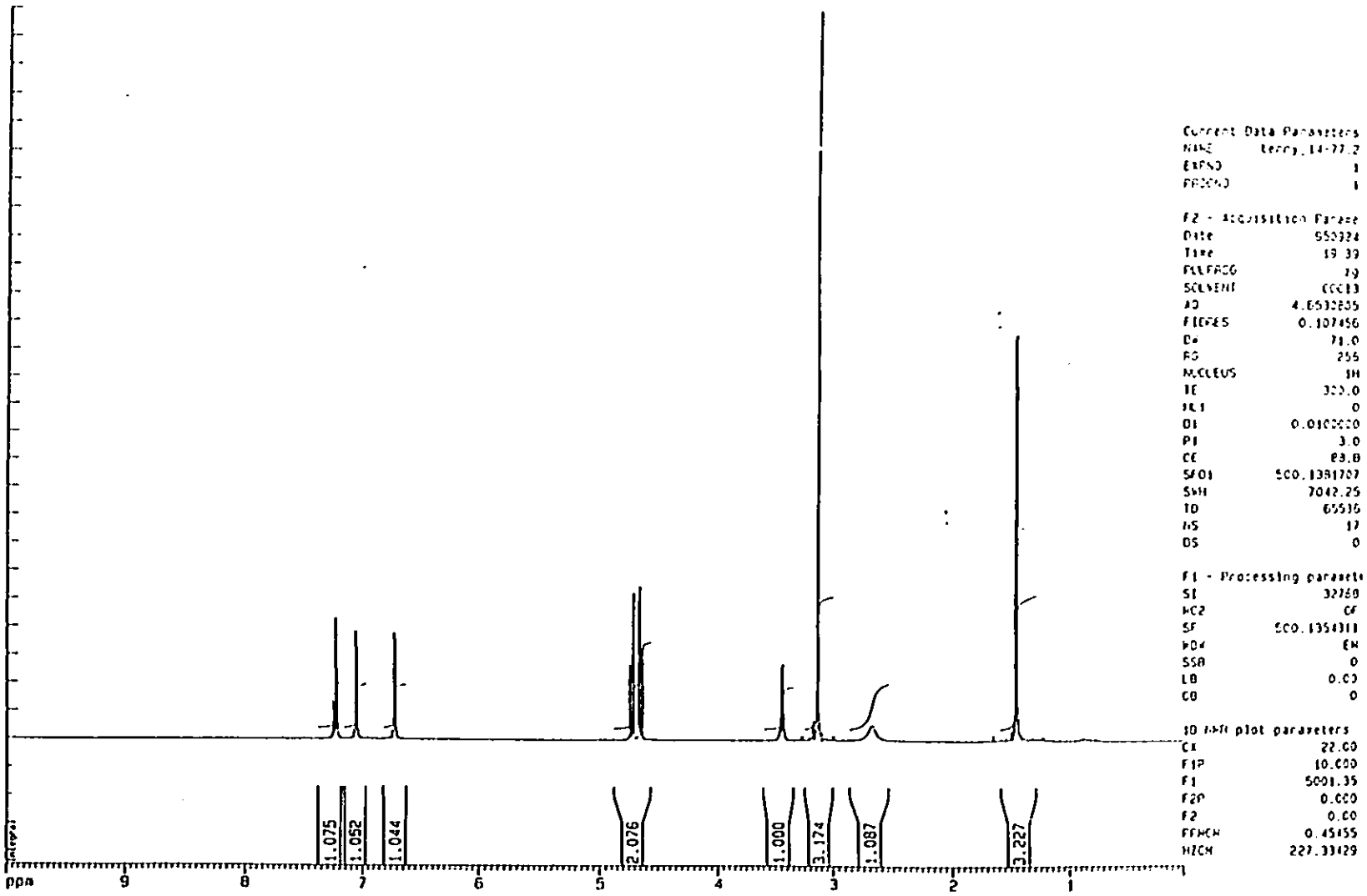
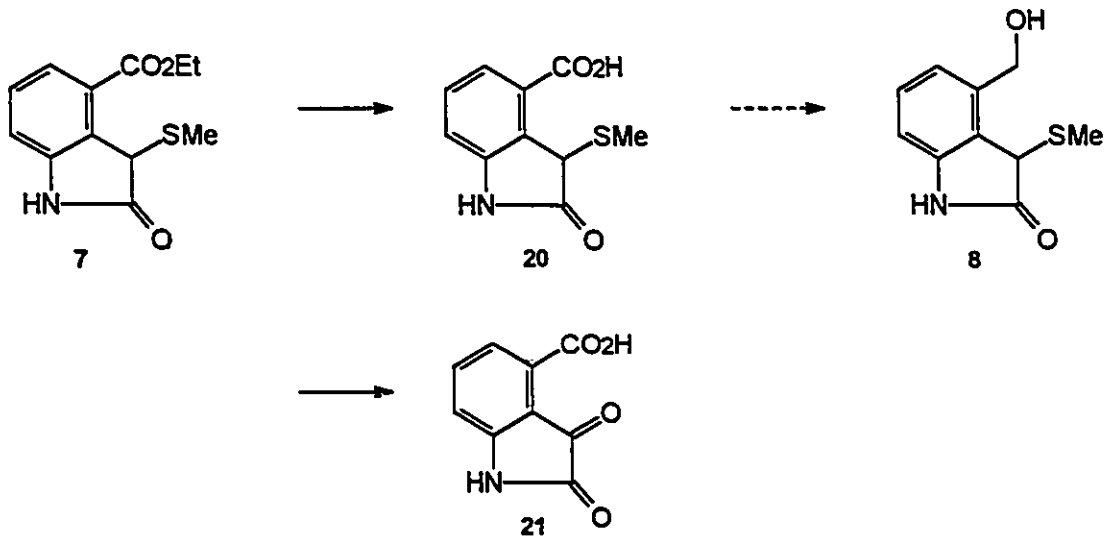


Figure 5.3 500 MHz ^{1}H-NMR Spectrum of Oxindole 19 in $CDCl_3$

Based on the previous results it appeared reasonable to suggest that the sequence of events in the reduction of 14 to 19 should be initial reduction of the ester followed by dethiomethylation. This result initiated a study on the reduction of oxindoles that is discussed in much greater detail in Chapter 7 of this thesis. With the realization that the sequence proposed in Scheme 5.5 could not be carried out, work in this area was abandoned.

5.3 Oxindole-Acid Approach

Because of the problems associated with the metal hydride mediated reduction of oxindole-ester 7, it was decided to investigate the possibility of hydrolyzing the ester and reducing the resulting carboxylic acid with a borane equivalent, as outlined in Scheme 5.7.



Scheme 5.7 - Proposed Route to 8 via Carboxylic Acid 14

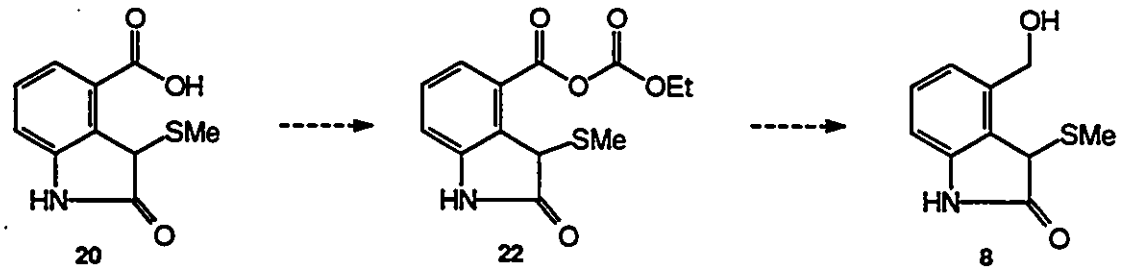
Hydrolysis of ester 7 by refluxing in EtOH in the presence of 20% KOH led to isatin derivative 21, rather than to the desired carboxylic acid. This was, in retrospect, not surprising, since Gassman had reported that 3-thioalkyl-2-oxindoles could be converted to isatins by streaming oxygen through a basic solution of the oxindole[7]. In addition, Taylor[9] had reported a similar conversion to isatin derivatives when

trying to hydrolyze the ester side chain of a different 3-thioalkyl oxindole. When the hydrolysis of **7** was carried out under conditions with the strict exclusion of oxygen, the conversion to carboxylic acid **20** (mp 208.5-209.0 °C) was achieved in near quantitative yield.

Disappointingly, exposing carboxylic acid **20** to reduction conditions with either BH_3•THF or BH_3•DMS in the absence or presence of Lewis acids like $B(OMe)_3$[10a] or BF_3•OEt_2[10b] led only to very complex reaction mixtures. Examination of the literature pointed out that borane had been known to give complex reaction mixtures when reacted with oxindoles[12], the presence of the carboxylic acid group in **20** no doubt complicated matters further. Due to these complications, this route to alcohol **8** was abandoned.

5.4 Oxindole-Anhydride Approach

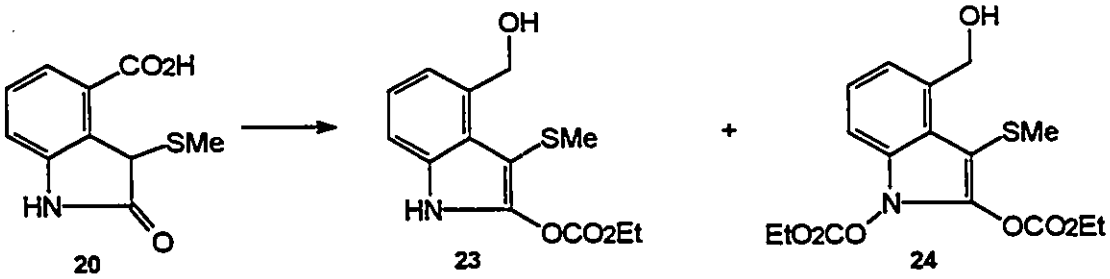
Due to the the complications associated with the borane mediated reduction of carboxylic acid **20**, the reduction of an activated derivative of the carboxylic acid was next attempted. To meet this end, conversion of acid **20** to the acid chloride was studied. However, reaction with thionyl chloride or oxalyl chloride, either neat or in solutions of CH_2Cl_2, led to complex reaction mixtures that could not be properly analyzed due to the sensitive nature of the intermediates. Attempted conversion of the acid **14** to a carboxylate salt and subsequent reaction with oxalyl chloride also failed to give the desired acid chloride. The case of enolization (*vide infra*) was blamed for this. Activation of the acid group according to Scheme 5.8 was then attempted.



Scheme 5.8 - Planned Synthesis of Alcohol **8** via Mixed Anhydride **22**

Using the procedure of Fraser et al[13], ethyl chloroformate and triethylamine were added to a solution of carboxylic acid 20 in THF, followed by portionwise addition of excess $NaBH_4$. After stirring at room temperature overnight, the reaction mixture was quenched by the slow addition of water. These conditions, followed by appropriate workup and column chromatography led to the isolation of two compounds.

The ^{1}H-NMR spectrum of the first compound that eluted (Fig. 5.4), isolated as a white crystalline solid, showed that two carboethoxy groups had been incorporated into the molecule due to two overlapping quartets centered at 4.35 and 4.30 ppm representing four protons, and two almost identical triplets at 1.35 and 1.36 ppm, integrating for six protons. The thiomethyl singlet had been shifted to a slightly lower field and now resonated at 2.50 ppm. Two rather broad singlets at 4.99 and 2.95 ppm indicated that reduction had occurred, since both of these signals were taken as evidence that the benzylic alcohol group was present. The most interesting aspect of the spectra was the appearance of the aromatic region. Two protons gave rise to a multiplet in the region of 7.10 to 7.20 ppm, and the remaining proton resonated at 8.00 ppm, appearing as a doublet with a 8.0 Hz coupling constant. This pattern was indicative of an indole with a strong electron withdrawing group on the nitrogen. Bands at 1779 and 1746 cm^{-1} in the IR spectra were consistent with the presence of carbonate and carbamate functionalities. Based on this spectroscopic data, structure 24 was proposed.



Scheme 5.9 - Products Formed by Mixed Anhydride Reduction Protocol of Acid 20

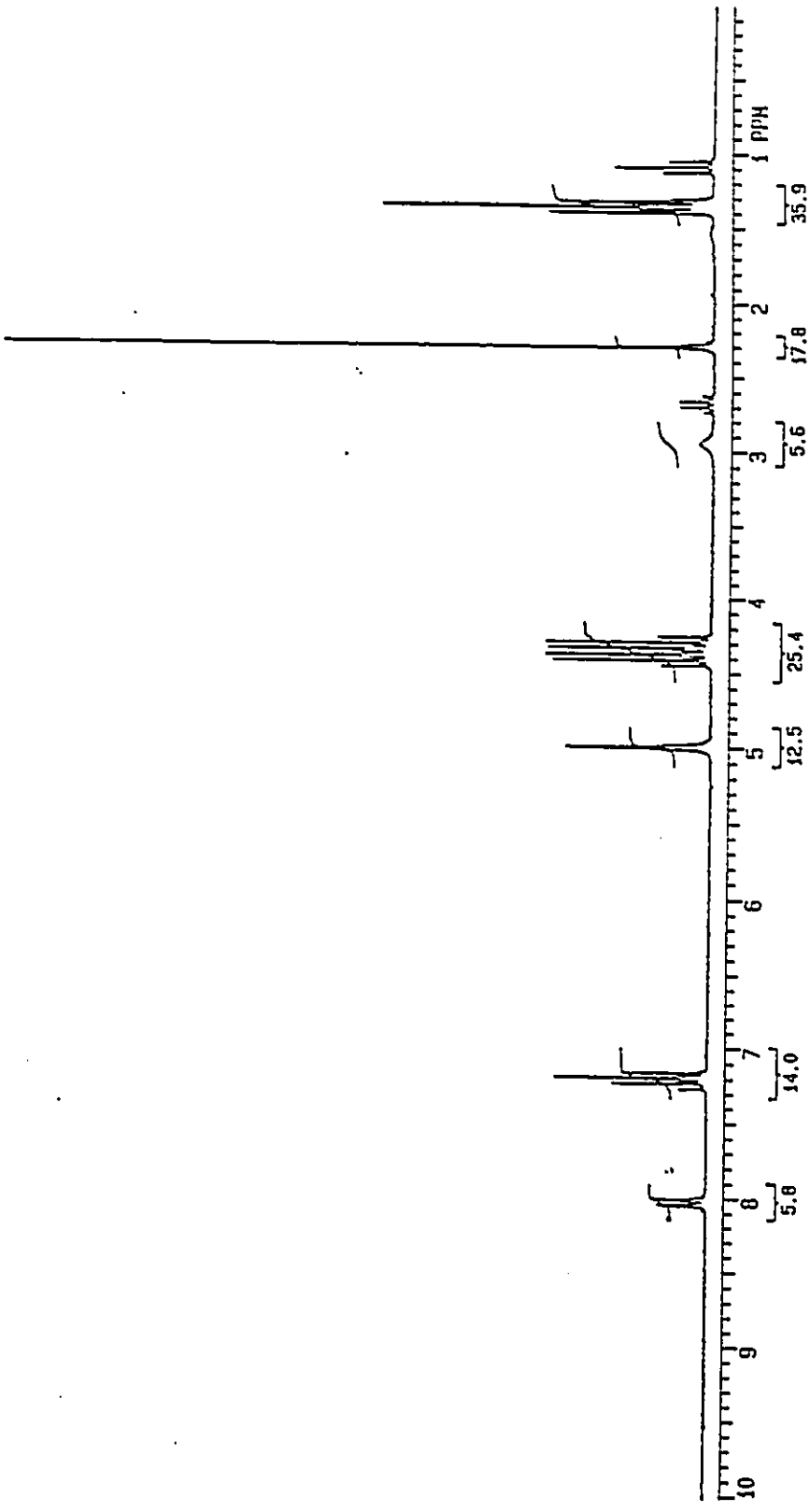


Figure 5.4 200 MHz ^{1}H-NMR Spectrum of Indole 24 in $CDCl_3$

The second product, isolated as a clear oil, was identified as 23. Its ^{1}H-NMR showed the presence of the thiomethyl group, benzylic alcohol, one carboethoxy group, three aromatic protons and an N-H group. The IR spectra showed the presence of a carbonate group (1772 cm^{-1}) and HRMS supported a molecular formula $C_{13}H_{15}NO_4S$.

The isolation of these compounds led to some very interesting speculation about the behavior of carboxylic acid 20. The formation of compounds 23 and 24, and the recovery of acid 20 indicated that carbonate formation occurred before activation of the acid group. Once the oxindole was tied up as a carbonate, carbamate formation became competitive with anhydride formation. This result seemed to indicate that either the methine proton of the oxindole was more acidic than the carboxylic acid, or that oxindole 20 had considerable enol character, and this was efficiently acylated with the chloroformate reagent. The ease of O-acylation and C-alkylation (*vide supra*) of these oxindoles makes the results of attempted trapping with silyl electrophiles even more puzzling.

The use of three equivalents of chloroformate and base and the change of reducing agent from $NaBH_4$ to $LiBH_4$[14] (more soluble in THF) resulted in a yield of 90% for the conversion of 20 to 24 without the need for chromatography; 24 being crystallized at the end of the reaction after a simple aqueous work up.

With 24 in hand, the hydrolysis to the desired 8 was attempted. Hydrolysis under a variety of basic conditions, including NaOH/MeOH and Na_2CO_3/MeOH led to very low yields of alcohol 8, and even after considerable experimentation, the best conditions found to convert 24 to 8 were the use of $LiEt_3BH$ in THF, and even then, the yield was only 35-40%.

Alcohol 8 was isolated as a slightly yellow solid (mp 154 °C) and was characterized by the presence of a thiomethyl group, resonating at 2.07 ppm in the ^{1}H-NMR (Fig. 5.5), a singlet at 4.41 ppm representing the methine proton, a very tight AB pattern for the benzylic methylene group, one doublet centered at 4.81 ppm, and the other at 4.87 ppm, with coupling constants of 12 Hz. In addition, the aromatic region showed the familiar pattern of three well defined and separated resonances, two doublets at 6.83 and 7.11 ppm and a triplet at 7.28 ppm with coupling constants of 7.0 Hz. A broad singlet at 8.00

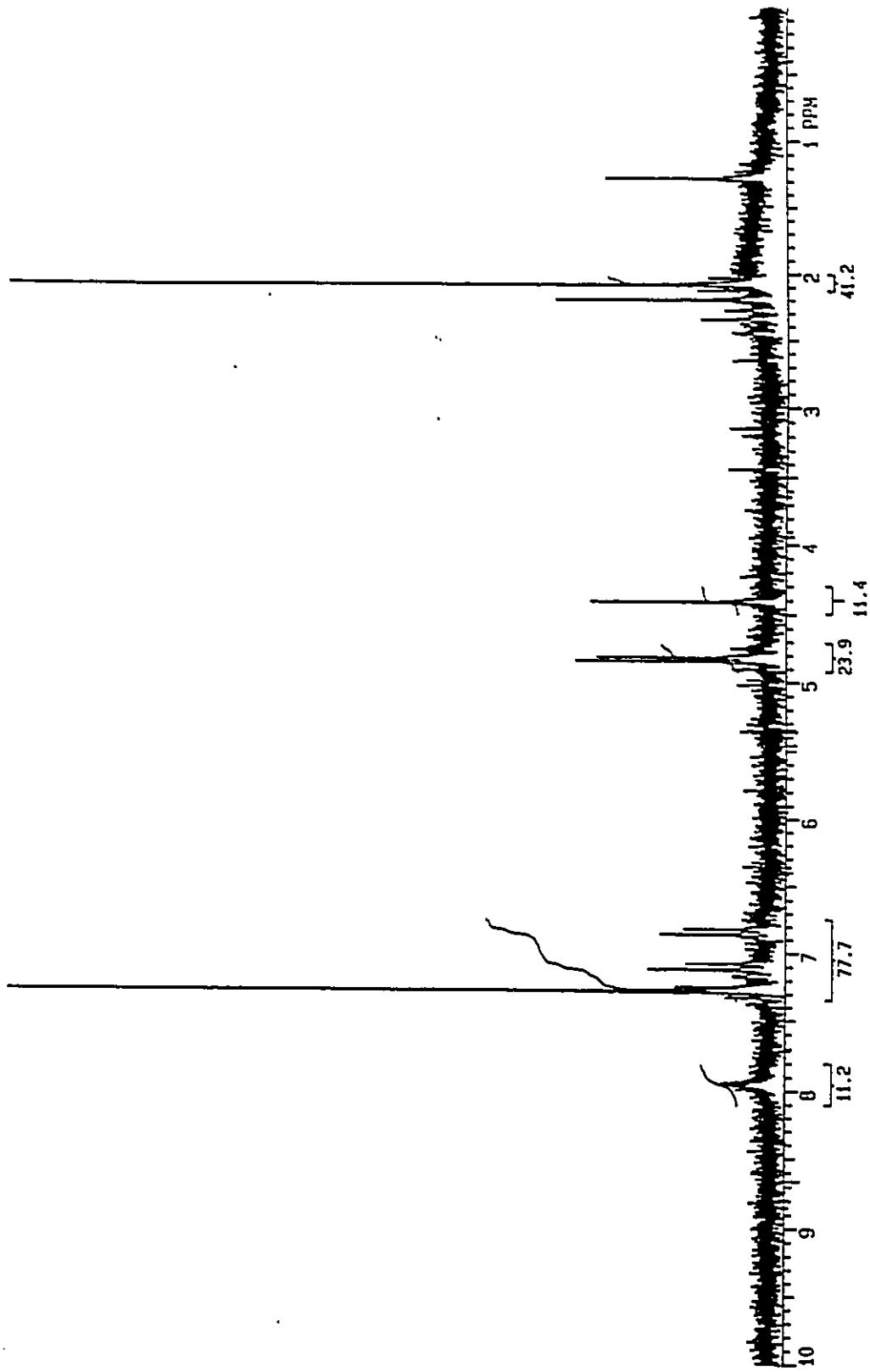
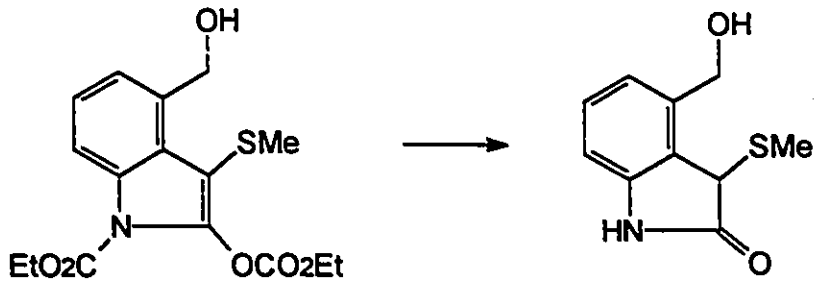


Figure 5.5 200 MHz ^{1}H-NMR Spectrum of Alcohol 8 in $CDCl_3$

ppm accounted for the amide N-H. In addition , the IR spectra showed a broad stretch at 3082 cm^{-1} and a sharp strong band at 1727 cm^{-1}, indicting that the alcohol and carbonyl functional groups were present.



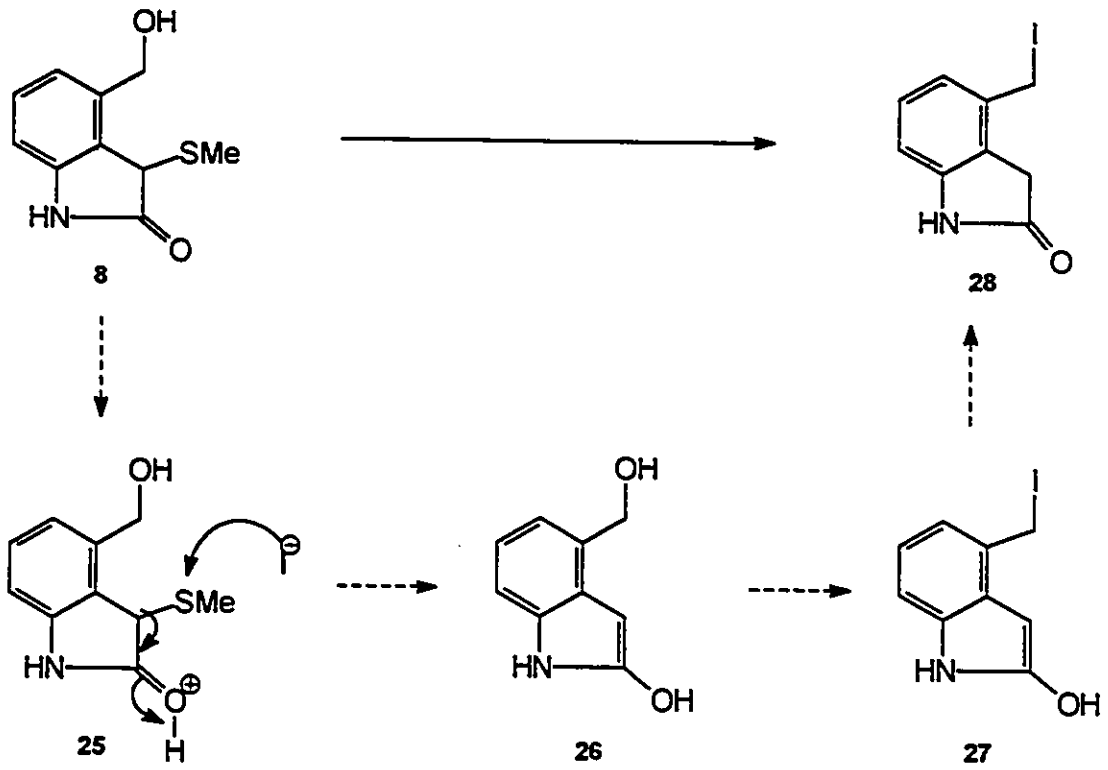
24 8

Scheme 5.10 - Conversion of 24 to Benzylic Alcohol 8

With 8 finally in hand, conversion to 9, as outlined in Scheme 5.1, was attempted. Disappointingly, the desired cyclization could not be achieved under either basic or acidic conditions, possibly due to the ease of enolization of the oxindole. Attempted activation of the hydroxymethyl group under basic conditions with MsCl and TEA led to a very complicated mixture. The ^{1}H-NMR of the crude product showed no methine group, and the pattern of the aromatic region resembled an indole rather than an oxindole. Addition of more than one equivalent did not lead to any of the desired compound. No pure products could be obtained after silica gel chromatography of the crude products obtained from any of the above attempts. The use of less reactive sulfonylating reagents such as TsCl or Ts_2O in the absence and presence of bulky bases like Huning's base or Proton Sponge™ over a broad temperature range failed to give any evidence for the formation of the desired product. In all cases, very complex reaction mixtures were formed, presumably due to the reason cited above.

Due to the failure of inducing cyclization under basic conditions, activation of the hydroxymethyl group under acidic conditions was attempted. Stirring a solution of 8 in CH_2Cl_2 in the presence of excess TsOH and NaI led to the very rapid formation of a nonpolar compound, as evident by tlc. Aqueous work up, followed by column chromatography led to the isolation of a slightly pale yellow solid. Examination of the EI-MS of the product showed a molecular ion at m/z 273, with a primary fragmentation showing loss

of 127 to give a base peak at m/z 146, a fragmentation consistent with the presence of one iodine. The ^{1}H-NMR spectrum (Fig. 5.6) showed peaks at 3.48 (s, 2H), 4.32 (s, 2H), 6.75 (d, 1H), 6.99 (d, 1H), 7.12 (d, 1H) and 7.80 (bs, 1H) ppm, all consistent with structure 28.



Scheme 5.11 - Proposed Mechanism for Reaction of Alcohol 8 With NaI and TsOH

Presumably protonation of the carbonyl group as in 25 activates the sulfur towards attack by the soft nucleophile I:⁻, leading to formation of enol 26. Subsequent conversion of the hydroxymethyl group to the benzylic iodide 27 followed by re-enolization on work up should provide the observed product 28. This non-reductive desulfenation was studied in more detail, and is the subject of Chapter 8 of this thesis. It is also possible that conversion to the hydroxymethyl group to the benzylic iodide preceded

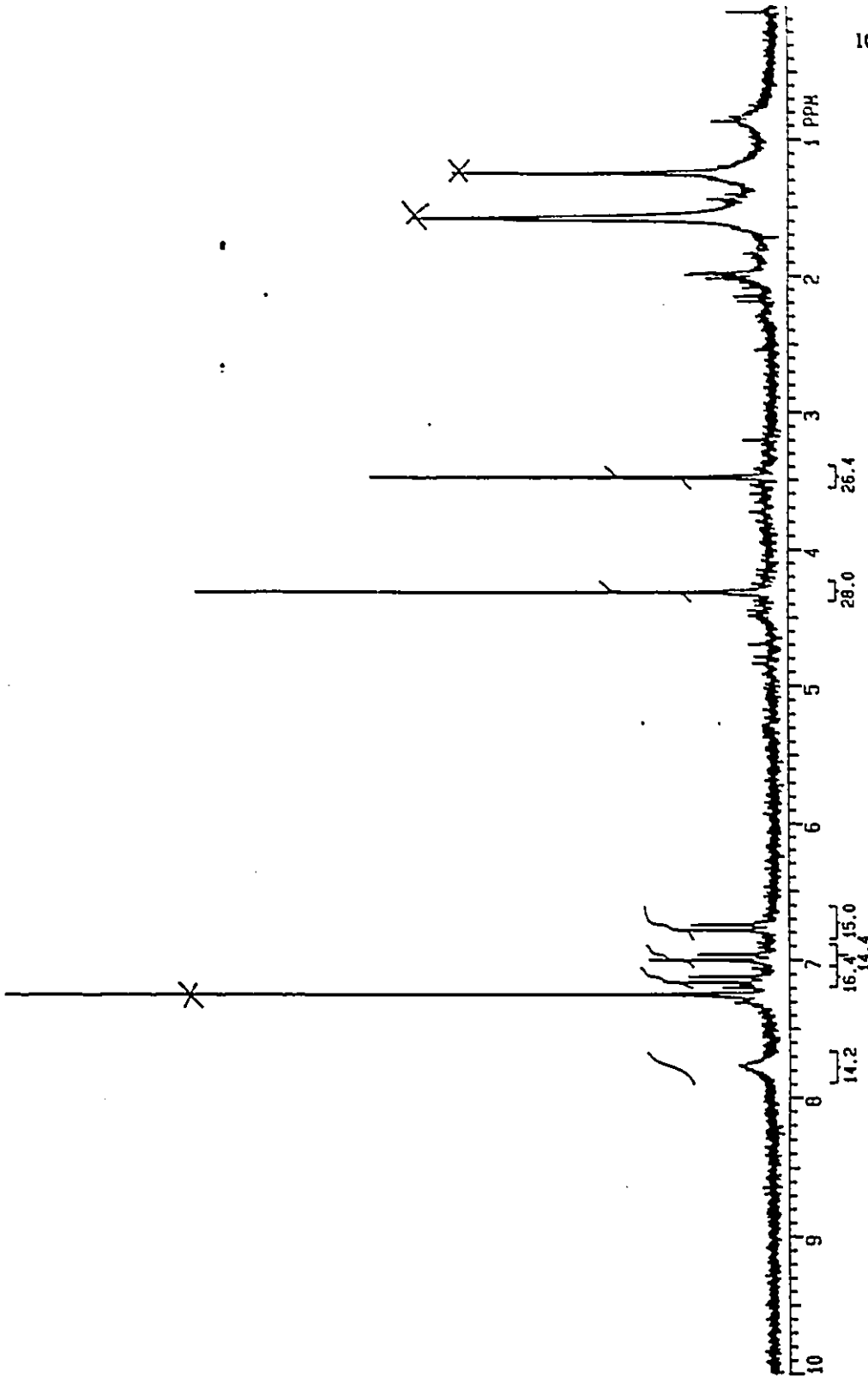
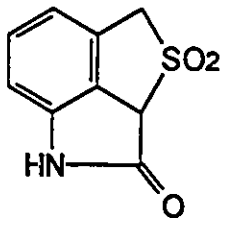


Figure 5.6 200 MHz ^{1}H-NMR Spectrum of Iodide 28 in $CDCl_3$

displacement of thiomethyl group, although ring closure might have been expected if this represented the pathway.

Based on the results described in this chapter, work directed towards the synthesis of tricyclic sulfone 29 was abandoned.

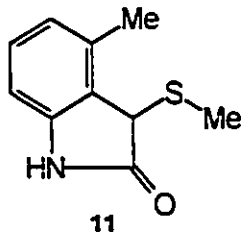


29

5.5 Experimental

For general comments regarding experimental, see chapter 3. Oxindole 7 was prepared as described in chapter 4.

Reduction of Oxindole 7 with $LiAlH_4$ (11).



11

A solution of oxindole 7 (100 mg, 0.40 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (150 mg, 3.95 mmol) in THF (10 mL). The resulting gray, cloudy solution was refluxed for 18 h, poured into a saturated solution of potassium sodium tartrate (50 mL) and EtOAc (50 mL), and stirred for 4 h. The organic phase was separated and subjected to normal work up followed by column chromatography (2:1 Hex:EtOAc) providing two compounds; recovered starting material (35 mg, 35%) and a less polar compound, **11**, isolated as an off white solid (30 mg, 43%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.50 (s, 3H), 4.25 (s, 1H), 6.70 (d, 1H, J=8.0 Hz), 6.80 (d, 1H, J=8.0 Hz), 7.20 (t, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.45, 17.85, 45.52, 107.17, 123.27, 124.31, 128.69, 135.96, 140.98, 177.17 ppm.

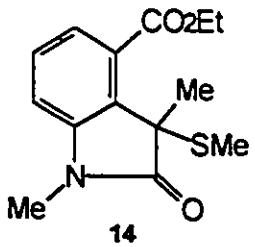
IR (CH_2Cl_2): 1724 cm^{-1}.

EI-MS (m/z, %): 193 (26.5, $M^{+\cdot}$), 146 (100), 118 (4.2).

HRMS: Calc. for $C_{10}H_{11}NOS$: 193.05614; Found: 193.05684.

mp: 154.3-155.9 °C.

1,3-Dimethyl-3-(thiomethyl)-2-oxo-2,3-dihydroindole (14).



14

A solution of freshly prepared LDA (2.1 equiv.) in THF was added dropwise to a cooled (0 °C) solution of oxindole 7 (500 mg, 1.99 mmol) in THF (20 mL). Stirring was continued for 1 h, after which time a solution of MeI (631 mg, 4.38 mmol) in THF (5 mL) was added dropwise. The resulting solution was allowed to slowly rise to RT over 12 h, poured into H_2O (50 mL) and extracted with Et_2O (4 x 20 mL). The combined organic extracts were worked up in the usual manner affording, after chromatography (2:1 Hex:EtOAc), the title compound 14 as a pale yellow oil (540 mg, <95%).

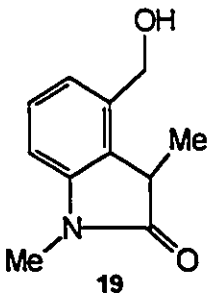
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.5 Hz), 1.80 (s, 3H), 2.02 (s, 3H), 3.21 (s, 3H), 4.40 (q, 2H, J=7.5 Hz), 6.98 (dd, 1H, J=7.0, 1.0 Hz), 7.38 (t, 1H, J=7.0 Hz), 7.59 (dd, 1H, J=7.0, 1.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.29, 14.20, 21.32, 26.55, 51.59, 61.40, 111.28, 124.61, 128.70 ,129.09, 130.93, 143.62, 165.99, 177.25 ppm.

EI-MS (m/z, %): 279 (12.2, $M^{+\cdot}$), 233 (100).

HRMS: Calc. for $C_{14}H_{17}NO_3S$: 279.09292; Found: 279.09141.

Reduction of Oxindole 14 with $LiAlH_4$ (19).



19

A solution of oxindole 14 (100 mg, 0.36 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (25 mg, 0.66 mmol) in THF (10 mL). The resulting gray cloudy solution was heated to reflux for 12 h, poured into a saturated solution of potassium sodium tartrate (50 mL) and extracted with EtOAc (4 x 25 mL). The combined organic extracts were combined and worked up in the normal manner, affording a yellow oil that was chromatographed (1:1 Hex:EtOAc), providing as the major, polar material, oxindole 19 as a pale yellow solid (45 mg, 66%).

^{1}H-NMR (500 Hz, $CDCl_3$): δ 1.44 (d, 3H, J=7.60 Hz), 2.70 (br, 1H), 3.14 (s, 3H), 3.44 (q, 1H, J=7.60 Hz),4.65 (d, 1H, J=13.0 Hz), 4.73 (d, 1H, J=13.0 Hz), 6.72 (d, 1H, J=8.0 Hz), 7.05 (d, 1H, J=8.0 Hz), 7.24 (t, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 15.43, 26.29, 40.11, 62.26, 107.42, 121.62, 127.93, 128.12, 137.15, 144.10, 178.81 ppm.

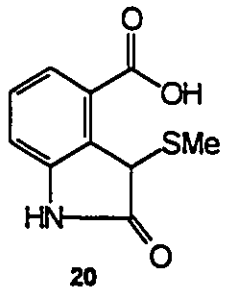
IR (CH_2Cl_2): 1710, 3603 cm^{-1}.

EI-MS (m/z, %): 191 (100, $M^{+\cdot}$), 173 (73.3), 144 (32.6).

HRMS: Calc. for $C_{11}H_{13}NO_2$: 191.09463; Found: 191.09650.

mp: 99.8-100.0 °C.

3-(Thiomethyl)-2-oxo-2,3-dihydroindole-4-carboxylic acid (20).



20

A solution of NaOH (5%, 10 mL) and EtOH (10 mL) was brought to reflux and a steady stream of nitrogen was passed through the solution for 30 min. After this period, oxindole 7 (500 mg, 1.99 mmol) was added as a neat solid, and refluxing was continued for another 30 min. The yellow solution was then cooled to RT, acidified with HCl (conc.) and the EtOH was stripped off. The white solid that formed was filtered off, affording the title compound **20** as white plates (430 mg, >95%).

^{1}H-NMR (200 MHz, acetone-d^6): δ 1.90 (s, 3H), 4.50 (s, 1H), 7.05 (d, 1H, J=8.0 Hz), 7.30 (t, 1H, J=8.0 Hz), 7.54 (d, 1H, J=8.0 Hz), 9.50 (br, 1H) ppm.

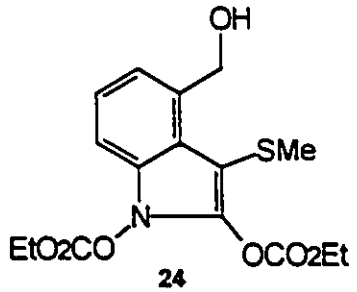
^{13}C-NMR (75 MHz, acetone-d^6): δ 16.89, 51.17, 118.14, 128.41, 133.36, 133.38, 134.07, 148.67, 171.20, 180.65 ppm.

EI-MS (m/z,%): 223 (10.2, $M^{+\cdot}$), 205 (1.6), 177 (100), 131 (9.4), 119 (9.0).

HRMS: Calc. for $C_{10}H_9NO_3S$: 223.03032; Found: 223.03021.

mp: 208.5-209.0 °C.

1-(Carboethoxy)-2-(oxo-carboethoxy)-3-(thiomethyl)-4-(hydroxymethyl)indole (24).



24

Ethyl chloroformate (0.80 g, 7.40 mmol) and triethylamine (1.10 g, 10.9 mmol) were added sequentially to a solution of carboxylic acid **20** (0.72 g, 3.23 mmol) in THF (100 mL). The resulting solution was allowed to stir at RT for 1 h, after which time $LiBH_4$ (0.28 g, 12.9 mol) was slowly added portionwise. After all the reducing agent was added, the solution was allowed to stir at RT for 1 h, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (6 x 50 mL). Usual work up afforded the title compound **24** as a white crystalline solid (0.75 g, 66%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=7.5 Hz), 1.33 (t, 3H, J=7.5 Hz), 2.28 (s, 3H), 2.95 (br, 1H), 4.28 (q, 2H, J=7.5 Hz), 4.32 (q, 2H, J=7.5 Hz), 5.00 (s, 2H), 7.23 (m, 2H), 8.10 (dd, 1H, J=7.5, 1.0 Hz) ppm.

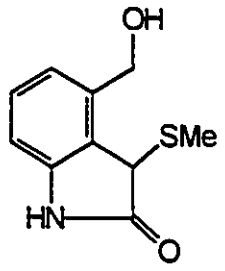
^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.78, 13.79, 20.07, 62.67, 63.68, 65.87, 101.42, 115.02, 124.40, 124.68, 124.95, 132.19, 133.48, 143.57, 149.21, 151.64 ppm.

IR (CH_2Cl_2): 1746, 1779, 3450 cm^{-1}.

EI-MS (m/z, %): 353 (10.0, $M^{+\cdot}$), 281 (31.2), 263 (52.8), 190 (43.2), 160 (70.1), 132 (47.6), 29 (100).

HRMS: Calc. for $C_{16}H_{19}NSO_6$: 353.09331; Found: 353.09242.

3-(Thiomethyl)-4-(hydroxymethyl)-2-oxo-2,3-dihydroindole (8).



8

A solution of $LiEt_3BH$ (3.0 mL, 1.0 M in THF, 3.0 mmol) was added dropwise to a solution of 24 (100 mg, 0.28 mmol) in THF (10 mL). The resulting solution was heated to reflux for 1 h, cooled to RT, acidified to pH 3 with HCl (10%), and extracted with EtOAc (4 x 50 mL). Usual work up on the combined organic extracts, followed by chromatography (1:1 Hex:EtOAc) afforded the title compound 8 as a pale yellow solid (21 mg, 35%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.07 (s, 3H), 4.41 (s, 1H), 4.78 (d, 1H, J=15.0 Hz), 4.88 (d, 1H, J=15.0 Hz), 6.83 (d, 1H, J=7.0 Hz), 7.11 (d, 1H, J=7.0 Hz), 7.28 (t, 1H, J=7.0 Hz), 8.00 (br, 1H) ppm.

^{13}C-NMR (75 MHz, d^4-MeOH): δ 11.65, 46.67, 61.70, 109.94, 122.41, 124.36, 130.25, 140.34, 143.50, 179.43 ppm.

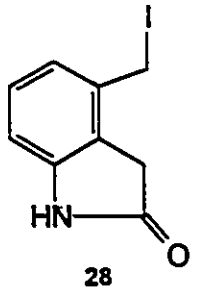
IR (CH_2Cl_2): 1727, 3423, 3682 cm^{-1}.

EI-MS (m/z, %): 209 (2.8, $M^{+\cdot}$), 161 (100), 145 (18.2).

HRMS: Calc. for $C_{10}H_{11}NO_2S$: 209.05105; Found: 209.05403.

mp: 154 °C.

2-Oxo-4-(iodomethyl)-2,3-dihydroindole (28).



28

A solution of alcohol **8** (20 mg, 0.10 mmol), NaI (30 mg, 0.20 mmol) and TsOH (36 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was stirred at RT until tlc showed complete consumption of starting material. Addition of H_2O (10 mL), and extraction with CH_2Cl_2 (2 x 5 mL) followed by washing the combined organic extracts with sodium thiosulfate (10%, 4 x 25 mL) and usual work up afforded the title compound as a slightly yellow solid (23 mg, 88%).

^{1}H-NMR (200 MHz, $CDCl_3$): 3.48 (s, 2H), 4.32 (s, 2H), 6.75 (d, 1H, J=7.5 Hz), 6.99 (d, 1H, J=7.5 Hz), 7.12 (t, 1H, J=7.5 Hz), 7.80 (br, 1H) ppm.

EI-MS (m/z,%): 273 (9.0, $M^{+\bullet}$), 146 (100), 128 (20.9).

HRMS: Calc. for C_9H_8NOI: 272.96507; Found: 272.96515.

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7) See footnote 4 in: Gassman, P.G.; Halweg, M. *J. Org. Chem.*, **1979**, *44*, 628.

8) For example see Karp, G.M. *J. Org. Chem.*, **1992**, *57*, 4765 and references therein.

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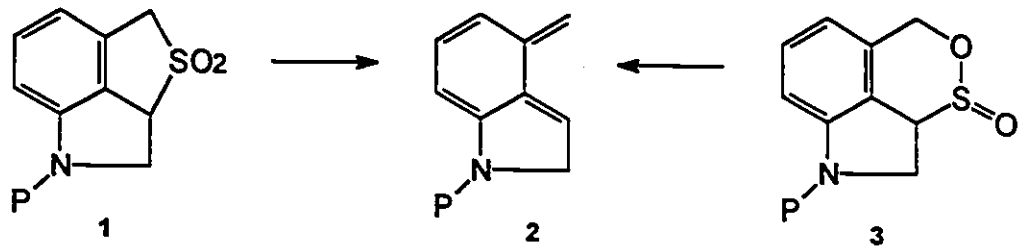
Chapter 6 - Sultine Approach

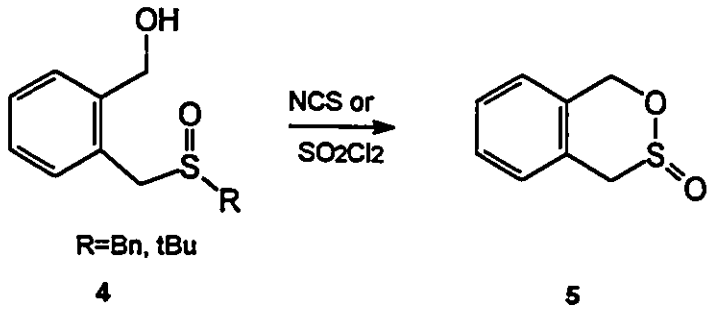
6.1 Introduction

Retrosynthetic analysis suggested that sulfone 1 could be a valuable intermediate in the synthesis of the ergot alkaloid ring system. Several attempts to prepare 1, or the precursor sulfide, have been described in the earlier chapters of this thesis, but none had been successful. One reason for the lack of success might have been that the 6,5,5- ring system of 1 is highly strained. It was believed that the sultine 3 would be a relatively unstrained precursor to 2. Additionally, with 3 in hand, it was hoped that its thermolysis in the absence of a dienophile would lead to sulfone 1 since a related sultine to sulfone isomerization has been reported[1].



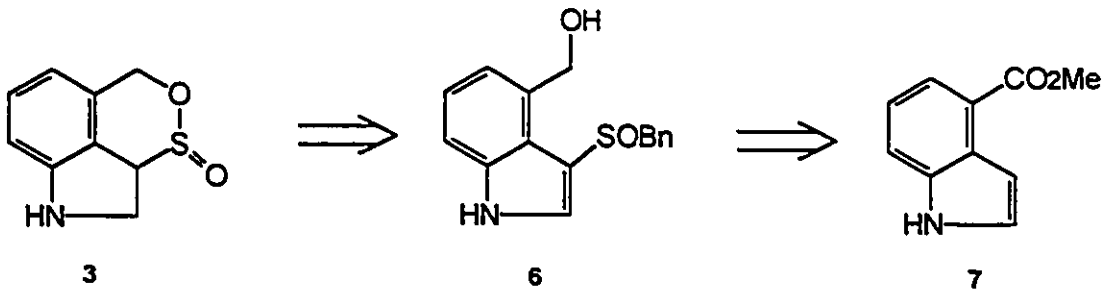
6.2 Indole-Sultine Approach

The first approach was based on previous work of Durst[1] who had shown that benzfused sultines could be formed efficiently from hydroxy-sulfoxides by reaction with NCS or SO_2Cl_2, as illustrated in Scheme 6.2 for the transformation of 4 to 5.



Scheme 6.1 - Durst's Sultine Synthesis via Hydroxy-Sulfoxides

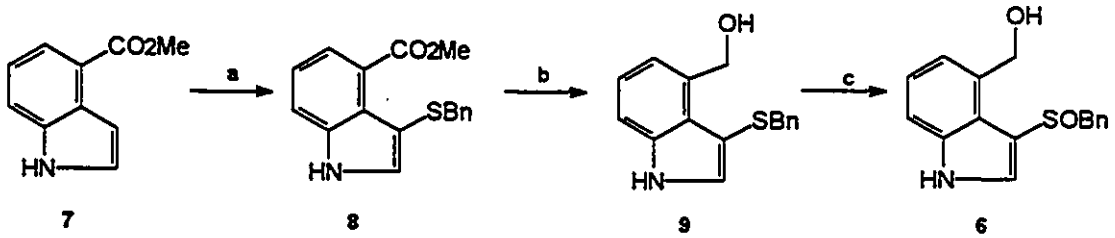
Using this as precedence, it was anticipated that sultine 3 could be formed from hydroxy sulfoxide 6, which should be accessible from indole 7. This is shown retrosynthetically in Scheme 6.2.



3 6 7

Scheme 6.2 - Retrosynthesis of 3 to indole 7

Starting with 4-carbomethoxyindole 7, readily available from 2-methyl-3-nitrobenzoic acid using the procedure of Leimgruber,[2] the thiobenzyl substituent was introduced at three position by the reaction with benzylsulfenyl chloride, generated in situ from benzyl disulfide and SO_2Cl_2 according to the procedure of Hamel[3]. Unfortunately, separation of the product from the starting material was not possible at this stage using column chromatography. The crude product 8 was subjected to reduction with $LiAlH_4$ in THF. Column chromatography afforded 9, characterized by ^1H- and ^{13}C-NMR, as a clear oil in a 56% yield based on crude 8.



7 8 9 6

Reagents: a) $(BnS)_2$, SO_2Cl_2, DMF; b) LAH, THF (56%); c) $NaIO_4$, $MeOH/H_2O$ (94%).

Scheme 6.3 - Synthesis of Hydroxy-Sulfoxide 6 from Indole 7

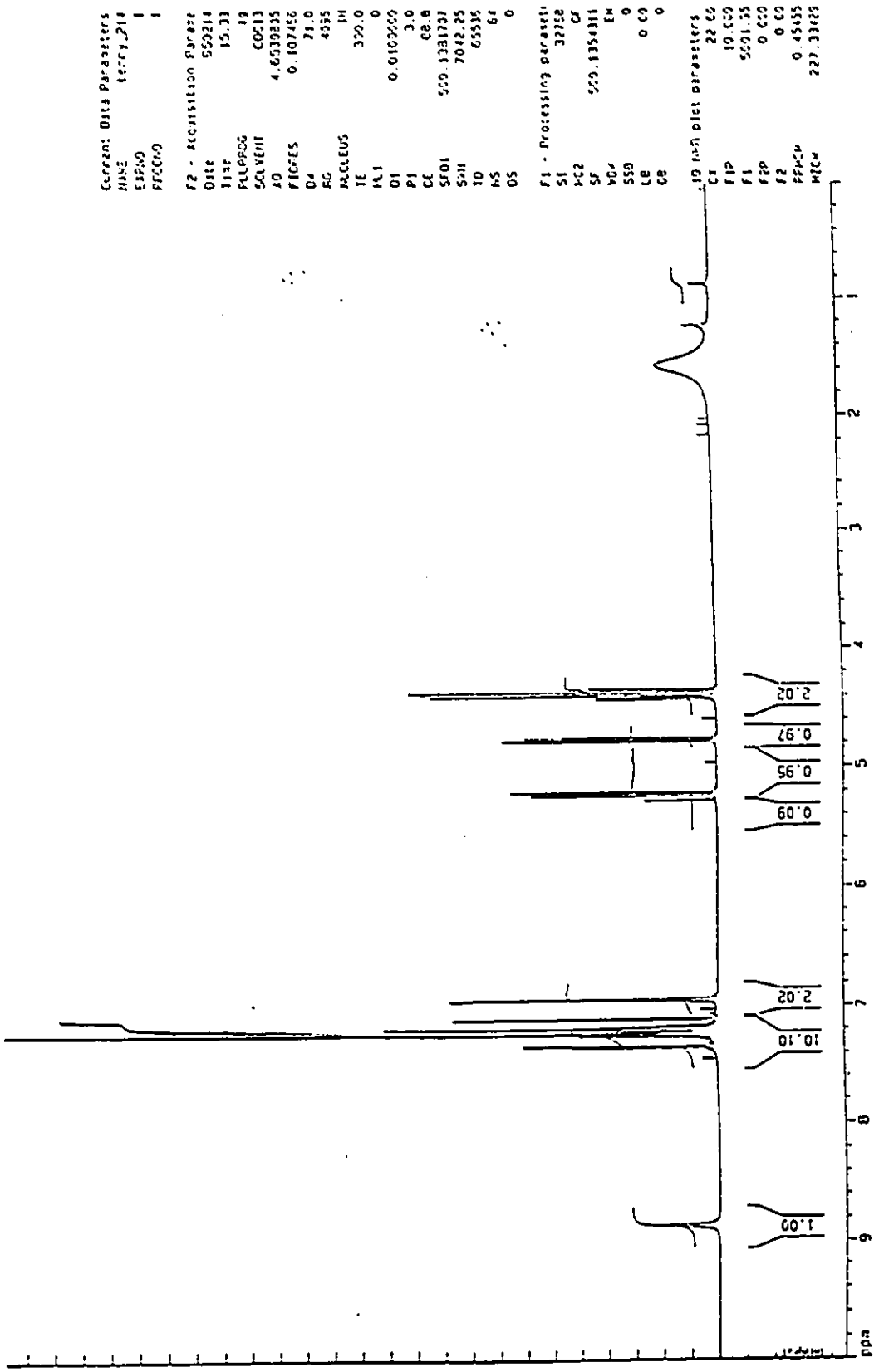
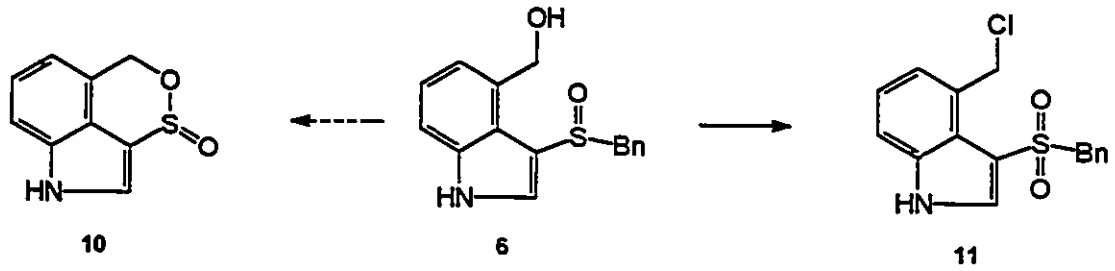


Figure 6.1 500 MHz ^{1}H-NMR Spectrum of Hydroxy-Sulfoxide **6** in $CDCl_3$

Oxidation of sulfide 9 to sulfoxide 6 was accomplished in 94% yield with $NaIO_4$ in MeOH[4]. The ^{1}H-NMR of sulfoxide 6 (Fig. 6.1), isolated as a beige solid after recrystallization from CH_2Cl_2/hexanes (mp 148 °C), showed the expected AB quartets at 4.35 and 4.42 ppm (J=12.4 Hz) due to the benzylic methylene group α to the sulfoxide and at 4.77 and 5.19 ppm (J=12.8 Hz) for the benzylic methylene group of the alcohol. Signals accounting for nine aromatic protons at 6.90 (d, 1H, J=8.0 Hz), 7.30 (d, 1H, J=8.0 Hz) and 7.10-7.25 (m, 7H) ppm and the indolic proton (broad singlet at 9.20 ppm) were also present.

With the desired sultine precursor 6 in hand, cyclization to afford sultine 10 was attempted. Addition of one equivalent of NCS in CH_2Cl_2 led to rapid and smooth conversion to a single product, isolated as a pale yellow solid (mp 178 °C) after chromatography. This compound showed a 3:1 ratio of $M^{+\cdot}$:($M^{+\cdot}$+2) peaks in the EI-MS, indicating that the a chlorine atom had been incorporated into the molecule. The ^{1}H-NMR showed singlets at 4.80 (2H) and 5.80 (2H) ppm. More importantly, integration of the aromatic region showed that there were still nine protons present, thus the pendant benzyl group had not been cleaved off as anticipated. A broad singlet at 8.90 ppm indicated that the indole nucleus was still intact. These data were consistent with chlorosulfone 11.



10 6 11

Scheme 6.4 - Reaction of Hydroxy-Sulfoxide 6 With NCS or SO_2Cl_2

To explain the formation of this unexpected product, a more critical look at the operative reaction mechanism was necessary. The key oxosulfoxonium salt intermediate 13 is expected to be generated by initial S- chlorination of sulfoxide 6 to chlorosulfoxonium salt 12, followed by intramolecular

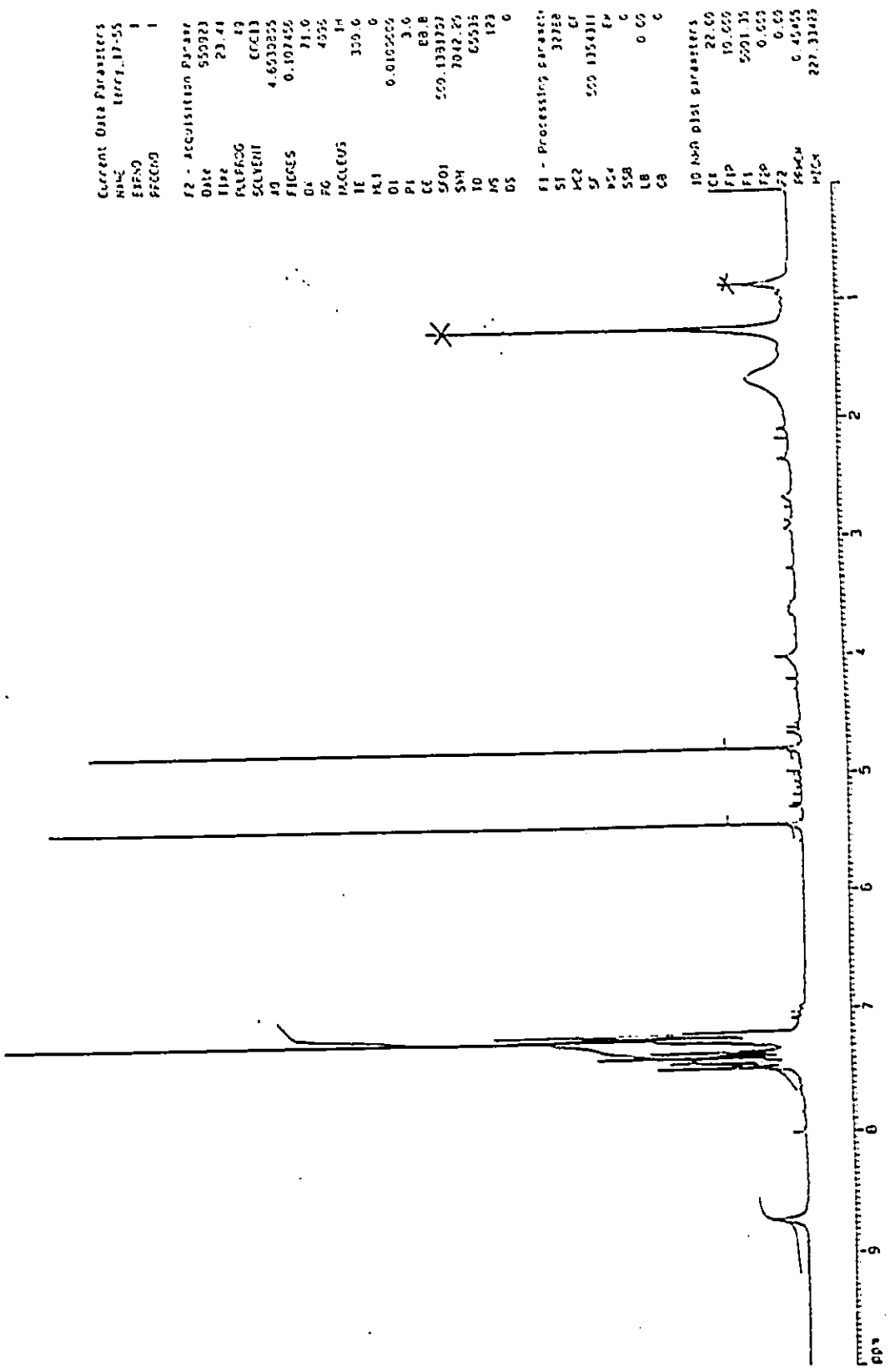
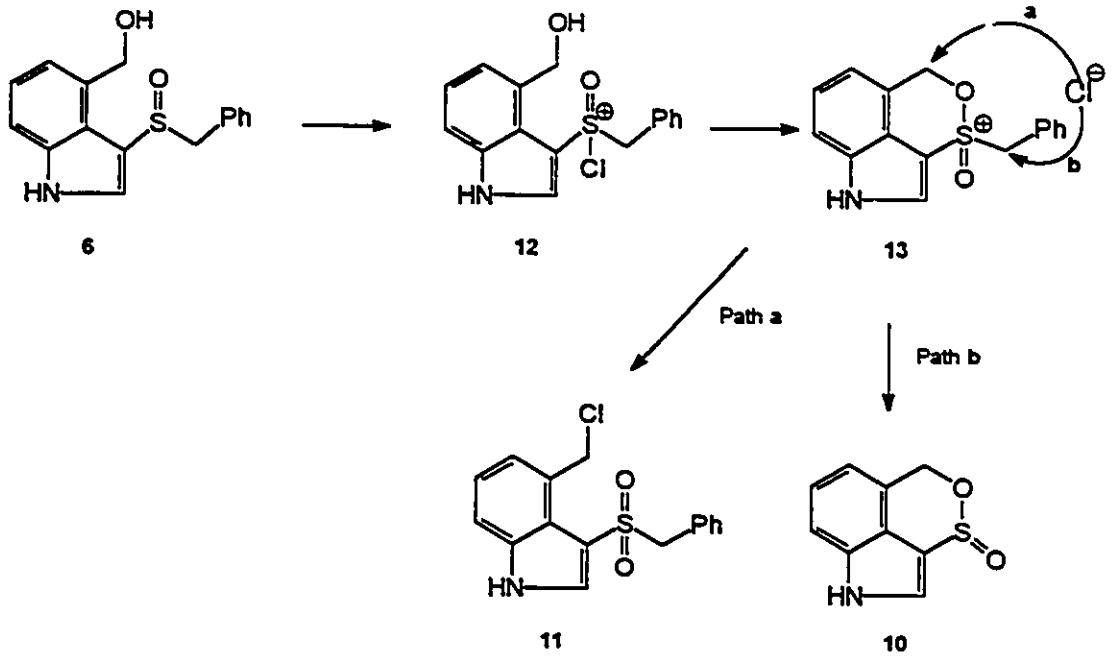


Figure 6.2 500 MHz ^{1}H-NMR Spectrum of Chloro-Sulfone 11 in $CDCl_3$

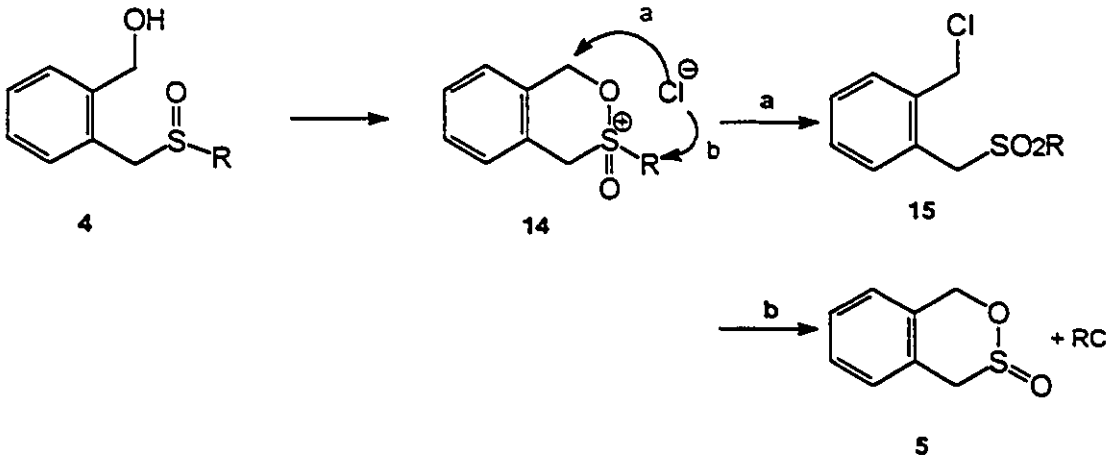
displacement of the halide by the hydroxy group producing 13. At this point, the chloride liberated in the previous step could react with 13 via either path a or path b, giving 11 or 10 respectively.



Scheme 6.5 - Mechanism for Reaction of 6 With NCS

Path b leads to the desired product. However, the reaction proceeded exclusively by pathway a, and 11 was the only product isolated. Using alternative chlorine sources, like SO_2Cl_2, led to the same product. Examination of the ^{1}H-NMR spectra of the crude product showed that in all cases, 11 was formed cleanly and exclusively. In stark contrast to this, Durst et al did not report products other than the sultines under identical reaction conditions. As shown in Scheme 6.6, the same type of intermediate and the same two possible reaction pathways occur for hydroxy-sulfoxide 4. Once oxosulfoxonium salt 14 is formed, pathway a or b can be followed.

Why in the case of 4 was the sultine 5 the only observable product, and no trace of 15 was found, whereas in the case of substrate 6, reaction occurred exclusively via pathway a, giving only chloro-sulfone 11, and none of the desired sultine 10?



Scheme 6.6 - Mechanism For Durst's Sultine Synthesis

In the case of **14** when R=Bn, reaction following either pathway **a** or **b** leads to a primary benzylic chloride. Inspection of the bond / no-bond resonance forms of either of the products arising from intermediate **14**, shown in Figure 6.3, clearly showed that there was little difference in the stability of products due to pathway **a** or **b**. Presumably in this case, pathway **b** is favored due to the enthalpic factors usually associated with ring forming reactions.

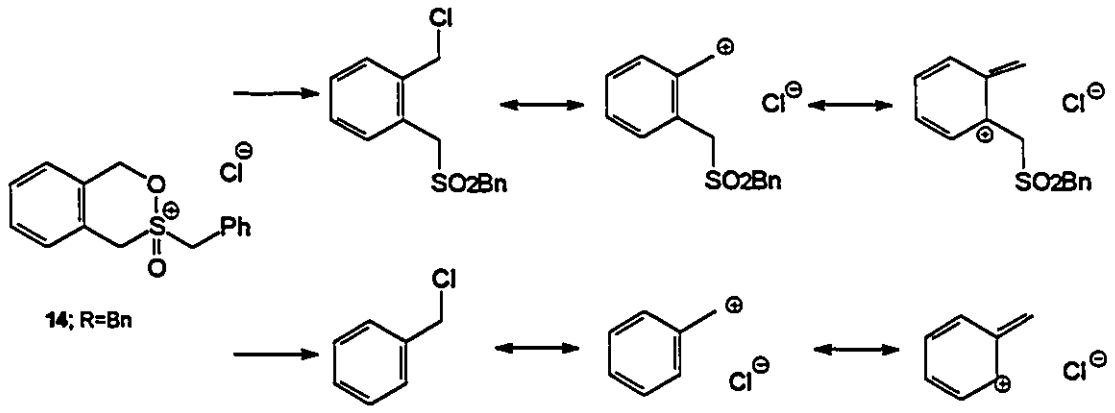


Figure 6.3 - Bond/No-Bond Resonance Structures of Products From Fragmentation of **14**

A possible answer comes from examination of the intermediate **13** and evaluation of its bond/no-bond resonance forms (Fig. 6.4). Fragmentation of the benzylic C-O bond may be facilitated by the lone

pair of the indole nitrogen. Such a reaction would lead to 11 via the stabilized benzylic cation 16. Such a fragmentation is not as readily available for the oxosulfoxonium intermediate 14

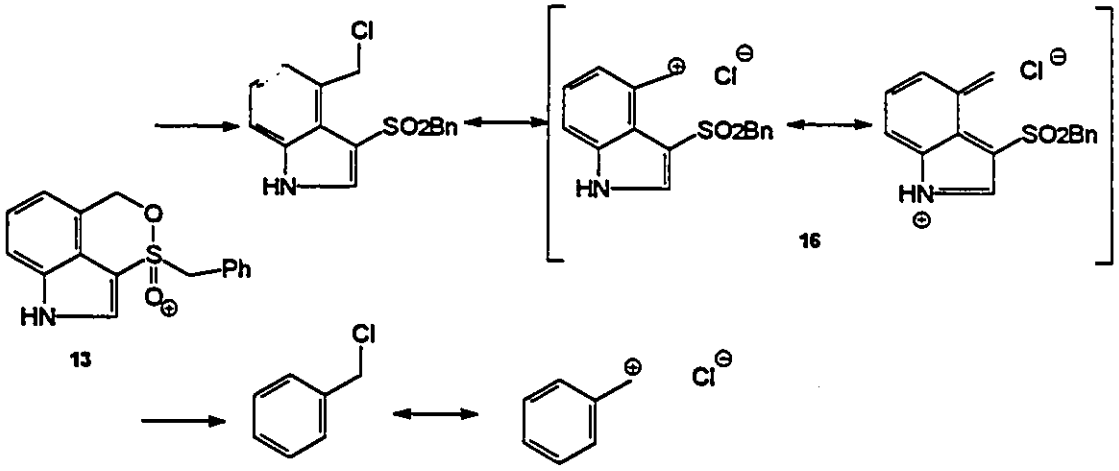
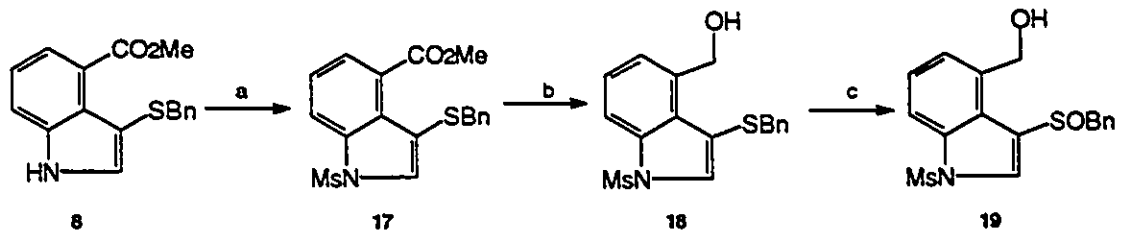


Figure 6.4 - Bond/No-Bond Resonance Structures of Products From Fragmentation of 13

Although the sequence discussed above had not provided the desired target sultine, the results were encouraging since it had shown that the key intermediate and new ring system 13 was formed quite easily, but had failed to fragment in the desired manner. With an understanding of the reaction mechanism, it was hoped that some way could be developed to suppress the alternative observed fragmentation of oxosulfoxonium salt 16 and return to the previously observed fragmentation to afford the desired sultine. One obvious alternative was to place a strong electron withdrawing group on the indolic nitrogen. By decreasing the electron donating ability of the nitrogen, it was hoped that the participation of resonance form 16 would be minimized, returning to the previously observed preference for these oxosulfoxonium salts to form benzyl chloride and sultines.

With this goal in mind, indole 8 was N-mesylated MsCl/TEA and then reduced with $LiAlH_4$ to afford 18 as a pale yellow oil in an overall yield of 47% from crude 8. The spectroscopic properties of both the ester and alcohol sulfonamides 17 and 18 agreed with the assigned structures.



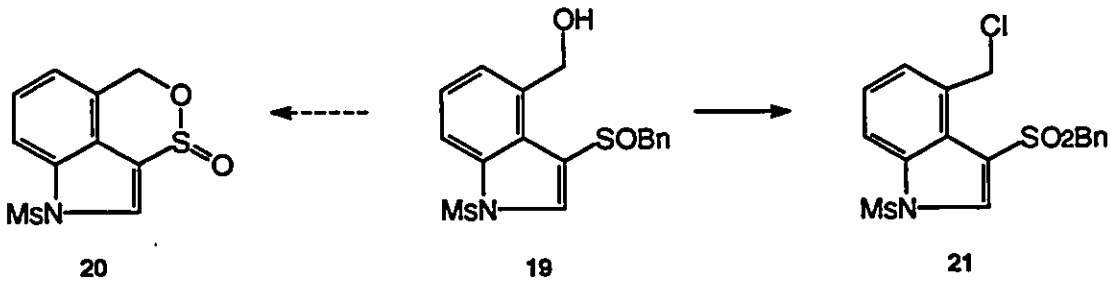
8 17 18 19

Reagents: a) MsCl, TEA, CH_2Cl_2 (70%); b) $LiAlH_4$, THF (67%); c) $NaIO_4$, MeOH-H_2O (95%).

Scheme 6.7 - Synthesis of Hydroxy-Sulfoxide **19** from Indole **8**

Oxidation of hydroxy-sulfide **18** to hydroxy-sulfoxide **19** was accomplished in 95% yield using $NaIO_4$ in MeOH-H_2O. The colorless solid isolated by crystallization and trituration with ether (mp 152 °C) had a ^{1}H-NMR spectrum (Fig. 6.5) consistent with **19**. Key peaks in the ^{1}H-NMR included a singlet at 3.00 ppm ($MeSO_2$-), two doublets at 4.33 and 4.43 ppm with a coupling constant of 12.7 Hz (-CH_2- α to the S=O) and two doublets at 4.79 and 5.06 ppm which also had a 12.7 Hz coupling ($ArCH_2O$). The presence of the sulfoxide moiety, which was quite obvious from examining the ^{1}H-NMR, was confirmed by IR spectroscopy which showed a band at 1150 cm^{-1}.

The cyclization of **19** to sultine **20** was attempted using the previously reported conditions of reaction with NCS in CH_2Cl_2. As with **6**, reaction led to the rapid consumption of starting material and the formation of a single product, as evident by tlc. Typical aqueous work up followed by column chromatography led to the isolation of a colorless solid (mp 215 °C) in a yield of 57% which was identified as chlorosulfone **21**. The simple proton spectrum (Fig. 6.6) showed peaks at 3.07 (s, 3H, $MeSO_2$-), 4.81 (s, 2H), 5.41 (s, 2H) and a total of nine aromatic protons.



20 19 21

Scheme 6.8 - Reaction of Hydroxy-Sulfoxide **19** With NCS

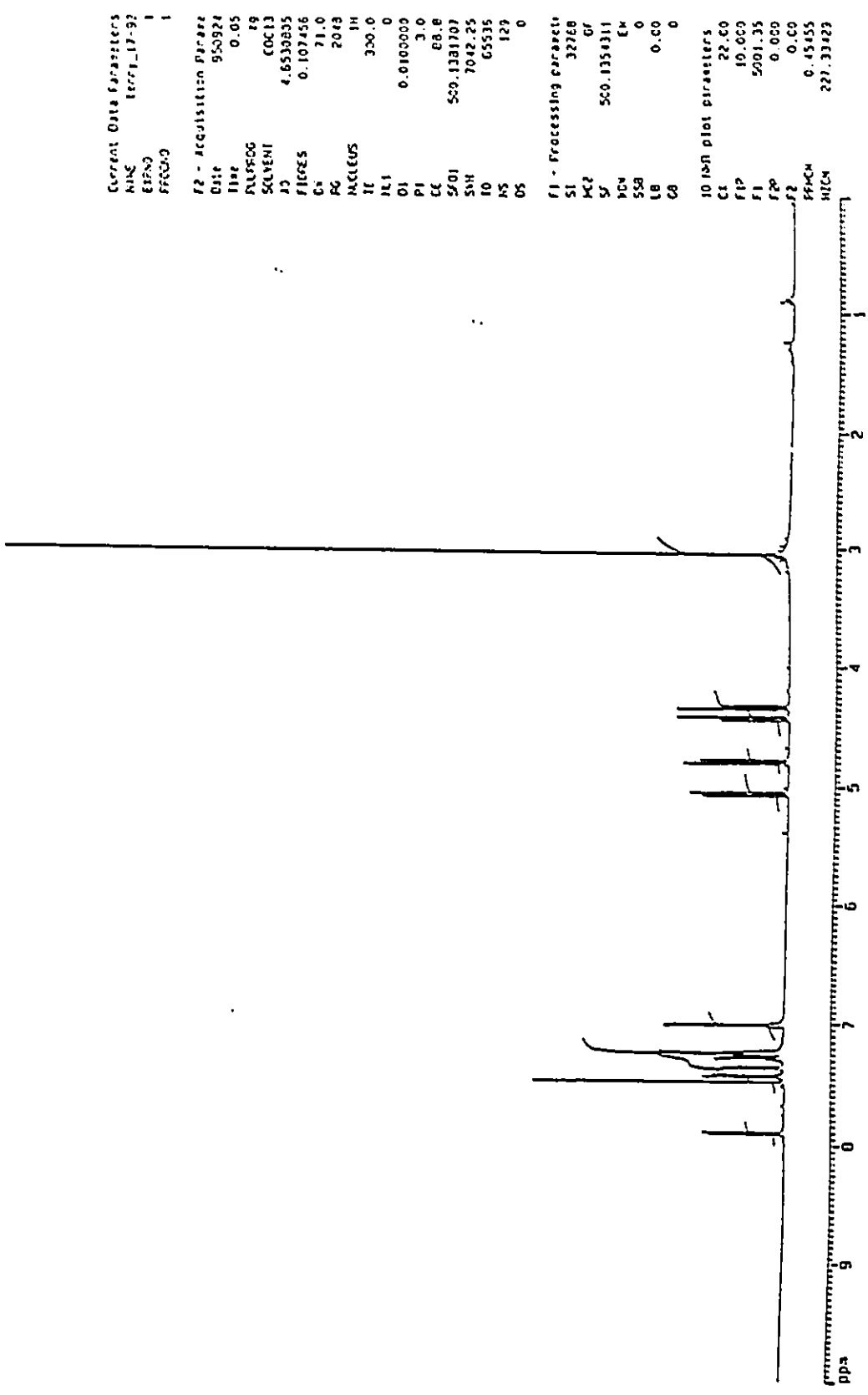


Figure 6.5 500 MHz ^{1}H-NMR Spectrum of Hydroxy-Sulfoxide 19 in $CDCl_3$

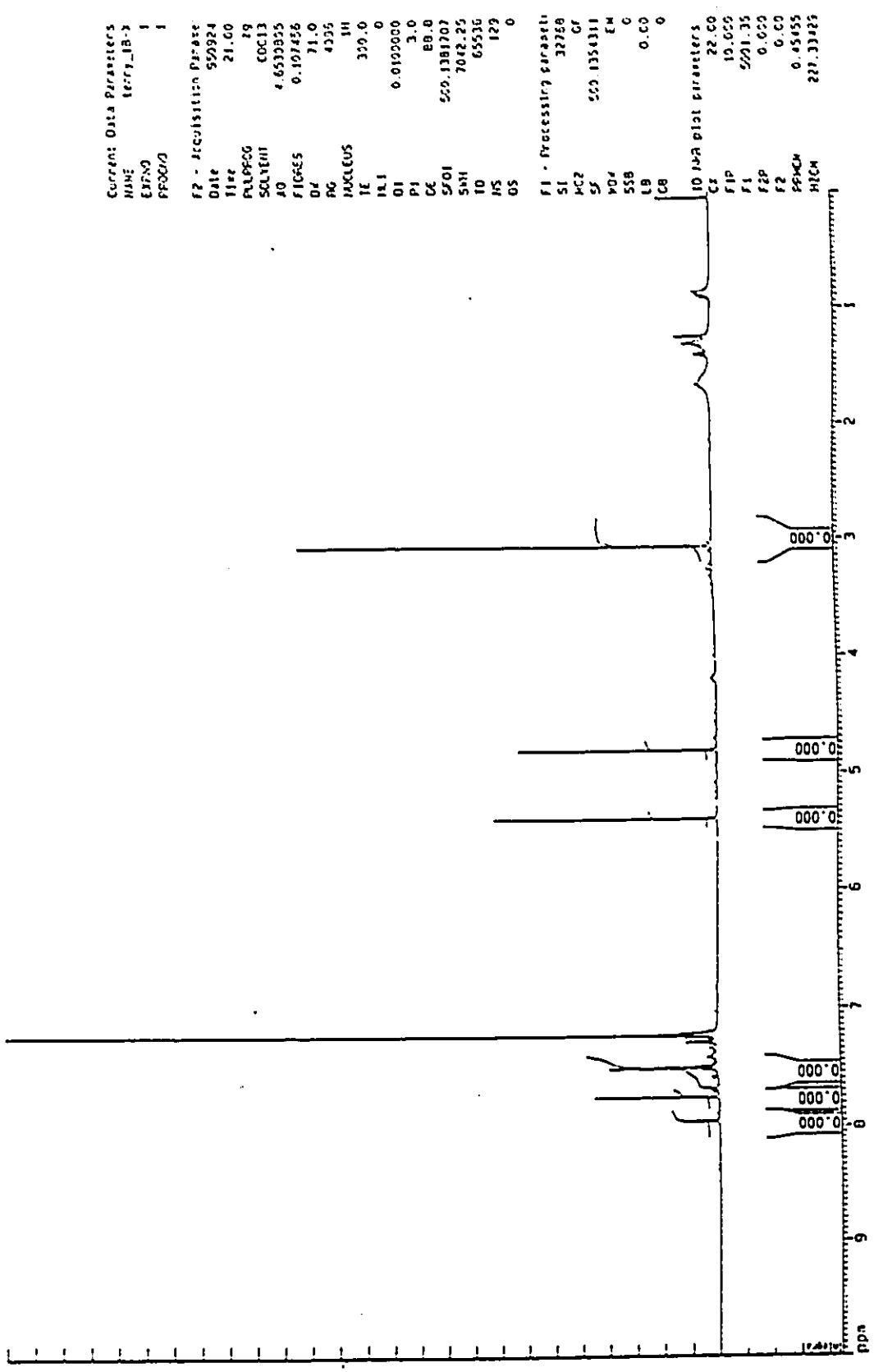
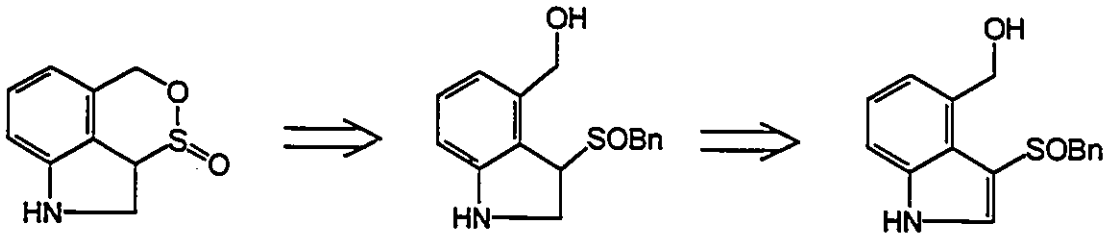


Figure 6.6 500 MHz ^{1}H-NMR Spectrum of Chloro-Sulfone 21 in $CDCl_3$

6.3 Indoline-Sultine Approach

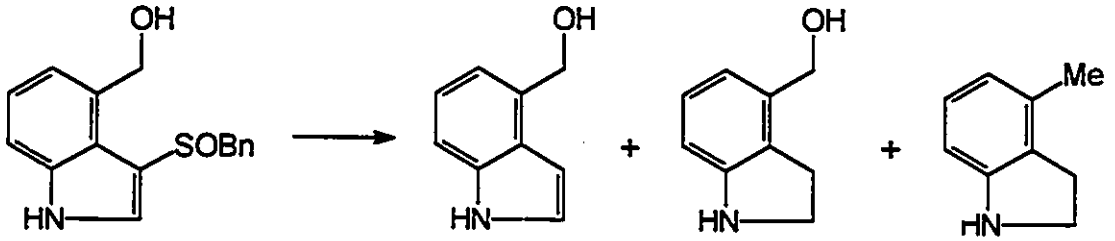
Having failed in the first attempt to favor sultine over sulfone formation, the next solution was to remove the indole double bond. It was believed that once the double bond was removed, there would be no conjugated pathway allowing the nitrogen to pump electron density in to the ring and a return to normal sultine forming behavior would be observed. By making 3 the target, there was actually very little deviation from the original retrosynthesis since the indole sultine 20 would have to be converted to the indoline sultine 3 in order to allow the chelotropic expulsion to occur. The only difference, therefore, was the order of the sequence. Whereas the first approach called for sultine formation, then indole reduction the modified or second approach called for indole reduction to precede sultine formation. The retrosynthesis of sultine 3 to the readily available hydroxy-sulfoxide 6 is shown in Scheme 6.9.



3 22 6

Scheme 6.9 - Retrosynthesis of Tricyclic Sultine 3 to Hydroxy-Sulfoxide 6

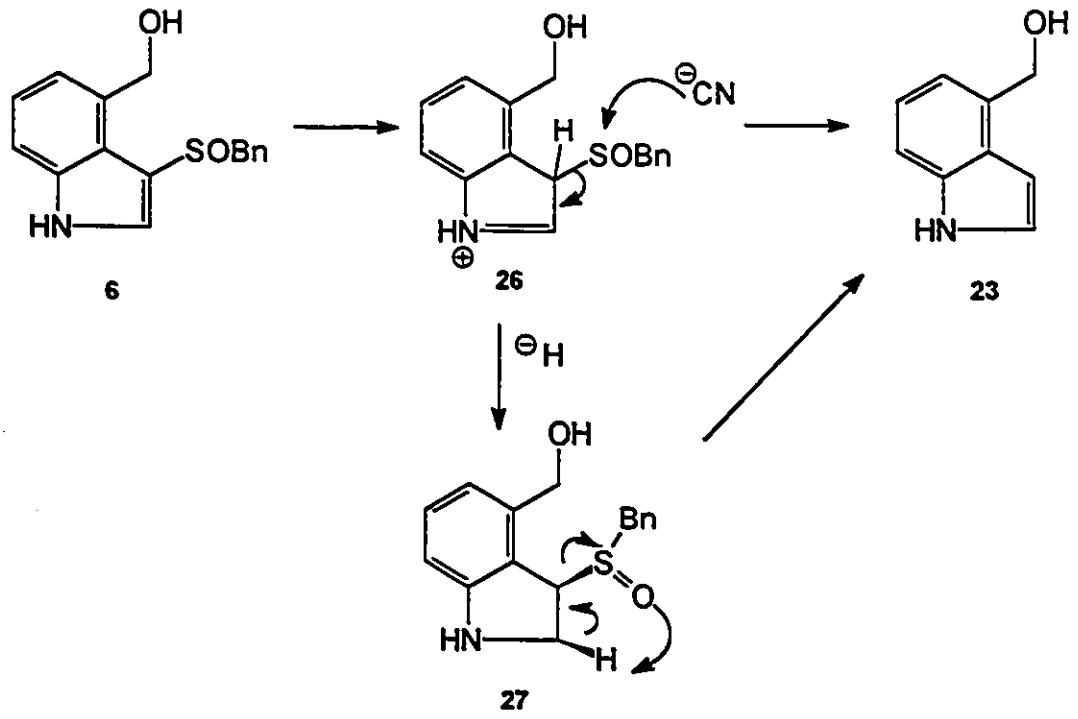
Reduction of 6 with $NaBH_3CN$ in HOAc[5] returned starting material. Using TFA as a solvent led to over-reduction and desulfenation as shown in Scheme 6.10.



6 23 24 25

Scheme 6.10 - Reduction of Indole 6 with $NaBH_3CN$ in TFA

It seemed obvious that indoline 24 resulted from further reduction of the initially formed indole 23, and indoline 25 was the result of reduction of the 4-hydroxymethyl group of 24, but there was some question as to how indole 23 had formed. Two mechanistic possibilities are offered. Undoubtedly, the first step in the reaction mechanism was C3 protonation of indole 6 to provide imine 26 as the key intermediate. Attack of some nucleophile, be it ^{-}CN or $^{-}OCOCF_3$, on the sulfoxide with concomitant displacement of the indole nucleus would result in formation of indole 23. Alternatively, imine 26 could have undergone typical reduction with addition of hydride at C2, giving indoline 27. Syn elimination of phenylmethansulfinic acid would also have led to indole 23. Since the temperatures usually required for elimination of sulfinic acids are typically greater than 110 °C[6], this pathway is not viewed as being likely. Both of these pathways are shown in Scheme 6.11. Although both pathways are, in principle, possible, the pathway involving nucleophilic attack on the sulfoxide moiety is viewed as being more reasonable based on the work reported by the Merck group[7]. Atkinson and coworkers[7] had reported that 3-alkylthio indoles undergo isomerizations and desulfenations when dissolved in strongly acidic mediums (PPA or TFA) in the presence of another nucleophile, usually a thiolate nucleophile. They have also reported that in the absence of an added nucleophile that the conjugate base of the acid is sufficiently nucleophilic to react at the sulfur center.



Scheme 6.11 - Possible Mechanisms for Formation of Indole 23 via Reduction of Indole 6

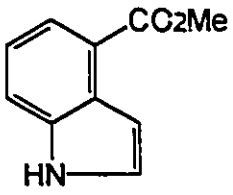
With the realization that reduction of an indole with an electron withdrawing group at C3 was not going to be a trivial transformation, work on this project was abandoned. However, a number of questions regarding the accessibility of the desired ring systems had been raised. All of the problems associated with the failures in this chapter were attributed to the aromatic indole nucleus. It was decided to remove both of these and focus a study based entirely on the dihydroindene skeleton. These studies are discussed in greater detail in Chapters 9 and 10.

6.4 Experimental

General

For comments regarding general experimental, see experimental section of chapter 3.

4-(Carbomethoxy)-indole (7).



7

Indole 7 was prepared according to the procedure of Leimgruber[2].

A solution of methyl (2-methyl-3-nitro)benzoate (50.00 g, 0.26 mol) and DMFDA (35.00 g, 0.29 mol) in DMF (100 mL) was heated to reflux for 12 h. The resulting dark red solution was poured into H_2O (1 L) and extracted exhaustively with Et_2O until the organic extract was clear. The combined organic extracts were worked up in the usual manner affording a dark red oil (58.5 g).

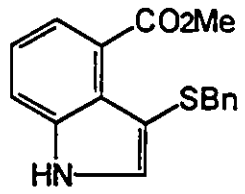
The resulting red oil was dissolved in EtOH (650 mL) and HOAc (glacial, 650 mL) and iron (195 g) was added. The resulting solution was stirred with a mechanical stirrer and heated to 50 °C for 1h, then warmed to reflux for 3 h. The solution was filtered through Celite™, extracted with Et_2O (6 x 100 mL), then washed with Na_2CO_3 (10 %) until neutral. Normal work up, followed by distillation at reduced pressure afforded the title compound 7 as a clear oil that slowly solidified on standing to a white solid (35.2 g).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 7.50 (m, 5H), 8.80 (br, 1H) ppm.

bp: 110 °C (0.15 torr)

mp: 65 °C (lit.[2] 63 °C).

3-(Thiobenzyl)-4-(carbomethoxy)-indole (8).

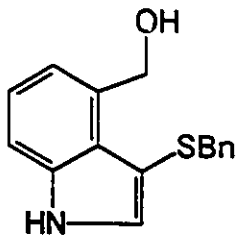


8

Sulfuryl chloride (0.74 g, 5.60 mmol) was added to a solution of benzyl disulfide (1.40 g, 5.70 mmol) in 1,2-dichloroethane (10 mL). The yellow solution that resulted was stirred at RT for 10 min, then added dropwise to a solution of indole 7 (2.00 g, 11.43 mmol) in DMF (20 mL). After stirring at RT for 1 h, the solution was poured into H_2O (100 mL) and extracted with Et_2O (4 x 50 mL). Usual work up followed by chromatography (3:1 Hex:EtOAc) provided the title compound **8** as a pale yellow oil, contaminated with starting indole 7. This material was used directly in the next step without further purification.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.50 (s, 2H), 7.0-7.5 (m, 9H), 8.80 (br, 1H) ppm.

3-(Thiobenzyl)-4-(hydroxymethyl)-indole (9).



9

A solution of crude ester 8 (500 mg, 1.68 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (65 mg, 1.71 mmol) in THF (10 mL). The cloudy gray reaction mixture was stirred at RT for 15 min, warmed to reflux for 2 h, cooled to RT and quenched by the addition of a saturated solution of potassium sodium tartrate (50 mL) and EtOAc (50 mL). Usual work up of the organic phase followed by column chromatography (3:1 Hex:EtOAc) afforded the title compound 9 as a clear oil (258 mg, 56% based on crude 8).

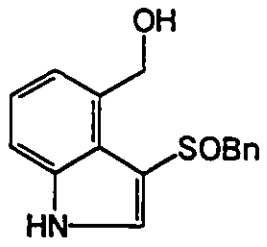
^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.40 (br, 1H), 3.88 (s, 2H), 5.05 (s, 2H), 6.88 (d, 1H, J=2.6 Hz), 7.0-7.3 (m, 8H), 8.90 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 43.59, 63.41, 102.36, 11.69, 120.94, 122.08, 126.25, 125.77, 128.03, 128.71, 131.61, 132.90, 136.70, 137.56 ppm.

IR (CH_2Cl_2): 3455 cm^{-1}.

CI-MS (isobutane): 270 (19.2, M^{+}+1).

3-(Thiobenzyl-S-oxide)-4-(hydroxymethyl)-indole (6).



6

A solution of $NaIO_4$ (103 mg, 0.50 mmol) in H_2O (2 mL) was added dropwise to a solution of sulfide 9 (130 mg, 0.48 mmol) in MeOH (5 mL). The resulting solution was stirred at RT for 6 h, after which time the MeOH was evaporated off under reduced pressure. The residue was extracted with CH_2Cl_2 (4 x 10 mL). Usual work up afforded a beige solid which was recrystallized from CH_2Cl_2/hexanes to afford the title compound as a white solid (130 mg, 94%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.35 (d, 1H, J=12.4 Hz), 4.42 (d, 1H, J=12.4 Hz), 4.77 (d, 1H, J=12.8 Hz), 5.19 (d, 1H, J=12.8 Hz), 6.90 (d, 2H, J=8.0 Hz), 7.20 (m, 7H), 7.30 (d, 1H, J=8.0 Hz), 9.20 (br, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 62.58, 65.02, 112.52, 123.05, 123.96, 128.22, 128.44, 128.53, 128.70, 130.10, 130.27, 130.86, 133.65, 137.85 ppm.

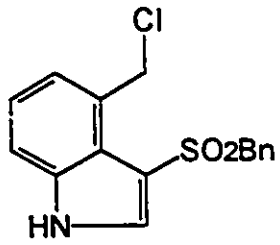
IR (CH_2Cl_2): 1109 cm^{-1}.

EI-MS (m/z, %): 285 (1.8, $M^{+\cdot}$), 237 (13.5), 176 (43.7), 148 (36.5), 91 (100).

HRMS: Calc. for $C_{16}H_{15}NO_2S$: 285.08235; Found: 285.08079.

mp: 148 °C.

Reaction of sulfoxide 6 with NCS (11).



11

NCS (26 mg, 0.20 mmol) was added in one portion to a solution of sulfoxide 5 (50 mg, 0.18 mmol) in CH_2Cl_2 (25 mL). The solution was stirred at RT for 1 h, then poured into H_2O (20 mL), extracted with CH_2Cl_2 (4 x 10 mL) then washed with Na_2CO_3 (3 x 20 mL) and subjected to usual work up. Chromatography afforded **11** as a pale yellow solid (30 mg, 54%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.80 (s, 2H), 5.40 (s, 2H), 7.2-7.4 (m, 9H), 8.90(br, 1H) ppm.

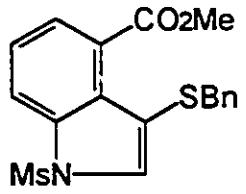
^{13}C-NMR (125 MHz, $CDCl_3$): δ 45.80, 62.05, 116.54, 117.23, 120.30, 122.05, 123.86, 125.67, 126.34, 130.09, 130.54, 132.64, 136.29, 138.02, 139.86 ppm.

IR (CH_2Cl_2): 1119, 1334 cm^{-1}.

EI-MS (m/z, %): 319 (3.5, $M^{+\cdot}$), 193 (10.0), 129 (222.0), 91 (100).

mp: 178 °C.

N-(Methanesulfonyl)-3-(thiobenzyl)-4-(carbomethoxy)-indole (17).



17

A solution of MsCl (360 mg, 31.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a cooled (0°C) solution of indole 8 (0.91 g, 3.06 mmol) and triethylamine (34.5 mmol) in CH_2Cl_2 (50 mL). The resulting solution was stirred at 0 °C for 1 h, then was poured into H_2O (50 mL) and was worked up in the usual manner. Purification via column chromatography afforded the title compound as white needled (0.82 g, 70% based on crude indole 8).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.91 (s, 3H), 3.980 (s, 2H), 3.982 (s, 3H), 7.22 (m, 6H), 7.40 (t, 1H, J=7.5 Hz), 7.61 (dd, 1H, J=7.5, 1.0 Hz), 8.03 (dd, 1H, J=7.5, 1.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 39.85, 40.79, 52.40, 114.40, 116.01, 124.57, 124.88, 126.41, 127.29, 128.08, 128.44, 128.83, 129.20, 135.75, 137.09, 168.33 ppm.

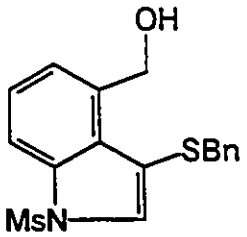
IR (CH_2Cl_2): 1162, 1371, 1720 cm^{-1}.

EI-MS (m/z, %): 375 (9.1, $M^{+\cdot}$), 296 (2.9), 264 (5.7), 91 (100).

HRMS: Calc. for $C_{18}H_{17}NO_4S_2$: 375.05990; Found: 375.05840.

mp: 111 °C.

N-(Methanesulfonyl)-3-(thiobenzyl)-4-(hydroxymethyl)-indole (18).



18

A solution of indole **17** (200 mg, 0.53 mmol) in THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ (25 mg, 0.66 mmol) in THF (10 mL). The resulting reaction mixture was stirred at RT for 30 min, reflux for 30 min, cooled to RT, and quenched with potassium sodium tartrate (saturated, 100 mL) and EtOAc (50 mL). Separation of the organic layer and usual workup, followed by column chromatography (3:1 Hex:EtOAc) afforded the title compound **18** as a slightly yellow oil (125 mg, 67%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.97 (s, 3H), 4.00 (s, 2H), 5.07 (s, 2H), 7.10-7.40 (m, 8H), 7.90 (d, 1H, J=7.0 Hz) ppm.

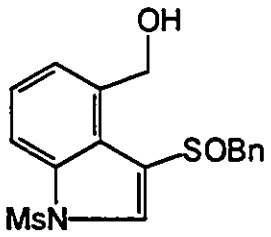
^{13}C-NMR (125 MHz, $CDCl_3$): δ 40.89, 41.81, 62.81, 100.77, 111.72, 113.07, 124.57, 125.56, 127.79, 128.57, 129.12, 130.30, 134.90, 135.71, 136.79 ppm.

IR (CH_2Cl_2): 1177, 1370, 3566 cm^{-1}.

EI-MS (m/z, %): 347 (14.3, $M^{+\cdot}$), 256 (10.9), 160 (9.9, 91 (100).

HRMS: Calc. for $C_{17}H_{17}NO_3S_2$: 347.06499; Found: 347.06294.

N-(Methanesulfonyl)-3-(thiobenzyl-S-oxide)-4-(hydroxymethyl)-indole (19).



19

A solution of $NaIO_4$ (80 mg, 0.37 mmol) in H_2O (2 mL) was added dropwise to a solution of **18** (120 mg, 0.35 mmol) in MeOH (10 mL). The resulting mixture was stirred at RT for 2 h, after which time the MeOH was stripped off at reduced pressure, H_2O (10 mL) was added and the solution was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were worked up in the usual manner, and the residue chromatographed (1:2 Hex:EtOAc) affording, in addition to recovered starting material (68.2 mg), the title compound **19** as a white waxy solid (58.5 mg, > 95%).

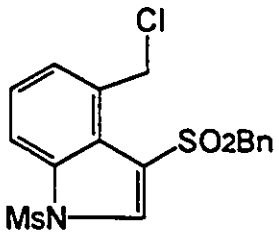
^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.00 (s, 3H), 4.33 (d, 1H, J=12.7 Hz), 4.43 (d, 1H, J=12.7 Hz), 4.79 (d, 1H, J=12.7 Hz), 5.06 (d, 1H, J=12.7 Hz), 7.00 (d, 2H, J=7.0 Hz), 7.2-7.3 (m, 3H), 7.35 (d, 1H, J=7.4 Hz), 7.43 (t, 1H, J=7.4 Hz), 7.47 (s, 1H), 7.90 (d, 1H, J=7.4 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 41.57, 61.85, 64.37, 113.34, 122.71, 124.55, 125.49, 126.35, 128.51, 128.58, 128.85, 129.55, 130.39, 134.49, 136.10 ppm.

IR (CH_2Cl_2): 961, 1179, 1375, 3334 cm^{-1}.

mp: 152 °C.

Reaction of 19 with SO_2Cl_2 (21).



21

A solution of SO_2Cl_2 (5 μL) in CH_2Cl_2 was added dropwise to a solution of sulfoxide **19** (20.5 mg, 0.06 mmol) in CH_2Cl_2 (5 mL). Stirring was continued at RT for 1 h, after which time tlc showed that no starting material remained, and the solvent was evaporated, leaving a white precipitate. Chromatography of the residue (2:1 Hex:EtOAc) afforded chloro-sulfone **21** as a white solid (13.6 mg, 57%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.07 (s, 3H), 4.81 (s, 2H), 5.41 (s, 2H), 7.2-7.3 (m, 5H), 7.50 (m, 2H), 7.75 (s, 1H), 7.95 (dd, 1H, J=7.5, 1.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 41.94, 44.86, 61.98, 113.98, 119.79, 126.86, 128.21, 128.50, 128.59, 128.66, 128.80, 128.91, 130.88, 131.63, 136.21 ppm.

IR (CH_2Cl_2): 1090, 1210, 1350, 1362 cm^{-1}.

CI-MS (iso): 398 (M^{+*}+1, 0.5), 362 (100).

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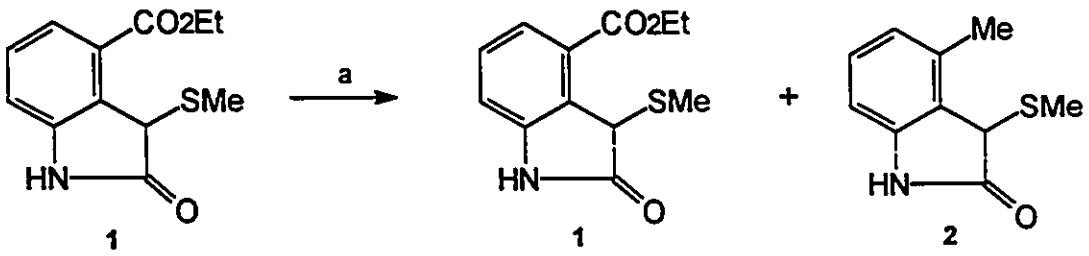
Chapter 7 - Studies on the Reductions of Oxindoles

7.1 Introduction

As mentioned earlier (cf. Chapter 5), the behavior of some of the 3-thioalkyl-2-oxindoles towards $LiAlH_4$ mediated reduction was atypical. Intrigued by these results, a series of structurally related oxindoles, which varied only in the position of the pendant ester group on the benzene ring, and the number of methyl groups in the 1 and 3 positions were prepared and their behavior towards reduction with $LiAlH_4$ and $LiEt_3BH$ was studied. The goal of this research was to gain an understanding of the factors influencing the ease of reduction of the pendant ester group on the aromatic ring.

7.2 3-Thiomethyl-4-carboethoxy-2-oxindole

Attempted reduction of 1 with a variety of reducing agents led to quantitative recovery of starting material. Only under rather forcing conditions (10 equivalents $LiAlH_4$, refluxing THF, 18 hours) was any reaction observed, and even under these conditions, 50% of the starting material was recovered with the remainder of the mass balance being 3-thiomethyl-4-methyl-2-oxindole 2.



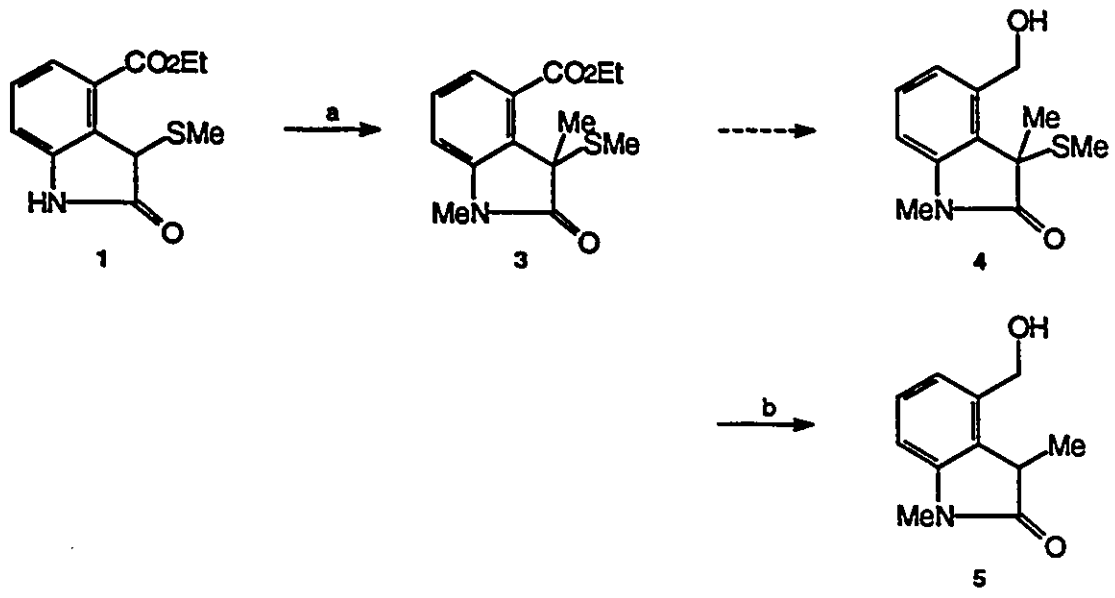
Reagents: a) (i) 10 equiv. $LiAlH_4$, THF, Δ, 18 h; (ii) Rochelle's Salt, EtOAc

Scheme 7.1 - Reduction of Oxindole 1 with $LiAlH_4$

The absence of any of the presumed intermediate to 2, the desired benzylic alcohol, led to the mechanistic proposal shown in Scheme 5.3. The initial resistance of the ester group of 1 towards reaction with $LiAlH_4$ and the subsequent high propensity for over reduction was ascribed to the high acidity of H_3.

7.3 1,3-Dimethyl-3-thiomethyl-4-carboethoxy-2-oxindole

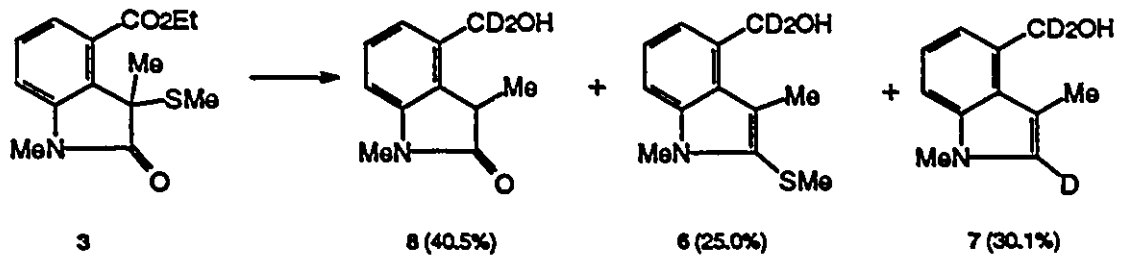
It was expected that removing the troublesome acidic protons α to the carbonyl group would allow the desired reduction to benzylic alcohol 4 to take place, thus 1 was permethylated to 3. However, treatment of 3 with $LiAlH_4$ in refluxing THF afforded 5 as the major polar product.



Reagents: a) 2LDA, THF, -78 °C (ii) MeI; b) $LiAlH_4$, THF

Scheme 7.2 - Synthesis and Initial Reduction of Oxindole 1

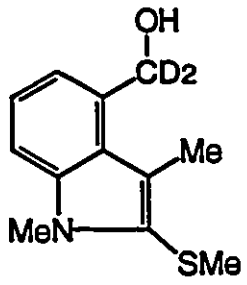
To gain insight into the reduction mechanism, the reaction was repeated using $LiAlD_4$ as the reducing agent. Reaction of 1 with $LiAlD_4$ in THF at RT, followed by careful chromatography led to the isolation of *three* products!



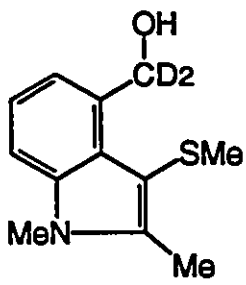
3 8 (40.5%) 6 (25.0%) 7 (30.1%)

Scheme 7.3 - Reduction of Oxindole 3 with $LiAlD_4$

The least polar product, isolated as a pale yellow solid (mp 106.3 - 107.0 °C) showed three methyl singlets in the ^{1}H-NMR at δ = 2.12, 2.58 and 3.75 ppm. The small separation of peaks and the pattern in the aromatic region of the ^{1}H-NMR suggested that the nucleus was now an indole, rather than the starting oxindole. The IR spectrum showed a broad stretch at 3400 cm^{-1}, indicating that ester reduction to the benzylic alcohol had occurred, and the absence of a C=O band confirmed that the oxindole carbonyl had also been reduced. In addition, the ^{13}C-NMR showed a 5 line pattern centered at 63.80 ppm and the ^{2}H-NMR showed a singlet at 4.87 ppm, consistent with a benzylic -CD_2OH group. EI-MS showed a molecular ion at m/z 223, and HRMS supported a molecular formula of $C_{12}H_{13}NOSD_2$. All of this spectroscopic evidence was consistent with two structures, 6a or 6b.



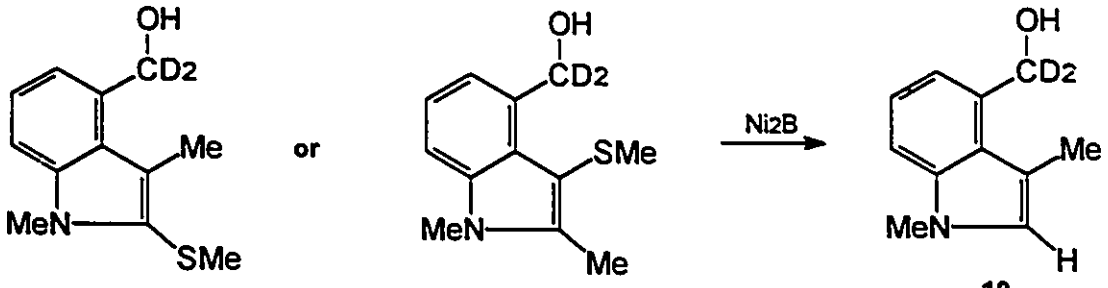
6a



6b

Distinguishing between 6a and 6b by spectroscopic methods proved difficult, so recourse was made to Ni_2B mediated desulfurization[1]. Desulfurization of either 6a or 6b would led to a C3 or C2 substituted indole respectively, which would be readily identifiable on the basis of the chemical shift of the proton

that would replace the sulfur substituent. For C3 substituted indoles, the C2 proton resonates close to 7 ppm, whereas for C2 substituted indoles, the C3 proton resonates at much higher chemical shifts, typically around 5 ppm[2].



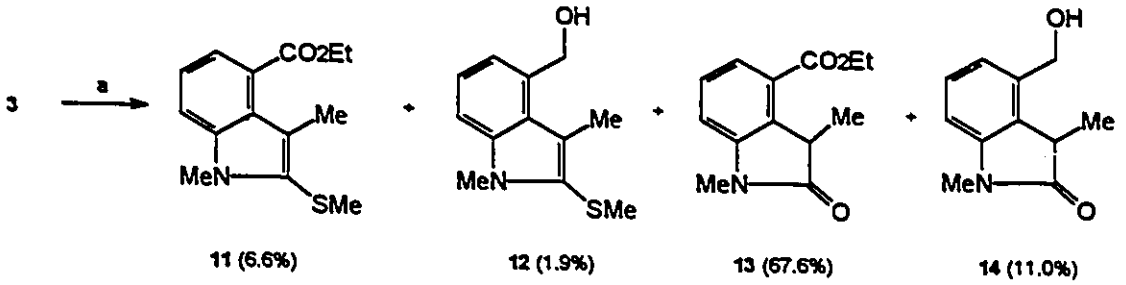
6a **6b** **10**

Exposure of a THF solution of the unknown indole to a methanolic solution of Ni_2B, generated *in situ* from $NaBH_4$ and $NiCl_2$, resulted in the formation of a single product which showed a new resonance in the ^{1}H-NMR at 6.78 ppm, indicative of an indolic C2 proton, and consistent with the precursor being **6a**.

The second compound, isolated as a pale yellow solid (mp 80.5 - 81.7 °C) was assigned structure 7. The ^{1}H-NMR spectrum showed that an indole had formed, but that only 2 methyl groups had been retained. Additionally, the ^{2}H-NMR spectrum indicated that *two deuteriums had been incorporated in a ratio of 2:1*, at chemical shifts of 4.68 and 6.78 ppm! Examination of the EI-MS did show a major peak at m/z 178, however HRMS was not possible due to slight contamination by 6, as evident from the ^{1}H-NMR and the EI-MS. The signal in the ^{2}H-NMR spectrum at 6.78 ppm was consistent with deuterium incorporation at C2 of the indole.

The most polar compound, also obtained as a pale yellow solid (mp 99.6 - 101.3 °C) had a ^{1}H-NMR that showed signals at 1.38 (d, 3), 3.08 (s, 3H), 3.42 (q, 1H) ppm. The aromatic region showed a doublet-doublet-triplet pattern associated with an oxindole nucleus at 6.65, 6.98 and 7.18 ppm. The IR spectrum showed the presence of an alcohol (3603 cm^{-1}) and a carbonyl group (1710 cm^{-1}), HRMS supported a molecular formula $C_{11}H_{11}NO_2D_2$ and the ^{2}H-NMR showed two singlets in a one to one ratio at 4.56 and 4.63 ppm. These data are consistent with structure 8.

The reaction was repeated using a milder, more controlled hydride source (Super-Hydride™). Careful chromatography led to the isolation of *four products*: 11 - 14. The isolation of 11 and 13 indicated that reduction of the oxindole carbonyl group preceded that of the C4 ester group.



Reagents: a) $LiEt_3BH$, THF

Scheme 7.4 - Super-Hydride™ Mediated Reduction of Oxindole 3

The inertness of the oxindole carbonyl when the oxindole was not substituted with an alkyl group at either the 1 or 3 position was in stark contrast to the reduction of oxindole 3 which was substituted at both the 1 and 3 positions. At this point, it was decided to investigate the reduction behavior of some oxindoles that were substituted at either the 1 or 3 positions.

7.4 1-Methyl-3-thiomethyl-4-carboethoxy-2-oxindole

As shown in Scheme 7.5, starting with commercially available material and adapting the procedure of Krishnamurthy[3], aniline 16 was converted into the requisite N-methyl oxindole 17 using the standard Gassman method[3]. Oxindole 17 (^{1}H-NMR shown in Fig. 7.1) was isolated as off- white needles (mp 82.5 - 82.8 °C) following chromatography and recrystallization from MeOH in an unoptimized yield of 12%.

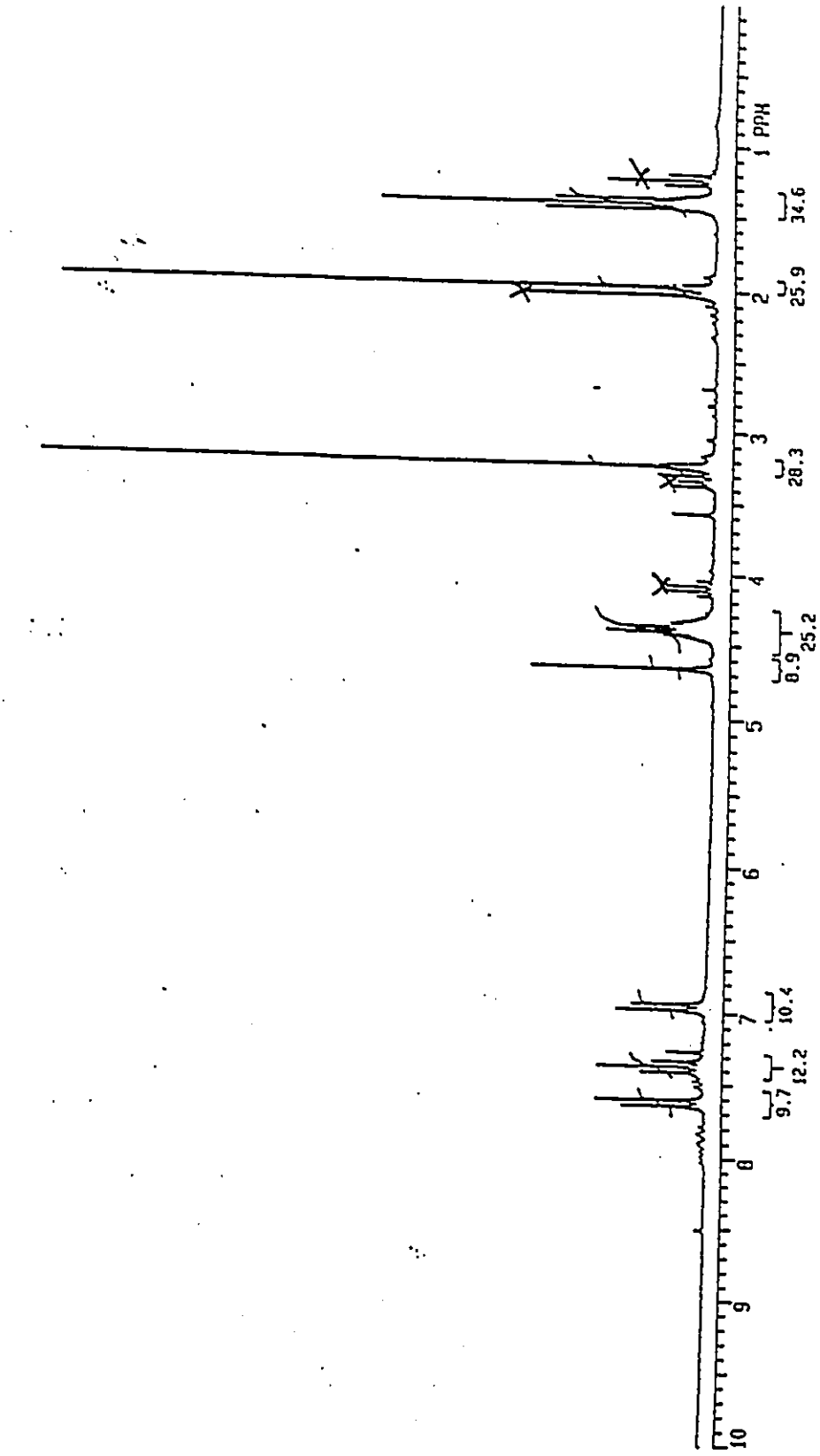
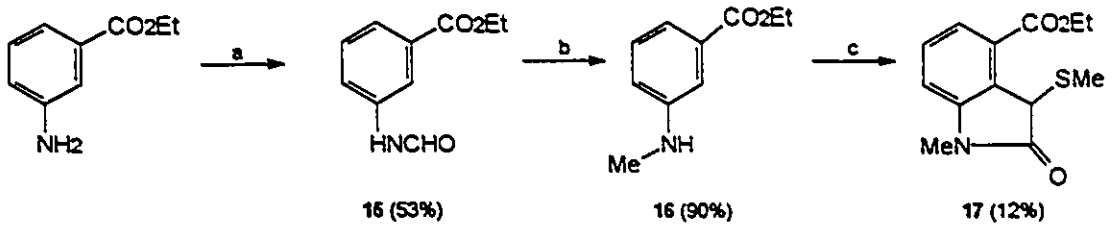


Figure 7.1 200 MHz ^{1}H-NMR Spectrum of Oxindole **17** in $CDCl_3$

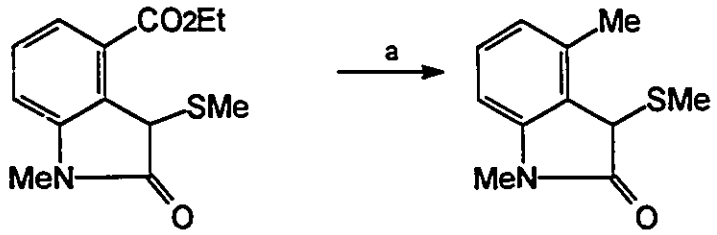


15 (53%) 16 (90%) 17 (12%)

Reagents: a) HCO_2H, PhMe, Δ; b) BMS, THF, Δ; c) (i) tBuOCl, (ii) $MeSCH_2CO_2Me$, (iii) TEA

Scheme 7.5 - Synthesis of Oxindole 17

Reaction of **17** with $LiEt_3BH$ in THF at temperatures ranging from 0 °C to reflux resulted in the recovery of starting material in near quantitative yield. Excess $LiAlH_4$, at room temperature, likewise failed to promote reaction, but in refluxing THF (67 °C) complete reduction of the ester group was observed. Oxindole **18** was isolated as an off-white solid (mp 100.0 - 101.3 °C) in 90% yield after column chromatography. Key changes in the ^{1}H-NMR spectrum (Fig. 7.2) included loss of the ethyl group and the appearance of a new singlet integrating for three protons at 2.43 ppm. An upfield shift of the aromatic protons was also consistent with conversion of **17** to **18**. Additionally, HRMS supported a molecular formula of $C_{11}H_{13}NOS$.



17 18 (90%)

Reagents: a) $LiAlH_4$, THF, Δ

Scheme 7.6 - Reduction of Oxindole 17

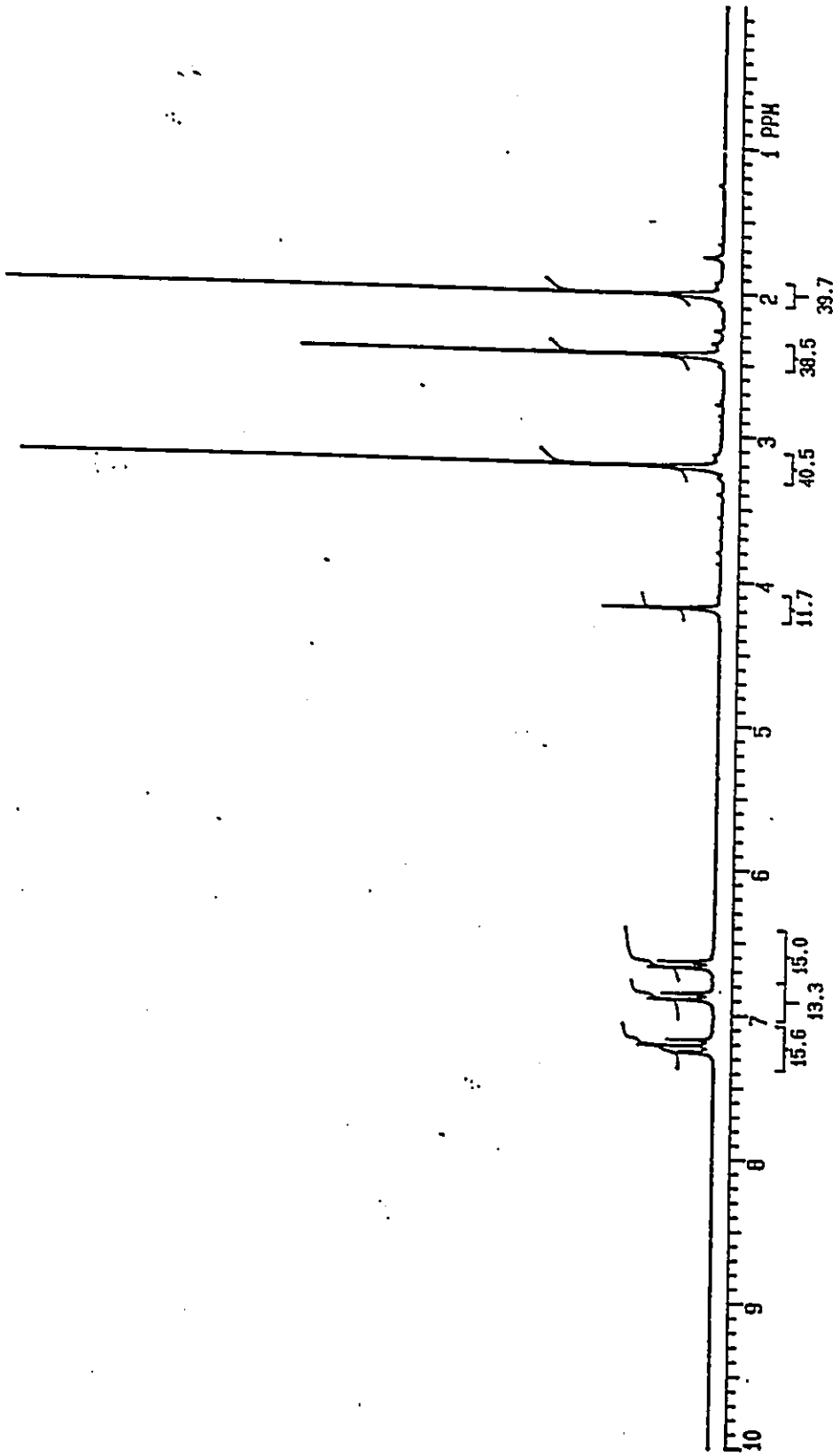
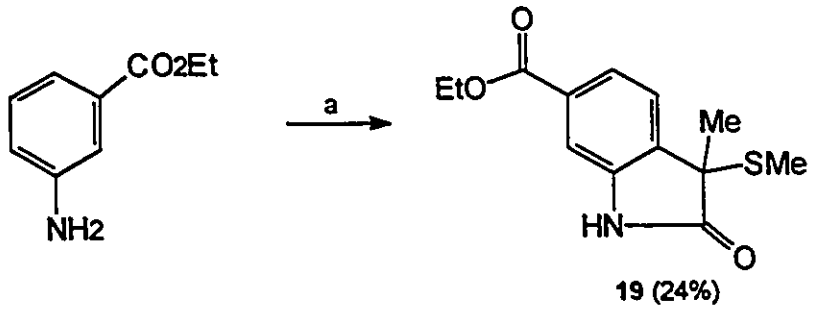


Figure 7.2 200 MHz ^{1}H-NMR Spectrum of Oxindole 18 in $CDCl_3$

7.5 3-Methyl-3-thiomethyl-6-carbcethoxy-2-oxindole

Having established the effect of an N-alkyl group, it was decided to investigate the reduction of a compound in which deprotonation at C3 was blocked by alkylation. Gassman methodology again provided the desired oxindole. Reactions as shown in Scheme 7.7 afforded oxindole 19 as an off-white solid (plates, mp 135.3 - 136.2 °C) in an unoptimized yield of 24%. This compound showed two carbonyl stretches in the IR spectrum at 1722 and 1730 cm^{-1}. The EI-MS showed a molecular ion at m/z 265, and HRMS supported a molecular formula of $C_{13}H_{15}NO_3S$. Examination of the aromatic region of the ^1H-NMR spectrum (Fig. 7.3) showed a splitting pattern indicative of a 1,2,5-trisubstituted system.



Reagents: a) (i) tBuOCl, CH_2Cl_2; (ii) $MeCH(SMe)CO_2Me$; (iii) TEA

Scheme 7.7 - Synthesis of Oxindole **19**

Although both 1,2,3- 1,2,5-trisubstituted oxindoles are possible products from this reaction, up to this point, only 1,2,3-trisubstituted oxindoles had been formed. As suggested in Scheme 7.8, the increased steric demand of the branched sulfide ester may have been responsible for this switch in regiochemistry.

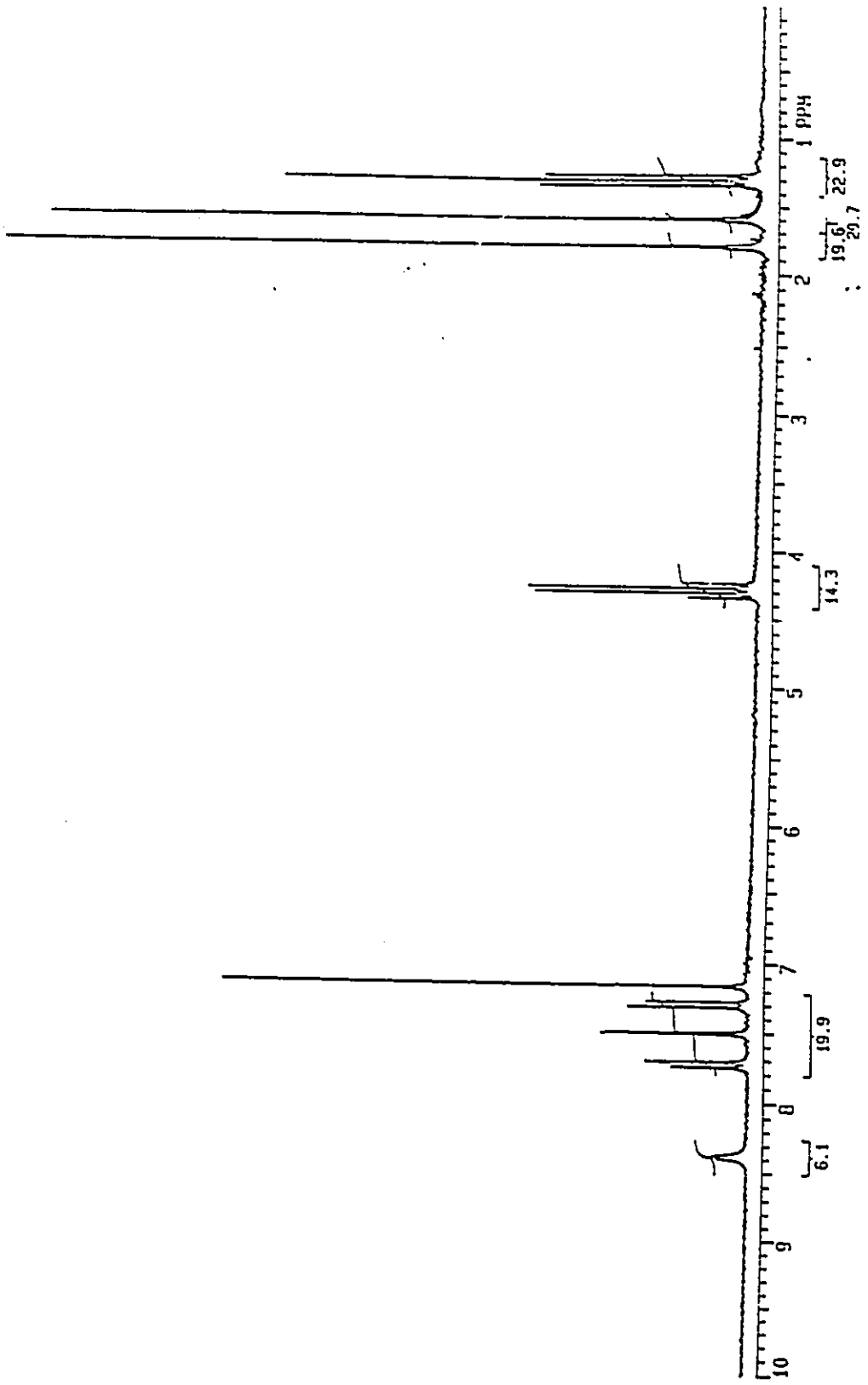
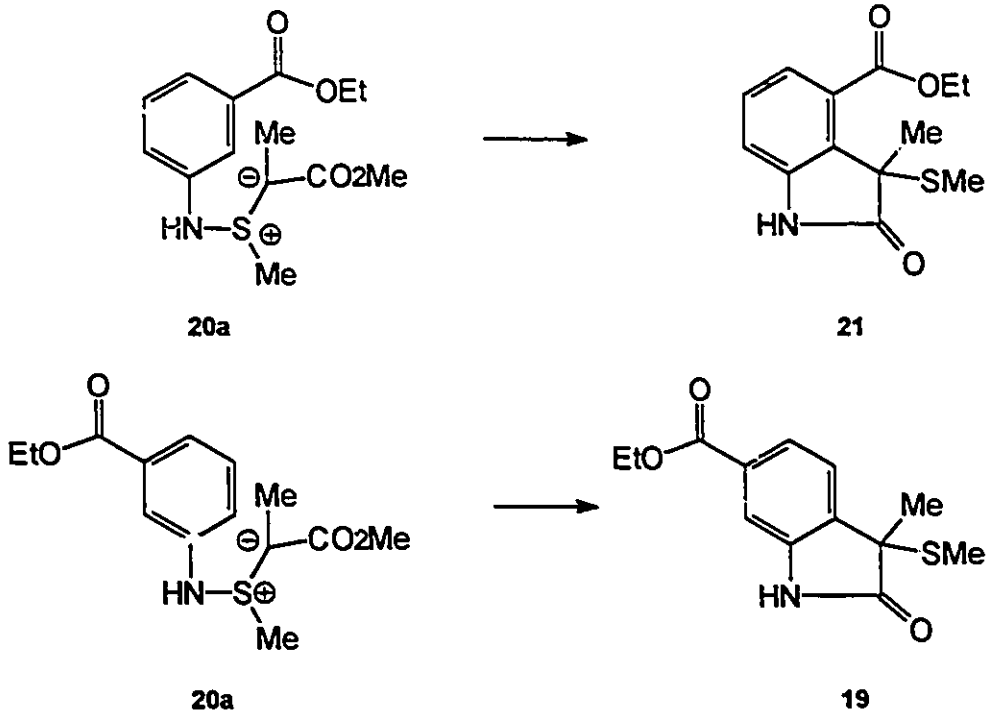


Figure 7.3 200 MHz ^{1}H-NMR Spectrum of Oxindole 19 in $CDCl_3$



Scheme 7.8 - Possible Intermediates in Synthesis of Oxindole 40

Since the ester groups of 19 and 21 are electronically very similar, the regiochemistry of the product made little difference for the reduction study. Reduction of a THF solution of oxindole 19 was accomplished by the addition of 2.5 equivalents of a solution of $LiEt_3BH$ (Scheme 7.9). Usual work up, chromatography and recrystallization afforded 22 as a white solid (prisms, mp 167.3 - 167.5 °C) in a yield of 88%. The IR spectrum of 22 showed bands consistent with reduction of the ester group to an alcohol (3604 cm^{-1}) with the oxindole remaining intact (1729 cm^{-1}). In addition, HRMS supported a molecular formula of $C_{11}H_{13}NO_2S$. Inspection of the ^{1}H-NMR spectrum (Fig. 7.4) showed that the resonances associated with the ethyl ester had disappeared and a new singlet at 4.60 ppm integrating for 2 protons had appeared.

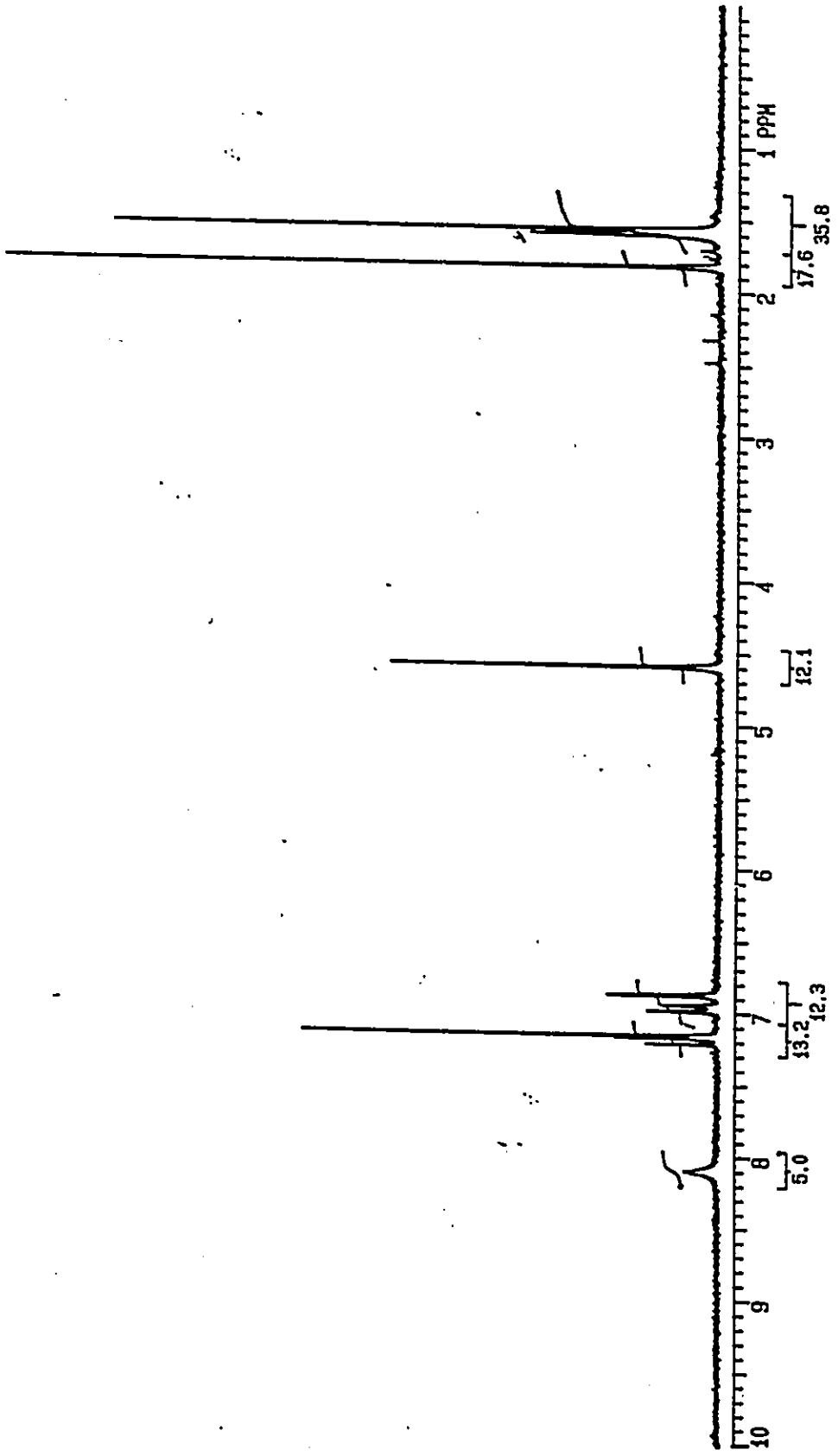
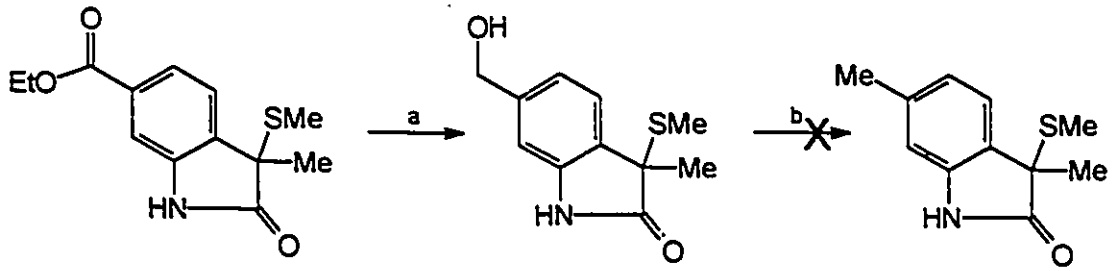


Figure 7.4 200 MHz ^{1}H-NMR Spectrum of Oxindole 22 in $CDCl_3$



19 22 23

Reagents: a) $LiEt_3BH$, THF; b) $LiAlH_4$, THF, Δ

Scheme 7.9 - Reduction of Oxindole 19

Oxindole 22 was not prone to over-reduction. This was demonstrated by the recovery of starting material when it was allowed to react with excess (5 equivalents) $LiAlH_4$ in refluxing THF (6 h).

7.6 3-Thiomethyl-7-carboethoxy-2-oxindole

Having established the effects of the benzylic methine proton on the reduction of the carbonyl groups, it remained to be seen if the anion generated on the amide nitrogen had any effect on reduction/over-reduction of the pendant ester group. The synthesis of the material required for this study, oxindole 24, was accomplished using modified Gassman conditions[5] as shown in Scheme 7.10. Oxindole 24 was obtained as a white crystalline solid (mp 87.3 - 88.2 °C) after usual work up, chromatography and recrystallization, in a non-optimized yield of 10.1%. The IR spectrum of 24 showed two C=O stretches (1697 and 1721 cm^{-1}). The ^{1}H-NMR spectrum (Fig. 7.5) was consistent with 24.

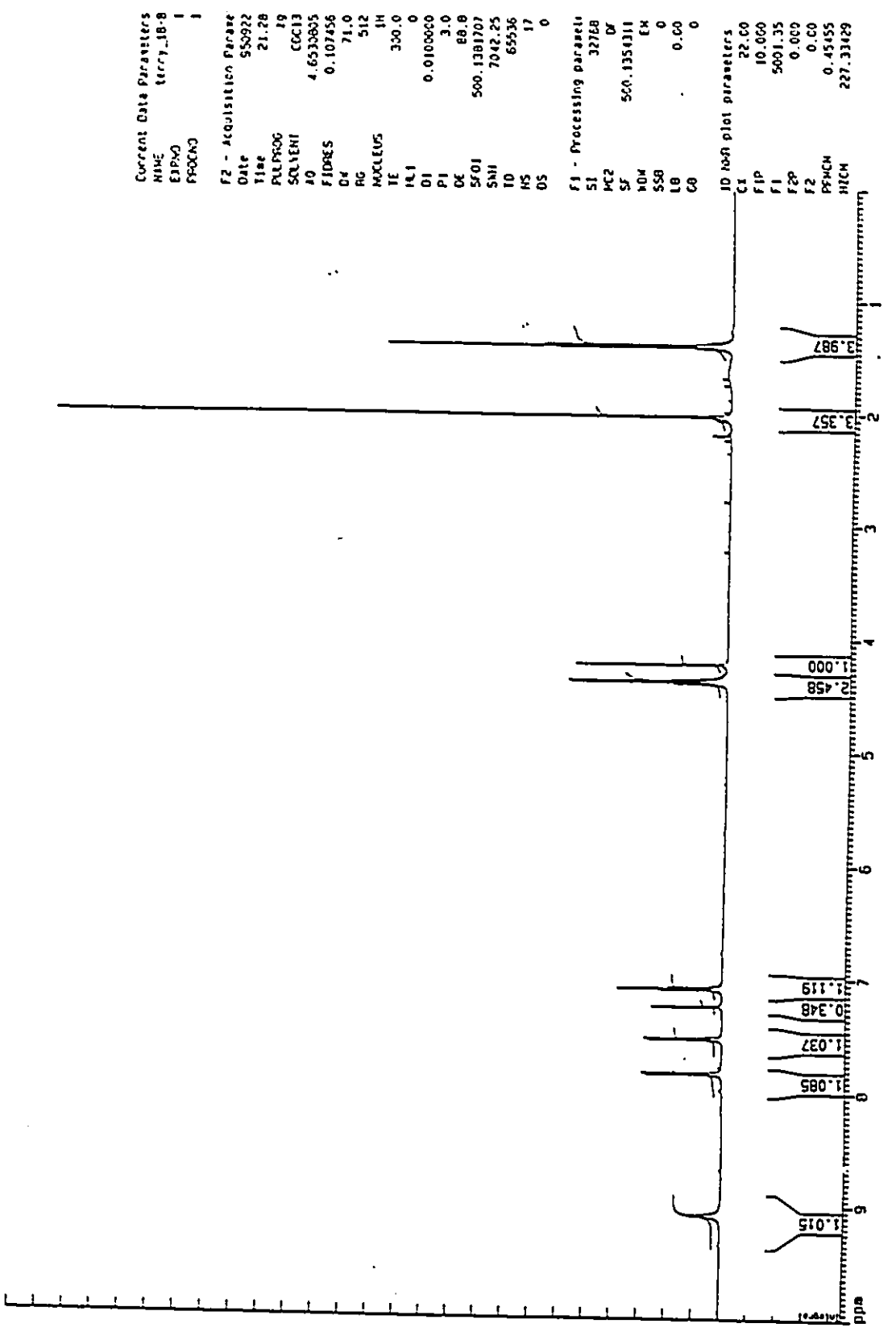
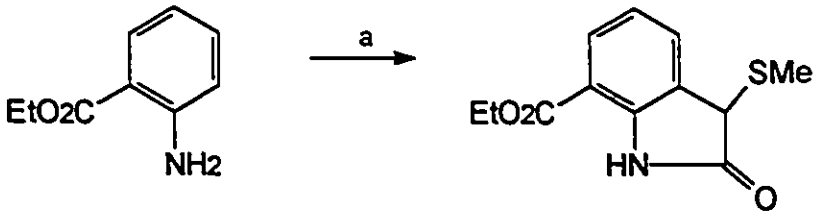


Figure 7.5 500 MHz ^{1}H-NMR Spectrum of Oxindole 24 in $CDCl_3$



24

Reagent: a) (i) SO_2Cl_2, CH_2Cl_2; (ii) $MeSCH_2CO_2Me$; (iii) TEA

Scheme 7.10 - Synthesis of Oxindole **24**

Reaction of oxindole **24** with either $LiEt_3BH$ or $LiAlH_4$ in THF at RT afforded smooth conversion to a single compound. Usual work up, chromatography and recrystallization afforded **25** as a pale yellow solid (mp 148.3 - 149.1 °C). The IR spectra showed that one carbonyl group remained (1721 cm^{-1}) and that an alcohol was now present (3620 cm^{-1}). The ^{1}H-NMR spectrum (Fig. 7.6) and HRMS provided additional support for **25**.

Once again, reduced oxindole **25** was subjected to forcing reduction conditions (excess $LiAlH_4$, refluxing THF). No further reduction of the benzylic alcohol to a methyl group was observed. After prolonged exposure to these harsh reduction conditions (18 h refluxing THF), a small amount of reduction of the oxindole group to provide **27** was noted (less than 5%). However, at no time was there any evidence to support formation of oxindole **26**. Indole **27** was characterized on the basis of its ^{1}H-NMR spectra and EI-MS which showed a molecular ion at m/z 147.

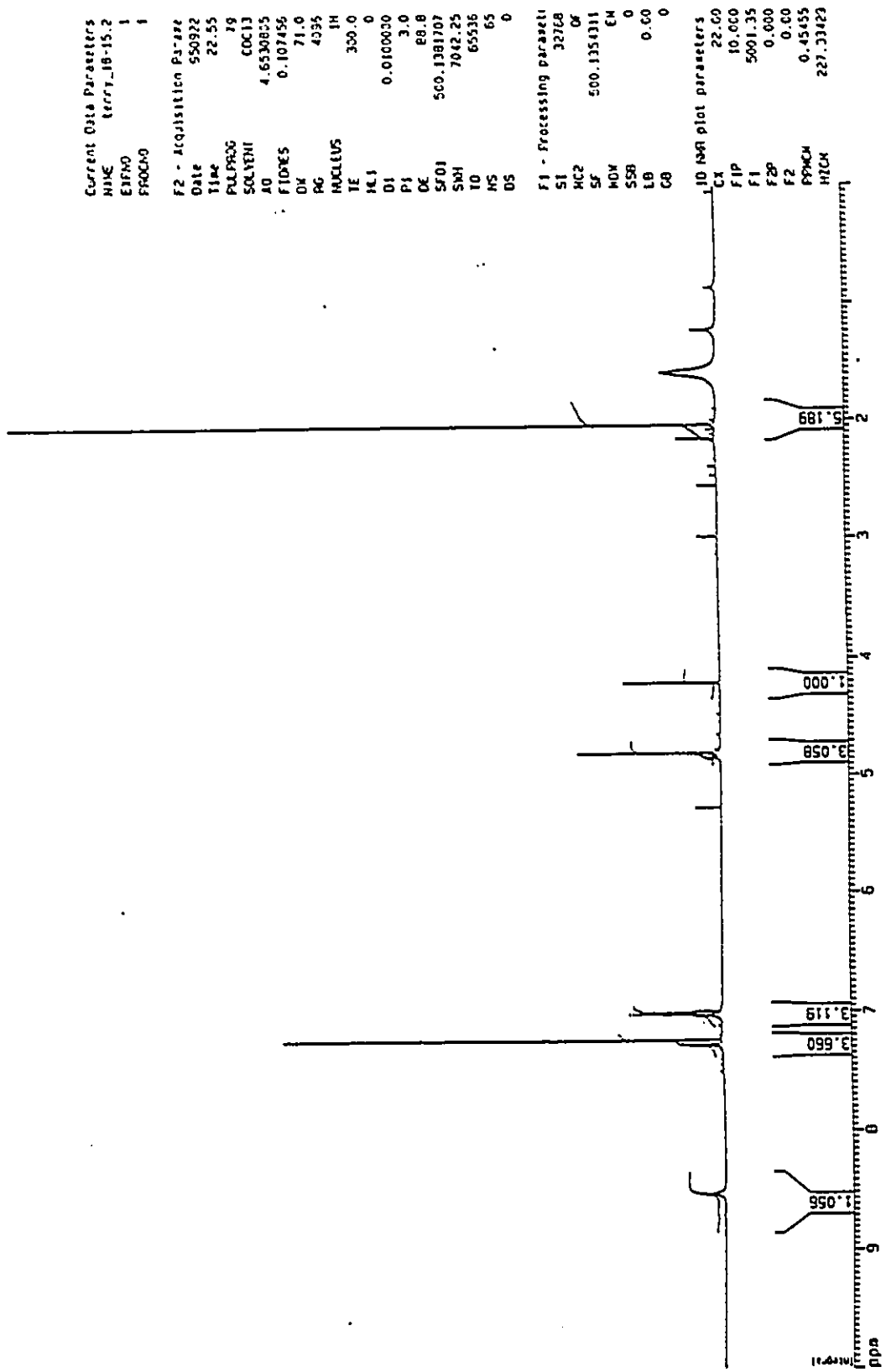
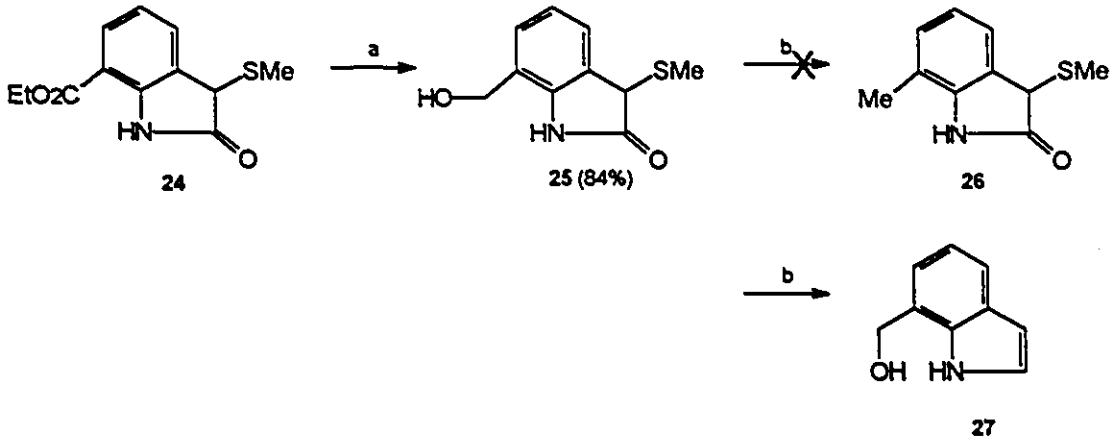


Figure 7.6 500 MHz ^{1}H-NMR Spectrum of Oxindole 25 in $CDCl_3$

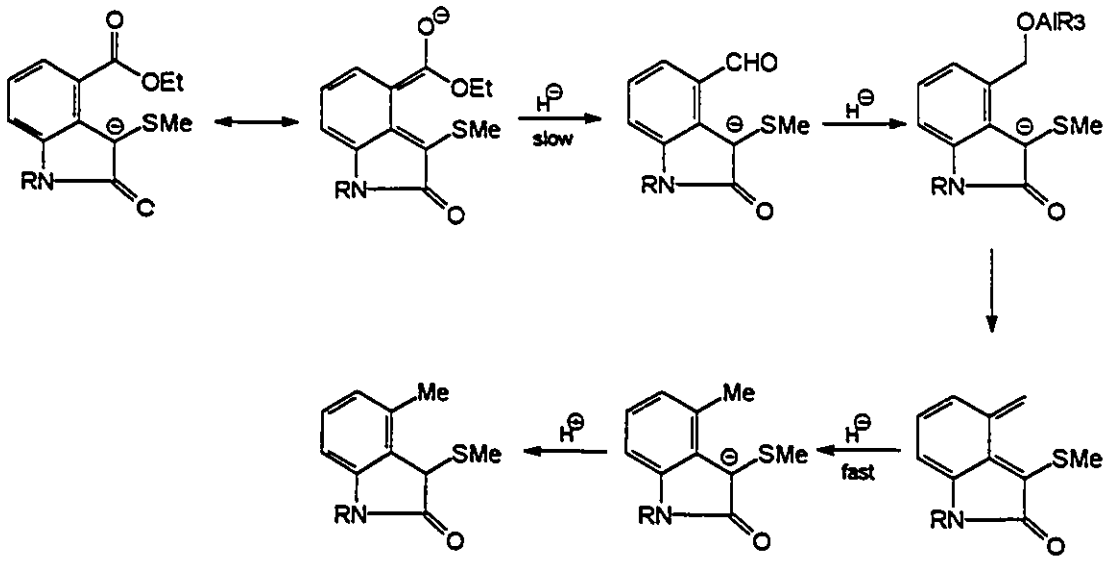


Reagents: a) $LiEt_3BH$ or $LiAlH_4$, THF; b) $LiAlH_4$, THF, Δ

Scheme 7.11 - Reduction of Oxindole 24, and Further Reduction of Product 25

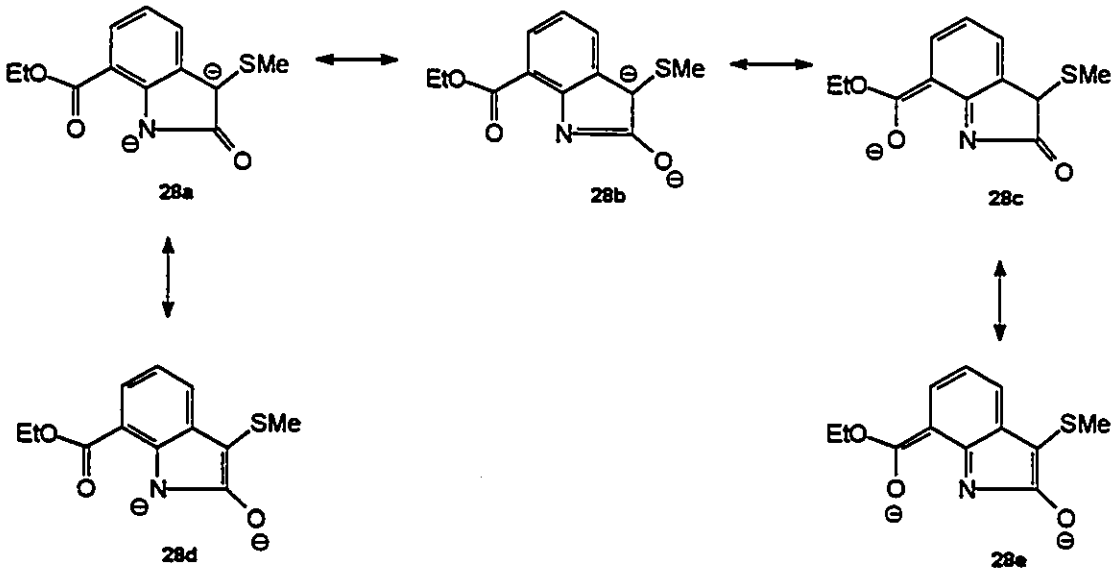
7.7 Conclusion

Considering the series of compounds prepared and the results of reductions discussed in this chapter, a general conclusion regarding the reduction of 3-thiomethyl-2-oxindoles bearing an ester on the benzene ring was reached. In all cases, except for 1,3-dimethyl-2-oxindole, the oxindole carbonyl was extremely inert to reduction, with only a small amount of reduction occurring at prolonged exposure to elevated temperatures and excess reducing agent. From this, it appears that having a proton α to the oxindole carbonyl protects this carbonyl group against reduction. Deprotonation of either the amide proton, or the benzylic methine proton leads to an electron rich carbonyl group that is not susceptible to the first addition of hydride. If the C3 anion is ortho to the ester functional group, then the ester becomes somewhat inert to initial addition of hydride. However, it also becomes extremely susceptible to subsequent over reduction.[6] The proposed mechanism for this case is shown in Scheme 7.12.

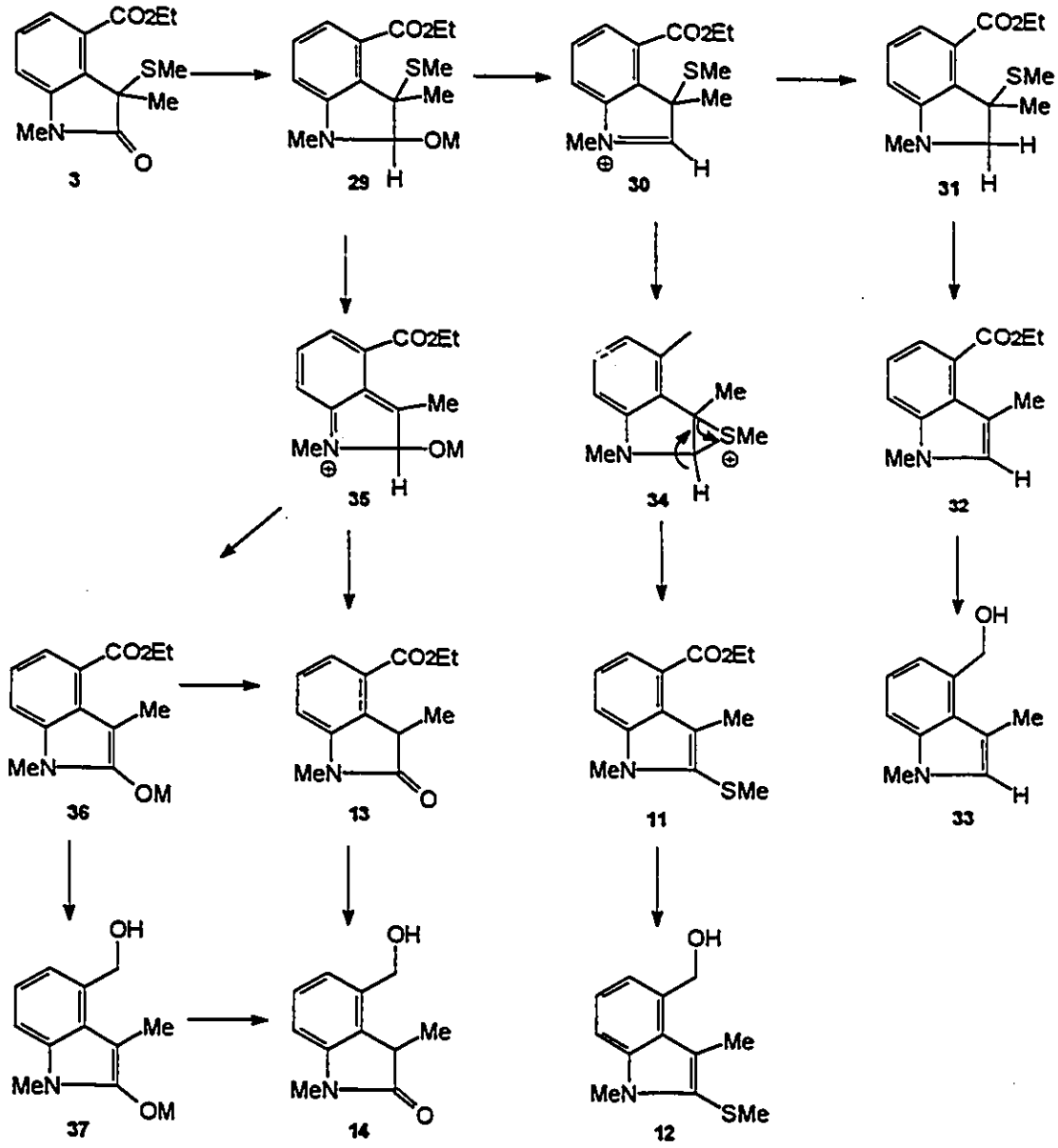


Scheme 7.12 - Proposed Reduction Mechanism for C3 Anion Case

If the amide anion is ortho to the ester group, then ester reduction is unimpeded, proceeding smoothly to the benzylic alcohol, and not going past the alcohol stage even under forcing conditions. This suggests that the contribution of resonance forms 28c and 28e are negligible. This is not surprising since any delocalization into the benzene ring would force the molecule to give up the amide resonance, and any resonance energy associated with this resonance, as well as a loss of aromaticity of the indole ring.



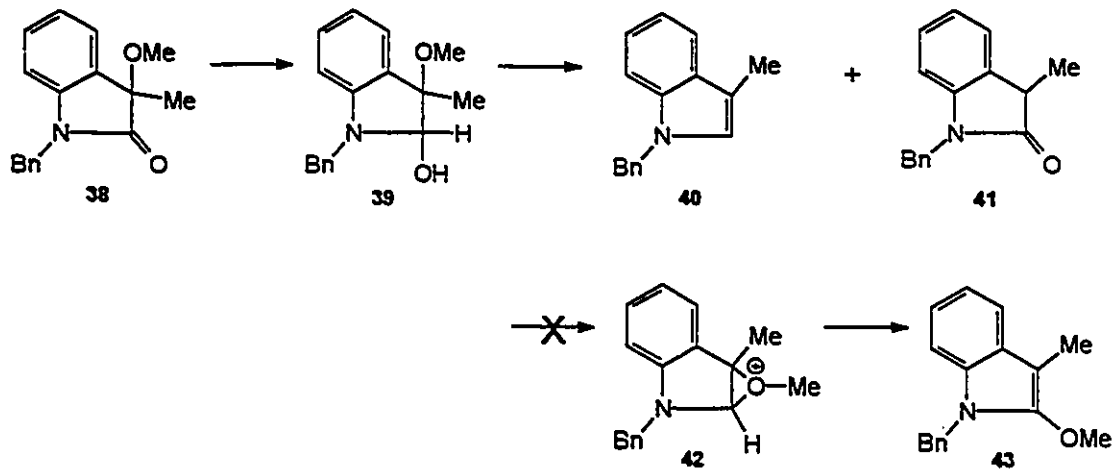
In the case of 2-oxindoles that have both of the positions α to the oxindole carbonyl group blocked to deprotonation, then oxindole carbonyl reduction occurs prior to that of the ester carbonyl group. The initial hemi-aminal 29 produced by addition of one hydride to the oxindole may follow a number of pathways. Addition of another hydride in a manner reminiscent of amide to amine reduction, followed by loss of HSMe from indoline 31 (cf Chapter 4) would afford indole 32.



Scheme 7.13 - Proposed Mechanism for Reduction of Oxindole 3

Further reduction of the ester side chain provides indole 33. Alternatively, nitrogen assisted elimination of the thiomethyl group from 29 through the putative intermediate 35 followed by deprotonation would result in the formation of enol 36. Further reduction of 36 to 37, followed by re-enolization on work up would result in 13 and 14 respectively. Another possible pathway which would result in the formation of 13 and 14 from 35 is a 1,2-hydride shift, forming 13 directly. Although no deuterium was incorporated at C3, this pathway cannot be ruled out due to the ease of enolization of 13 and the possibility of scrambling.

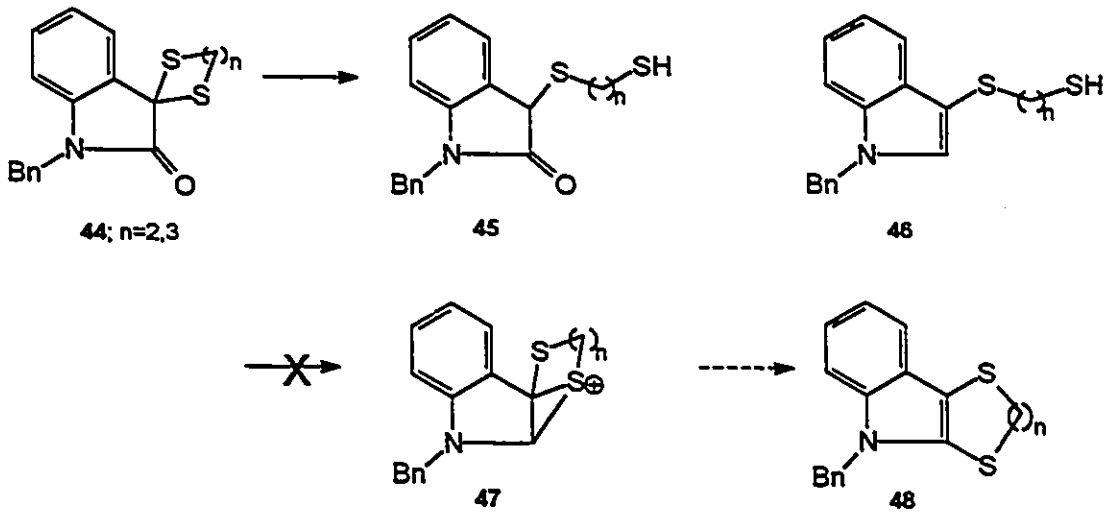
Finally, a rather unusual rearrangement of the thioalkyl group from the 3 to 2 position occurred. One possible pathway would involve the intermediacy of epi-sulfonium salt 34. In an attempt to gain more insight into this rearrangement, a number of analogues were prepared.



Scheme 7.14 - Reaction of 3-Alkoxy Substituted 2-Oxindoles

As shown in Scheme 7.14, reduction of oxindole 38 (three steps from isatin) with $LiEt_3BH$ afforded hemi-aminal 39 in greater than 90% yield after chromatography. Hemi-aminal 39 was characterized by HRMS and a large coupling of the new methine proton to the hydroxy proton (16 Hz). This coupling disappeared upon addition of one drop of D_2O. Further reduction of 39, or use of $LiAlH_4$ for the reduction of 38 provided indole 40 and oxindole 41, characterized by ^{1}H-NMR and HRMS. There was never any evidence of 43 being formed under the reaction conditions. The failure of 38 or 39 to form

43 lends further support to the mechanism proposed in Scheme 7.13. Due to the longer C-S bond, an intermediate such as epi-sulfonium salt 34 may be possible, whereas an intermediate like 42 is not accessable due to the shorter C-O bond.



Scheme 7.15 - Reductions of Oxindoles 44

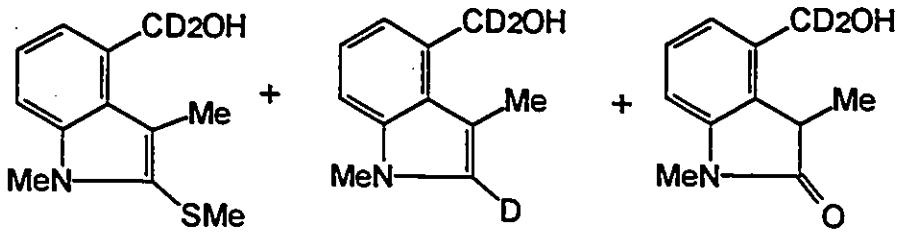
The reactive carbonyl group was also transformed into a dithiane and a dithiolane as in 44. Reaction of 44 with $LiEt_3BH$ or $LiAlH_4$ resulted in the isolation of two compounds, tentatively assigned as 45 and 46 on the basis on their ^{1}H-NMR. These compounds did not give informative MS results, presumably as a result of the ready autooxidation of the free thiol to disulfides. Compound 45 was identified on the basis of the pattern of the aromatic region of the ^{1}H-NMR, which showed the diagnostic doublet and triplet of the oxindole, the other doublet being somewhat obscured due to the signal from the benzyl group. Likewise, 46 was identified on the basis of the indole-like pattern of the aromatic region, with all protons being fairly close together, and the integration accounting for 10 aromatic protons, eliminating compound 48 as a possibility. The failure to form 48 is probably the result the rather unlikely nature of forming intermediate 47, an idea which again supports the intermediary of an epi-sulfonium salt as in intermediate in the migration of SMe from the 3 to 2 position reported earlier.

7.8 Experimental

General

General experimental was as reported in the experimental section of Chapter 3. In addition to this, ^{2}H-NMR were recorded in CH_2Cl_2 solutions on a Varian XL-300 spectrometer, operating at a frequency of 46.06 MHz and are referenced to the natural abundance of CD_2Cl_2 at 5.20 ppm. The synthesis of compounds 1, 2 and 3 was as reported in Chapters 4 and 5. tBuOCl was prepared immediately before use as reported[7]. Once again, all manipulation involving tBuOCl, including the preparation, were carried out in the dark.

Reduction of Oxindole 3 with $LiAlD_4$ (6, 7, 8)



6 7 8

A solution of oxindole 3 (200 mg, 0.72 mmol) was added dropwise to a suspension of $LiAlD_4$ (50 mg, 1.19 mmol) in THF (10 mL) at RT. After stirring at RT for 7 h, the resulting gray cloudy solution was poured into a solution (50 mL) of saturated potassium sodium tartrate and EtOAc (20 mL). After stirring for 4 h, the organic phase was separated, and subjected to normal work up, affording 180 mg of a pale yellow oil. Chromatography with a gradient of 2:1 to 1:1 Hex:EtOAc provided three compounds.

Indole 6: 40.3 mg (25.0%), R_f=0.5 (1:1 Hex:EtOAc), pale yellow solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.58 (s, 3H), 3.75 (s, 3H), 6.95 (d, 1H, J=7.5 Hz), 7.10 (m, 2H) ppm.

^{2}H-NMR (46 MHz, CH_2Cl_2): δ 4.87 (s) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.03, 19.61, 29.89, 63.80 (quintet), 109.45, 116.38, 119.24, 122.11, 124.65, 130.10, 132.91, 137.88 ppm.

IR (CH_2Cl_2): 3392 cm^{-1}.

EI-MS (m/z, %): 223 (100), 205 (15.0), 190 (48.5), 175 (28.5).

HRMS: Calc for $C_{12}H_{13}NOSD_2$: 223.10309, Found: 223.09989.

mp: 106.3 - 107.0 °C.

Indole 7, 38.4 mg (30.1%), R_f =0.40 (1:1 Hex:EtOAc), pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.62 (s, 3H), 6.90 (d, 1H, J=7.5 Hz), 7.15 (t, 1H, J=7.5 Hz), 7.23 (d, 1H, J=7.5 Hz).

^{2}H-NMR (46 MHz, CH_2Cl_2): δ 4.86 (s, 2D), 6.78 (s, 1D).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.14, 32.54, 63.80 (quintet), 109.42, 109.75, 119.42, 121.36, 122.86, 128.72, 132.48, 138.62 (doublet).

IR (CH_2Cl_2): 3391 cm^{-1}.

EI-MS (m/z, %): 178 (96.3) ($M^{+\cdot}$), 160 (100).

mp: 80.5 - 81.7 °C.

Oxindole 8, 56.0 mg (40.5 %), R_f= 0.1 (1:1 Hex:EtOAc), pale yellow solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.38 (d, 3H, J=7.5 Hz), 3.08 (s, 3H), 3.42 (q, 1H, J=7.5 Hz), 6.65 (d, 1H, J=7.5 Hz), 6.98 (d, 1H, 7.5 Hz), 7.18 (t, 1H, J=7.5 Hz).

^{2}H-NMR (46 MHz CH_2Cl_2): δ 4.56 (s, 1D), 4.63 (s, 1D).

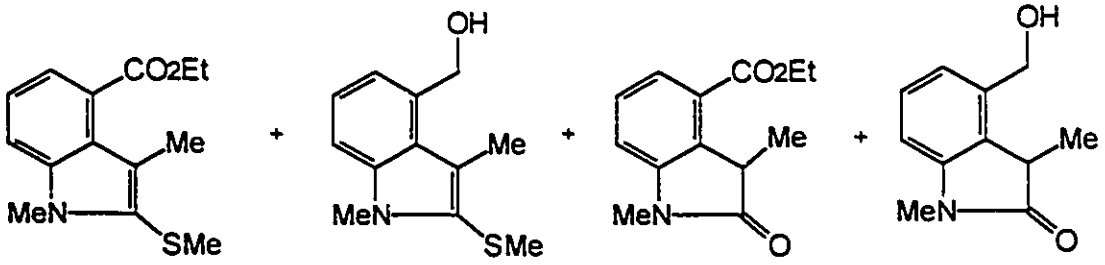
IR (CH_2Cl_2): 3603, 1710 cm^{-1}.

EI-MS (m/z, %): 193 (45.6, $M^{+\cdot}$), 175 (32.9), 160 (23.9), 43 (100).

HRMS: Calc for $C_{11}H_{11}NO_2D_2$: 193.11028, Found: 193.10784.

mp: 99.6 - 101.3 °C.

Reduction of Oxindole 3 with $LiEt_3BH$ (11, 12, 13, 14).



11 **12** **13** **14**

A solution of $LiEt_3BH$ (2.80 mL, 2.80 mmol, 1.0 M in THF) was added dropwise via syringe to a solution of oxindole 3 (156.3 mg, 0.56 mmol) in THF (15 mL) at RT. The resulting bright yellow solution was stirred at RT for 3 h, after which time the yellow solution was poured into H_2O (20 mL), adjusted to pH 3 by the dropwise addition of HCl (10%) and extracted with EtOAc (4 x 20 mL). The combined organic extracts were worked up as usual, affording a pale yellow oil (120 mg) which was chromatographed with a gradient of 2:1 to 1:1 Hex:EtOAc and afforded four compounds.

Indole 11, yellow oil, 9.8 mg (6.6 %), R_f=0.9 (1:1 Hex:EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.5 Hz), 2.25 (s, 3H), 2.51 (s, 3H), 3.88 (s, 3H), 4.42 (q, 2H, J=7.5 Hz), 7.20 (t, 1H, J=7.5 Hz), 7.41 (d, 1H, 7.5 Hz), 7.52 (d, 1H, J=7.5 Hz).

EI-MS (m/z, %): 263 (57.3, $M^{+\cdot}$), 248 (12.6), 234 (14.0), 219 (24.3), 205 (53.3), 57.0 (100).

HRMS: Calc for $C_{14}H_{17}NO_2S$: 263.09800, Found: 263.09847.

Indole 12, white solid, 2.4 mg (1.9%), R_f=0.75 (1:1 Hex:EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.68 (s, 3H), 3.85 (s, 3H), 5.05 (s, 2H), 7.04 (d, 1H, J=7.5 Hz), 7.20 (m, 2H).

EI-MS (m/z, %): 221 (100, $M^{+\cdot}$), 188 (43.3), 173 (32.2), 145 (36.5).

HRMS: Calc for $C_{12}H_{15}NOS$: 221.08744, Found: 221.08616.

mp: 115.0 - 116.1 °C.

Oxindole **13**, pale yellow solid, 88.2 mg (67.6 %), R_f=0.50 (1:1 Hex:EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.5 Hz), 1.48 (d, 3H, J=7.5 Hz), 3.22 (s, 3H), 3.86 (q, 1H, 7.5 Hz), 4.38 (q, 2H, 7.5 Hz), 6.98 (d, 1H, J=7.5 Hz), 7.32 (t, 1H, J=7.5 Hz), 7.68 (d, 1H, J=7.5 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.89, 15.93, 26.00, 41.65, 60.86, 111.36, 123.46, 126.58, 127.59, 132.41, 144.66, 165.55, 178.66.

IR (CH_2Cl_2): 1714 cm^{-1}.

EI-MS (m/z, %): 233 (100, $M^{+\cdot}$), 204 (40.3), 188 (29.7), 160 (83.7).

HRMS: Calc for $C_{13}H_{15}NO_3$: 233.10519, Found: 233.10495.

mp: 70.0 - 70.5 °C.

Oxindole **14**, pale yellow solid, 11.8 mg (11.0 %), R_f=0.10 (1:1 Hex:EtOAc).

^{1}H-NMR (500 MHz, CDC_3): δ 1.44 (d, 3H, J=7.6 Hz), 2.70 (br, 1H), 3.14 (s, 3H), 3.44 (q, 1H, J=7.6 Hz), 4.65 (d, 1H, 13.0 Hz), 4.73 (d, 1H, J=13.0 Hz), 6.72 (d, 1H, J=8.0 Hz), 7.05 (d, 1H, J=8.0 Hz), 7.24 (t, 1H, 8.0 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 15.43, 26.29, 40.11, 62.26, 107.42, 121.62, 127.93, 128.12, 137.15, 144.10, 178.81.

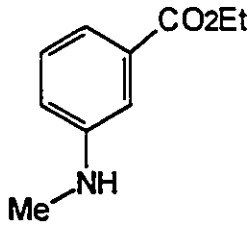
IR (CH_2Cl_2): 3603, 1710 cm^{-1}.

EI-MS (m/z, %): 191 (100, $M^{+\cdot}$), 173 (73.3), 144 (32.7).

HRMS: Calc for $C_{11}H_{13}NO_2$: 191.09463, Found: 191.09650.

mp: 99.8 - 100.0 °C.

Ethyl-3(N-Methyl-amino)benzoate.



A toluene (50 mL) solution of ethyl 3-aminobenzoate (5g, 30.30 mmol) and formic acid (5 mL, 98%) was fitted with a Dean-Stark trap and heated to reflux for 12 h. The solvent was removed and the resulting purple residue was suspended in CH_2Cl_2 (50 mL), and washed sequentially with H_2O (2 x 20 mL), HCl (10%, 2 x 20 mL) and $NaHCO_3$ (5%, 2 x 20 mL). The organic phase was worked up in the usual manner, triturated with Et_2O, and filtered. The purplish solid was recrystallized from CH_2Cl_2/Hexanes and filtered, affording 3.12 g of ethyl (N-formyl-amino)benzoate 15 (53 %) as white cubes.

The resulting N-formyl derivative (3.0 g, 15.54 mmol) was dissolved in THF (50 mL), and heated to reflux, at which point, a solution of borane-methyl sulfide complex was added (3.0 mL, 10 M, 30.00 mmol) dropwise via syringe. After 12 h at reflux, the solution was cooled to RT, and MeOH (20 mL) was added slowly (CAUTION! H_2 Evolution!). Stirring was continued until hydrogen evolution stopped, and then for 15 min more, after which time the solution was concentrated to dryness, and the residue purified by column chromatography (2:1 Hex:EtOAc), affording the title compound as a clear oil (2.5 g, 90 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.35 (t, 3H, J=6.8 Hz), 2.82 (s, 3H), 3.80 (br, 1H), 4.32 (q, 2H, J=6.8 Hz), 6.74 (d, 1H, J=6.5 Hz), 7.20 (t, 1H, J=6.5 Hz), 7.25 (d, 1H, J=6.5 Hz), 7.35 (d, 1H, J=6.5 Hz) ppm.

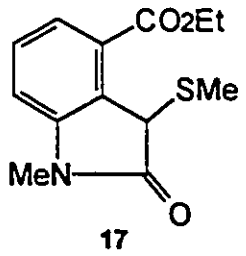
^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.32, 30.62, 60.79, 112.84, 116.77, 118.23, 129.04, 131.35, 149.34, 167.13 ppm.

IR (CH_2Cl_2): 3435, 1713 cm^{-1}.

EI-MS (m/z, %): 179 (100, $M^{+\bullet}$), 150 (76.0), 134 (40.3), 106 (58.5), 77 (23.2).

HRMS: Calc for $C_{10}H_{13}NO_2$: 179.09463, Found: 179.09484.

1-Methyl-3-thiomethyl-2-oxo-2,3-dihydroindole 17.



17

A solution of freshly prepared tBuOCl (0.60 g, 5.49 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a cooled (-78°C) solution of ethyl (3-(N-methyl)-amino)benzoate (0.98 g, 5.47 mmol) in CH_2Cl_2 (25 mL). The resulting bright yellow mixture was stirred at this temperature for 10 min, at which point a solution of methyl (thiomethyl)acetate (0.66 g, 5.47 mmol) in CH_2Cl_2 (5 mL) was added and stirring continued for 2.5 h. A solution of triethylamine (0.56 g, 5.54 mmol) in CH_2Cl_2 (5 mL) was added, and the initially yellow solution was allowed to warm to RT over 12 h. The reddish solution that resulted was poured into a solution of H_2O (100 mL), the organic phase separated and worked up in the usual manner to provide an orange solid. Recrystallization from CH_2Cl_2 afforded the title compound as a white solid (.75 mg, 12%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.1 Hz), 1.97 (s, 3H), 3.22 (s, 3H), 4.36 (m, 2H), 4.66 (s, 1H), 6.96 (d, 1H, J=7.1 Hz), 7.41 (t, 1H, J=7.1 Hz), 7.65 (d, 1H, J=7.1 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.32, 14.04, 26.33, 46.01, 61.30, 111.40, 124.02, 127.33, 127.86, 128.99, 144.72, 165.55, 174.86 ppm.

IR (CH_2Cl_2): 1717 cm^{-1}.

EI-MS (m/z, %): 265 (5.2, $M^{+\cdot}$), 219 (100), 190 (18.6), 174 (33.8).

HRMS: Calc for $C_{13}H_{15}NO_3S$: 265.07727, Found: 265.08194.

mp: 82.5 - 82.8 °C.

Reduction of Oxindole 17 with $LiAlH_4$ (18).

18

A solution of oxindole **17** (40 mg, 0.15 mmol) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (10 mg, 0.26 mmol) in THF (5 mL). The resulting gray cloudy solution was stirred at reflux for 2h, then poured into a saturated solution of potassium sodium tartrate (50 mL) and Et_2O (50 mL). Stirring was continued for 4 h, after which time the organic phase was separated, and worked up in the usual manner, affording, after column chromatography (1:1 Hex:EtOAc) compound **18** as off-white needles (28 mg, 90 %).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.43 (s, 3H), 3.21 (s, 3H), 4.18 (s, 1H), 6.66 (d, 1H, J=7.5 Hz), 6.88 (d, 1H, J=7.5 Hz), 7.21 (t, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.66, 17.78, 26.01, 44.79, 105.27, 122.54, 124.31, 128.58, 135.53, 143.77, 174.81 ppm.

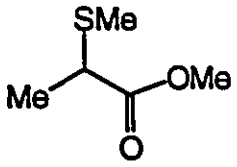
IR (CH_2Cl_2): 1712 cm^{-1}.

EI-MS (m/z, %): 207 (14.2, $M^{+\cdot}$), 160 (100), 130 (9.4), 117 (10.4), 77 (7.9).

HRMS: Calc for $C_{11}H_{13}NOS$: 207.07179, Found: 207.07322.

mp: 100.0 - 101.3 °C.

Methyl (2-thiomethyl)propionate.



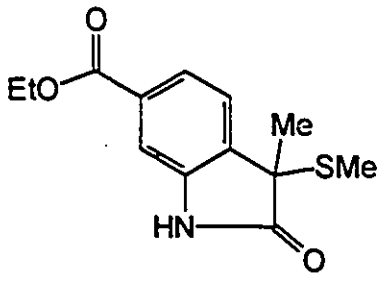
Freshly cut sodium metal (2.2 g, 95.65 mmol) was dissolved in MeOH (150 mL). To this was added thiolactic acid (5g, 47.17 mmol), and the resulting cloudy solution was stirred at RT for 1 h, after which time MeI (7.4 g, 52.11 mmol) was added, and stirring was continued for 18 h. The solution was acidified with H_2SO_4 (conc.) and the resulting precipitate was filtered off. The resulting clear, reddish solution was refluxed for 3 h, the solvent was evaporated, and the residue dissolved in CH_2Cl_2 (100 mL), washed with H_2O (50 mL), then $NaHCO_3$ (5 %, 4 x 20 mL). Usual work up of the organic phase, followed by purification via distillation afforded the title compound as a clear liquid (3.01 g, 48 %).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (d, 3H, J=7.1 Hz), 2.02 (s, 3H), 3.37 (q, 2H, J=7.1 Hz), 3.61 (s, 3H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.58, 16.22, 41.46, 51.85, 172.84 ppm.

bp: 75 - 77 °C (20 torr).

3-Methyl-3-thiomethyl-6-carboethoxy-2-oxo-2,3-dihydroindole (19).



19

Standard Gassman methodology as reported for the synthesis of **17** afforded the title compound **19** in a yield of 24% after purification via column chromatography (4:1 Hex:EtOAc) and recrystallization from CH_2Cl_2/Hexanes.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7.2 Hz), 1.59 (s, 3H), 1.80 (s, 3H), 4.28 (q, 2H, J=7.2 Hz), 7.29 (d, 1H, J=7.9 Hz), 7.50 (d, 1H, J=1.4 Hz), 7.73 (dd, 1H, J=7.9, 1.4 Hz), 8.38 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.82, 14.01, 21.16, 50.19, 60.98, 110.29, 123.53, 124.53, 130.91, 136.38, 139.61, 165.63, 178.90 ppm.

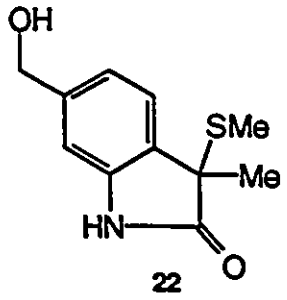
IR (CH_2Cl_2): 3421, 1722, 1730 cm^{-1}.

EI-MS (m/z, %): 265 (2.9, $M^{+\cdot}$), 218 (100), 190 (34.5).

HRMS: Calc for $C_{13}H_{15}NO_3S$: 265.07727, Found: 265.07661.

mp: 135.3 - 136.2 °C.

Reduction of Oxindole 19 with $LiEt_3BH$ (22).



22

A solution of $LiEt_3BH$ (0.45 mL, 1.0M, 0.45 mmol) was added dropwise to a cooled (0 °C) solution of oxindole **19** (45 mg, 0.17 mmol) in THF (5 mL). Stirring was continued at 0 °C for 1h, after which time the pale yellow solution was poured into a solution of H_2O (10 mL) and made acidic by the dropwise addition of HCl (10 %). Extraction with EtOAc (4 x 20 mL), followed by normal work-up and chromatography (2:3 Hex:EtOAc) afforded, in addition to returned starting material (7.8 mg), the title compound **22** (27.4 mg, 88%), which was recrystallized from CH_2Cl_2/Hexanes as white prisms.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.54 (s, 3H), 1.80 (s, 3H), 4.60 (s, 2H), 6.85 (s, 1H), 6.95 (d, 1H, J=7.5 Hz), 7.19 (d, 1H, J=7.5 Hz), 8.10 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.79, 21.29, 49.98, 64.77, 108.11, 121.13, 123.71, 130.72, 139.78, 141.78, 179.22 ppm.

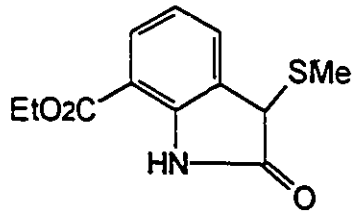
IR (CH_2Cl_2): 3604, 1729 cm^{-1}.

EI-MS (m/z, %): 223 (6.7, $M^{+\bullet}$), 176 (100), 148 (2.8).

HRMS Calc for $C_{11}H_{13}NO_2S$: 223.06670, Found: 223.06858.

mp: 167.2 - 167.5 °C.

3-Thiomethyl-7-carboethoxy-2-oxo-2,3-dihydroindole (24).



24

A solution of sulfuryl chloride (2.26 g, 16.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a cooled solution (-78 °C) of methyl (methylthio)acetate (1.83 g, 15.3 mmol) in CH_2Cl_2 (50 mL), resulting in the slow formation of a white precipitate. After stirring for 1 h, a solution of ethyl (2-amino)benzoate (2.50 g, 15.1 mmol) in CH_2Cl_2 (50 mL) was added dropwise, resulting in slow dissolution of the white precipitate with the solution slowly turning pale yellow. After stirring for 2 h, triethylamine (1.59 g, 15.8 mmol) was added, and the solution was allowed to warm to RT overnight. Water (50 mL) was added, and the aqueous layer separated and subjected to normal work up conditions, resulting in a yellow semi-solid which was dissolved in Et_2O (50 mL) and HCl (10%, 10 mL). The two phase mixture was refluxed for 12 h, cooled, the organic phase separated and worked up in the usual manner. Column chromatography (5:1 Hex:EtOAc) afforded a yellow solid which was recrystallized from CH_2Cl_2/Hexanes, affording the title compound **24** as white flakes (383.8 mg, 10.1%).

^{1}H-NMR (500 MHz, $CDCl_3$): 1.39 (t, 3H, J=7.0 Hz), 2.02 (s, 3H), 4.23 (s, 1H), 4.38 (q, 2H, J=7.0 Hz), 7.08 (t, 1H, J=7.5 Hz), 7.50 (d, 1H, J=7.5 Hz), 7.81 (d, 1H, J=7.5 Hz), 9.20 (br, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 12.23, 14.32, 45.32, 61.39, 111.73, 122.14, 127.57, 129.58, 129.66, 143.79, 165.85, 175.92 ppm.

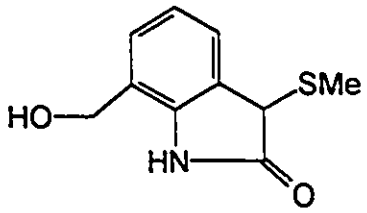
IR (CH_2Cl_2): 3403, 1721, 1697 cm^{-1}.

EI-MS (m/z, %): 251 (3.4, $M^{+\cdot}$), 205 (100), 158 (40.9), 130 (14.1).

HRMS: Calc. for $C_{12}H_{13}NO_3S$: 251.06162, Found: 251.06239.

mp: 87.3 - 88.2 °C.

Reduction of Oxindole 24 with $LiAlH_4$ (25).



25

A solution of oxindole 24 (50 mg, 19.9 mg) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (10 mg, 26.3 mmol) in THF (10 mL). The resulting gray cloudy mixture was heated to reflux for 18 h, then cooled to RT, and poured into a saturated solution of sodium potassium tartrate (20 mL) and EtOAc (50 mL). The biphasic solution was stirred for 4 h, the organic phase was separated and worked up in the usual manner, affording, after purification via column chromatography (1:1 Hex:EtOAc), 25 as a white crystalline solid (35 mg, 84%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.00 (s, 3H), 4.30 (s, 1H), 4.80 (s, 2H), 7.02 (m, 2H), 7.28 (d, 1H, J=7.5 Hz), 8.50 (br, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.33, 45.79, 63.43, 120.20, 122.56, 124.54, 127.24, 138.76, 142.36, 168.20 ppm.

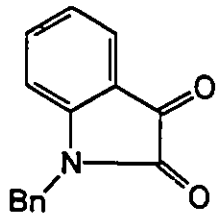
IR (CH_2Cl_2): 3620, 1721 cm^{-1}.

EI-MS (m/z, %): 209 (7.6, $M^{+\cdot}$), 163 (100), 144 (42.0), 116 (48.6).

HRMS: Calc. for $C_{10}H_{11}NO_2S$: 209.05105, Found: 209.04985.

mp: 148.3 - 149.1 °C.

N-(Benzyl)-isatin.



To a solution of isatin (5.00 g, 33.98 mmol) in CH_2Cl_2 (25 mL) was added benzyl bromide (5.81 g, 33.98 mmol), a solution of NaOH (10 mL, 20%), and benzyl triethylammonium bromide (100 mg). The dark red solution was stirred at RT for 4 h, after which time the organic phase was separated and worked up in the usual manner, affording the title compound as an orange solid (6.85 g, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.82 (s, 2H), 6.68 (d, 1H, J=8.0 Hz), 6.98 (t, 1H, J=8.0 Hz), 7.20 (s, 1H), 7.35 (td, 1H, J=8.0, 1.0 Hz), 7.50 (dd, 1H, J=8.0 1.0 Hz) ppm.

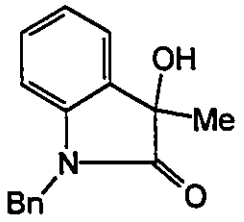
^{13}C-NMR (75 MHz, $CDCl_3$): δ 50.62, 110.68, 117.39, 123.54, 125.11, 127.11, 127.86, 128.74, 134.19, 137.98, 150.43, 157.96, 182.91 ppm.

EI-MS (m/z, %): 237 (62.2, $M^{+\cdot}$), 180 (38.4), 146 (100).

HRMS: Calc. for $C_{15}H_{11}NO_2$: 237.07898; Found: 237.07912.

mp: 124.2-125.1 °C

1-Benzyl-3-methyl-3-hydroxy-2-oxo-2,3-dihydroindole.



A solution of MeMgBr (0.85 mL, 3.0 M in Et_2O, 2.55 mmol) was added dropwise to a cooled (0 °C) solution of N-benzyl-isatin (500 mg, 2.11 mmol) in THF (20 mL). The resulting yellow solution was allowed to warm to RT over 12 h, and the red solution that resulted was poured into a solution of NH_4Cl (10%, 20 mL) and extracted with EtOAc (4 x 10 mL). Usual work up afforded a reddish oil that was subjected to column chromatography (2:1 Hex:EtOAc), providing the title compound as a yellow solid (346.2 mg, 65%).

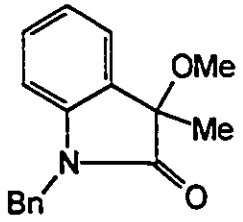
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.63 (s, 3H), 4.80 (d, 1H, J=15.0 Hz), 4.95 (d, 1H, J=15.0 Hz), 6.70 (d, 1H, J=8.0 Hz), 7.05 (t, 1H, J=8.0 Hz), 7.18 (dd, 1H, J=8.0, 1.0 Hz), 7.30 (s, 5H), 7.42 (dd, 1H, J=8.0, 1.0 Hz) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 24.78, 43.44, 73.41, 109.28, 122.96, 123.21, 126.90, 127.43, 128.56, 129.26, 131.01, 135.16, 141.63, 178.30 ppm.

EI-MS (m/z,%): 253 (24.7, $M^{+\bullet}$), 235 (20.5), 149 (38.3), 91 (100).

HRMS: Calc. for $C_{16}H_{15}NO_2$: 253.11078; Found: 253.11042.

1-Benzyl-3-methyl-3-methoxy-2-oxo-2,3-dihydroindole.



A solution of N-benzyl-3-methyl-3-hydroxy-2-oxo-2,3-dihydroindole (150 mg, 0.59 mmol) was added dropwise to a suspension of NaH (20 mg, 0.83 mmol) in THF (5 mL). The pale yellow solution was stirred at RT for 1 h, excess MeI was added, and the still pale yellow solution was stirred at RT for 18 h, after which time it was evaporated to dryness, leaving a pale yellow solid that was recrystallized from CH_2Cl_2/Hexanes, affording the title compound as a bright yellow solid (81.2 mg, 51%).

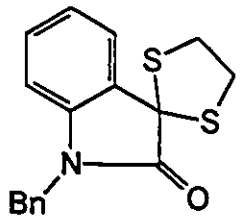
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.60 (s, 3H), 3.06 (s, 3H), 4.91 (d, 1H, J=16.0 Hz), 4.92 (d, 1H, J=16.0 Hz), 6.70 (d, 1H, J=8.0 Hz), 7.05 (t, 1H, J=8.0 Hz), 7.20-7.40 (m, 7H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 23.83, 43.44, 52.87, 79.33, 109.21, 122.82, 123.51, 126.93, 127.44, 128.29, 128.55, 129.31, 135.37, 142.23, 176.31 ppm.

EI-MS (m/z, %): 267 (23.4, $M^{+\cdot}$), 237 (25.3), 176 (14.5), 144 (28.6), 91 (100).

HRMS: Calc. for $C_{17}H_{17}NO_2$: 267.12593; Found: 267.12731.

1-Benzyl-3,3-ethylenedithio-2-oxo-2,3-dihydroindole.



A solution of N-benzylisatin (250 mg, 1.05 mmol) in CH_2Cl_2 (15 mL) containing ethane-1,2-dithiol (119 mg, 1.27 mmol) was stirred at RT while $BF_3 \bullet OEt_2$ (1 mL) was added dropwise. The resulting solution was stirred at RT for 2 h, then quenched by the addition of H_2O (20 mL), washed with sodium carbonate (10%, 3 x 20 mL), and worked up in the usual manner. Chromatography (5:1 Hex:EtOAc) afforded the title compound as a pale yellow solid (222 mg, 67%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.65 (m, 2H), 3.95 (m, 2H), 4.90 (s, 2H), 6.65 (d, 1H, J=8.0 Hz), 7.10 (t, 1H, J=8.0 Hz), 7.15 (t, 1H, J=8.0 Hz), 7.30 (s, 5H), 7.55 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.34, 43.82, 109.22, 123.13, 125.34, 125.94, 126.99, 127.54, 128.54, 128.69, 129.73, 135.31, 142.22, 177.96 ppm

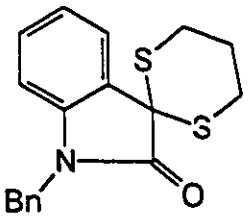
IR (CH_2Cl_2): 1717 cm^{-1}.

EI-MS (m/z, %): 313 (33.1, $M^{+\bullet}$), 254 (54.2), 222 (53.2), 162 (51.0), 91 (100).

HRMS: Calc. for $C_{17}H_{15}NOS_2$: 313.05951; Found: 313.06144.

mp: 107.8-108.0 °C.

1-Benzyl-3,3-propylenedithio-2-oxo-2,3-dihydroindole.



The title compound was prepared as above, except that propane-1,3-dithiol was used in the place of ethane-1,2-dithiol. Chromatography (6:1 Hex:EtOAc) afforded the title compound as a pale yellow solid (241.8 mg, 70.1%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.0-2.3 (m, 2H), 2.65 (dt, 2H, J=14.0, 2.0 Hz), 4.09 (td, 2H, J=14.0, 2.0 Hz), 4.85 (s, 2H), 6.63 (d, 1H, J=7.6 Hz), 7.00 (t, 1H, J=7.6 Hz), 7.15 (t, 1H, J=7.6 Hz), 7.30 (s, 5H), 7.45 (d, 1H, 7.6 Hz) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 24.18, 25.88, 43.16, 109.17, 122.94, 124.99, 126.80, 127.48, 128.71, 129.90, 135.39, 141.43, 175.67 ppm.

IR (CH_2Cl_2): 1708 cm^{-1}.

EI-MS (m/z, %): 327 ($M^{+\cdot}$, 23.2), 294 (22.0),, 254 (39.5), 162 (61.5), 91 (100).

HRMS: Calc. for $C_{18}H_{17}NOS_2$: 327.07516; Found: 327.07519.

mp: 148.8-149.2 °C.

References

1) a) Back, T.G. *J. Chem. Soc., Chem. Commun.* **1984**, 1417.
b) Back, T.G.; Yang, K.; Krouse, H.R. *J. Org. Chem.*, **1992**, *57*, 1986.

2) The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra, C.J. Pouchert and J. Behnke, Aldrich Chemical, Milwaukee, WI, 1992.

3) Krishnamurthy, S. *Tetrahedron Lett.*, **1982**, *23*, 3315.

4) Gassman, P.G.; van Bergen, T.J. *J. Amer. Chem. Soc.*, **1974**, *96*, 5508.

5) Weirengs, W.; Griffin, J.; Warpehaski, M.A. *Tetrahedron Lett.*, **1983**, *24*, 2437.

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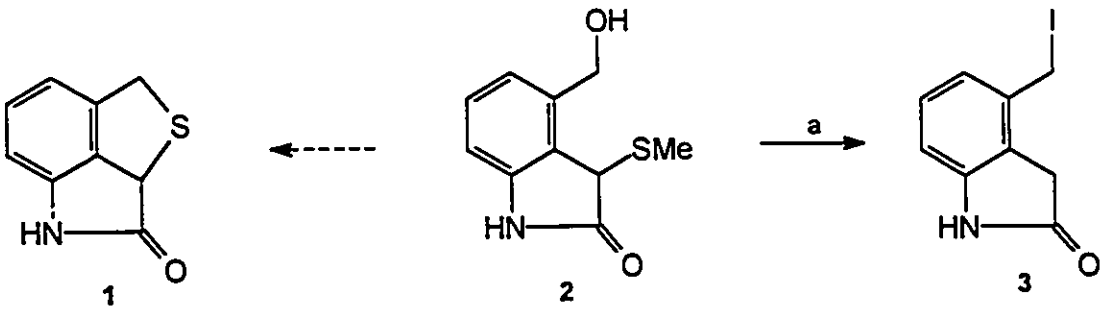
Chapter 8

Non-reductive Desulfenation of 3-Thioalkyl-2-Oxindoles

8.1 Introduction

Although Gassman's oxindole synthesis[1] is an extremely powerful method for the construction of the oxindole nucleus, the general utility of this sequence could be extended if mild conditions could be found for the removal of the necessary thioalkyl group. A survey of the literature showed that the only methods used were Raney Ni[1] and Zn[2]. Work from this laboratory had shown that Ni_2B[3, 4] worked as well as Raney Ni with the added advantages of being prepared rapidly and in situ, and being non-pyrophoric. However, all of these mentioned methods suffer from at least one serious drawback; selectivity. Although all three reagents mentioned are very powerful desulfenating reagents, they are also very powerful reducing agents, limiting the choice of substrates.

In the course of studies directed towards the synthesis of a new tricyclic heterocycle (1), acid promoted ring closure of oxindole 2 was expected to provide 1 via a sulfonium salt intermediate. However, treatment of 2 with excess TsOH and NaI in CH_2Cl_2 led to the formation of 3. Further study of this reaction has led to the development of a mild, general high yielding method for the desulfenation of 3-thioalkyl oxindoles, the results of which are presented in the remainder of this chapter.

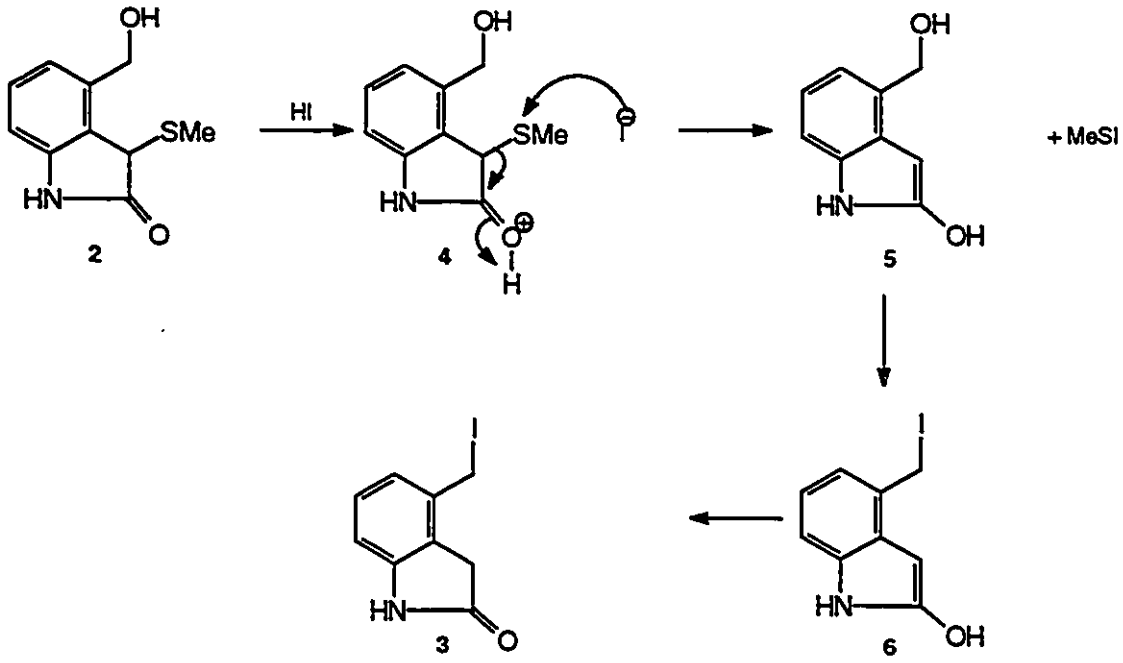


Reagents: a) TsOH, NaI, CH_2Cl_2, RT.

Scheme 8.1 - Reaction of Oxindole 2 with NaI and TsOH.

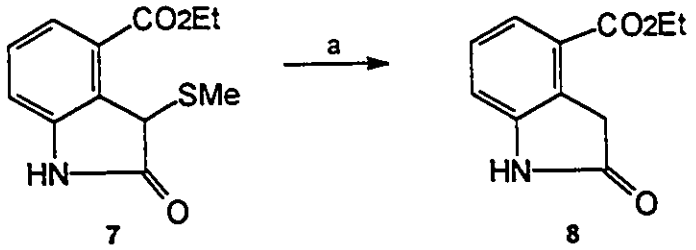
8.2 Study of the Reaction Mechanism and Design of a Reagent Pair

A mechanism to account for the unexpected convversion of 2 to 3 upon treatment with HI as shown in Scheme 8.2 was proposed: Initial addition of a proton to 2 leads to protonation of the amide carbonyl forming 4. This protonation of the carbonyl results in the activation of the sulfur substituent at C3 towards attack by a thiophile. Thus a soft nucleophile such as I^- present would generate a sulfenyl iodide and the enol 5 which can tautomerize back to the oxindole form.



Scheme 8.2 - Proposed Mechanism for Desulfenation of Oxindole 2

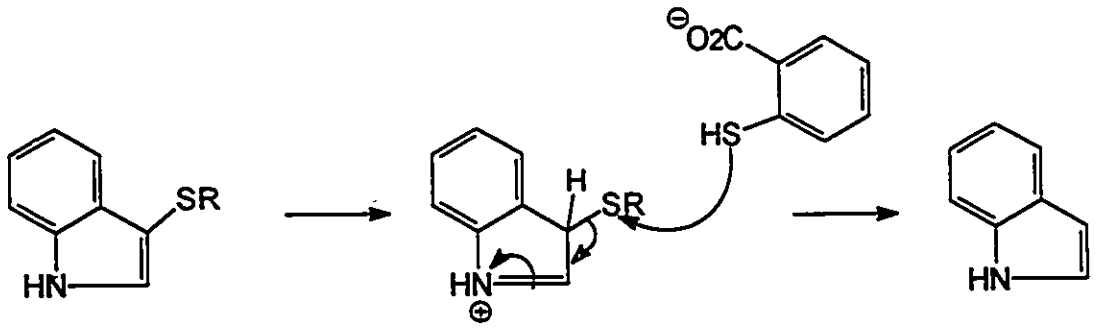
To test the generality of this reaction, oxindole 7 was subjected to the same reaction conditions as 2. When stirred with 1.5 equivalents of TsOH and NaI, 7 was rapidly converted into product 8 in a yield of 80%.



Reagents: a) TsOH, NaI, CH_2Cl_2.

Scheme 8.3 - Reaction of Oxindole 7 with TsOH and NaI.

Although using TsOH and NaI as a reagent pair resulted in excellent yields of the desulfenated products, the reaction was somewhat messy, giving I_2 and $(MeS)_2$ as by products. Inspection of the proposed mechanism showed that, in principle, all that was necessary was a proton source to cause formation of 4 from 2, and a thiophile to effect the conversion of 4 to 5. With this idea in mind, the search for another reagent pair was initiated. Workers at Merck[5] had reported on the use o-mercaptobenzoic acid as a method of desulfenating 3-thioalkyl indoles. Reaction in this case occurs by initial C3 protonation, followed by nucleophilic attack of the added sulfur nucleophile on the sulfur of the 3-thioalkyl indole.



Scheme 8.4 - Merck Methodology for Desulfenation of 3-Thioalkylindoles.

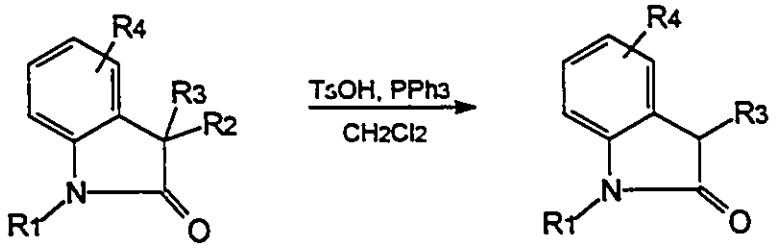
It was anticipated that a similar reaction could take place between a 3-thioalkyl oxindole and o-mercaptobenzoic acid. However, treatment of oxindole 7 with 1.5 equivalents of o-mercaptobenzoic acid

led to the quantitative recovery of starting material. Failure of this reagent to effect the desired transformation was believed to be the result of either: a) insufficient acidity of the benzoic acid moiety or b) inadequate nucleophilicity of the benzenethiol portion of the reagent. When this reaction was repeated using one equivalent of TsOH as the acidic reagent, starting material was again recovered. Since TsOH was previously shown to be acidic enough to protonate the amide carbonyl, it was concluded that the reaction failed due to the low thiophilicity of o-mercaptobenzoic acid.

Rapoport[6] had used PPh_3 as a thiophile in his modification of the Eschenmoser ring contraction[7], thus desulfenation with the reagent pair PPh_3/TsOH was attempted. Reaction of oxindole 7 with 1.5 equivalents of both PPh_3 and TsOH in CH_2Cl_2 at RT resulted in smooth and rapid conversion to the desulfenated product 8 (89% yield) after a base wash and elution through a plug of silica gel. Both the TsOH and PPh_3 were necessary to effect the desired transformation. With a reagent pair that provided the desired product cleanly and in high yields, with a relatively simple purification, a survey of the generality of this non-reductive desulfenation was carried out.

8.3 Scope of the Reaction

As can be seen from Table 8.1, the reaction is quite general and high yielding. The reaction worked well for both 3- thiomethyl and thiobenzyl substituents (entries 1 and 2). Desulfinylation also occurred in acceptable yields (entry 10), but desulfonylation could not be carried out (entry 11). Presumably, the reaction failed because the nucleophile (PPh_3) was too soft to react at the sulfone center, a hard electrophilic site.



Entry	R_1	R_2	R_3	R_4	Yield (%)	Conditions/ Notes
1	H	SMe	H	4-CO_2Et	87	a
2	H	SBn	H	4-CO_2Et	97	a
3	Me	SMe	H	4-CO_2Et	85	a
4	Me	SMe	H	4-Me	97	a
5	H	SMe	Me	6-CO_2Et	89	a
6	Me	SMe	Me	4-CO_2Et	98	b
7	H	SMe	H	5-Br	93	a
8	H	SMe	H	4-NO_2	90	a
9	Allyl	SMe	Allyl	4-CO_2Et	87	b
10	Propargyl	SMe	Propargyl	4-CO_2Et	85	b
11	H	SOMe	H	4-CO_2Et	76	a
12	H	SO_2Me	H	4-CO_2Et	0	d
13	H	SMe	H	7-CH_2OH	0	c
14	H	SBn	H	4-CO_2Et	80	e

a) RT; b) Reflux; c) no products identified; d) recovered starting material; e) polymer bound PPh_3 used.

Table 8.1 - Summary of Non-Reductive Desulfenation Results

The reaction proceeded well for both 1- and 3-alkyl substituted oxindoles, as shown by entries 3 through 5. For 1,3-dialkyl substituted oxindoles (entries 6, 9 and 10), the reaction was somewhat sluggish at RT, being only 70% complete after 24 h. The reaction, when conducted in refluxing CH_2Cl_2, was rapid and high yielding, providing the desulfenated product in near quantitative yield after 2 h (entry 6). The reaction was also relatively insensitive to the nature of the substituent on the benzene ring, tolerating alkyl groups and acyl groups, the only exception being entry 13. In this case, the benzylic alcohol was also susceptible to reaction with the nucleophile under acidic conditions, leading to, presumably, a phosphonium salt, since no organic material was isolated following standard work up.

The utility of the methodology was best illustrated by entries 7-10. As shown by the high yields of the reaction, easily reduced groups such as halogens, nitro, and isolated double bonds are not touched under the reaction conditions.

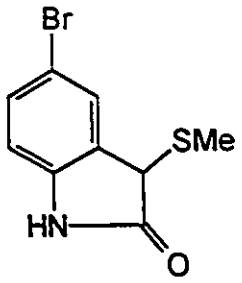
In the case of entry 14, polymer bound PPh_3 was used. It was hoped that the work up would become even easier, since filtering would remove the excess PPh_3 and the by-product. However, use of this reagent did not offer any advantages. The reaction was much slower with the polymer bound phosphine, which was acceptable, but a small amount of the polymer always remained in solution, making chromatography necessary. Due to these difficulties, recourse was made to the $TsOH/PPh_3$ pair which worked best.

8.4 Experimental

General

For general experimental, see the experimental section of chapter 3. All starting oxindoles were prepared as described in chapter 7, except 3-thiomethyl-4-nitro-2-oxindole, which was prepared according to Gassman[1] and those noted below.

3-Thiomethyl-5-bromo-2-oxo-2,3-dihydroindole



A solution of tBuOCl (0.63 g, 5.82 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a cooled (-78 °C) solution of 4-bromoaniline (1.00 g, 5.82 mmol) in CH_2Cl_2 (50 mL). The resulting yellow solution was stirred at -78 °C for 15 min, after which time a solution of methyl (methylthio)acetate (0.70 g, 5.82 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The yellow solution was stirred for 1 h, then a solution of triethylamine (0.59 g, 5.82 mmol) in CH_2Cl_2 (5 mL) was added, and the resulting solution was allowed to warm to RT over a period of 16 h. The dark red solution was poured into H_2O (50 mL) separated and concentrated to dryness. The residue was dissolved in Et_2O (100 mL) and HCl (10%, 25 mL) was added and the solution refluxed for 2 h. Separation of the organic phase followed by usual work up afforded a pale yellow solid (500 mg, 33%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 3H), 4.29 (s, 1H), 6.82 (d, 1H, J=8.2 Hz), 7.42 (dd, 1H, J=8.2, 1.0 Hz), 7.52 (d, 1H, J=1.0 Hz), 9.00 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.15, 46.35, 111.44, 115.68, 128.44, 132.01, 140.25, 177.08 ppm.

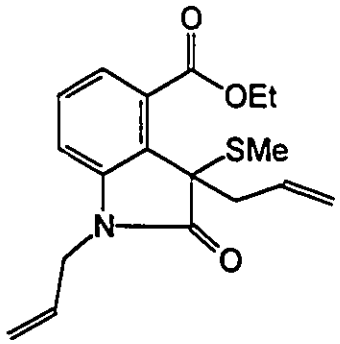
IR (CH_2Cl_2): 1726 cm^{-1}.

EI-MS (m/z, %): 259 (M^{+}+2, 17.5), 257 (M^{+}, 16.8), 211 (100), 213 (97.9), 182 (15.2).

HRMS: Calc for C_9H_8NOSBr: 256.95099; Found: 256.95057.

mp: 174.0-175.0 °C.

3,3-Di(3-propenyl)-3-thiomethyl-2-oxo-2,3-dihydroindole.



A solution of freshly prepared LDA (2.1 equiv.) in THF was added dropwise to a cooled (-78 °C) solution of 3-thiomethyl-4-carboethoxy-2-oxo-2,3-dihydroindole (100 mg, 0.40 mmol) in THF (10 mL). Stirring was continued for 1 h, after which time a solution of allyl bromide (145 mg, 1.20 mmol) in THF (5 mL) was added dropwise. The resulting solution was allowed to slowly rise to RT over 12 h, then poured into H_2O (50 mL) and extracted with Et_2O (4 x 20 mL). The combined organic extracts were worked up in the usual manner affording, after chromatography (7:1 Hex:EtOAc), the title compound as a pale yellow oil (110 mg, 83%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.35 (t, 3H, J=7.5 Hz), 1.80 (s, 3H), 2.80 (dd, 1H, J=16.0, 11.0 Hz), 3.50 (dd, J=16.0, 11.0 Hz), 4.20 (m, 1H), 4.35 (m, 3H), 4.80 (dd, 1H, J=11.0, 1.0 Hz), 5.00 (dd, 1H, J=18.0, 1.0 Hz), 5.15 (m, 2H), 5.25 (m, 1H), 5.80 (m, 1H), 6.80 (dd, 1H, J=8.0, 1.0 Hz), 7.25 (t, 1H, J=8.0 Hz), 7.60 (dd, 1H, J=8.0, 1.0 Hz) ppm.

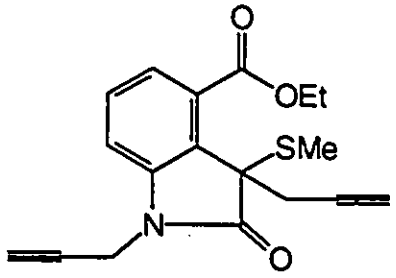
^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.01, 14.23, 39.04, 42.49, 55.45, 61.40, 112.07, 117.78, 118.99, 124.41, 128.63, 128.67, 129.52, 130.96, 132.03, 143.43, 166.05, 175.77 ppm.

IR (CH_2Cl_2): 1719 cm^{-1}.

EI-MS (m/z, %): 331 ($M^{+\cdot}$, 8.6), 285 (87.5), 244 (49.5), 41 (100).

HRMS: Calc. for $C_{18}H_{21}NO_3S$: 331.12422; Found: 331.12528.

3,3-Di(3-propynyl)-3-thiomethyl-2-oxo-2,3-dihydroindole.



A solution of freshly prepared LDA (2.1 equiv.) in THF was added dropwise to a cooled (-78 °C) solution of 3-thiomethyl-4-carbocthoxy-2-oxo-2,3-dihydroindole (100 mg, 0.40 mmol) in THF (10 mL). Stirring was continued for 1 h, after which time a solution of propargyl bromide (150 mg, 80% wt. in toluene, 1.00 mmol) in THF (5 mL) was added dropwise. The resulting solution was allowed to slowly rise to RT over 12 h, then poured into H_2O (50 mL) and extracted with Et_2O (4 x 20 mL). The combined organic extracts were worked up in the usual manner affording, after chromatography (7:1 Hex:EtOAc), the title compound as a pale yellow solid (105 mg, 81%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.41 (t, 3H, J=7.0 Hz), 1.65 (t, 1H, 2.6 Hz), 2.15 (s, 3H), 2.21 (t, 1H, J=2.5 Hz), 3.00 (dd, 1H, J=16.0, 2.5 Hz), 3.80 (dd, 1H, J=16.0, 2.5 Hz), 4.38 (q, 2H, J=7.0 Hz), 4.45 (dd, 1H, J=16.0, 2.5 Hz), 4.68 (1H, J=16.0, 2.5 Hz), 7.22 (dd, 1H, J=8.0, 1.0 Hz), 7.42 (t, 1H, J=8.0 Hz), 7.70 (1H, dd, J=8.0, 1.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.28, 14.19, 25.09, 29.59, 30.87, 54.42, 61.49, 70.50, 72.58, 76.42, 78.39, 112.51, 125.30, 128.81, 129.04, 142.78, 165.51, 174.64 ppm.

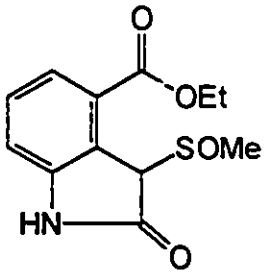
IR (CH_2Cl_2): 3303, 1727 cm^{-1}.

EI-MS (m/z, %): 327 ($M^{+\bullet}$, 12.3), 281 (100).

HRMS: Calc. for $C_{18}H_{17}NO_3S$: 327.09292; Found: 327.09347.

mp: 105.4 °C.

3-Thiomethyl-4-carboethoxy-2-oxo-2,3-dihydroindole-S-oxide.



To a cooled (-78 °C) solution of 3-thiomethyl-4-carboethoxy-2-oxo-2,3-dihydroindole (150 mg, 0.60 mmol) in CH_2Cl_2 (15 mL) was added in one portion mCPBA (121 mg, 85%, 0.60 mmol). The resulting mixture was stirred and slowly allowed to reach RT. After 12 h, H_2O (10 mL) was added, and the organic phase separated and washed with sodium bisulfite (10%, 2x10 mL) and sodium bicarbonate (10%, 2x10 mL). Usual work up afforded a slighly reddish solid which was triturated with cold (0 °C) Et_2O (2 mL) and filtered, providing the title compound as a white solid (88 mg, 62%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7.0 Hz), 3.05 (s, 3H), 4.25 (q, 2H, J=7.0 Hz), 4.85 (s, 1H), 6.95 (d, 1H, J=7.5 Hz), 7.30 (t, 1H, J=7.5 Hz), 7.65 (d, 1H, J=7.5 Hz), 8.20 (br, 1H) ppm.

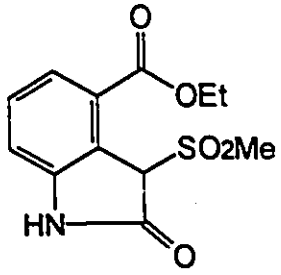
^{13}C-NMR (75 MHz, $CDCl_3$): 13.88, 35.58, 61.04, 64.24, 114.19, 123.53, 123.92, 126.64, 129.66, 143.60, 165.13, 169.98 ppm.

IR (CH_2Cl_2): 3400, 1716, 1029 cm^{-1}.

EI-MS (m/z, %): 267 ($M^{+\cdot}$, 0.6), 205 (100).

mp: 149.0-149.5 °C.

3-Thiomethyl-4-carbocthoxy-2-oxo-2,3-dihydroindole-S,S-dioxide.



To a cooled (0 °C) solution of 3-thiomethyl-4-carbocthoxy-2-oxo-2,3-dihydroindole (150 mg, 0.60 mmol) in CH_2Cl_2 (15 mL) was added in one portion mCPBA (240 mg, 85%, 1.20 mmol). The resulting mixture was stirred and slowly allowed to reach RT. After 12 h, H_2O (10 mL) was added, and the organic phase separated and washed with sodium bisulfite (10%, 2x10 mL) and sodium bicarbonate (10%, 2x10 mL). Usual work up afforded a slightly reddish solid which was triturated with cold (0 °C) Et_2O (2 mL) and filtered, providing the title compound as a white solid (85 mg, 50%).

^{1}H-NMR (200 MHz, $CDCl_3$): 1.35 (t, 3H, J=7.0 Hz), 3.20 (s, 3H), 4.35 (q, 2H, J=7.0 Hz), 5.45 (s, 1H), 7.00 (d, 1H, J=8.0 Hz), 7.40 (t, 1H, J=8.0 Hz), 7.60 (d, 1H, J=8.0 Hz), 7.80 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): 14.03, 39.70, 61.46, 67.86, 113.37, 117.36, 124.06, 130.76, 131.13, 143.14, 164.38, 169.23 ppm.

IR (CH_2Cl_2): 3400, 1716, 1330, 1110 cm^{-1}.

EI-MS (m/z, %): 283 ($M^{+\cdot}$, 5.6), 238 (1.2), 204 (100), 176 (19.0).

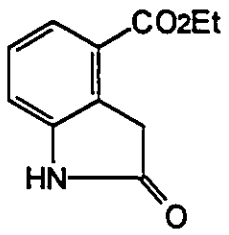
HRMS: Calc. for $C_{12}H_{13}NO_5S$: 283.05144; Found: 283.05114.

mp: 156.3-157.0 °C.

General Procedure for Non-Reductive Desulfenation.

A solution of oxindole (1.00 mmol) in CH_2Cl_2 (10 mL) was stirred at RT as PPh_3 (1.10 mmol) and TsOH (1.10 mmol) were added. The resulting solution was stirred at RT, except for 1,3-disubstituted substrates, in which cases the reaction mixtures were refluxed, until tlc showed complete consumption of starting material. The solution was washed with H_2O (2 x 5 mL) and $NaHCO_3$ (2 x 5 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed.

4-Carboethoxy-2-oxo-2,3-dihydroindole



^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.5 Hz), 3.86 (s, 2H), 4.36 (q, 2H, J=7.5 Hz), 7.05 (d, 1H, J=6.5 Hz), 7.30 (t, 1H, J=6.5 Hz), 7.70 (d, 1H, J=6.5 Hz), 8.50 (br, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.30, 37.97, 61.14, 113.52, 123.58, 126.85, 127.47, 127.9, 143.27, 165.83, 177.91 ppm.

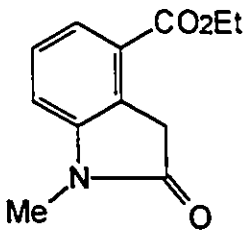
IR (CH_2Cl_2): 1719, 3430 cm^{-1}.

EI-MS (m/z,%): 205 ($M^{+\cdot}$, 100), 176 (35.0), 160 (33.8).

HRMS: Calc. for $C_{11}H_{11}NO_3$: 205.07389; Found: 205.07317.

mp: 181.3-182.1 °C (white solid).

1-Methyl-4-carbocthoxy-2-oxo-2,3-dihydroindole



^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.37 (t, 1H, J=7.0 Hz), 3.22 (s, 3H), 3.82 (s, 2H), 4.33 (q, 2H, J=7.0 Hz), 6.94 (d, 1H, J=8.0 Hz), 7.31 (t, 1H, J=8.0 Hz), 7.68 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.31, 26.28, 37.47, 61.14, 111.64, 123.46, 126.61, 126.88, 127.97, 145.97, 165.85, 175.11 ppm.

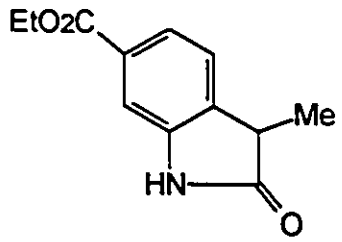
IR(CH_2Cl_2): 1714 cm^{-1}.

EI-MS (m/z, %): 219 ($M^{+\cdot}$, 100), 190 (63.4), 173 (31.8), 146 (27.6).

HRMS: Calc. for $C_{12}H_{13}NO_3$: 219.08954; Found: 219.08867.

mp: 108.0-108.5 °C (white solid).

3-Methyl-6-carbocthoxy-2-oxo-2,3-dihydroindole



^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.37 (t, 3H, J=7.0 Hz), 1.51 (dd, 3H, J=7.0 Hz), 3.49 (q, 1H, J=7.0 Hz), 4.35 (q, 2H, J=7.0 Hz), 7.25 (d, 1H, J=8.0 Hz), 7.55 (s, 1H), 7.75 (d, 1H, J=8.0 Hz), 8.60 (br, 1H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.32, 15.01, 41.11, 61.17, 110.32, 123.62, 124.25, 130.42, 136.23, 141.30, 166.21, 180.71 ppm.

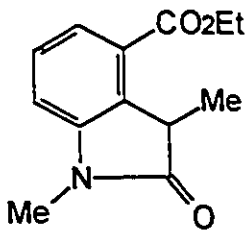
IR (CH_2Cl_2): 1720 cm^{-1}.

EI-MS (m/z, %): 219 ($M^{+\cdot}$, 100), 174 (55.3), 146 (76.3).

HRMS: Calc. for $C_{12}H_{13}NO_3$: 219.08954; Found: 219.08968.

mp: 135.3-136.2 °C (white solid).

1,3-Dimethyl-4-Carboethoxy-2-oxo-2,3-dihydroindole.



^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.43 (t, 3H, J=7.0 Hz), 1.49 (d, 3H, J=7.0 Hz), 3.22 (s, 3H), 3.85 (q, 1H, J=7.0 Hz), 4.38 (q, 2H, J=7.0 Hz), 6.98 (d, 1H, J=7.5 Hz), 7.35 (t, 1H, J=7.5 Hz), 7.65 (d, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.17, 16.22, 26.28, 41.93, 61.13, 111.62, 123.73, 126.90, 127.86, 132.71, 144.96, 165.82, 178.92 ppm.

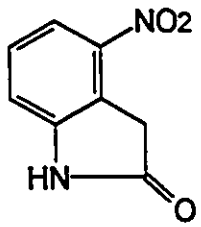
IR (CH_2Cl_2): 1714 cm^{-1}.

EI-MS (m/z, %): 233 ($M^{+\bullet}$, 100), 204 (39.5), 188 (31.7), 160 (89.7).

HRMS: Calc. for $C_{13}H_{15}NO_3$: 233.10519; Found: 233.10528.

mp: 70.0-70.5 °C (pale yellow solid).

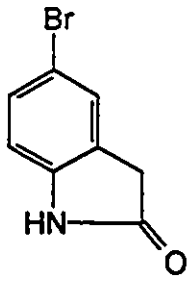
4-Nitro-2-oxo-2,3-dihydroindole



^{1}H-NMR (200 MHz, $CDCl_3$): 4.00 (s, 2H), 7.15 (d, 1H, J=8.0 Hz), 7.40 (t, 1H, J=8.0 Hz), 7.89 (d, 1H, J=8.0 Hz), 8.30 (br, 1H) ppm.

mp: 156.3-157.0 °C (white solid).

5-Bromo-2-oxo-2,3-dihydroindole



^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.45 (s, 2H), 6.73 (d, 1H, J=7.5 Hz), 7.32 (m, 2H), 8.00 (br, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 35.91, 110.87, 114.95, 127.26, 127.88, 130.82, 141.24, 176.24 ppm.

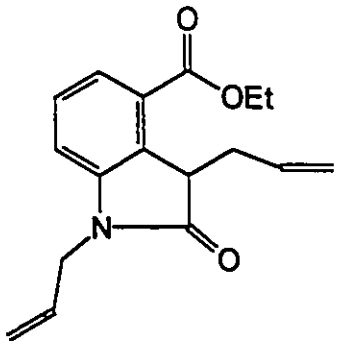
IR (CH_2Cl_2): 1714 cm^{-1}.

EI-MS: (m/z, %): 213 (M^{+}+2, 98.2), 211 (M^{+}, 100), 132 (14.2).

HRMS: Calc. for C_8H_6BrNO: 210.96327; Found: 210.96311.

mp: 220 °C (white solid).

3,3-Di(3-propenyl)-2-oxo-2,3-dihydroindole.



^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.0 Hz), 2.85 (m, 1H), 2.95 (m, 1H), 4.03 (m, 1H), 4.21 m, 1H), 4.38 (q, 2H), 4.45 (m, 1H), 4.83 (dd, 1H, J=14.0, 1.0 Hz), 4.94 (dd, 1H, J=14.0, 1.0 Hz), 5.15 (m, 1H), 5.20 (m, 1H), 5.35 (m, 1H), 5.75 (m, 1H), 6.80 (d, 1H, J=7.5 Hz), 7.20 (t, 1H, J=7.5 Hz), 7.80 (d, 1H, J=7.5 Hz) ppm.

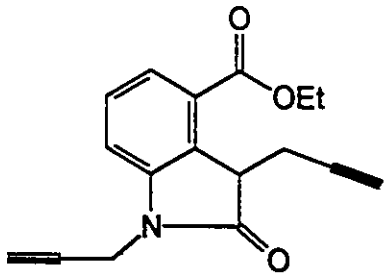
^{13}C-NMR (125 MHz, $CDCl_3$): 14.21, 34.53, 42.22, 46.69, 61.16, 112.41, 117.56, 118.28, 123.68, 127.22, 127.89, 130.13, 131.23, 132.64, 144.70, 165.92, 177.13 ppm.

IR (CH_2Cl_2): 1712 cm^{-1}.

EI-MS (m/z, %): 285 ($M^{+\cdot}$, 36.3), 240 (53.2), 212 (100).

HRMS: Calc. for $C_{17}H_{19}NO_3$: 285.13649; Found: 285.13655.

3,3-Di(3-propynyl)-2-oxo-2,3-dihydroindole.



^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.5 Hz), 1.60 (t, 1H, J=2.5 Hz), 2.10 (t, 1H, J=2.5 Hz), 3.03 (m, 1H), 3.22 (m, 1H), 4.00 (t, 1H, J=2.5 Hz), 4.36 (q, 2H, J=7.5 Hz), 4.55 (m, 2H), 7.20 (d, 1H, J=7.5 Hz), 7.40 (t, 1H, J=7.5 Hz), 7.80 (d, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.20, 20.11, 29.25, 45.30, 61.28, 70.29, 72.38, 76.61, 78.77, 112.79, 124.27, 127.10, 128.49, 129.34, 144.17, 165.59, 175.70 ppm.

IR (CH_2Cl_2): 3303, 1719 cm^{-1}.

CA: Calc. for $C_{17}H_{15}NO_3$: C (72.58), H (5.37), N (4.98); Found: C (72.55), H (5.55), N (4.75).

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4) a) Back, T.G. *J. Chem. Soc., Chem. Commun.*, **1984**, 1417.
b) Back, T.G.; Yang, K.; Krouse, H.R. *J. Org. Chem.*, **1992**, *57*, 1986.

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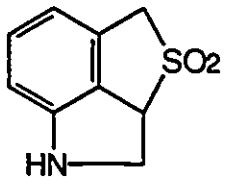
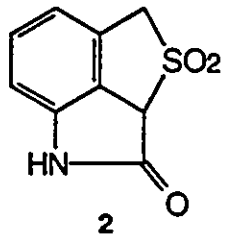
Chapter 9
Photochemically Generated Bicyclic ortho-Quinodimethanes

9.1 Introduction

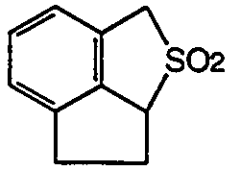
Due to the problems associated with the synthesis of a bicyclic o-quinodimethane precursor containing an indole nucleus, the direction of research was changed. Evaluation of research done to date had shown that although a number of interesting studies had been conducted and some unusual behavior uncovered and new methodology developed, major questions remained. Can a 6-5-5 tricyclic ring system such as **1**, **2** or **3** be prepared, and if so, can it be used to generate o-quinodimethanes?



1



2

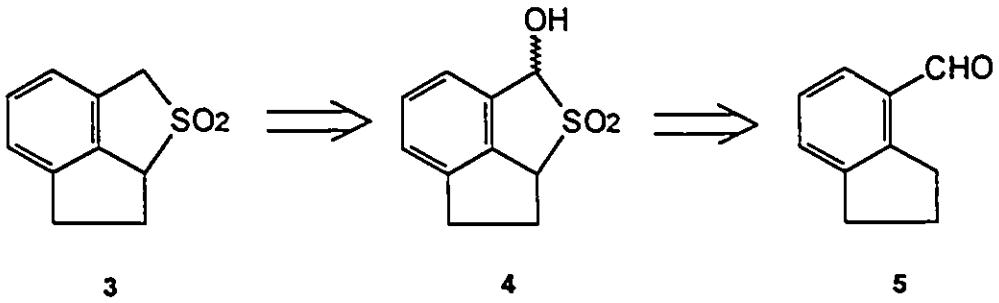


3

Since considerable effort had been invested in exploring routes to **1** and **2**, it was decided to investigate routes to **3**. Since **3** was a derivative of the dihydroindene skeleton, one problem associated with the synthesis of **1** and **2**, aromatization to the indole ring system, would not be encountered in the synthesis of **3**.

9.2 Photoenolization Strategy to 3

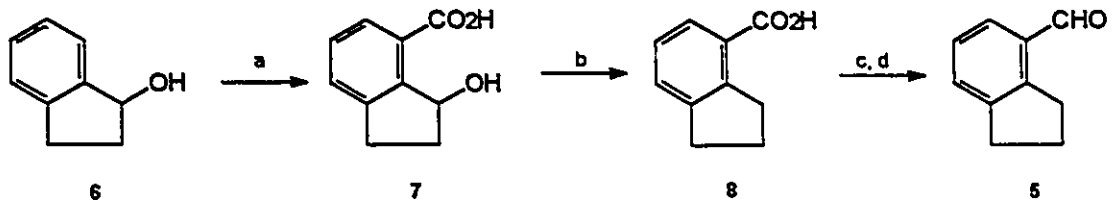
A synthetic route to **3** was devised. This sequence relied on the successful trapping of the photoenol of **5** with SO_2 and is shown retrosynthetically in Scheme 9.1.



3 4 5

Scheme 9.1 - Retrosynthetic Analysis of Tricyclic Sulfone 3

The aldehyde 5 had been reported in the literature[2], although its synthesis was not selective, and resulted in a mixture of isomers that had to be carried through a number of steps before separation could be achieved. To circumvent these problems, a new synthesis of 5 was developed and is shown in Scheme 9.2.



6 7 8 5

Reagents: a) (i)2.2 nBuLi, TMEDA, Pentane,Δ; (ii) CO_2 (s); (iii) HCl (65%); b) H_2, 10% Pd/C, HOAc (90%); c) $LiAlH_4$, THF, Δ (90%); d) MnO_2, CH_2Cl_2, Δ (93%).

Scheme 9.2 - Synthesis of Aldehyde 5

Alkoxide directed ortho-metallation of 1-indanol using the conditions described by Seebach[3], followed by a low temperature quench of the di-anion with CO_2 afforded the carboxylic acid 7 as a white solid (mp 128 °C) in an overall yield of 65%. Hydrogenolysis of the benzylic alcohol to the acid 8 (mp 150 °C) was best accomplished by bubbling H_2 through a solution of hydroxy-acid 7 in glacial HOAc in the presence of a catalytic amount of 10% Pd/C. Finally, the desired aldehyde 5 was obtained via a two step sequence consisting of $LiAlH_4$ mediated reduction, followed by MnO_2 oxidation. Aldehyde 5,

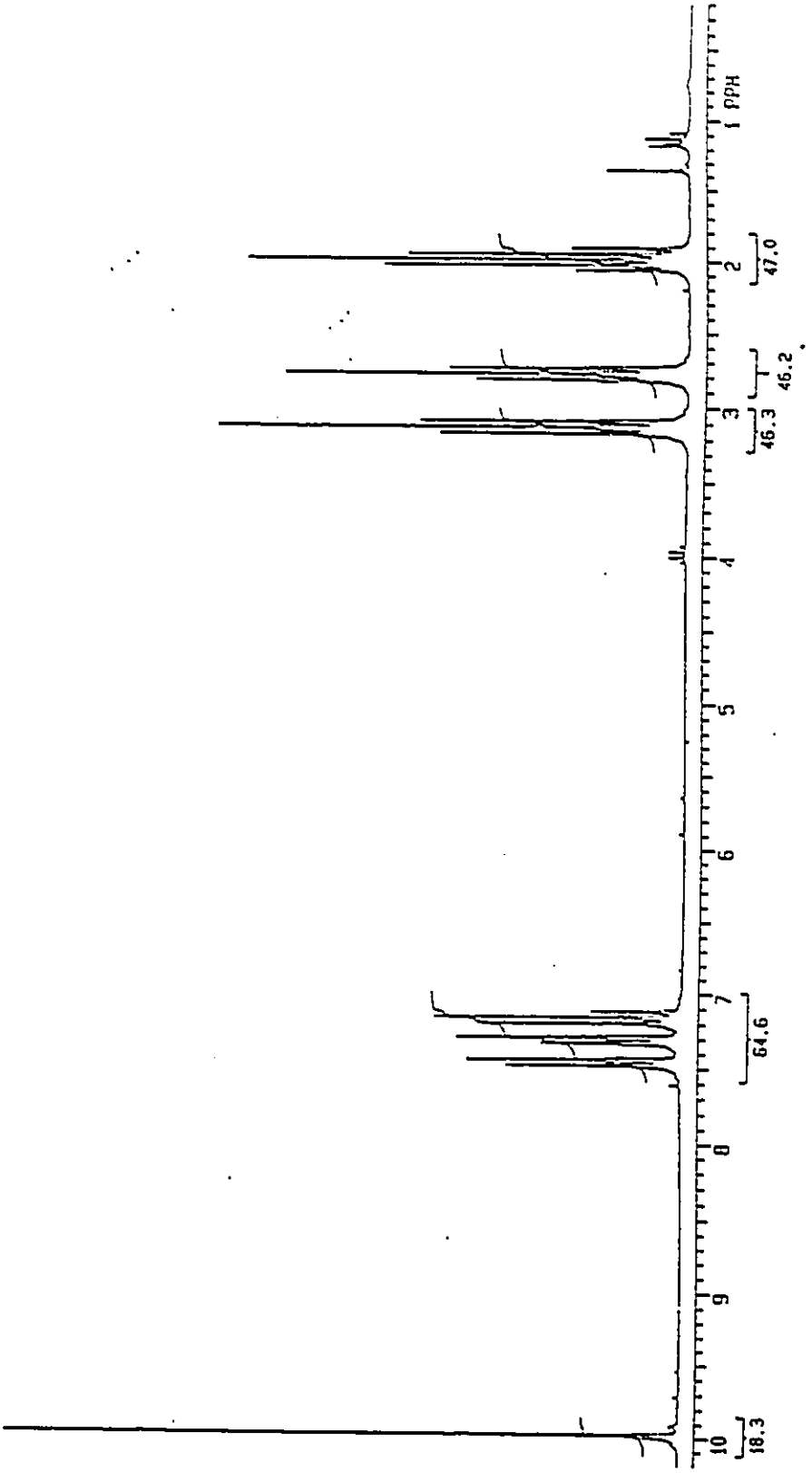


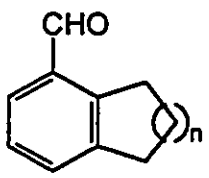
Figure 9.1 200 MHz ^{1}H-NMR Spectrum of Aldehyde 5 in $CDCl_3$

isolated as a clear oil in yields greater than 90%, was identified on the basis of its ^{1}H-NMR spectrum (Fig. 9.1), which showed a sharp singlet at 9.97 ppm, a quintet and two triplets for the aliphatic protons at 1.98, 2.77 and 3.12 ppm respectively, and a pattern in the aromatic region indicative of a 1,2,3-trisubstituted benzene.

Irradiation of a solution of aldehyde 5 in benzene in the presence of SO_2[5] led only to recovered starting material, and carboxylic acid 8. With the envisioned route to 4 and 5 failing in the key step, the focus of the current study was modified once again. At this point, it was not known if the desired aldehyde 5 would form an enol under irradiation conditions. It was then decided to synthesize a number of compounds related to 5 and enlist the help of Professor Tito Scaiano. Professor Scaiano's group has made significant contributions in the field of laser flash photolysis, particularly in the area of studying photo-enols[6]. The goal of this research was gain a better understanding of the geometric factors influencing photo-enolization. At the time of the writing of this thesis, these studies are still in progress. What follows is a report on the synthesis of a number of putative photo-enol precursors, and the results of trapping experiments using classical dieneophiles.

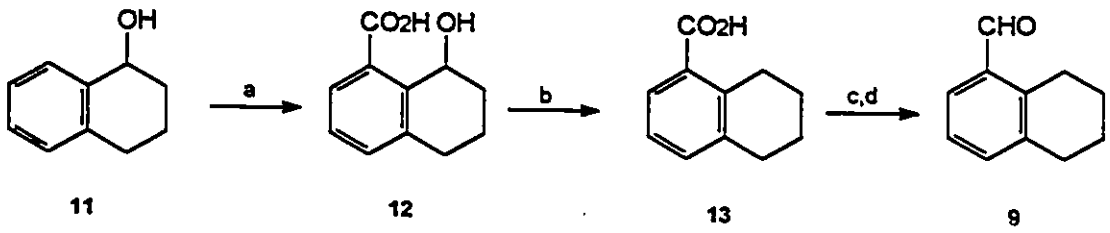
9.3 Other Bicyclic Aldehydes

Since the goal of this research was to identify the effects of imposing physical constraints on the photo-enol precursors, a series of compounds was desired that had a predictable differences in the angle and distance between the reactive carbonyl center and the γ-hydrogen. It was believed that a series of compounds that differed only in the number of methylene units in the saturated ring would best fit this criterion, i.e. **5, 9** and **10.**



5; n=1
9; n=2
10; n=3

The synthesis of 9 was accomplished in a manner identical to the synthesis of 5, except that 1,2,3,4-tetrahydro-1-napthol was the starting material. This synthesis is shown in Scheme 9.3.



11 12 13 9

Reagents: a) (i)2.2 nBuLi, TMEDA, Pentane,Δ; (ii) CO_2 (s); (iii) HCl (70%); b) H_2, 10% Pd/C, HOAc (75%); c) $LiAlH_4$, THF, Δ (87%); d) MnO_2, CH_2Cl_2, Δ (78%).

Scheme 9.3 - Synthesis of Aldehyde 9

Again, all intermediates in Scheme 9.3 had spectroscopic properties consistent with the proposed structures. Key ^{1}H-NMR resonances for aldehyde 9 (Fig. 9.2), which was isolated as a clear oil after column chromatography, included the aromatic pattern, which was typical of a 1,2,3-trisubstituted benzenoid aromatic, a singlet at 10.15 ppm indicative of the aldehyde, and a multiplet at 1.65 ppm accounting for 4 protons and two triplets at 2.73 and 3.10 ppm, each representing two protons.

With a secure route to aldehydes 5 and 9, attention was turned towards the synthesis of aldehyde 10. The benzylic alcohol 15 was prepared in near quantitative yield via a standard $LiAlH_4$ reduction from commercially available benzosuberone 14. Ortho-metallation with nBuLi/TMEDA and quenching with CO_2 followed by acidic work up afforded lactone 16 as a white crystalline solid (mp 74.8 °C) in a 75% yield. However, lactone 16 could not be converted to acid 17 via hydrogenolysis[7].

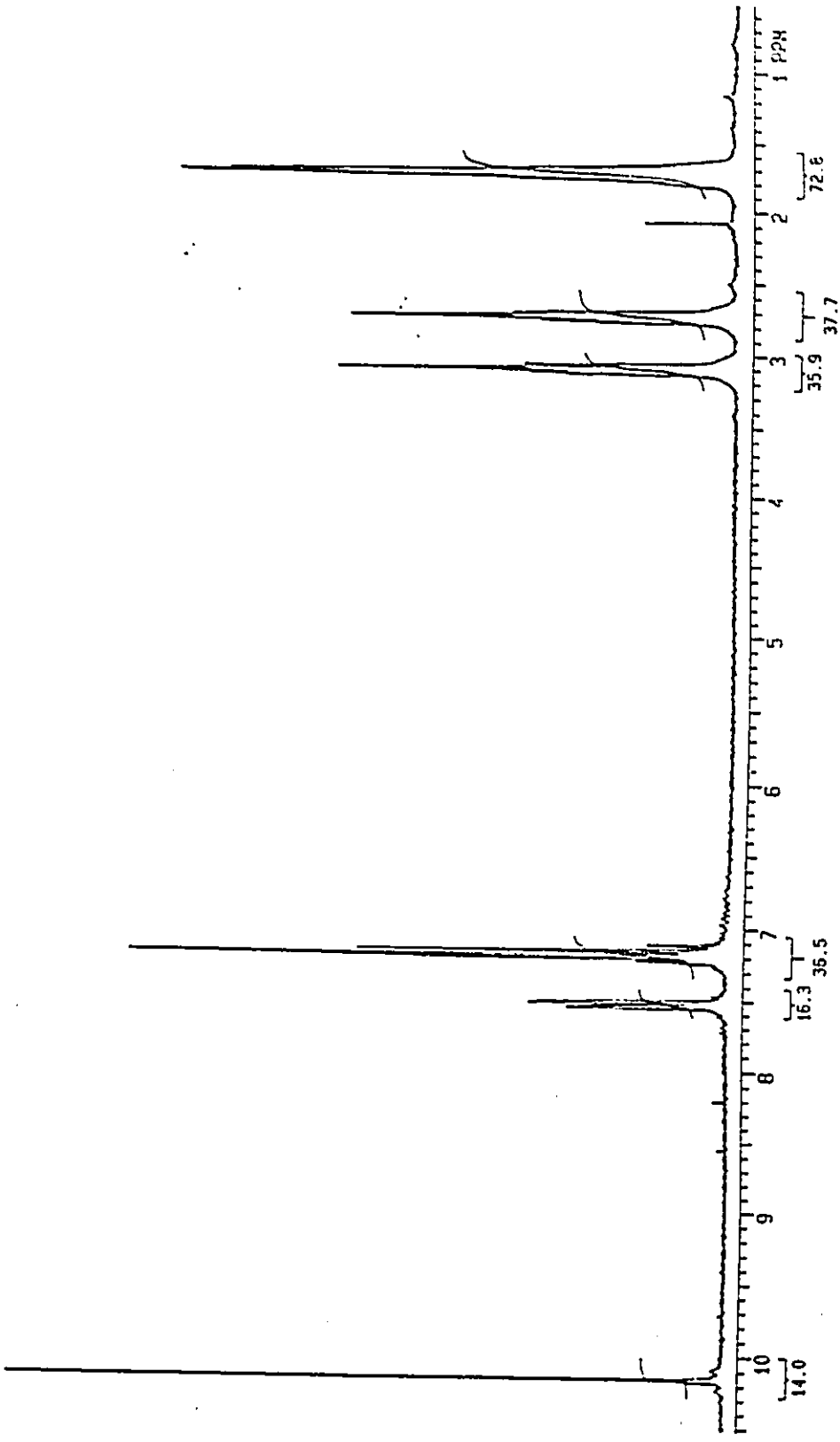
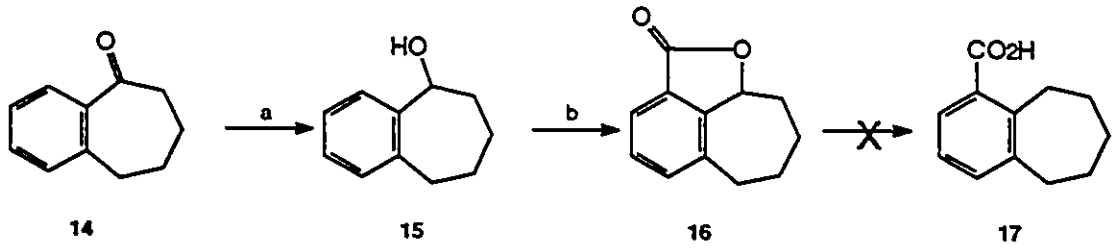


Figure 9.2 200 MHz ^{1}H-NMR Spectrum of Aldehyde 9 in $CDCl_3$



Scheme 9.4 - Attempted Synthesis of Acid **17** from Alcohol **15**

After investigating a number of alternative routes in the hope of converting **16** to **17**, this route was abandoned and a longer sequence was adopted. Reduction of lactone **16** to diol **18** (white solid, mp 77 °C) was accomplished in 89% yield with $LiAlH_4$. Protection of the primary benzylic alcohol with TBDMSCl[8] proceeded in quantitative yield affording **19** as a white solid (mp 62 °C). Activation of the secondary benzylic alcohol with Ts_2O and pyridine in CH_2Cl_2 generated the alkene **20**, which was characterized solely on the basis of its ^{1}H-NMR which showed a doublet at 6.60 ppm and a doublet of triplets at 6.15 ppm accounting for the olefinic protons. Hydrogenation of **20** followed by deprotection of the silyl ether with TBAF[9] in THF afforded alcohol **22** as a clear oil in 85% yield after chromatography. Oxidation to aldehyde **10** was accomplished in 80% yield with PDC[10] in CH_2Cl_2. Aldehyde **10** was isolated as a clear oil and had spectroscopic properties consistent with its structure. Its ^{1}H-NMR spectrum is shown in Fig. 9.3.

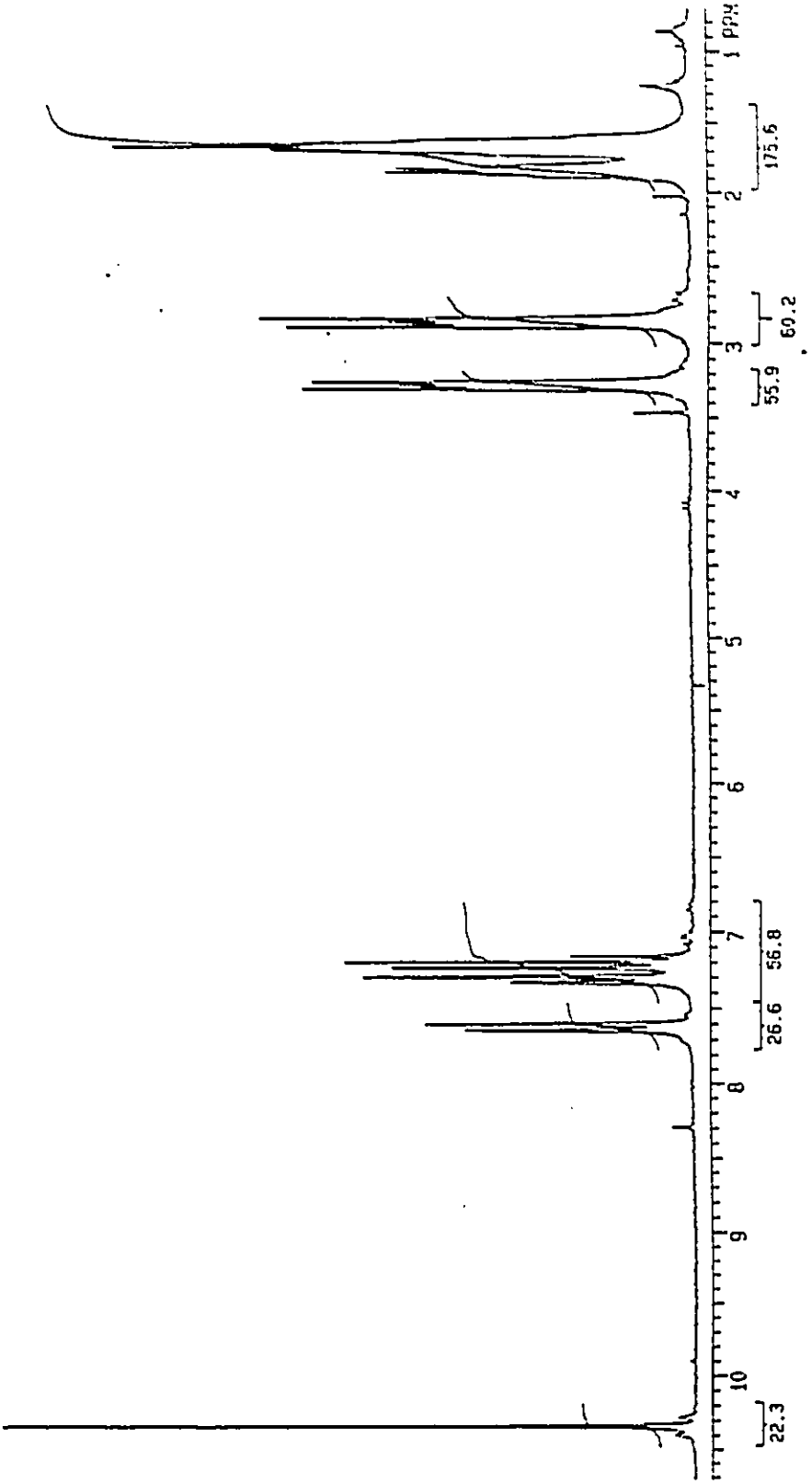
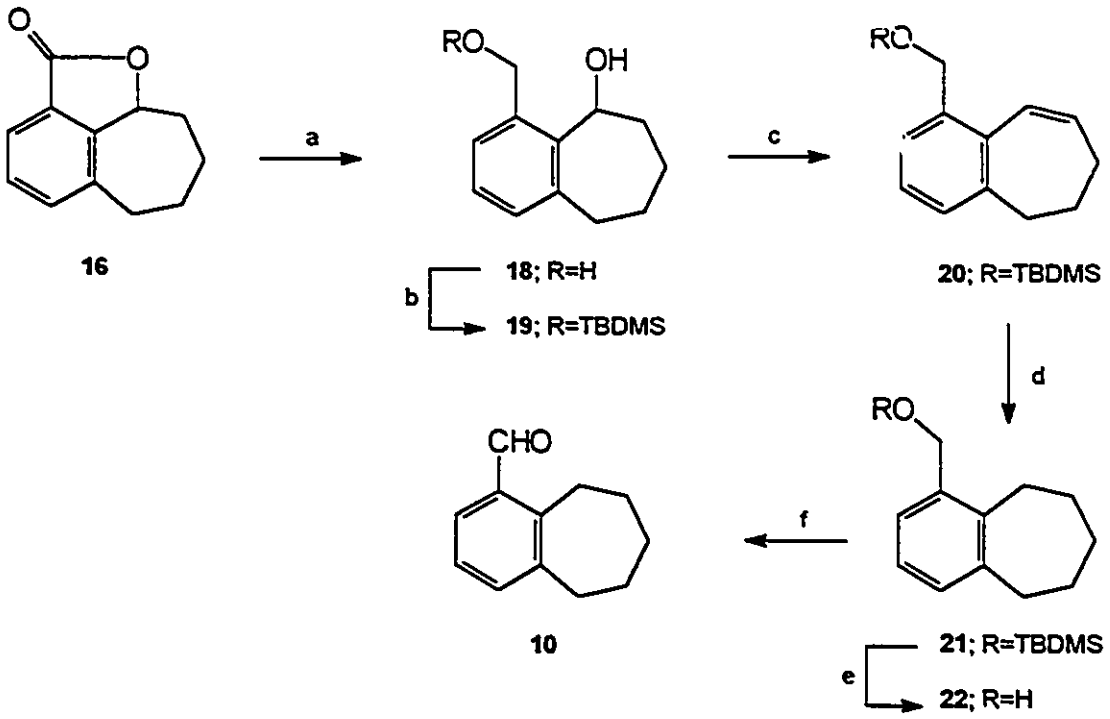


Figure 9.3 200 MHz ^{1}H-NMR Spectrum of Aldehyde 10 in $CDCl_3$

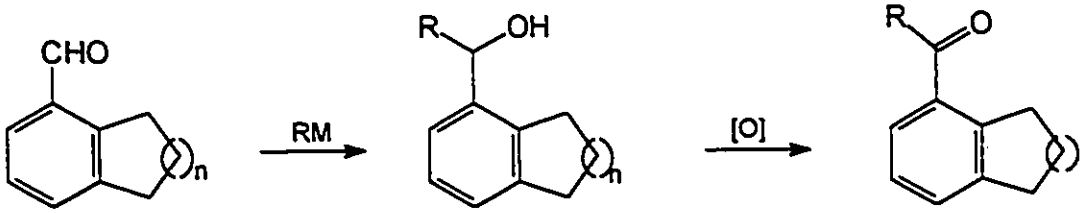


Reagents: a) $LiAlH_4$, THF, Δ (89%); b) TBDMSCl, Et_3N, DMAP, CH_2Cl_2 (>95%); c) Ts_2O, pyr, DMAP, CH_2Cl_2 (85%); d) H_2, 10% Pd/C, MeOH (83%); e) TBAF, THF (85%); f) PDC, CH_2Cl_2 (80%).

Scheme 9.5 - Synthesis of Aldehyde **10**

9.4 Synthesis of Bicyclic Ketones

As part of the laser flash photolysis study, accessibility to the methyl, phenyl and pentafluorophenyl ketones was desirable. These compounds were prepared via a two-step sequence involving addition of a Grignard reagent or organolithium to the aldehydes, followed by oxidation of the generated secondary alcohol to the desired ketone. This general sequence is shown in Scheme 9.6.



5; n=1
9; n=2
10; n=3

a; R=Me
b; R=Ph
c; R=Pf

23; n=1
24; n=2
25; n=3

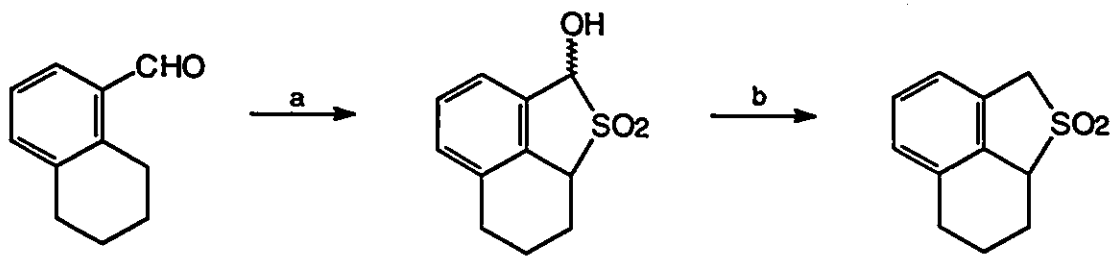
Scheme 9.6 - Synthesis of Bicyclic Ketones

Acetophenone derivatives **23a**, **24a**, and **25a** were prepared by dropwise addition of MeMgBr (Aldrich) to a THF solution of the appropriate aldehyde. The secondary alcohol intermediates were identified on the basis of the high field doublet and quartet that appeared in the ^{1}H-NMR spectra in a 3:1 ratio. The crude products were immediately oxidized to the desired methyl ketones with MnO_2 in CH_2Cl_2. The methyl ketones were readily identified by the loss of the aforementioned doublet and quartet, and the appearance of a new singlet, typically resonating around 2.5 ppm in the ^{1}H-NMR spectrum.

The benzophenone derivatives **23b**, **24b**, and **25b** and the pentafluorophenyl analogues **23c-25c** were prepared by dropwise addition of PhLi (prepared at -78 °C via metal-halogen exchange of bromobenzene and nBuLi) and pentafluorophenyllithium[11] respectively to a THF solution of the appropriate aldehyde. The intermediate alcohols were identified by the presence of a new singlet in the ^{1}H-NMR at 6 ppm, which accounted for the doubly benzylic methine proton. Oxidation caused a decrease in polarity, as well as loss of the signal at 6 ppm in the ^{1}H-NMR spectra.

9.5 Trapping of Photoenols

As mentioned earlier in this chapter, the reaction between the presumed photoenol of 5 and SO_2 failed to provide any cycloadduct. However, when a benzene solution of 9 was irradiated in the presence of SO_2, a new product, tentatively assigned as 26 was isolated by base washing and then re-acidification and extraction with Et_2O. This intermediate was converted into the sulfone 27 by reaction with $NaBH_4$ and then concentrated HCl[12].



9 26 27

Reagents: a) hv, SO_2, PhH; b) (i) $NaBH_4$, MeOH; (ii) HCl (25% from 9).

Scheme 9.7 - Synthesis of Sulfone 27 from Aldehyde 9 via SO_2 Trapping of Photoenol.

The 500 MHz ^{1}H-NMR (Fig. 9.4) of 27 showed a number of multiplets for the aliphatic protons. Key signals included a doublet of doublets at 4.19 ppm, accounting for the methine proton adjacent to the sulfur, and an AB pattern with doublets centered at 4.15 and 4.50 ppm (J=15.8 Hz) for the benzylic methylene group adjacent to the sulfonyl group. Although the EI-MS did not show a molecular ion, a peak accounting for loss of SO_2 from the parent structure was readily apparent; this is suggestive of a ready extrusion of SO_2. CI-MS did show a peak at m/z 209, accounting for the $[M^{+\bullet}+1]$ peak.

This result, which proved that bicyclic ortho-quinodimethanes could be prepared photochemically, made the failure of 5 to react with SO_2 even more interesting. A brief survey of the

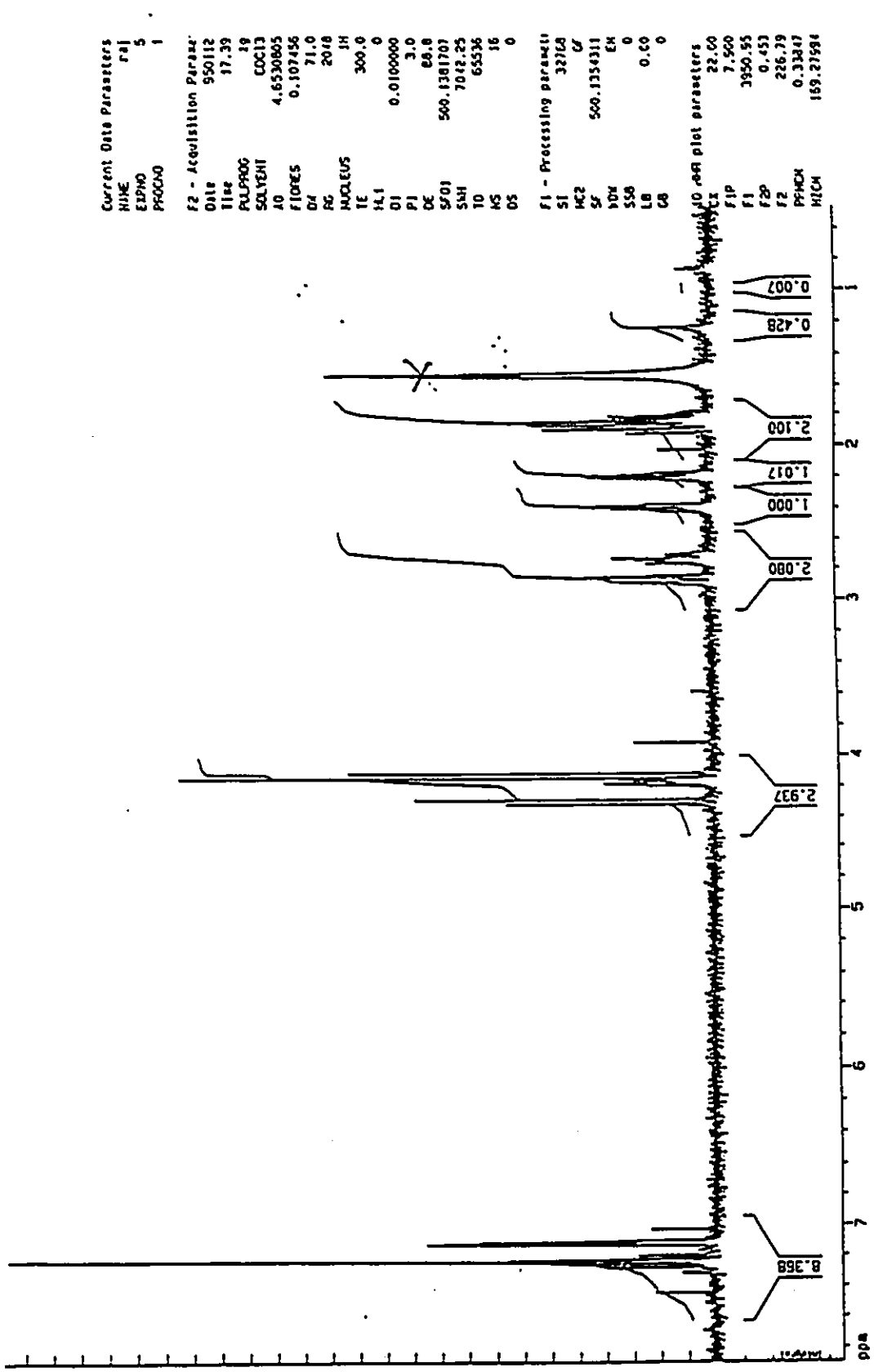
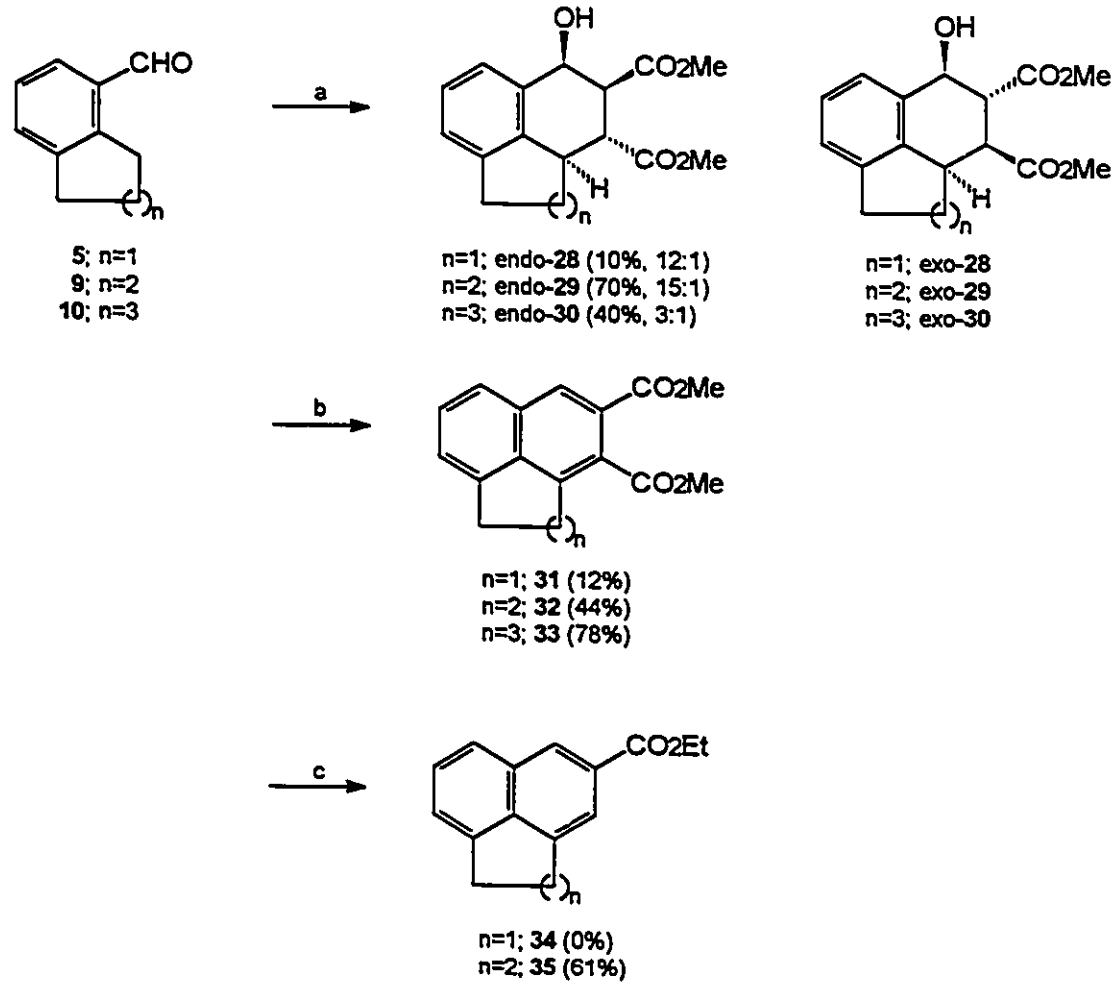


Figure 9.4 500 MHz ^{1}H-NMR Spectrum of Sulfone 27 in $CDCl_3$

photochemistry of aldehydes 5, 9 and 10 was then undertaken. The results are summarized in Scheme 9.8.



Reagents: a) Dimethyl Fumarate, CH_3CN, hv. b) (i) Dimethylacetylenedicarboxylate, CH_3CN, hv; (ii) TsOH. c) (i) Ethylpropiolate, CH_3CN, hv; (ii) TsOH.

Scheme 9.8 - Summary of Aldehyde Photochemistry Results

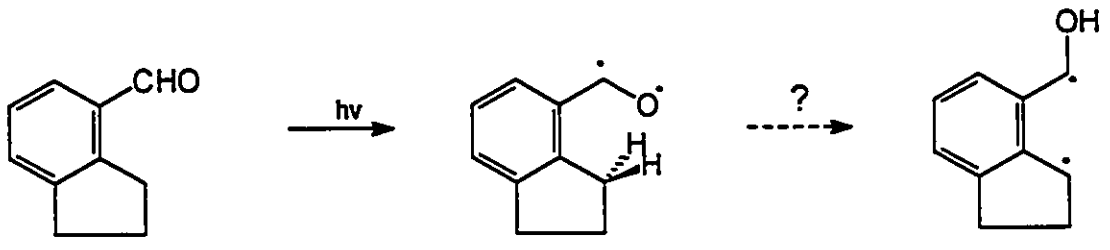
As is immediately obvious from inspecting the above data, the yields associated with trapping the photoenol of 5 were always lower than the yields of the same reactions using either 9 or 10. It appeared that the photoenol of 5 was not a willing participant in [4+2] cycloadditions, since no reaction was observed when SO_2 or methyl propiolate were used as dienophiles. Even when the very reactive

dienophiles dimethyl fumarate and dimethylacetylene dicarboxylate (DMAD) were used as trapping reagents, the yields were still quite low. Because of this poor yield, cycloadducts 28 and 31 could not be fully characterized. In the case of reactions with DMAD, the intermediate dihydronapthols were dehydrated with TsOH to simplify work-up and product identification.

The reactions with dimethyl fumarate provided two isomers resulting from endo and exo addition of the dienophile to the intermediate ortho-quinodimethane. These isomers were readily identified by the size of the coupling constant between the benzylic methine proton and the adjacent methine proton. The benzylic methine proton resonated around 5 ppm, and typically displayed a 3 Hz coupling constant for the endo cycloadduct whereas the exo cycloadduct had a 10 Hz coupling constant.

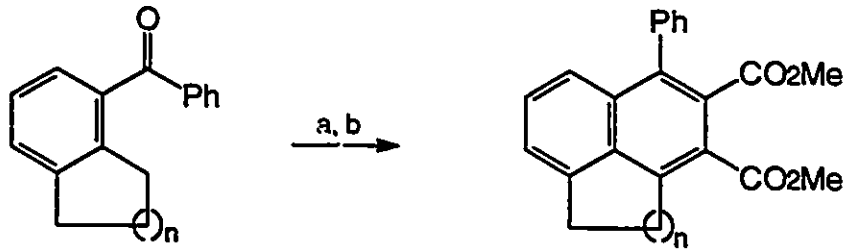
The reaction between the photoenol of 9 and methyl propiolate led to only one regioisomer. Again, the intermediate dihydonapthol was dehydrated to the naphthalene derivative 35 to simplify product isolation and identification. The regiochemistry was confirmed by the presence of two lowfield doublets at 7.80 and 8.40 ppm with a coupling constant of 1 Hz. The resonance were assigned to the isolated aromatic protons of the B aromatic ring which flanked the carbomethoxy group. The size of the coupling constant was indicative of a meta coupling, confirming the expected regiochemistry as shown in 35.

The consistently lower yields associated with reaction of photoenol 5 were the observations that initiated the laser flash photolysis study. It was unknown at this time if the lower yields were the result of a poor geometry making proton abstraction in triplet 36 difficult. If this were so, then it would explain the lower yields, since the yields of diradical 37 and the photoenol would be lower.



5 36 37

To finish off the photoenol trapping project, acetonitrile solutions of the benzophenone derivatives **23b**, **24b**, and **25b** were irradiated in the presence of DMAD. Again, the initially formed dihydronapthols were dehydrated to form the naphthalene derivatives. The results of this series of reactions is shown in Scheme 9.12.



n=1; **23b**
n=2; **24b**

n=1; **38** (43%)
n=2; **39** (59%)

Reagents: a) DMAD, hv, CH_3CN; b) TsOH.

Scheme 9.9 - Summary of Photochemical Trapping Results of Ketones **23b** and **24b**.

The cycloadducts **38** and **39** displayed spectroscopic data consistent with the proposed structures. The ^{1}H-NMR spectra for **38** and **39** are shown in Fig. 9.5 and 9.6 respectively. Somewhat surprising was the formation of **38** in a yield of 43%. This bright yellow solid (mp 150 °C) displayed two singlets in the ^{1}H-NMR spectrum (Fig. 9.5) at 3.56 and 3.92 ppm, accounting for the methyl esters. The methylene groups of the five membered ring appeared as two triplets with a 7.5 Hz coupling constant at 3.44 and 3.70 ppm. This result spurned the notion that photoenolization of the indane substrates was not possible due to some geometry constraint. In retrospect, it is more likely that photoenolization of aldehyde **5** resulted in poor trapping yields due to rapid oxidation to the corresponding carboxylic acid, irrespective of the amount of care taken during sample preparation and isolation. The photochemistry of benzophenone **25b** was not investigated.

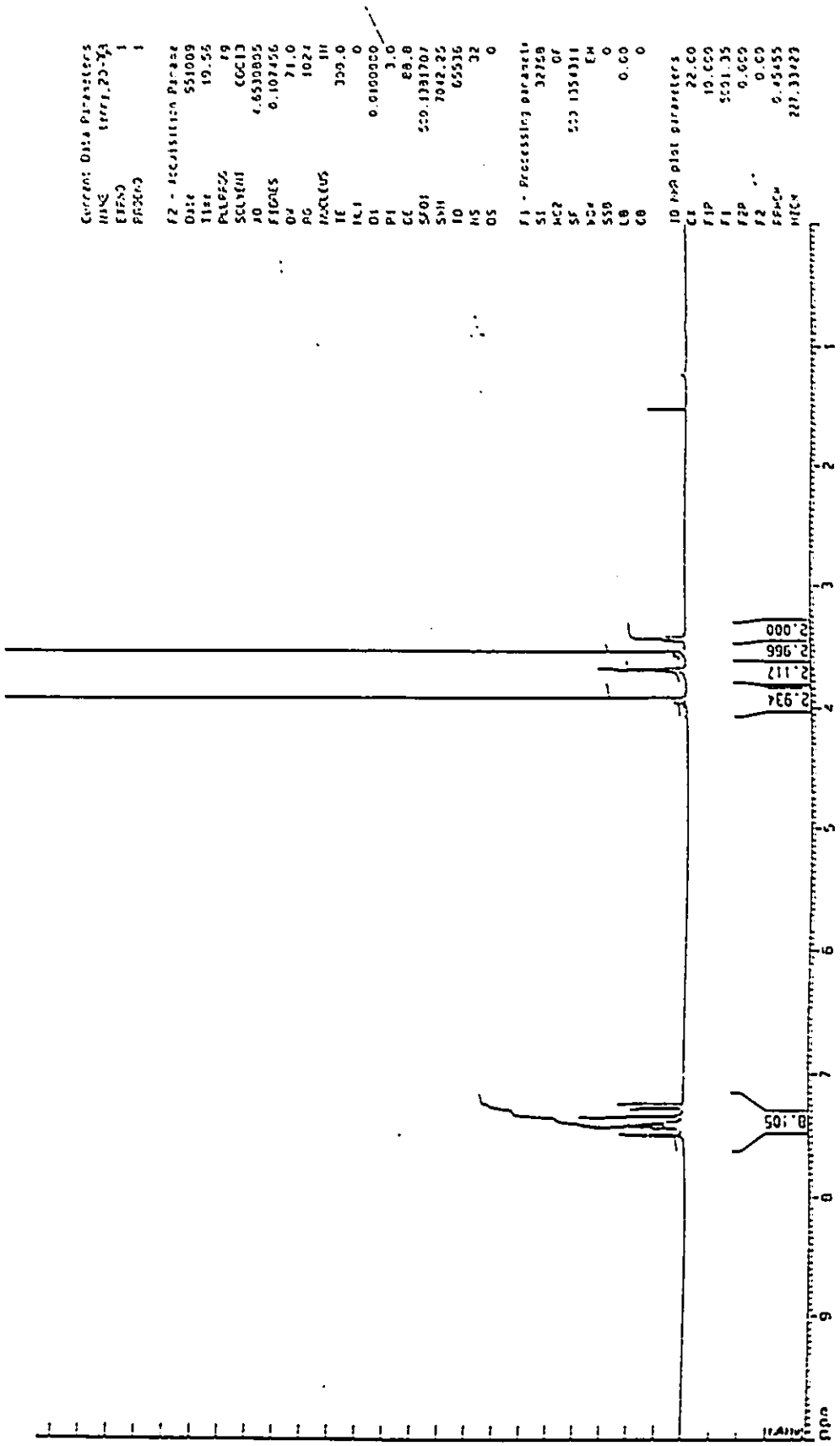


Figure 9.5 500 MHz ^{1}H-NMR Spectrum of Cycloadduct 38 in $CDCl_3$

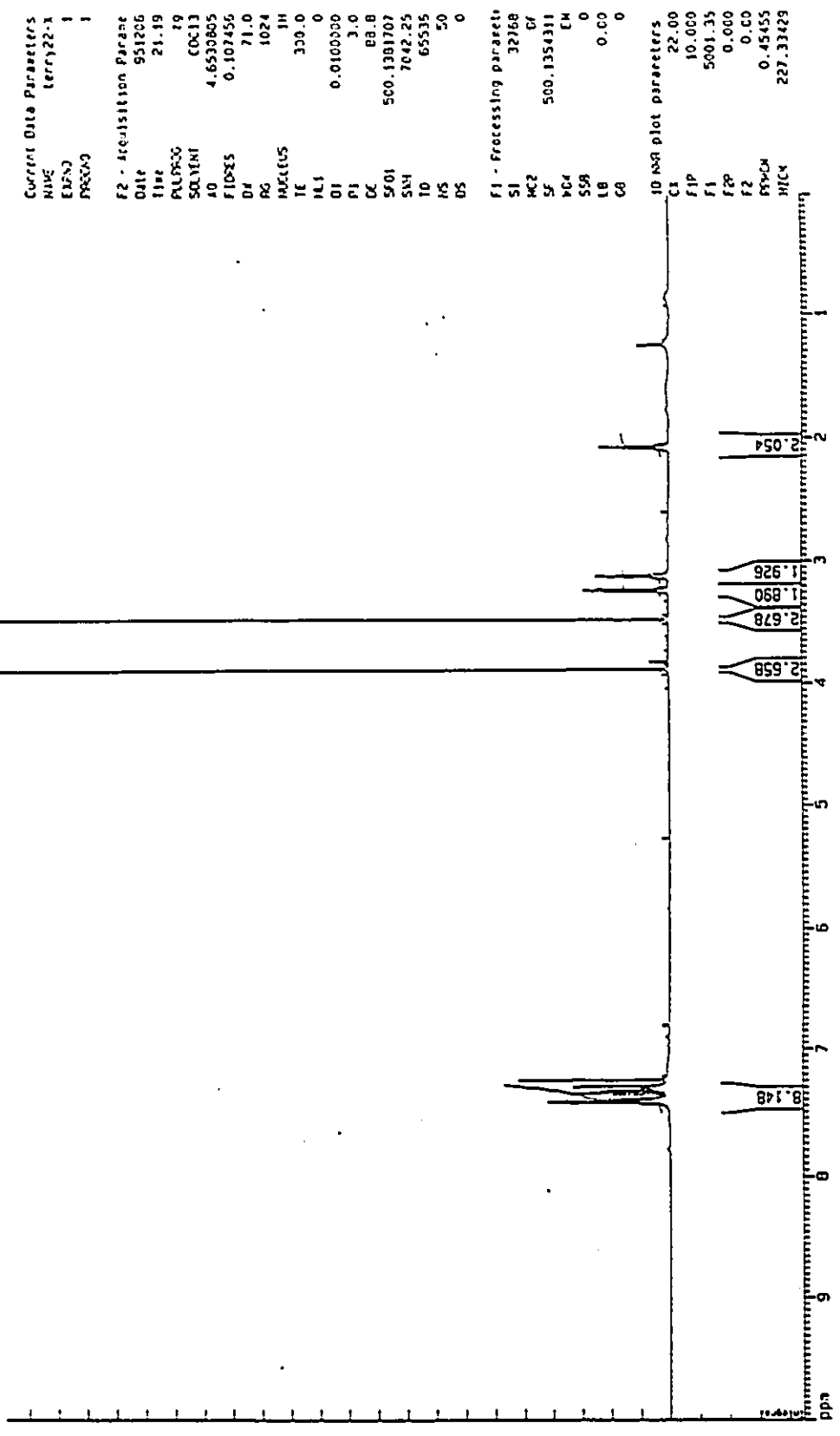
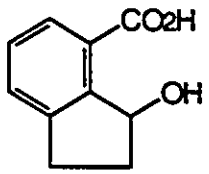


Figure 9.6 500 MHz ^{1}H-NMR Spectrum of Cycloadduct 39 in $CDCl_3$

9.6 Experimental

For comments regarding general experimental, see the experimental section of Chapter 3. Methylmagnesium bromide was purchased from Aldrich as a 3.0 M solution in Et_2O and was used as received. Phenyllithium was prepared in THF from bromobenzene via metal-halogen exchange with nBuLi at -78 °C. Pentafluorophenyllithium was prepared from bromopentafluorobenzene according to the literature method[11]. Photochemical reactions were conducted with a water-cooled Hanovia medium pressure mercury arc lamp. Acetonitrile (BDH, reagent grade) solutions of the carbonyl compounds were placed in Pyrex test tubes, sealed with rubber septa and were degassed with nitrogen for 30 min prior to irradiation. After this time, the flow of nitrogen was reduced, and the samples were irradiated for the specified time 5 cm from the arc lamp.

1(H)-2,3-Dihydro-3-hydroxy-4-indenoic acid (7).



7

A solution of nBuLi (33 mL, 2.5 M in Hexanes, 82.5 mmol) was added dropwise to a solution of indanol (5.00 g, 37.3 mmol) and TMEDA (12.5 mL, 9.63 g, 83.0 mmol) in pentane (500 mL). The resulting reddish mixture was heated to reflux for 12 h, cooled to -78 °C, and excess Dry Ice was added as a solid. The yellow solution was allowed to slowly warm to RT over 6 h. Water was added and the reaction mixture was adjusted to pH 1 with concentrated HCl, and extracted with Et_2O (5 x 100 mL). The combined organic extracts were subjected to standard work-up, providing a thick, red oil. The title compound could be crystallized as a white solid (3.93 g, 65%) by the addition of Et_2O and hexanes.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.15 (m, 1H), 2.40 (m, 1H), 2.85 (m, 1H), 3.18 (m, 1H), 5.64 (dd, 1H, J=8.0, 4.0 Hz), 7.37 (t, 1H, J=7.5 Hz), 7.51 (d, 1H, J=7.5 Hz), 7.96 (d, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 29.86, 32.16, 75.02, 125.21, 128.24, 129.27, 130.43, 145.27, 146.93, 171.33 ppm.

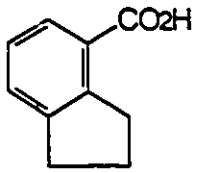
IR (CH_2Cl_2): 3495, 1684 cm^{-1}.

EI-MS (m/z, %): 178 ($M^{+\bullet}$, 3.1), 160 (56.6), 115 (100).

HRMS: Calc. for $C_{10}H_{10}O_3$: 178.06299; Found: 178.06371.

mp: 128 °C.

1(H)-2,3-Dihydro-4-indenoic acid (8).



8

A solution of hydroxy-acid 7 (3.50 g, 19.7 mmol) in HOAc (20 mL) was added dropwise to a suspension of 10% Pd/C (500 mg) in glacial acetic acid (50 mL). The reaction mixture was sealed with a rubber septum, and hydrogen was bubbled through the solution for 6 h. An aliquot was worked up by filtering through a pad of Celite™, rinsing with Et_2O, then concentrating the filtrate to dryness. ^{1}H-NMR analysis of the crude product showed reaction was complete. The remainder of the reaction mixture was worked up in the same manner affording 8 as a white solid (3.20 g, 90%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.26 (m, 2H), 3.09 (t, 2H, J=7.5 Hz), 3.46 (t, 2H, J=7.5 Hz), 7.35 (t, 1H, J=8.0 Hz), 7.58 (d, 1H, J=8.0 Hz), 8.04 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.47, 33.14, 34.70, 126.25, 126.83, 129.36, 130.07, 146.62, 148.29, 173.54 ppm.

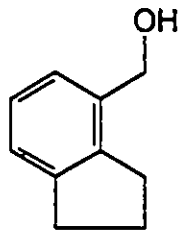
IR (CH_2Cl_2): 3500, 1689 cm^{-1}.

EI-MS (m/z, %): 162 ($M^{+\bullet}$, 59.7), 117 (100).

HRMS: Calc. for $C_{10}H_{10}O_2$: 162.06808; Found: 162.06783.

mp: 150 °C.

1(H)-2,3-Dihydro-4-hydroxymethyl-indene.



A solution of carboxylic acid **8** (3.00 g, 18.3 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (1.40 g, 37.0 mmol) in THF (20 mL). After addition was complete, the reaction mixture was refluxed for 2 h, cooled to RT and *carefully* poured into a solution of potassium sodium tartrate (10%, 200 mL). EtOAc (100 mL) was added and the mixture stirred at RT overnight. Separation of the organic phase and usual work up afforded the title compound as a clear oil (2.46 g, 90%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.00 (quintet, 2H, J=7.0 Hz), 2.80 (m, 4H), 4.54 (s, 2H), 7.08 (s, 3H) ppm.

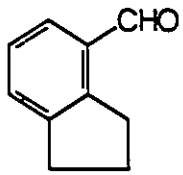
^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.93, 30.60, 32.71, 63.37, 123.63, 124.57, 126.40, 136.28, 142.05, 144.53 ppm.

IR (CH_2Cl_2): 3605 cm^{-1}.

EI-MS (m/z, %): 148 ($M^{+\cdot}$,20.0), 130 (100).

HRMS: Calc. for $C_{10}H_{12}O$: 148.08882; Found: 148.09103.

1(H)-2,3-dihydro-4-indenecarboxaldehyde (5).



5

A mixture of 1(H)-2,3-dihydro-4-hydroxymethylindene (4) (2.00 g, 13.5 mmol) and activated MnO_2 (5.00 g, 57.5 mmol) in CH_2Cl_2 (100 mL) was refluxed for 10 h, cooled to RT and filtered through Celite™. The filter cake was washed thoroughly with CH_2Cl_2 and the resulting clear solution was concentrated to dryness. Column chromatography (8:1 Hex: EtOAc) afforded the title compound as a clear oil (1.83 g, 93%).

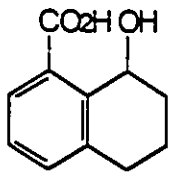
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.98 (quintet, 2H, J=7.6 Hz), 2.77 (t, 2H, J=7.6 Hz), 3.12 (t, 2H, J=7.6 Hz), 7.15 (t, 1H, J=7.3 Hz), 7.30 (d, 1H, J=7.3 Hz), 7.45 (d, 1H, J=7.3 Hz), 9.97 (s, 1H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.78, 31.31, 31.62, 126.28, 128.77, 129.48, 131.88, 145.79, 145.85, 192.20 ppm.

EI-MS: (m/z, %): 146 ($M^{+\cdot}$, 86.8), 145 (27.0), 117 (100).

HRMS: Calc. for $C_{10}H_{10}O$: 146.07317; Found: 147.07645.

5,6,7,8-Tetrahydro-8-hydroxy-1-napthoic acid (12):



12

The title compound was prepared in 70% yield according to the procedure of Seebach[3].

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.70 (m, 2H), 2.00 (m, 2H), 2.80 (m, 2H), 5.05 (t, 1H, J-5.0 Hz), 7.1-7.30 (m, 2H), 7.75 (d, 1H, J=8.0 Hz) ppm.

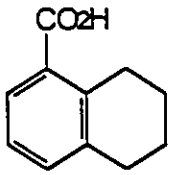
^{13}C-NMR ($CDCl_3$, 75 MHz): 16.57, 29.67, 30.01, 63.32, 126.96, 129.07, 129.25, 134.61, 138.12, 139.29, 172.22 ppm.

EI-MS (m/z, %): 192 (8.4, $M^{+\cdot}$), 174 (67.1), 146 (54.3), 118 (100).

HRMS for $C_{11}H_{12}O_3$; Calc: 192.07864; Found: 192.07682.

mp: 125 °C (lit.[3] :115-118 °C).

5,6,7,8-Tetrahydro-1-napthoic acid (13)



13

A solution of hydroxy acid **12** (4.00 g, 20.8 mmol) in glacial HOAc (50 mL) was added dropwise to a suspension of Pd/C (10%, 500 mg) in glacial acetic acid (10 mL). The resulting solution was stirred at room temperature as hydrogen was continuously bubbled through the solution for 4 h. Workup as for **8** followed by recrystallization from EtOAc/Hex afforded white prisms (2.75 g, 75%).

^{1}H-NMR (500 MHz, $CDCl_3$): 1.78 (m, 4H), 2.82 (t, 2H, 7.5 Hz), 3.12 (t, 2H, 7.5 Hz), 7.15 (t, 1H, J=8.0 Hz), 7.25 (d, 1H, 8.0 Hz), 8.30 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 22.36, 23.09, 27.96, 30.28, 125.03, 128.69, 129.03, 134.15, 138.58, 139.86, 172.87 ppm.

IR (CH_2Cl_2): 3495, 1690 cm^{-1}.

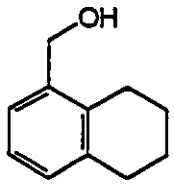
EI-MS (m/z, %): 176 ($M^{+\bullet}$, 71.5), 158 (81.7), 131 (100).

HRMS for $C_{11}H_{12}O_2$; Calc. 176.08373; Found: 176.08472.

CA: Calc: C (74.98), H (6.86); Found: C (74.94), H (6.55).

mp: 150 °C.

5,6,7,8-Tetrahydro-1-hydroxymethylnapthylene.



A solution of carboxylic acid **13** (2.50 g, 14.2 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (1.10 g, 28.9 mmol) in THF (20 mL). After addition was complete, the reaction mixture was refluxed for 2 h, cooled to RT and *carefully* poured into a solution of potassium sodium tartrate (10%, 200 mL). EtOAc (100 mL) was added and the mixture stirred at RT overnight. Separation of the organic phase and usual work up afforded the title compound as a clear oil (2.00 g, 87%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.75 (m, 4H), 2.71 (t, 2H, J=7.0 Hz), 2.85 (t, 2H, J=7.0 Hz), 4.65 (s, 2H), 7.2 (m, 3H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.45, 22.77, 25.05, 29.63, 62.70, 124.39, 125.00, 128.48, 134.62, 137.08, 138.31 ppm.

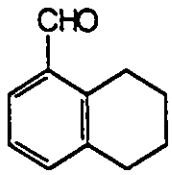
IR (CH_2Cl_2): 3605 cm^{-1}.

EI-MS (m/z, %): 162 ($M^{+\cdot}$, 5.5), 144 (100).

HRMS: Calc. for $C_{11}H_{14}O$: 162.10446; Found: 162.10399.

CA: For $C_{11}H_{14}O$, Calc: C (81.44), H (8.70); Found: C (81.73), H (8.86).

5,6,7,8-Tetrahydro-1-napthaldehyde (9).



9

A mixture of 5,6,7,8-tetrahydro-1-napthaldehyde (2.00 g, 12.3 mmol) and activated MnO_2 (4.00 g, 46.0 mmol) in CH_2Cl_2 (100 mL) was refluxed for 10 h, cooled to RT and filtered through Celite™. The filter cake was washed thoroughly with CH_2Cl_2 and the resulting clear solution was concentrated to dryness. Column chromatography (8:1 Hex: EtOAc) afforded 9 as a clear oil (1.54 g, 78%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.65 (m, 4H), 2.73 (t, 2H, J=7.1 Hz), 3.10 (t, 2H, J=7.1 Hz), 7.15 (m, 2H), 7.52 (d, 1H, J=7.5 Hz), 10.15 (s, 1H) ppm.

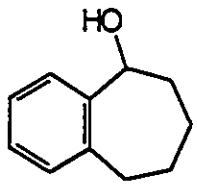
^{13}C-NMR (75 MHz, $CDCl_3$): 21.90, 22.30, 26.00, 29.98, 124.80, 130.62, 134.00, 135.20, 138.20, 139.40, 192.86 ppm.

IR (CH_2Cl_2): 1691 cm^{-1}.

EI-MS (m/z, %): 160 ($M^{+\cdot}$, 100), 159 (10.4), 131 (74.8).

HRMS: Calc. for $C_{11}H_{12}O$: 160.08881; Found: 160.08961.

Benzosuberan-1-ol (15).



15

A solution of benzosuberone (25.00 g, 0.16 mol) in THF (150 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (6.00 g, 0.16 mol) in THF (50 mL). The resulting solution was stirred at RT for 1 h, and was *carefully* poured into a solution of potassium sodium tartrate (10%, 250 mL). EtOAc (150 mL) was added, and the mixture was stirred for 10h. The organic phase was then separated and subjected to standard work up, affording the title compound **15** as a white solid (25.00 g, >95%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.50 (m, 2H), 1.80 (m, 2H), 2.00 (m, 1H), 2.10 (m, 1H), 2.75 (m, 1H), 3.00 (m, 1H), 5.00 (d, 1H, J=4.0 Hz), 7.20 (m, 3H), 7.50 (d, 1H, J=7.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.30, 28.80, 35.70, 36.50, 74.30, 124.52, 125.35, 127.46, 129.46, 141.32, 143.67 ppm.

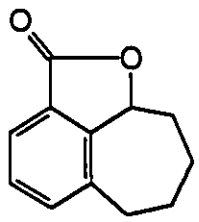
IR (CH_2Cl_2): 3601 cm^{-1}.

EI-MS (m/z, %): 162 ($M^{+\cdot}$, 6.2), 144 (83.4), 129 (100).

HRMS: Calc. for $C_{11}H_{14}O$: 162.10447; Found: 162.10475.

mp: 106.0 °C

5-Hydroxy-benzosuberane-7-carboxylic acid lactone (16).



16

A solution of nBuLi (27.2 mL, 2.5 M in Hexanes, 68.0 mmol) was added dropwise to a solution of alcohol **15** (5.00 g, 30.9 mmol) and TMEDA (7.90 g, 67.9 mmol) in pentane (500 mL). The resulting cloudy yellow reaction mixture was refluxed for 12 h, cooled to -78 °C, and treated with an excess of Dry Ice. The reaction mixture was slowly allowed to warm to RT, acidified with concentrated HCl, and the aqueous phase extracted with Et_2O (5 x 100 mL). The combined organic extracts were concentrated, and the title compound was isolated as an off-white solid. Recrystallization from Et_2O/hexanes provided the title compound as white plates (4.35 g, 75%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (m, 2H), 1.80 (m, 1H), 2.10 (m, 1H), 2.30 (m, 1H), 2.50 (m, 1H), 2.80 (m, 2H), 5.20 (dd, 1H, J=12.0, 3.6 Hz), 7.30 (m, 2H), 7.80 (d, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 27.53, 27.72, 32.86, 35.16, 82.58, 122.92, 125.57, 129.03, 133.39, 138.19, 150.68, 170.80 ppm.

IR (CH_2Cl_2): 1762 cm^{-1}.

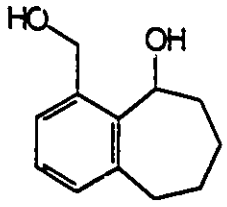
EI-MS (m/z, %): 188 ($M^{+\cdot}$, 100), 159 (99.3), 131 (82.2).

HRMS: Calc. for $C_{12}H_{12}O_2$: 188.08373; Found: 188.08726.

CA: Calc. for $C_{10}H_{10}O_2$: C (76.57), H (6.43); Found: C (76.67), H (6.45).

mp: 75.0 °C.

7-Hydroxymethyl-5-hydroxybenzosuberane (18).



18

A solution of lactone **17** (4.00 g, 21.3 mmol) in THF (50 mL) was added dropwise to a suspension of $LiAlH_4$ (0.80 g, 21.1 mmol) in THF (100 mL). The resulting mixture was stirred at RT for 1 h, refluxed for 2 h, cooled to RT, and was poured *carefully* into a solution of potassium sodium tartrate (10%, 100 mL). EtOAc (150 mL) was then added and the mixture was stirred for 10 h. Separation of the organic phase and usual work up afforded the title compound as a thick, clear oil that slowly solidified on standing. Recrystallization from Et_2O/hexanes afforded diol **18** as a white crystalline solid (3.62 g, 89%).

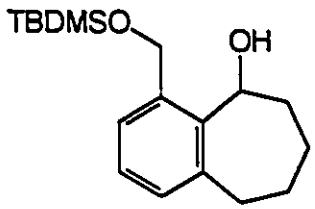
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (m, 1H), 1.65 (m, 1H), 1.80 (m, 2H), 2.05 (m, 1H), 2.10 (m, 1H), 2.65 (m, 1H), 3.20 (m, 1H), 4.40 (d, 1H, J=12.5 Hz), 4.70 (d, 1H, J=12.5 Hz), 5.25 (dd, 1H, J=12.0, 1.0 Hz), 7.10 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 24.46, 27.62, 33.35, 35.36, 65.04, 69.84, 127.48, 127.91, 131.03, 138.06, 141.71, 143.61 ppm.

IR (CH_2Cl_2): 3596, 3392 cm^{-1}.

CA: For $C_{12}H_{16}O_2$: Calc. C (74.97), H (8.39); Found: C (74.72), H (8.61).

7-(tert-Butyldimethylsiloxy)methyl-5-hydroxybenzosuberane (19).



19

A solution of TBDMSCl (3.02 g, 20.0 mol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of diol **18** (3.50 g, 18.2 mmol), Et_3N (2.80 mL, 20.1 mmol) and DMAP (200 mg) in CH_2Cl_2 (150 mL). The resulting clear solution was stirred at RT for 1h, after which time tlc analysis indicated the complete consumption of starting material. The reaction mixture was poured into H_2O (100 mL) and the organic phase separated and subjected to standard work up. The resulting clear oil was purified by passing it through a short column of silica gel (10:1 hexanes:EtOAc). The resulting clear oil solidified on standing, providing the title compound **19** as a white solid (5.60 g, >95%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.80 (m, 4H), 2.10 (m, 2H), 2.65 (m, 2H), 3.10 (br, 1H), 4.65 (d, 1H, J=12.0 Hz), 4.90 (d, 1H, J=12.0 Hz), 5.35 (dd, 1H, J=3.5, 1.5 Hz), 7.05 (s, 3H) ppm.

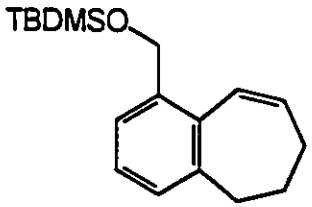
^{13}C-NMR (50 MHz, $CDCl_3$): δ -5.25, -5.17, 24.59, 25.64, 25.91, 27.70, 33.10, 35.42, 65.53, 69.63, 127.14, 127.20, 130.61, 138.01, 141.86, 143.34 ppm.

IR (CH_2Cl_2): 3599 cm^{-1}.

CA: For $C_{18}H_{30}SiO_2$: Calc. C (70.53), H (9.86); Found C (70.93), H (9.76).

mp: 62 °C.

7-(tert-Butyldimethylsiloxy)methyl-4,5-dehydro-benzosuberane (20).



20

A solution of alcohol **19** (2.00 g, 6.54 mmol), pyridine (1.20 mL, 14.8 mmol) and DMAP (100 mg) in CH_2Cl_2 (100 mL) was stirred at RT while Ts_2O (2.13 g, 6.54 mmol) was added portionwise. The resulting solution was stirred at RT for 6 h, poured into H_2O (75 mL) and the organic phase separated and subjected to standard work up. The resulting clear oil was chromatographed with hexanes, affording the title compound as a clear oil (1.60 g, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.90 (s, 9H), 2.10 (m, 4H), 2.70 (t, 2H, J=6.5 Hz), 4.75 (s, 2H), 6.15 (dt, 1H, 10.0, 6.5 Hz), 6.60 (d, 1H, J=10.0 Hz), 7.15 (m, 2H), 7.38 (d, 1H, J=7.0 Hz) ppm.

7-(tert-Butyldimethylsiloxy)methylbenzosuberane (21).

21

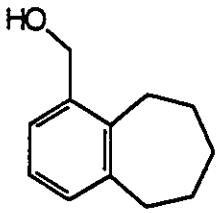
A solution of olefin **20** (1.50 g, 5.19 mmol) in MeOH (50 mL) was *carefully* added dropwise to a cooled (0 °C) suspension of Pd/C (10%, 200 mg) in MeOH (10 mL). Hydrogen was bubbled through the resulting solution for 4 h. The dark solution was then filtered through a pad of Celite™. The filter cake was then washed with Et_2O, and the combined organic solutions evaporated to dryness. The resulting clear oil was passed through a plug of silica gel, affording the title compound as a clear oil (1.27 g, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.95 (s, 9H), 1.60 (m, 4H), 1.80 (m, 2H), 2.80 (m, 4H), 4.70 (s, 2H), 7.05 (m, 2H), 7.20 (dd, 1H, J=7.0, 1.0 Hz) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ -5.83, 18.30, 25.21, 26.00, 26.42, 27.43, 32.52, 36.08, 64.16, 125.00, 126.20, 127.32, 128.16, 131.62, 139.72 ppm.

CA: For $C_{18}H_{30}SiO$: Calc. C (74.42), H (10.41); Found: C (74.26), H (10.88).

7-hydroxymethylbenzosuberane (22).



22

A solution of TBAF (5.0 mL, 1.0 M in THF, 5.00 mmol) was added dropwise to a solution of silyl ether **21** (1.20 g, 3.44 mmol) in THF (50 mL). The resulting solution was stirred at RT for 12 h, poured into H_2O (50 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were subjected to standard work up and the resulting clear, oily residue was purified via column chromatography (5:1 Hex:EtOAc) affording the title compound as a clear colorless oil (0.60 g, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.60 (m, 4H), 1.85 (m, 2H), 2.85 (m, 4H), 4.62 (s, 2H), 7.10 (m, 3H) ppm.

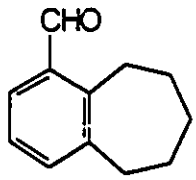
^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.19, 28.80, 30.05, 33.15, 37.03, 64.65, 126.30, 127.22, 129.64, 138.18, 142.76, 145.15 ppm.

IR (CH_2Cl_2): 3602 cm^{-1}.

EI-MS (m/z, %): 176 ($M^{+\bullet}$, 11.9), 158 (50.2), 143 (28.9), 130 (100).

HRMS: Calc. for $C_{12}H_{16}O$: 176.12012; Found: 176.11881.

Benzosuberan-7-carboxaldehyde (10).



10

A mixture of alcohol **22** (0.95 g, 5.38 mmol) and PDC (3.05 g, 8.11 mmol) in CH_2Cl_2 (75 mL) was stirred at RT for 12 h, after which time a 1:1 mixture of Celite™ and silica gel (2g) was added. Stirring was continued for 2 h, and the mixture was filtered through Celite™. The filter cake was washed thoroughly with Et_2O, and the combined organic solutions subjected to standard work up. The resulting yellow oil was purified via column chromatography (10:1 Hex:EtOAc) affording the title compound as a clear oil (0.75 g, 80%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.60 (m, 4H), 1.80 (m, 2H), 2.85 (m, 2H), 3.25 (m, 2H), 7.15 (t, 1H, J=7.0 Hz), 7.30 (d, 1H, J=7.0 Hz), 7.65 (d, 1H, J=7.0 Hz), 10.31 (s, 1H) ppm.

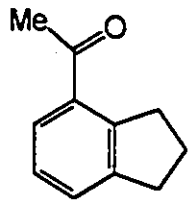
^{13}C-NMR (50 MHz, $CDCl_3$): δ 27.17, 27.53, 27.78, 32.09, 35.85, 126.00, 129.01, 133.70, 134.36, 145.59, 146.07, 192.94 ppm.

EI-MS (m/z, %): 174 ($M^{+\bullet}$, 100), 173 (25.7), 145 (75.6).

HRMS: Calc. for $C_{12}H_{14}O$: 174.10447; Found: 174.10407.

General Experimental for the synthesis of Methyl Ketones (23a-25a).

4-Acetyl-1(H)-2,3-dihydroindene (23a).



23a

A solution of MeMgBr (0.25 mL, 3.0 M in Et_2O, 0.75 mmol) was added dropwise to a cooled (0 °C) solution of aldehyde 5 (100 mg, 0.68 mmol) in THF (10 mL). The resulting solution was stirred at 0 °C for 30 min, warmed to RT and stirred for 1 h. The pale yellow solution was then poured into a saturated solution of NH_4Cl (25 mL) and extracted with Et_2O (5 x 15 mL). The combined organic extracts were subjected to standard work up, affording a clear oil (108.3 mg, >95%). The intermediate alcohol was dissolved in CH_2Cl_2 (20 mL) and activated MnO_2 was added (118 mg, 1.36 mmol). The resulting dark solution was refluxed for 10 h, cooled to RT and filtered through Celite™. The filter cake was washed thoroughly with CH_2Cl_2, and resulting clear solution concentrated to dryness. The resulting pale yellow oil was chromatographed (5:1 Hex:EtOAc) affording the title compound as a clear oil (88 mg, 80% from 5).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.05 (quintet, 2H, J=7.0 Hz), 2.57 (s, 3H), 2.90 (t, 2H, J=7.0 Hz), 3.24 (t, 2H, J=7.30 Hz), 7.21 (t, 1H, J=7.0 Hz), 7.38 (d, 1H, J=7.0 Hz), 7.64 (d, 1H, J=7.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.00, 28.27, 32.27, 34.01, 126.10, 127.42, 128.50, 133.85, 145.34, 146.20, 199.83 ppm.

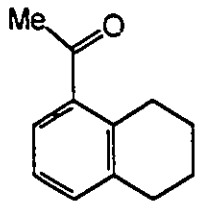
IR (CH_2Cl_2): 1680 cm^{-1}.

EI-MS (m/z, %): 160 ($M^{+\cdot}$, 60.0), 145 (100), 117 (61.1).

HRMS: Calc. for $C_{11}H_{12}O$: 160.08881; Found: 160.08735.

CA: For $C_{11}H_{12}O$: C (82.45), H (7.55); Found: C (82.74), H (7.86).

6-Acetyl-1,2,3,4-tetrahydronapthylene (24a).



24a

Using the above procedure, aldehyde 9 (100 mg, 0.63 mmol) was converted to **24a** (92 mg, 84%). Ketone **24a** was purified via column chromatography (10:1 Hex:EtOAc) and was isolated as a clear oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.75 (m, 4H), 2.51 (s, 3H), 2.80 (t, 2H, J=6.0 Hz), 2.93 (t, 2H, J=6.0 Hz), 7.15 (m, 2H), 7.40 (d, 1H, J=7.0 Hz) ppm.

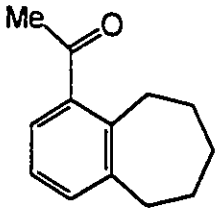
^{13}C-NMR (50 MHz, $CDCl_3$): δ 22.37, 23.06, 27.63, 30.08, 30.12, 124.88, 126.21, 132.50, 132.52, 136.67, 139.56, 202.86 ppm.

IR (CH_2Cl_2): 1685 cm^{-1}.

EI-MS (m/z, %): 174 ($M^{+\bullet}$, 72.0), 159 (100), 131 (60.8).

HRMS: Calc. for $C_{12}H_{14}O$: 174.10447; Found: 174.10396.

7-Acetyl-benzosurberane (25a).



25a

Using the above procedure, aldehyde **10** (150 mg, 0.86 mmol) was converted into ketone **25a** (117 mg, 72%). Ketone **25a** was isolated as a clear, colorless oil after chromatography (10:1 Hex:EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): 1.60 (m, 4H), 1.85 (m, 2H), 2.50 (s, 3H), 2.82 (m, 4H), 7.20 (m, 3H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): 27.40, 27.82, 30.66, 30.94, 32.10, 36.21, 124.68, 125.32, 131.12, 140.43, 140.94, 145.20, 204.81 ppm.

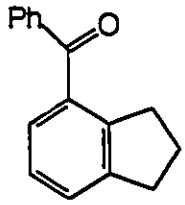
IR (CH_2Cl_2): 1680 cm^{-1}.

EI-MS (m/z, %): 188 (M•+, 59.4), 173 (100), 145 (32.2).

HRMS: Calc. for $C_{13}H_{16}O$: 188.12012; Found: 188.11934.

General Experimental for the synthesis of Phenyl Ketones (23b-25b).

4-Benzoyl-1(H)-2,3-dihydroindene (23b).



23b

A solution of nBuLi (0.81 mL, 2.5 M in Hexanes, 2.03 mmol) was added dropwise to a cooled (-78 °C) solution of bromobenzene (320 mg, 2.04 mmol) in THF (10 mL). The resulting solution was stirred at -78 °C for 30 min, after which time it was added via cannula to a cooled (-78 °C) solution of aldehyde 5 (150 mg, 1.02 mmol) in THF (10 mL). The resulting solution was stirred at -78 °C for 30 min, warmed to RT and stirred for 1 h. The pale yellow solution was then poured into a saturated solution of NH_4Cl (25 mL) and extracted with Et_2O (5 x 15 mL). The combined organic extracts were subjected to standard work up, affording a clear oil. The intermediate alcohol was dissolved in CH_2Cl_2 (20 mL) and activated MnO_2 was added (173 mg, 2.00 mmol). The resulting dark solution was refluxed for 10 h, cooled to RT and filtered through Celite™. The filter cake was washed thoroughly with CH_2Cl_2, and resulting clear solution concentrated to dryness. The resulting pale yellow oil was chromatographed (15:1 Hex:EtOAc) affording the title compound as a clear oil (132 mg, 58% from 5).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.06 (quintet, 2H, J=7.5 Hz), 2.95 (t, 2H, J=7.5 Hz), 3.01 (t, 2H, J=7.5 Hz), 7.40 (m, 6H), 7.78 (dd, 2H, J=7.5, 1.1 Hz) ppm.

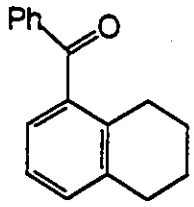
^{13}C-NMR (125 MHz, $CDCl_3$): δ 25.33, 32.64, 32.77, 125.69, 127.48, 127.77, 128.29, 130.00, 132.52, 134.43, 138.21, 144.83, 145.83, 197.81 ppm.

IR (CH_2Cl_2): 1658 cm^{-1}.

EI-MS (m/z, %): 222 ($M^{+\bullet}$, 100), 145 (19.2), 117 (26.6).

HRMS: Calc. for $C_{16}H_{14}O$: 222.10447; Found: 222.10422.

6-Benzoyl-1,2,3,4-tetrahydronapthylene (24b).



24b

Using the above procedure, aldehyde **9** (150 mg, 0.95 mmol) was converted to **24b** (140 mg, 63%). Ketone **24b** was purified via column chromatography (25:1 Hex:EtOAc) and was isolated as a clear colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.75 (m, 4H), 2.65 (t, 2H, J=6.0 Hz), 2.85 (t, 2H, J=6.0 Hz), 7.10 (m, 3H), 7.50 (m, 3H), 7.80 (d, 2H, J=7.0 Hz) ppm.

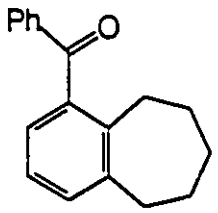
^{13}C-NMR (50 MHz, $CDCl_3$): δ 22.62, 22.85, 27.05, 29.79, 124.70, 125.34, 128.37, 130.04, 131.04, 133.11, 135.29, 137.60, 138.04, 136.82, 199.11 ppm.

IR (CH_2Cl_2): 1675 cm^{-1}.

EI-MS (m/z, %): 236 ($M^{+\cdot}$, 100), 159 (7.2), 131 (15.9).

HRMS: Calc. for $C_{17}H_{16}O$: 236.12011; Found: 236.11904.

7-Benzoyl-benzosurberane (25b).



25b

Using the above procedure, aldehyde **10** (150 mg, 0.86 mmol) was converted into ketone **25b** (120 mg, 56%). Ketone **25b** was isolated as a clear, colorless oil after chromatography (10:1 Hex:EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.50 (m, 2H), 1.60 (m, 2H), 1.75 (m 2H), 2.65 (m, 2H), 2.85 (m, 2H), 7.10 (m, 3H), 7.45 (d, 2H, J=8.0 Hz), 7.50 (m, 1H, J=8.0 Hz), 7.80 (m, 2H, J=8.0 Hz) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.50, 27.90, 31.73, 32.22, 36.43, 125.17, 125.22, 128.34, 130.09, 130.56, 133.18, 137.84, 139.05, 140.92, 144.77, 199.53 ppm.

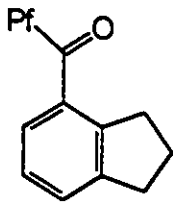
IR (CH_2Cl_2): 1662 cm^{-1}.

EI-MS (m/z, %): 250 ($M^{+\bullet}$, 88.4), 249 (100), 173 (47.6), 145 (16.6), 105 (40.1), 77 (68.4).

HRMS: Calc. for $C_{18}H_{18}O$: 250.13577; Found: 250.13619.

General Experimental for the synthesis of Pentafluorophenyl Ketones (23c-25c).

4-Pentafluorobenzoyl-1(H)-2,3-dihydroindene (23c).



23c

A solution of nBuLi (0.81 mL, 2.5 M in Hexanes, 2.03 mmol) was added dropwise to a cooled (-78 °C) solution of bromopentafluorobenzene (504 mg, 2.04 mmol) in THF (25 mL). After stirring at -78 °C for 30 min, it was added via cannula to a cooled (-78 °C) solution of aldehyde 5 (150 mg, 1.02 mmol) in THF (10 mL). The resulting solution was stirred at -78 °C for 30 min, warmed to RT and stirred for 1 h, after which time the pale yellow solution was poured into a saturated solution of NH_4Cl (25 mL) and extracted with Et_2O (5 x 15 mL). The combined organic extracts were subjected to standard work up, affording a clear oil. The intermediate alcohol was dissolved in CH_2Cl_2 (50 mL) and activated MnO_2 was added (173 mg, 2.00 mmol). The resulting dark solution was refluxed for 10 h, then cooled to RT and filtered through Celite™. The filter cake was washed thoroughly with CH_2Cl_2, and resulting clear solution concentrated to dryness. Chromatography (15:1 Hex:EtOAc) afforded the title compound as a white solid (168 mg, 52% from 5).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.14 (quintet, 2H, J=7.6 Hz), 2.96 (t, 2H, J=7.6 Hz), 3.29 (t, 2H, J=7.60 Hz), 7.22 (d, 1H, J=6.9 Hz), 7.24 (t, 1H, J=6.9 Hz), 7.48 (d, 1H, J=6.9 Hz) ppm

^{13}C-NMR (125 MHz, $CDCl_3$): δ 24.95, 32.25, 33.74, 126.65, 129.48, 130.52, 132.41, 137 (dm), 142 (dm), 143 (dm) ppm.

IR (CH_2Cl_2): 1678 cm^{-1}.

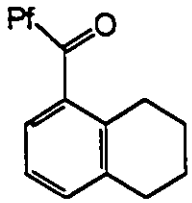
EI-MS (m/z, %): 312 ($M^{+\cdot}$, 44.6), 233 (99.4), 203 (35.3), 159 (100).

HRMS: Calc. for $C_{16}H_9F_9O$: 312.05736; Found: 312.05640.

CA for $C_{16}H_9F_9O$: Calc. C (61.55) H (2.91); Found: C (62.32) H (2.96).

mp: 80.1-81.2 °C (white needles from MeOH).

6-Pentafluorobenzoyl-1,2,3,4-tetrahydronapthylene (24c).



24c

Using the above procedure, aldehyde **9** (150 mg, 0.95 mmol) was converted to **24c** (114 mg, 37%). Ketone **24c** was purified via column chromatography (25:1 Hex:EtOAc) and was isolated as a white solid. Recrystallization from MeOH afforded an analytical sample.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.81 (m, 4H), 2.85 (t, 2H, J=6.0 Hz), 3.11 (t, 2H, J=6.0 Hz), 7.14 (t, 1H, J=7.0 Hz), 7.24 (d, 1H, J=7.0 Hz), 7.29 (d, 1H, J=7.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.17, 22.91, 27.85, 30.15, 125.20, 129.73, 135.07, 135.66, 137.80 (dm), 139.35, 139.76, 142.50 (dm), 143.80 (dm) ppm.

IR (CH_2Cl_2): 1679 cm^{-1}.

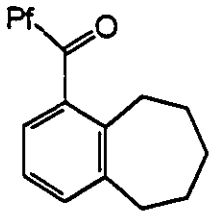
EI-MS (m/z, %): 326 ($M^{+\cdot}$, 100).

HRMS: Calc. for $C_{17}H_{11}F_5O$: 326.07301; Found: 326.07199.

CA for $C_{17}H_{11}F_5O$: Calc. C (62.58), H (3.40); Found: C (62.67), H (3.50).

mp: 110 °C.

7-Pentafluorobenzoyl-benzosuberane (25c).



25c

Using the above procedure, aldehyde **10** (90 mg, 0.52 mmol) was converted into ketone **25c** (50 mg, 28%). Ketone **25c** was isolated as a clear, colorless oil which slowly solidified to a white solid after chromatography (20:1 Hex:EtOAc).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.60 (m, 4H), 1.80 (m, 2H), 2.80 (m, 2H), 3.00 (m, 2H), 7.10 (m, 2H), 7.40 (d, 1H, J=7.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 27.01, 27.73, 30.12, 31.99, 36.14, 110.30 (dm), 125.55, 127.45, 133.48, 137.01 (dm), 137.61, 142.50, 144.04, 144.80, 146.08, 188.18 ppm.

IR (CH_2Cl_2): 1681 cm^{-1}.

EI-MS (m/z, %): 340 ($M^{+\cdot}$, 54.3), 195 (100), 167 (23.3).

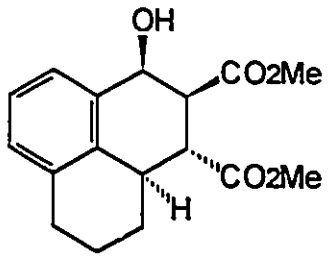
HRMS: Calc. for $C_{18}H_{13}F_5O$: 340.08866; Found: 340.08699.

mp: 58 °C.

General Procedure for the Generation and Trapping of Photoenols

A solution of the appropriate aldehyde or ketone (50-100 mg) in CH_3CN (10 mL) and the desired dieneophile (2 equivalents) was placed in a Pyrex test tube and was sealed with a rubber septum. The solution was degassed with nitrogen for 30 min, after which time the flow of nitrogen was reduced, the test tube was placed 5 cm from a water-cooled Hanovi medium pressure mercury arc lamp and the sample irradiated for 12h. The solvent was evaporated and the product purified by column chromatography. In the cases where DMAD was used as the dienophile, the reaction mixture was transferred to a round-bottom flask, a crystal of TsOH added and the resulting mixture refluxed for 1h. The solvent was evaporated and the product isolated as above.

Cycloadduct 29



29

Using the general procedure, aldehyde 9 (90 mg, 0.56 mmol) was converted into a 15:1 mixture of endo:exo cycloadducts, which was purified via column chromatography (3:1 Hex:EtOAc). Cycloadduct 29 was obtained as a white solid (120 mg, 70%).

^{1}H-NMR(500 MHz, $CDCl_3$): δ 1.45 (m, 1H), 1.75 (m, 1H), 1.92 (m, 2H), 2.75 (m, 1H), 2.81 (m, 2H), 3.03 (dd, 2H, J=10.0, 3.0 Hz), 3.75 (s, 3H), 3.77 (s, 3H), 5.13 (d, 1H, J=3H), 7.10 (m, 1H), 7.20 (m, 2H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.13, 27.56, 28.89, 29.60, 43.66, 49.35, 51.87, 52.17, 68.18, 126.78, 126.88, 129.34, 134.10, 135.39, 137.19, 172.57, 175.50 ppm.

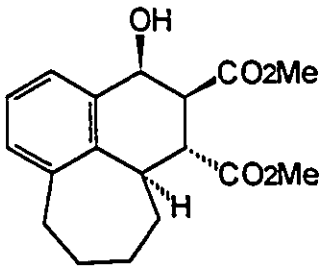
IR (CH_2Cl_2): 3550, 1734 cm^{-1}.

CI-MS(iso, m/z,%): 305 (M^{+}+1).

HRMS: Calc. for $C_{17}H_{18}O_4$ [(M^{+})-H_2O]: 286.12051; Found: 286.12103.

mp: 167 °C.

Cycloadduct 30



30

Using the general procedure, aldehyde **10** (50 mg, 0.29 mmol) was converted into a 3:1 mixture of endo:exo cycloadducts, which was purified via column chromatography (3:1 Hex:EtOAc). Cycloadduct **30** was obtained as a clear oil (35 mg, 40%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (m, 1H), 1.40 (m, 1H), 1.64 (m, 1H), 1.90 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.70 (m, 2H), 2.80 (m, 1H), 3.10 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 5.00 (d, 1H, 3.0 Hz), 7.10 (m, 3H) ppm.

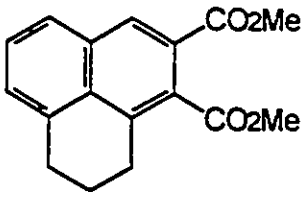
^{13}C-NMR (125 MHz, $CDCl_3$): 27.29, 31.74, 36.28, 36.61, 40.97, 44.61, 47.03, 52.22, 52.26, 69.08, 126.36, 127.68, 130.62, 135.07, 139.14, 143.41, 173.72, 175.96 ppm.

IR (CH_2Cl_2): 3589, 1733 cm^{-1}.

EI-MS (m/z, %): 318 ($M^{+\cdot}$, 1.5), 300 (5.9), 240 (100).

HRMS: Calc. for $C_{18}H_{22}O_5$: 318.14672; Found: 318.14676.

Cycloadduct 32



32

Using the general procedure, aldehyde **9** (90 mg, 0.56 mmol) was converted into cycloadduct **32** which was purified via column chromatography (5:1 Hex:EtOAc). Cycloadduct **32** was obtained as a pale yellow solid (70 mg, 44%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.03 (quintet, 2H, J=8.0 Hz), 3.05 (t, 2H, J=8.0 Hz), 3.09 (3, 2H, J=8.0 Hz), 3.92 (s, 3H), 3.96 (s, 3H), 7.35 (dd, 1H, J=8.0, 1.0 Hz), 7.45 (t, 1H, J=8.0 Hz), 7.74 (dd, 1H, J=8.0, 1.0 Hz), 8.38 (s, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.53, 28.21, 30.74, 52.46, 52.50, 122.14, 124.40, 127.19, 127.20, 127.35, 129.84, 131.44, 132.59, 134.63, 137.17, 166.63, 170.17 ppm.

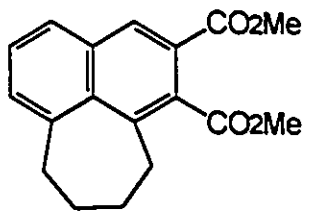
IR (CH_2Cl_2): 1727 cm^{-1}.

EI-MS (m/z, %): 284 ($M^{+\cdot}$, 5.6), 225 (36.8), 165 (13.5), 113 (100).

HRMS: Calc. for $C_{17}H_{16}O_4$: 284.10486; Found: 284.10503.

mp: 78 °C.

Cycloadduct 33



33

Using the general procedure, aldehyde **10** (50 mg, 0.29 mmol) was converted into cycloadduct **33** which was purified via column chromatography (5:1 Hex:EtOAc). Cycloadduct **33** was obtained as a pale yellow solid (67 mg, 78%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.98 (m, 4H), 3.10 (m, 2H), 3.22 (m, 2H), 3.90 (s, 3H), 3.95 (s, 3H), 7.35 (m, 2H), 7.71 (dd, 1H, J=8.0, 1.0 Hz), 8.35 (s, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 26.06, 26.19, 29.90, 34.26, 52.44, 52.54, 124.12, 126.86, 128.30, 130.43, 130.72, 131.06, 133.94, 135.59, 138.77, 142.13, 166.41, 170.63 ppm.

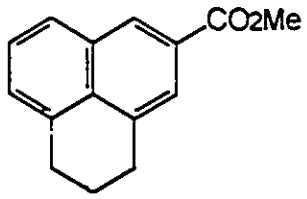
IR (CH_2Cl_2): 1717 cm^{-1}.

EI-MS (m/z, %): 298 ($M^{+\cdot}$, 20.6), 266 (100).

HRMS: Calc. for $C_{18}H_{18}O_4$: 298.12051; Found: 298.12056.

mp: 138 °C.

Cycloadduct 35



35

Using the general procedure, aldehyde 9 (90 mg, 0.56 mmol) was converted into cycloadduct 35 which was purified via column chromatography (10:1 Hex:EtOAc). Cycloadduct 35 was obtained pale yellow oil (83 mg, 61%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.42 (t, 3H, J=7.5 Hz), 2.06 (quintet, 2H, J=7.5 Hz), 3.08 (t, 2H, J=7.5 Hz), 3.11 (t, 2H, J=7.5 Hz), 4.45 (q, 2H, J=7.5 Hz), 7.20 (dd, 1H, J=8.0, 1.0 Hz), 7.40 (t, 1H, J=8.0 Hz), 7.76 (dd, 1H, J=8.0, 1.0 Hz), 7.80 (d, 1H, J=1.0 Hz), 8.40 (d, 1H, J=1.0 Hz) ppm.

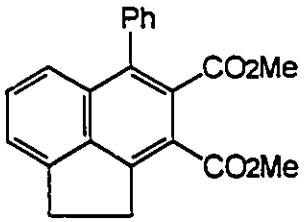
^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.42, 22.96, 31.24, 60.98, 122.99, 126.12, 126.18, 127.09, 127.35, 128.87, 132.23, 132.88, 136.48, 136.81, 167.11 ppm.

IR (CH_2Cl_2): 1711 cm^{-1}.

EI-MS (m/z, %): 240 ($M^{+\bullet}$, 100), 195 (49.5), 167 (76.6).

HRMS: Calc. for $C_{16}H_{16}O_2$: 240.11503; Found: 240.11391.

Cycloadduct 38



38

Using the general procedure, ketone **23a** (50 mg, 0.23 mmol) was converted into cycloadduct **38** which was purified via column chromatography (5:1 Hex:EtOAc). Cycloadduct **38** was obtained pale yellow solid (33 mg, 43%).

^{1}H-NMR (500 MHz, $CDCl_3$): 3.44 (t, 2H, J=7.5 Hz), 3.56 (s, 3H), 3.70 (t, 2H, J=7.5 Hz), 3.92 (s, 3H), 7.2-7.6 (m, 8H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 30.53, 32.74, 51.99, 52.10, 119.12, 121.30, 122.05, 127.77, 128.01, 130.11, 130.84, 132.20, 132.77, 135.20, 136.54, 138.83, 147.78, 151.09, 166.91, 169.87 ppm.

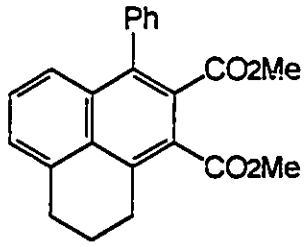
IR (CH_2Cl_2): 1725 cm^{-1}.

EI-MS (m/z, %): 346 ($M^{+\bullet}$, 39.7), 314 (100), 228 (35.5).

HRMS: Calc. for $C_{22}H_{18}O_4$: 346.12051; Found: 346.111975.

mp: 150 °C.

Cycloadduct 39



39

Using the general procedure, ketone **24a** (75 mg, 0.32 mmol) was converted into cycloadduct **39** which was purified via column chromatography (10:1 Hex:EtOAc). Cycloadduct **39** was obtained pale yellow oil (68 mg, 59%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.08 (quintet, 2H, J=7.5 Hz), 3.12 (t, 2H, J=7.5 Hz), 3.23 (t, 2H, J=7.5 Hz), 3.47 (s, 3H), 3.89 (s, 3H), 7.2-7.4 (m, 8H) ppm.

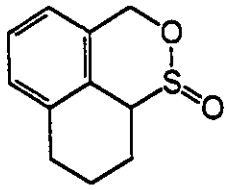
^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.75, 29.21, 31.19, 51.97, 52.37, 125.58, 125.85, 126.17, 127.39, 127.58, 127.92, 128.71, 129.61, 129.99, 130.20, 133.07, 136.01, 137.49, 138.09, 168.91, 169.07 ppm.

IR (CH_2Cl_2): 1730 cm^{-1}.

EI-MS (m/z, %): 360 ($M^{+\cdot}$, 16.0), 328 (100).

HRMS: Calc. for $C_{23}H_{20}O_4$: 360.13616; Found: 360.13705.

Sultine 27



27

In a Pyrex test tube containing a solution of aldehyde 9 (70 mg, 0.44 mmol) in benzene (10 mL) was added SO_2 (0.4g, 6.25 mmol). The resulting solution was sealed with a rubber septa, and irradiated for 12 h. The reaction mixture was then evaporated to dryness, and the resulting dark residue was dissolved in Et_2O (10 mL) and extracted with $NaHCO_3$ (10%, 4 x 5 mL). The combined basic extracts were acidified with HCl (10%), and extracted with Et_2O (4 x 25 mL). The combined organic extracts were subjected to usual work up, affording a white solid. The solid was dissolved in MeOH (5 mL) and $NaBH_4$ (50 mg) was added. The reaction mixture was stirred at RT for 2 h, then evaporated to dryness. Concentrated HCl (5 mL) was added *carefully* and the resulting mixture was heated to 50 °C for 30 min. The solution was then cooled to RT, and extracted with CH_2Cl_2 (4 x 15 mL) and worked up in the usual manner. The clear oil was chromatographed (8:1 Hex:EtOAc) affording sultine 27 as a clear oil (12 mg, 13% from 9).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.85 (m, 2H), 2.20 (m, 1H), 2.40 (m, 1H), 2.78 (m, 1H), 2.89 (m, 1H), 4.15 (d, 1H, J=15.8 Hz), 4.19 (dd, 1H, J=10.5, 4.0 Hz), 4.30 (d, 1H, J=15.8 Hz), 7.10 (d, 1H, J=7.0 Hz), 7.20 (m, 2H) ppm.

IR (CH_2Cl_2): 1133 cm^{-1}.

CI-MS (iso, m/z, %): 209 $M^{\bullet+}$+1, 100).

HRMS: Calc. for $C_{11}H_{12}$ [(M•+)-SO_2]: 144.09390; Found: 144.09180.

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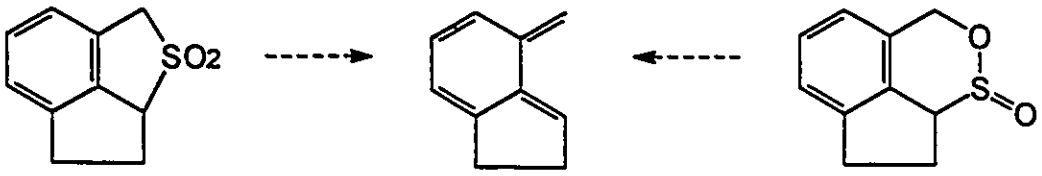
Chapter 10

Synthesis of New Sulfur-Containing Heterocycles and the Thermal Generation of Bicyclic ortho-Quinodimethanes

10.1 Introduction

Although the work discussed in the previous chapter did show that bicyclic ortho-quinodimethanes could be prepared photochemically and trapped with a number of reagents, there still remained one nagging question: Could the tricyclic compounds 1 or 2 be prepared easily, and once prepared, could they be used to thermally generate ortho-quinodimethane 3?



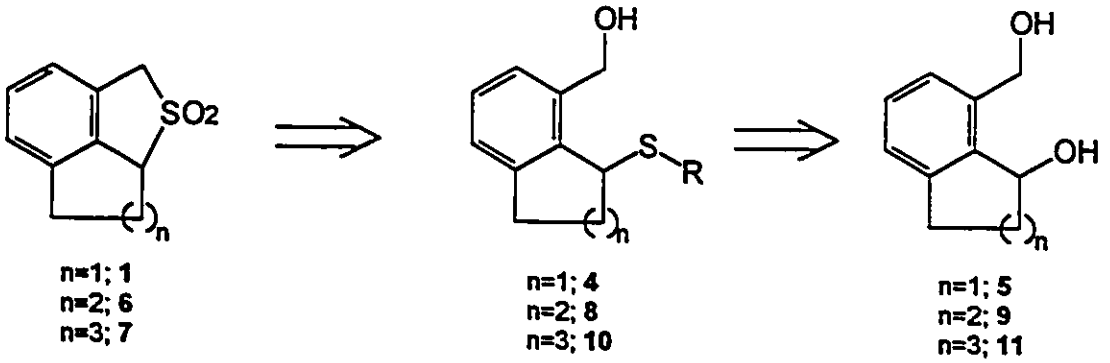
1 3 2

Scheme 10.1 - Postulated Thermal Generation of ortho-Quinodimethane 3

With the goal of answering these questions, studies directed towards the synthesis of 3 and analogues were initiated. The results of these studies are presented in the remainder of this chapter.

10.2 Studies on the Synthesis of Tricyclic Sulfones 1, 6 and 7

The route chosen was an extension of the work discussed in Chapter 3 and is represented retrosynthetically in Scheme 10.2.



Scheme 10.2 - Retrosynthetic Analysis of Tricyclic Sulfones 1, 6 and 7.

10.2.1 Synthesis of Tricyclic Sulfone 6

The synthesis of sulfone 6 started with hydroxy-acid 12 which was prepared in connection with another project (cf Chapter 9). Reduction of hydroxy-acid 12 with $LiAlH_4$ in THF afforded the diol 9 in a yield of 77%. Diol 9 was isolated as a white solid (mp 74 °C) and was readily identified by the presence of a new AB pattern in the ^{1}H-NMR representing the newly created benzylic methylene group. Addition of ZnI_2 to a CH_2Cl_2 solution of diol 9 and a thiol resulted in smooth conversion to hydroxy-sulfides 8a-c, in yields ranging from 82 to 88%. Incorporation of the sulfur nucleophile at the secondary benzylic center was confirmed by the significant upfield shift of the benzylic methine proton. Ring closure to tricyclic sulfide 13 was best accomplished with TsOH and NaI. Thus stirring together a solution of the hydroxy-sulfide in CH_2Cl_2 with one equivalent of TsOH and NaI afforded smooth conversation to the much less polar sulfide 13. Tricyclic sulfide 13 displayed spectroscopic properties consistent with its structure. The smelly, dark oil obtained was immediately oxidized to sulfone 6 with $RuCl_3$ and $NaIO_4$ in $CCl_4/CH_3CN/H_2O$[1] in a yield of 73%. Sulfone 6, isolated as a pale yellow solid (mp 130 °C), displayed the stretches diagnostic of a sulfone group in the IR spectrum; 1133 and 1317 cm^{-1}. Its ^{1}H-NMR spectrum is shown in Fig. 10.1

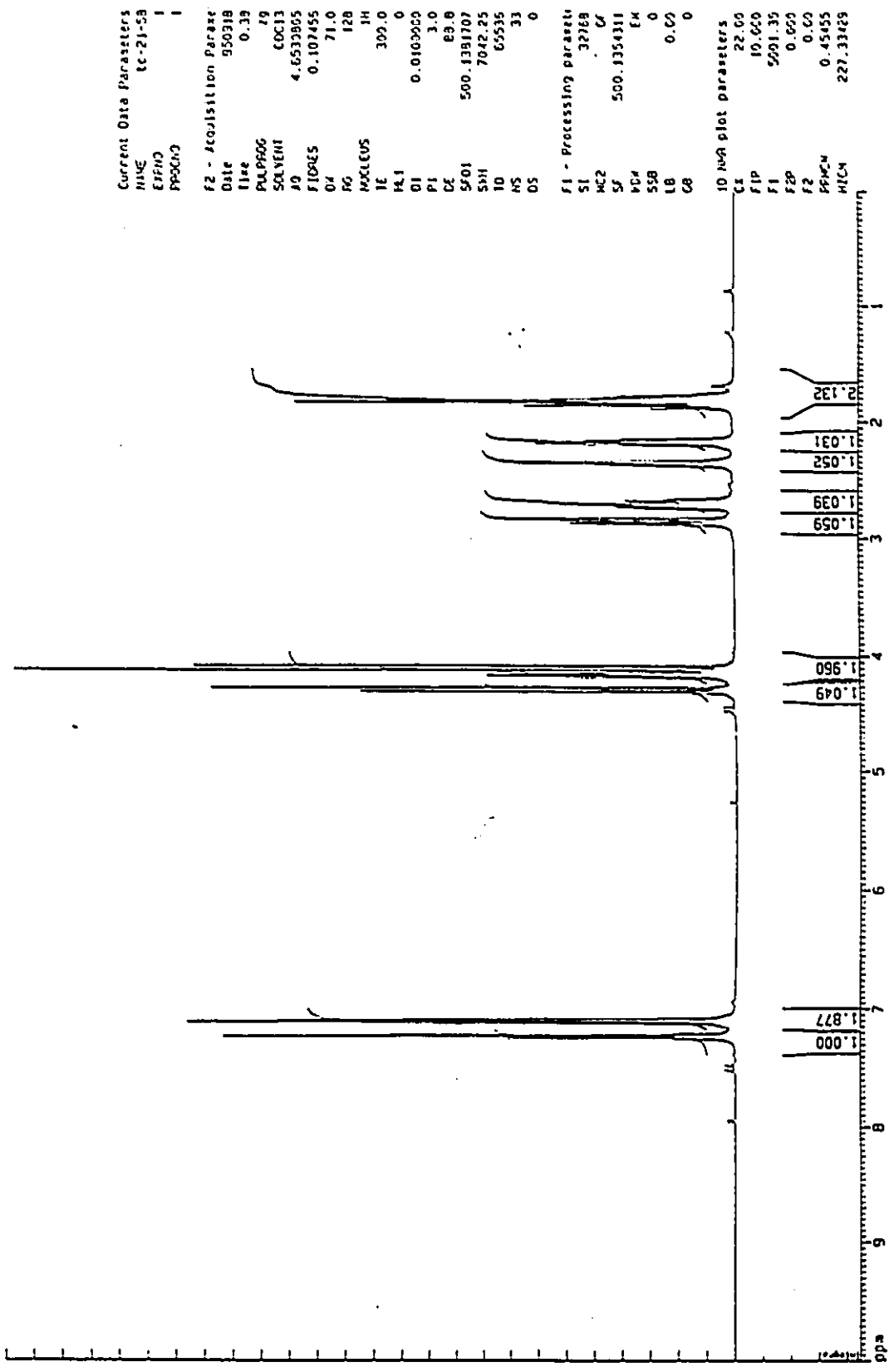
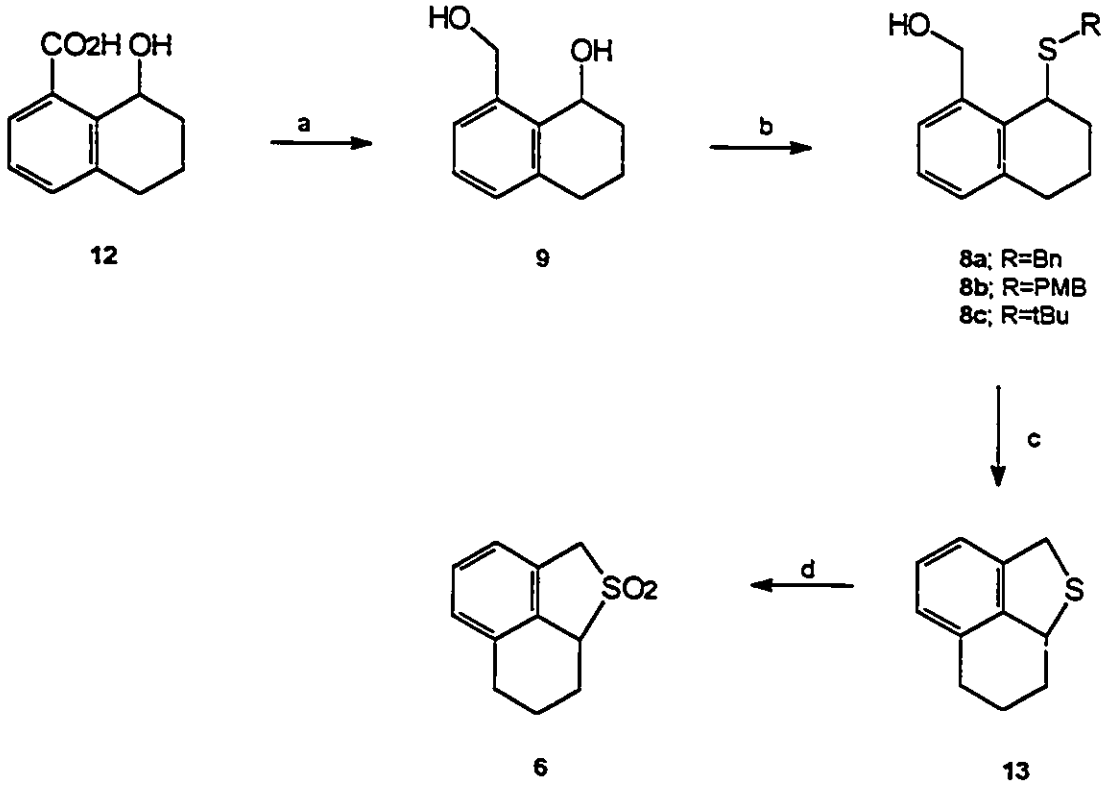


Figure 10.1 500 MHz ^{1}H-NMR Spectrum of Sulfone 6 in $CDCl_3$



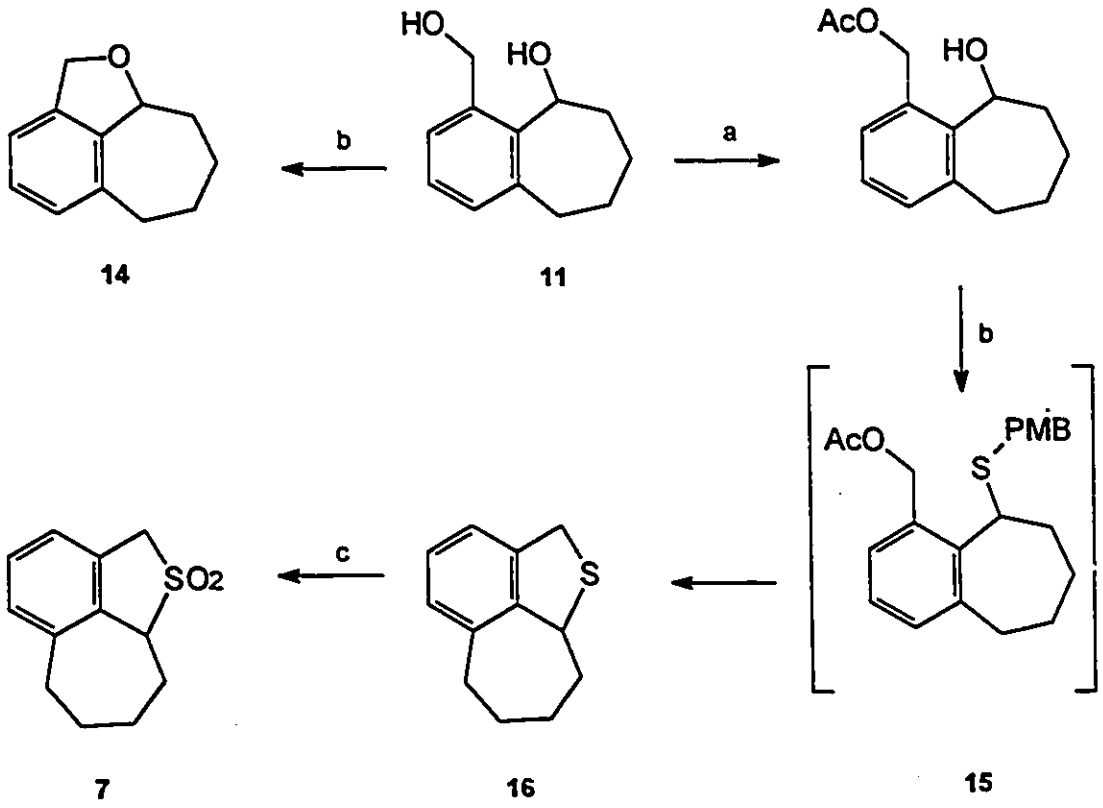
Reagents: a) $LiAlH_4$, THF, Δ (77%); b) RSH, ZnI_2, CH_2Cl_2 (82-88%); c) TsOH, NaI, CH_2Cl_2 (80%); d) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$ (73%).

Scheme 10.3- Synthesis of Tricyclic Sulfone 6.

10.2.2 Synthesis of Tricyclic Sulfone 7.

Based on the successful synthesis of tricyclic sulfone 6, an attempt was made to extend the methodology to the synthesis of 7. Treatment of diol 11, a compound that had been prepared previously (Chapter 9), with ZnI_2 in the presence of PMB-SH led to the formation of tricyclic ether 14, identified on the basis of its ^{1}H-NMR and EI-MS. However, acetylation of the primary benzylic alcohol, which could be done selectively with Ac_2O in CH_2Cl_2 at 0 °C, followed by reaction with p-methoxybenzylmercaptan (PMB-SH) and ZnI_2 led directly to tricyclic sulfide 16 in an overall yield of 50%. Oxidation of the sulfide as reported earlier led to the desired sulfone 7 in a yield of 87%. Sulfone 7, isolated as a pale yellow solid

(mp 135 °C), displayed spectroscopic properties consistent with its structure including two IR stretches at 1118 and 1312 cm^{-1}. Its ^{1}H-NMR spectrum is shown in Fig. 10.2.



Reagents: a) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (77%); b) ZnI_2, PMB-SH, CH_2Cl_2 (50%); c) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (87%).

Scheme 10.4 - Synthesis of Tricyclic Sulfone 7.

10.2.3 Attempted Synthesis of Tricyclic Sulfone 1.

Tricyclic sulfone 1 became the next target. Reduction of hydroxy-acid 17 with $LiAlH_4$ in THF afforded diol 5 as a clear oil in a yield of 70%. Conversion of diol 5 to hydroxy-sulfide 4 was accomplished as described above in a yield of 82%. Reaction of hydroxy-sulfide 4 with TsOH and NaI in CH_2Cl_2 rapidly led to a new, much less polar compound, as evident from tlc analysis. However, ^{1}H-NMR

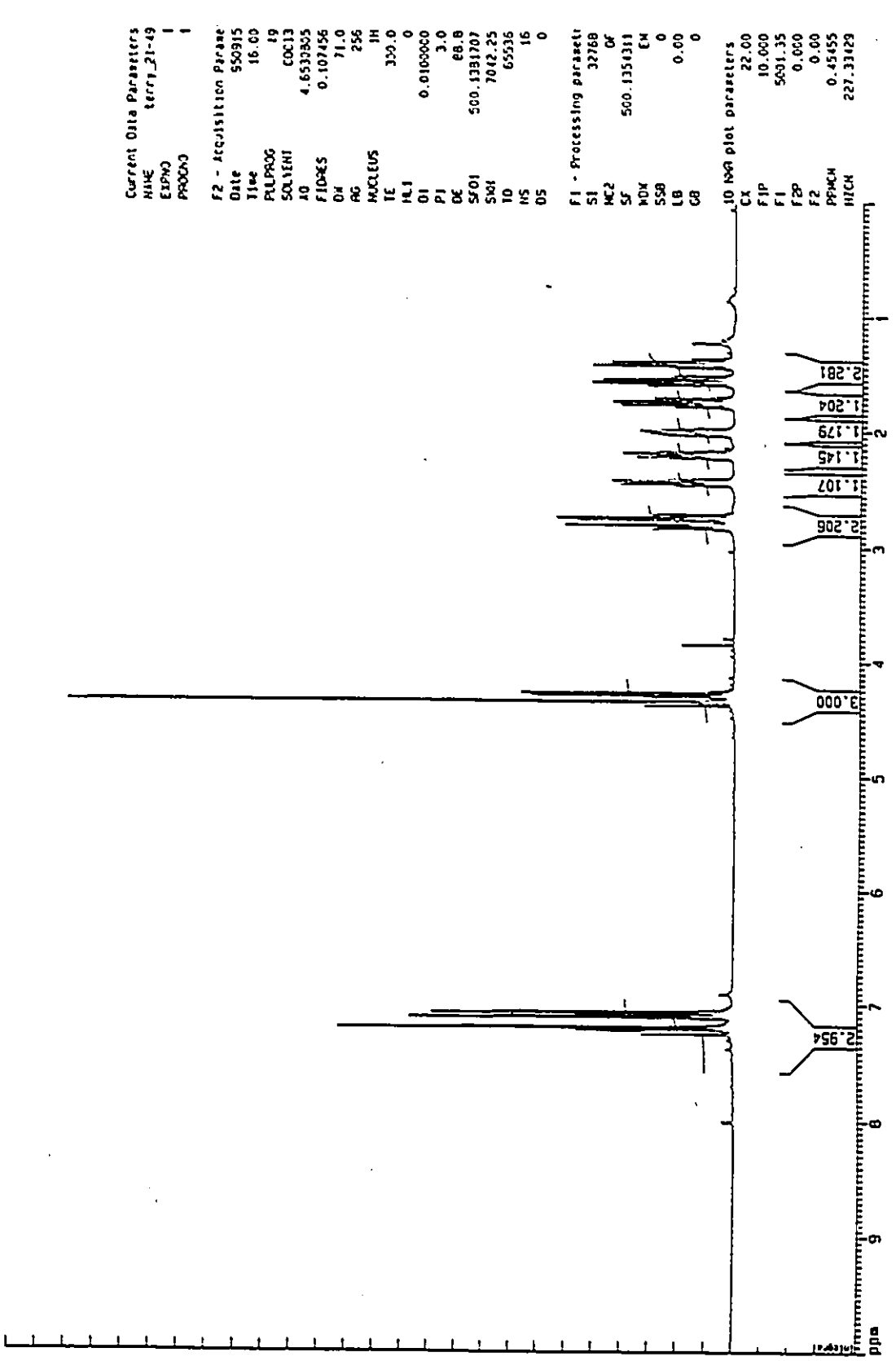
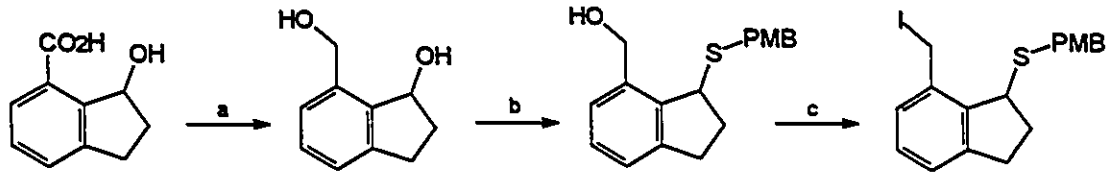


Figure 10.2 500 MHz ^{1}H-NMR Spectrum of Sulfone 7 in $CDCl_3$

analysis of the isolated compound showed that the PMB group still remained. The only difference in the spectrum was a slight downfield shift of the AB pattern representing the isolated benzylic methylene group, consistent with conversion of the benzylic alcohol to the benzylic iodide. In addition, analysis of the IR spectrum showed that the OH group was not present, and CI-MS showed a peak at 411, consistent with an $[M^{+\cdot}+1]$ peak for compound **18**. Higher reaction temperatures led to decomposition of the benzylic iodide, with no trace of the desired tricyclic sulfide.



17 **5** **4** **18**

Reagents: a) $LiAlH_4$, THF, Δ (70%); b) ZnI_2, PMB-SH, CH_2Cl_2 (82%); c) NaI, TsOH, CH_2Cl_2 (83%).

Scheme 10.5 - Synthesis of Iodo-Sulfide **20**

Another approach to tricyclic sulfone **1** involving an intramolecular Mitsunobu reaction[2] as the key step was undertaken. The sequence of reactions is shown in Scheme 10.6. Conversion of diol **5** to hydroxy-thiol **20** was accomplished using the two-step sequence published by workers at Merck[3]. Accordingly, diol **5** was converted to thioacetate **19** in 78% yield. Thioacetate **19** was readily identified by the appearance of a new singlet accounting for three protons at 2.35 ppm, as well as the IR spectrum, which showed stretches at 3355 and 1688 cm^{-1}. The pale yellow oil was hydrolyzed to hydroxy-thiol **20** with KOH in MeOH in a yield greater than 95%. The greenish oil, which showed stretches in the IR spectra at 3602 and 2592 cm^{-1} was immediately dissolved in benzene and added dropwise to a benzene solution of PPh_3 and DIAD. After the disappearance of starting material (tlc), the reaction was subjected to an aqueous work up. However, analysis of the crude reaction mixture did not provide any evidence supporting the formation of tricyclic sulfide **21**.

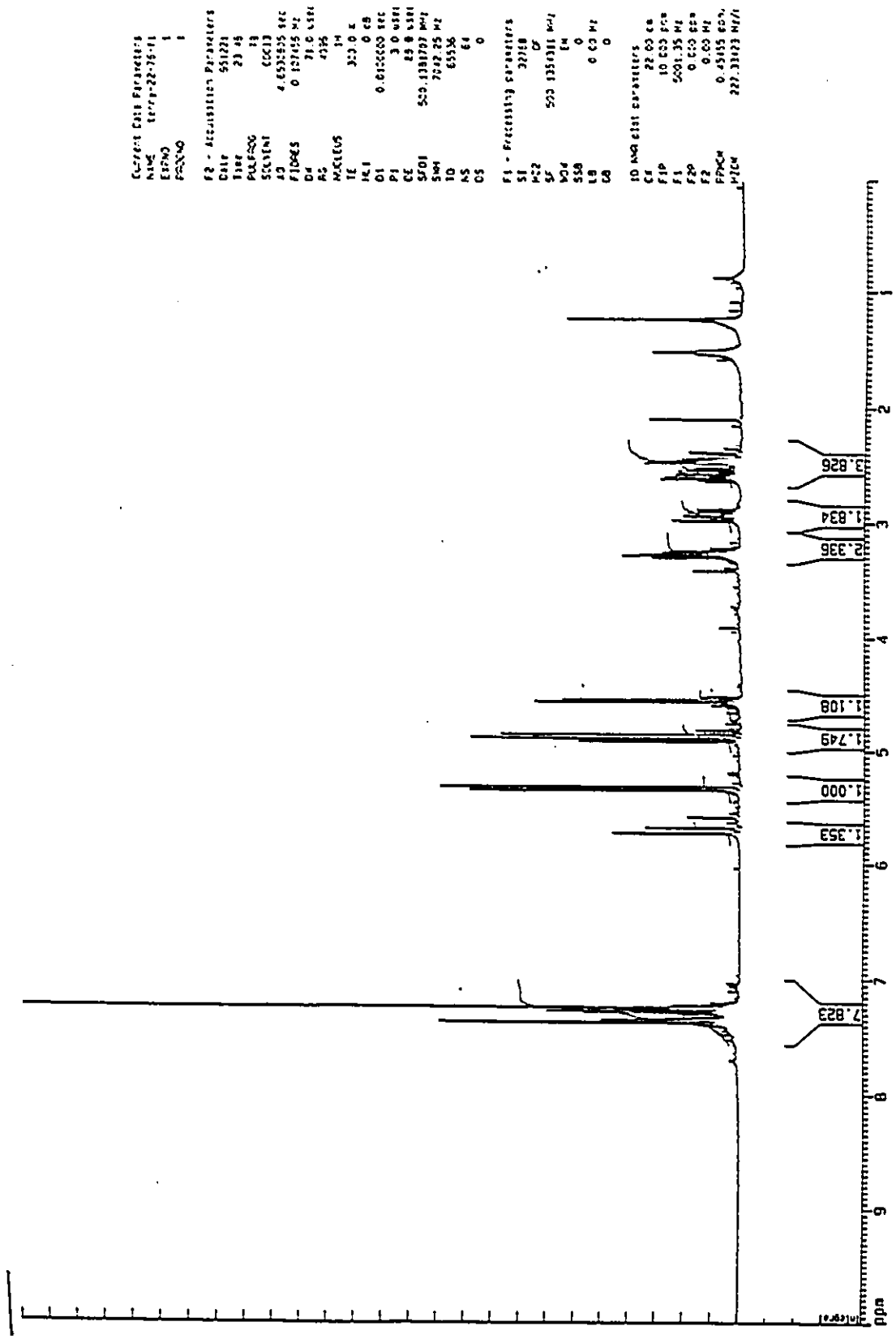
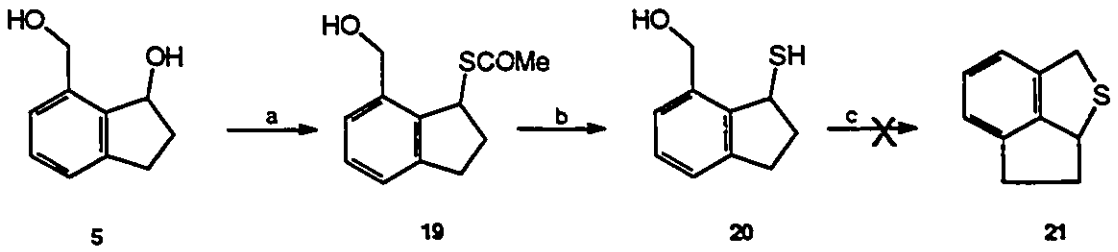


Figure 10.3 500 MHz ^{1}H-NMR Spectrum of Hydroxy-Sulfide 20 in $CDCl_3$



5 19 20 21

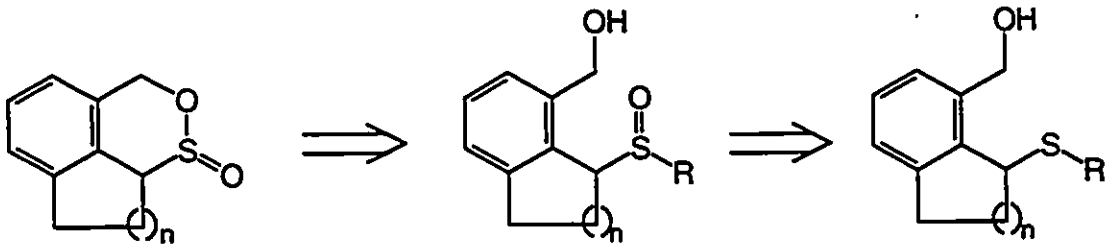
Reagents: a) ZnI_2, HSCOMe, CH_2Cl_2 (78%); b) KOH, MeOH (>95%); c) DIAD, PPh_3, PhH

Scheme 10.6 - Mitsunobu Approach to Tricyclic Sulfide **21**.

Based on these difficulties, work towards the synthesis of **1** was abandoned and studies directed towards the synthesis of **2** were initiated.

10.3 Synthesis of Tricyclic Sultines

As mentioned earlier in this thesis, one of the methods used in the synthesis of sultines is the reaction of a hydroxy-sulfoxide with a halogen source[4]. The proposed synthesis of tricyclic sultines **2** and **22** is shown retrosynthetically in Scheme 10.7.



n=1; **2**
n=2; **22**

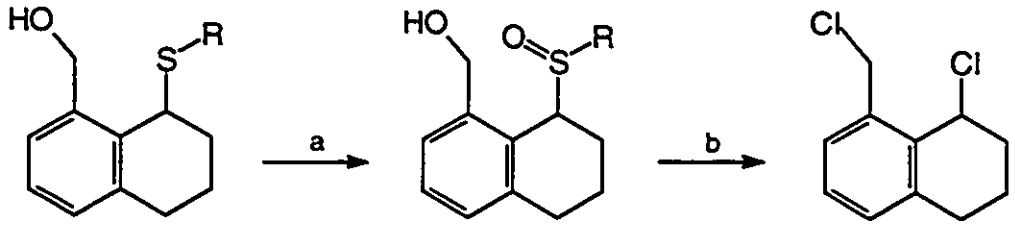
n=1; **23**
n=2; **24**

n=1; **4**
n=2; **8**

Scheme 10.7 - Retrosynthesis of Tricyclic Sultines **2** and **22**.

Due to the problems that had been encountered while trying to prepare any of the ortho-quinodimethane precursors for the indane series, it was decided to conduct the sequence on the tetrahydronapthalene series.

Starting with hydroxy-sulfide **8a**, oxidation to hydroxy-sulfoxide **24a** (mp 95°C, IR: 3683, 1053 cm^{-1}) was accomplished in 82% yield using $NaIO_4$ in $MeOH/H_2O$[5]. Treatment of a solution of **24a** in CH_2Cl_2 with either NCS or SO_2Cl_2 led rapidly and cleanly to a much less polar compound, identified as dichloride **25** on the basis of it ^{1}H-NMR spectrum and EI-MS.



8a; R=Bn
8b; R=PMB
8c; R=tBu

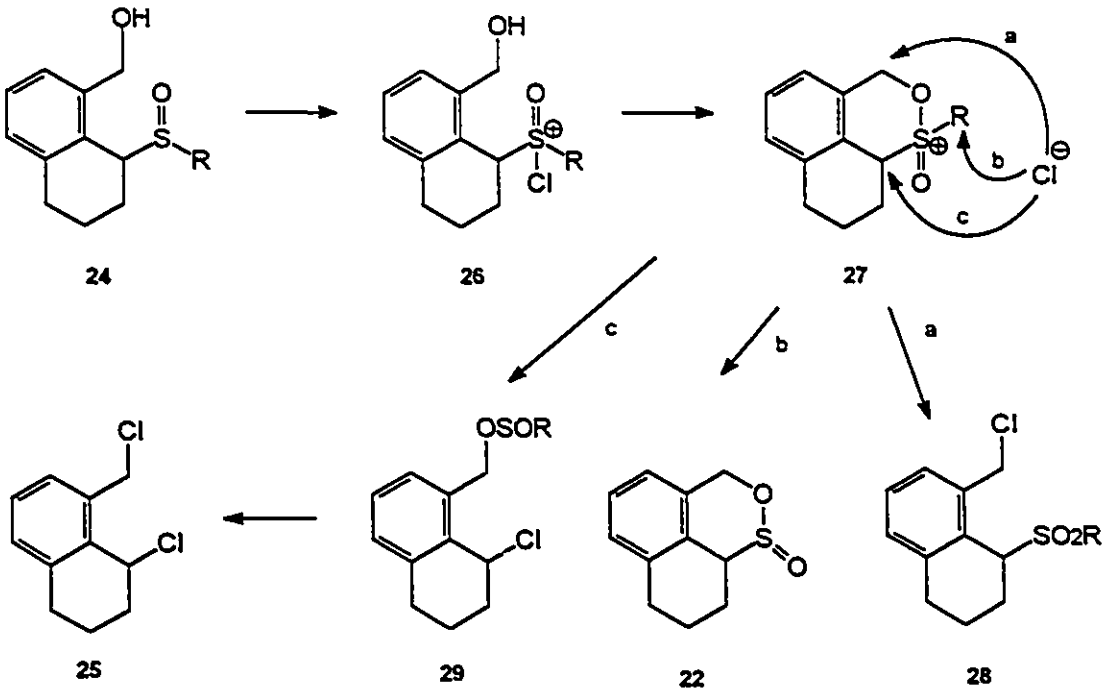
24a; R=Bn
24b; R=PMB
24c; R=tBu

25

Reagents: a) $NaIO_4$, $MeOH/H_2O$ (65-85%); b) NCS or SO_2Cl_2, CH_2Cl_2 (52-75%).

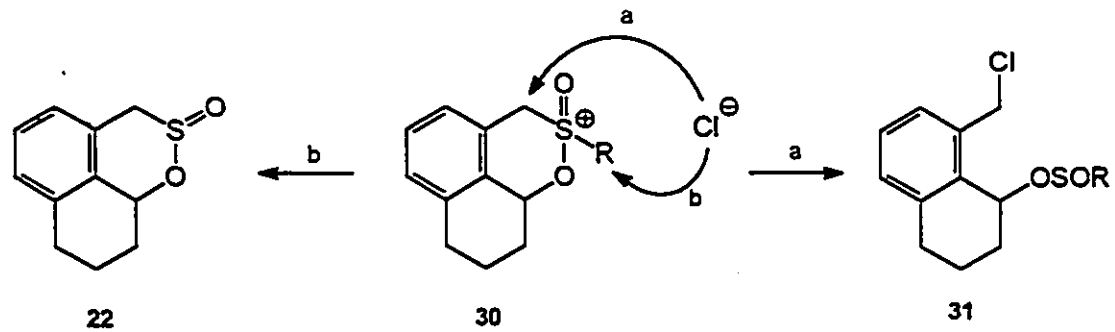
Scheme 10.8 - Approach 1 to Tricyclic Sultine **22**.

A mechanistic explanation to account for the formation of this unexpected product is shown in Scheme 10.9. Initial S-chlorination of **24**, followed by intramolecular ring closure would give the oxo-sulfoxonium salt **27**. Intermediate **27** is then capable of fragmenting via three pathways. Pathway a need not be considered since the carbons α to the positive sulfur center would be more electrophilic. The competition between pathways b and c may be rationalized on the stability of the carbocation at the electrophilic center. Thus, for **27a** (R=Bn), reaction via pathway b gives a secondary benzylic carbocation, whereas reaction via pathway c would give a primary benzylic carbocation. An attempt was made to favor pathway c by making a more stable carbocation at this electrophilic carbon. However, changing the R group to p-methoxybenzyl or t-butyl failed to give any of the desired product. Presumably, excess chloride reacts at the primary benzylic center of **29** giving rise to the observed **25**.



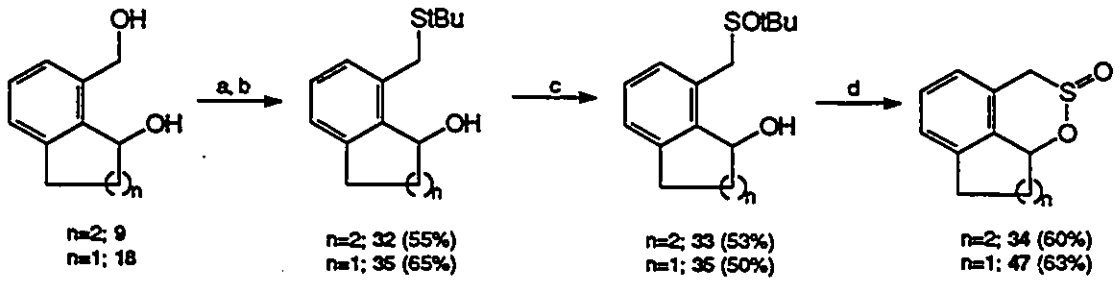
Scheme 10.9 - Proposed Mechanism for Formation of 25 from 24

Evaluation of the reaction mechanism, and more importantly, the key intermediate 27, indicated that transposing the position of the oxygen and sulfur atoms may lead to the correct fragmentation. If the intermediate was 30, then once again there would be a competition between reaction at the electrophilic carbons adjacent to the sulfur. In this case, however, reaction via pathway b should be favored,[4] especially if R=t-Bu. This is shown in Scheme 10.10.



Scheme 10.10 - Proposed Route to Sultine 22 via Intermediate 30.

To test this idea, diol 9 and pyridine were dissolved in CH_2Cl_2 and cooled to -78 °C. A solution of $POCl_3$ in CH_2Cl_2 was then added dropwise, and the temperature was slowly allowed to reach RT. Tlc showed that as starting material was consumed, a new, less-polar spot appeared. Attempts to purify this intermediate led to considerable solvolysis, returning starting material. However, addition of sodium t-butyl mercaptide to a THF solution of the crude product led to hydroxy-sulfide 32 in a yield of 65% from diol 9. Hydroxy-sulfide was identified on the basis of its ^{1}H-NMR spectrum, which showed an upfield shift of the AB pattern of the benzylic methylene group, consistent with incorporation of sulfur at this center. Oxidation with $NaIO_4$ afforded 33 as mixture of diastereomers in a non-optimized yield of 53%. Addition of SO_2Cl_2 to a solution of 33 in CH_2Cl_2 led to sultine 34 (60%). Sultine 34 was obtained as a single diastereomer after column chromatography. The clear oil displayed a ^{1}H-NMR spectrum (Fig. 10.4) that showed the expected AB pattern for the benzylic methylene group (4.85 and 5.55 ppm, J=14.1 Hz) and a triplet for the benzylic methine (5.63 ppm, J=3.0 Hz). The high-field region of the spectrum was quite complicated due to the extensive couplings and the non-symmetry of the sultines. Examination of the IR spectra showed a band at 1116 cm^{-1}, further supporting the proposed structure. Although EI-MS did not show a molecular ion, there was a peak at m/z 144, corresponding to loss of SO_2 from the parent ion. Inspection of the CI-MS did show a ($M^{+\bullet}$+1) peak at m/z 209. The synthetic sequence is shown in Scheme 10.11.



Scheme 10.11 - Synthesis of Tricyclic Sultines 37 and 40.

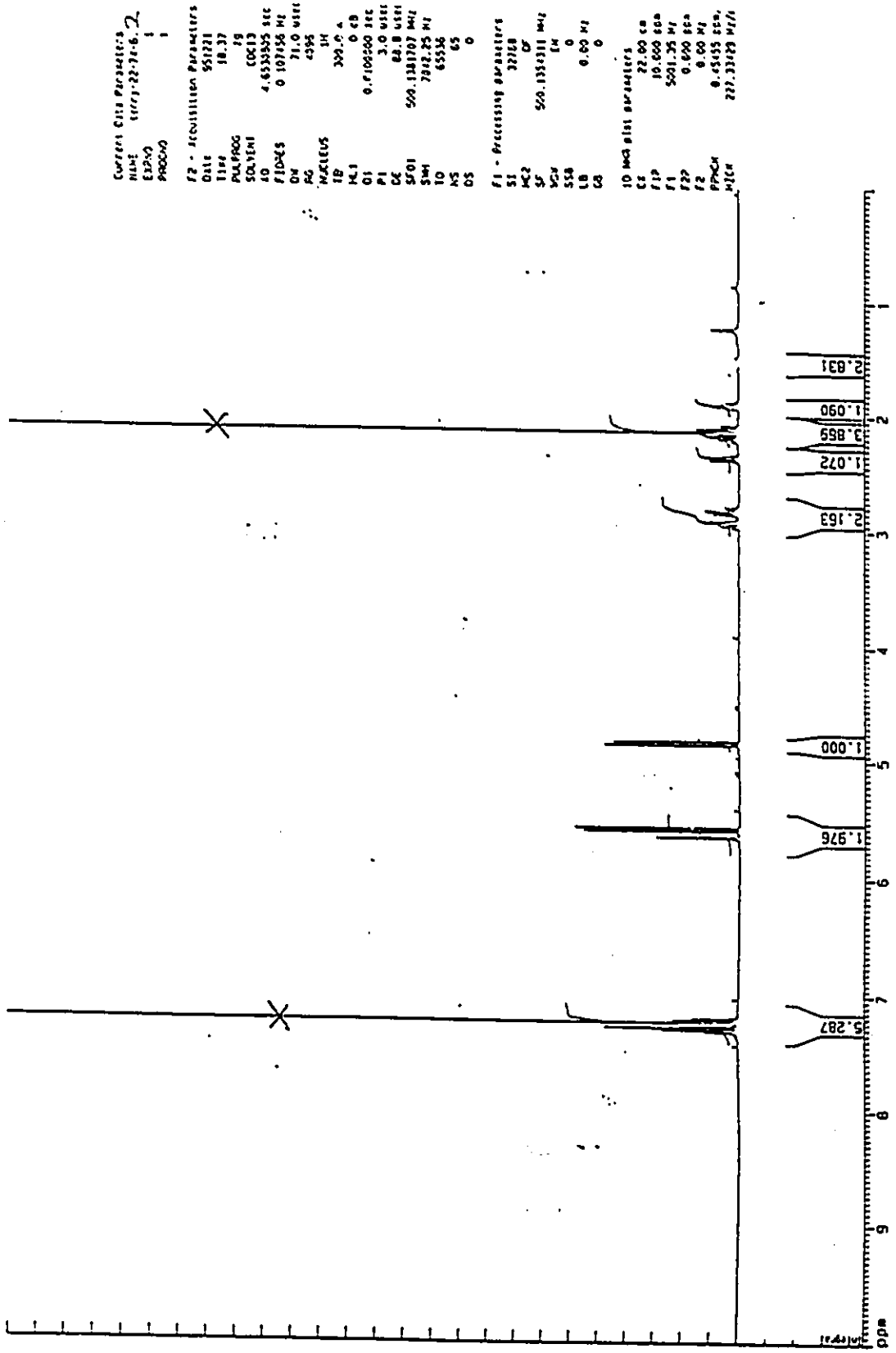


Figure 10.4 500 MHz ^{1}H-NMR Spectrum of Sultine 34 in $CDCl_3$

As can be seen in Scheme 10.11, this methodology was also successfully extended to the indane series, culminating in the successful synthesis of the 6-6-5 tricyclic sultine 37. The ^{1}H-NMR of sultine 37 is shown in Fig. 10.5. As is readily apparent, separation of the diastereomers was not achieved in this case, making the ^{1}H-NMR spectrum quite complicated. The isolated material seems to be a 1:1 mixture of diastereomers, as estimated by comparing the integrated area of the two AB patterns for the benzylic methylene groups. One diastereomer displayed a pattern of AB doublets at 4.86 and 5.35 ppm (J=14.5 Hz), with the methine proton appearing as a doublet of doublets at 5.74 ppm (J=8.0, 1.0 Hz). The other diastereomer displayed an AB pattern at 4.56 and 4.91 ppm (J=12.9 Hz). The benzylic methine appeared as a doublet of doublets at 5.67 ppm (J=8.0 Hz, 1.0 Hz).

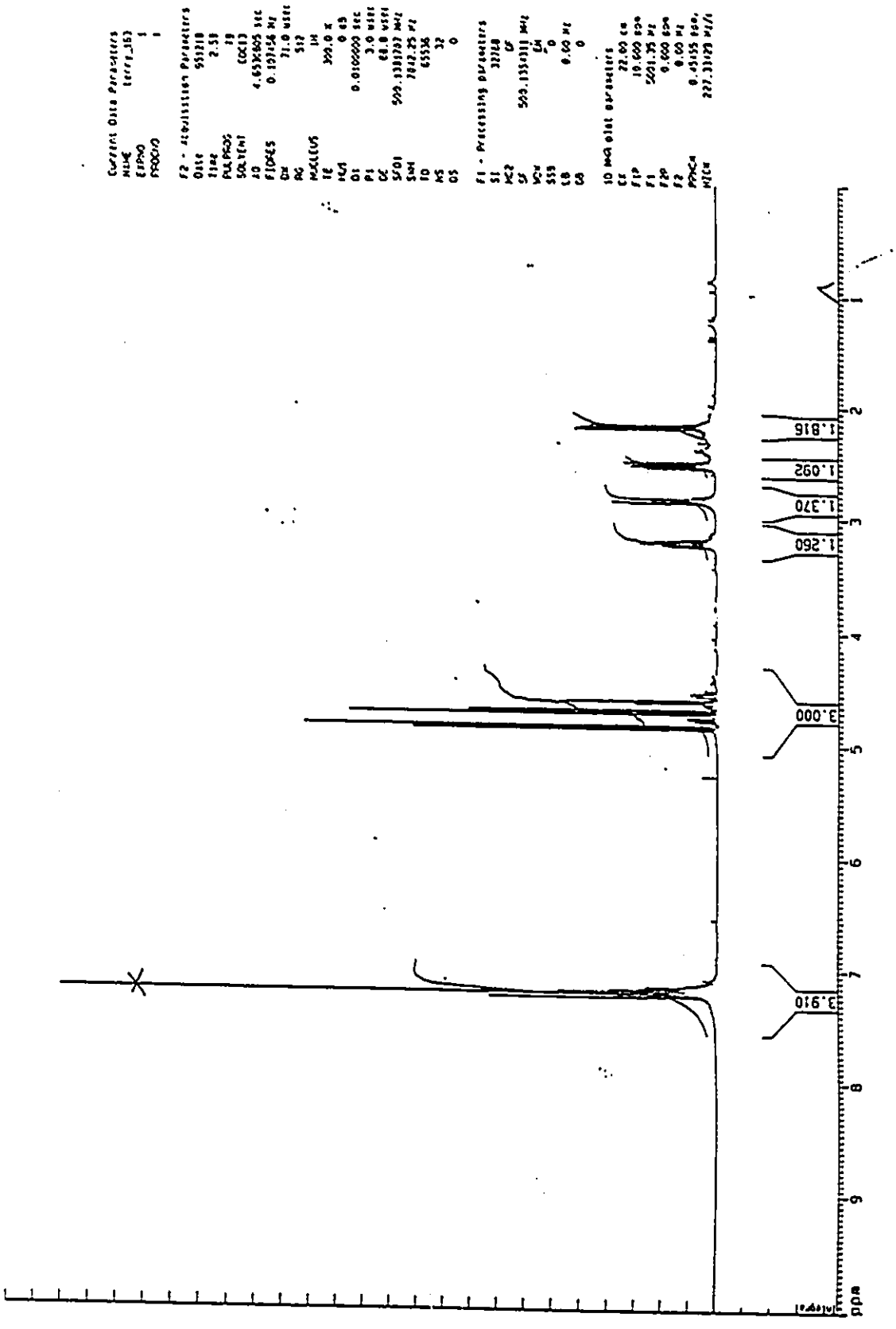
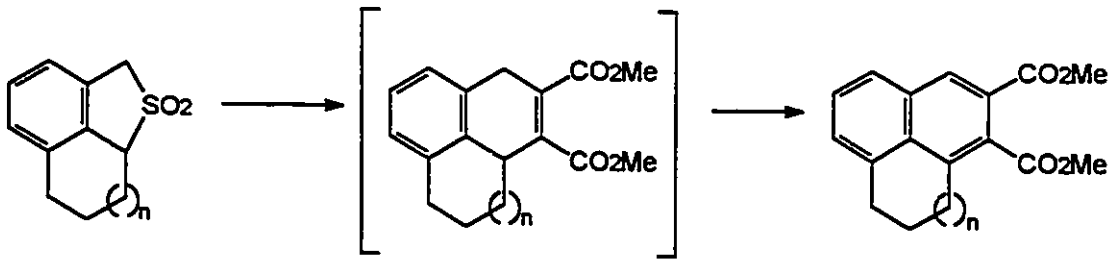


Figure 10.5 500 MHz ^{1}H-NMR Spectrum of Suline 35 in $CDCl_3$

10.4 Thermal Generation of Bicyclic ortho-Quinodimethanes

It now remained to find conditions that would allow for the generation and trapping of these bicyclic ortho-quinodimethanes from sulfones 6 and 7 and sultines 34 and 37. Unfortunately, time constrains did not allow for a systematic study of the thermal behavior of sultine 34 and 37 (activation temperatures, isomerization reactions, trapping). However, a reliable route to these compounds was developed, and the remainder of the study should be quite straightforward.

The thermal generation of bicyclic ortho-quinodimethanes from sulfones 6 and 7 was investigated. The best conditions found for the expulsion of SO_2 from sulfones 6 and 7 were to add excess dienophile to the sulfone, in the present cases, DMAD was used as a dienophile, and, in the absence of a solvent, heat the mixture from 250-320 °C for 15-20 min. Column chromatography of the crude products afforded the expected cycloadducts. In both cases, the intermediate dihydronapthalene was oxidized to the naphthalene derivative. The yields were acceptable, 65% for sulfone 6 and 45% for sulfone 7. The lower yield for the cycloaddition of 7 is presumably a reflection of the slightly longer reaction time and higher temperature used as compared to 6. The results of this study are shown in Scheme 10.12. The cycloadducts 38 and 39 were found to be identical to the same compounds prepared in Chapter 9 of this thesis.



n=1; 6
n=2; 7

n=1; 38
n=2; 39

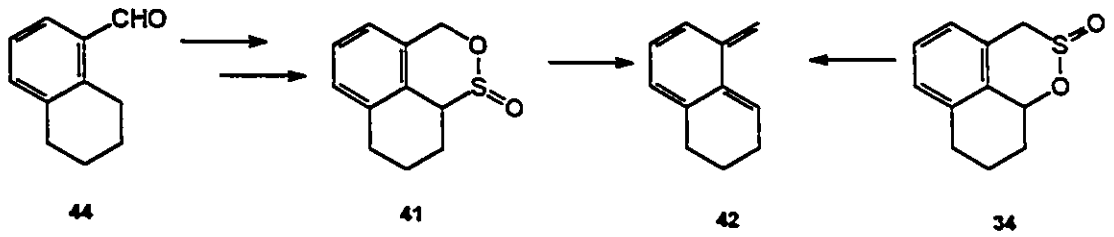
Scheme 10.12 - Generation and Trapping of Bicyclic ortho-Quinodimethanes from Sulfones 6 and 7

10.5 Conclusions and Suggestions for Further Research

Having completed a fairly comprehensive study on various routes to bicyclic ortho-quinodimethanes, there are still some questions that must be addressed. This final section poses some of these questions, and suggests some synthetic sequences that could be used to answer them.

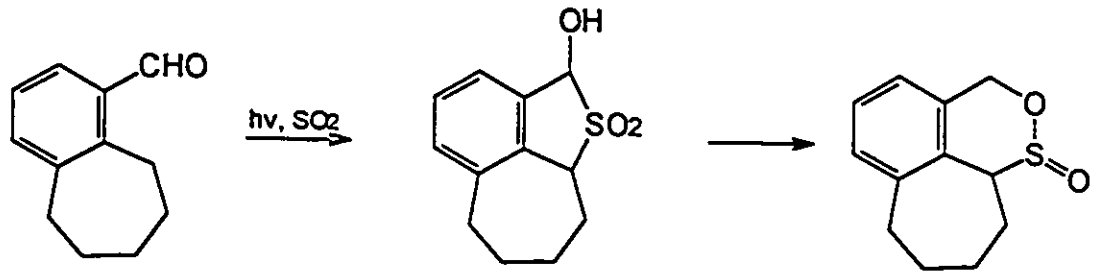
10.5.1 Tricyclic Sultines

With a viable route to these compounds, a systematic study of their reactivity should be done. This would involve repeating the sequences reported in Chapters 9 and 10. Since the photochemistry in Chapter 9 complements the ionic chemistry of chapter 10, it should be possible to compare the chemistry of the isomeric sultines as shown in Scheme 10.13.



Scheme 10.13 - Comparison of Thermal Chemistry of Sultines 41 and 34.

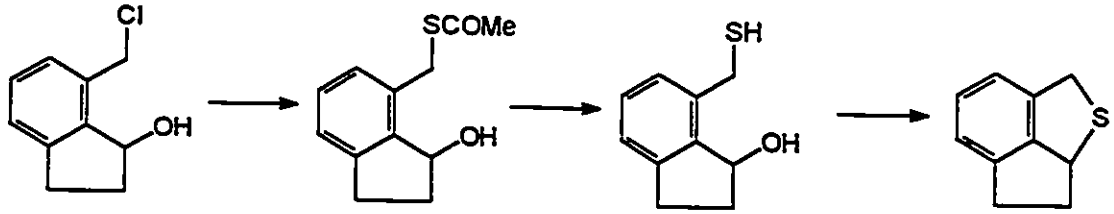
The photochemistry developed in Chapter 9 should also provide the only route to the 6-6-7 sultine ring system. Activation of the primary hydroxy group of diol 11 would be expected to result in the formation of the tricyclic ether 14 in a manner similar to what is reported in section 10.2, facilitating against the use of ionic chemistry. A photochemical route to sultine 45 is shown in Scheme 10.14.



43 44 45

Scheme 10.14 - Proposed Route to Tricyclic Sultine 45.

If the thermolysis of sultine 37 in the absence of a dienophile does not result in the formation of the 6-5-5 sulfone 21, then one other route that had not been explored is shown in Scheme 10.15. Synthesis of the primary benzylic chloride as reported in this chapter, followed by displacement with thiolacetic acid to thioacetate 46 and hydrolysis to the thio-alcohol 47. Addition of a Lewis acid will ionize the benzylic alcohol, and if 21 is an accessible compound, then this reaction should result in its preparation.

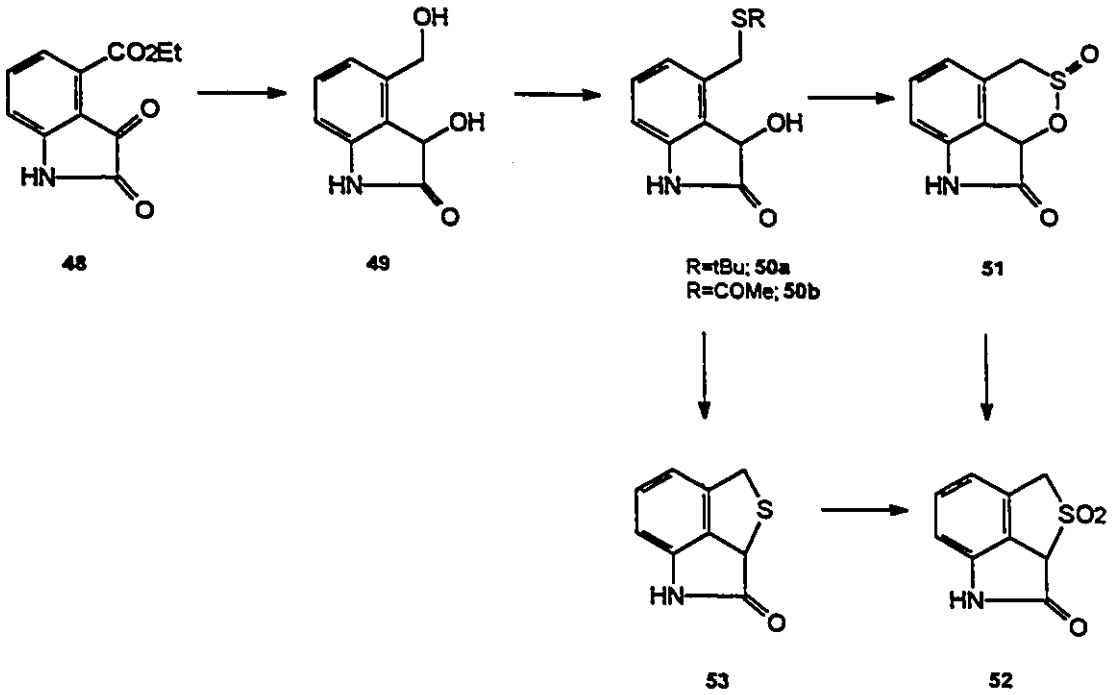


46 47 21

Scheme 10.15 - Possible Route to Tricyclic Sulfide 21

Finally, it is fitting that this thesis end the way it started, with a proposed route to tricyclic sulfone 52, a possible intermediate in the synthesis of lysergic acid. Isatin 48 is accessible via Gassman chemistry[6]. Based on the studies of oxindole reductions (Chapter 7), reduction of isatin 48 is expected to be facile, providing diol 49. Diol 49 could then be converted to sulfide 50a via the methodology discussed in this

chapter and then converted to sultine 51. Sultine 51 could then be used as an oxindole derived ortho-quinodimethane, or it could be isomerized to sulfone 62. Alternatively, diol 49 could be converted to thioacetate 50b. Hydrolysis of the thioacetate to the free thiol, followed by Lewis acid induced ring closure could provide a route to sulfide 53, an obvious precursor to sulfone 52. These reactions sequences are shown in Scheme 10.16.

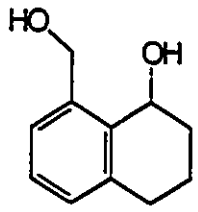


Scheme 10.16 - Possible Route to Sulfone 52 and Sultine 51.

10.6 Experimental

General experimental was as reported in Chapter 3. Hydroxy-acids 8 and 17 and diol 12 were prepared as described in Chapter 9. Final products and intermediates in this chapter are *not* characterized fully. Most of the sequences in this chapter were conducted when many of the analytical services of the department were not available. However, as the time of the writing of this thesis, an undergraduate student is repeating the sequences to sultines 34 and 35.

1-Hydroxy-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene (9).



9

A solution of hydroxy-acid 8 (5.00g, 26.04 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (2.00 g, 52.63 mmol) in THF (25 mL). After addition was complete, the reaction mixture was stirred at RT for 30 min, then was refluxed for 2 h. The reaction mixture was then cooled to RT and quenched by the *careful* addition of potassium sodium tartrate (10%, 250 mL) and EtOAc (100 mL). The resulting mixture was stirred for 6h, the organic phase separated and subjected to standard work up, affording the title compound as white plates (3.57 g, 77%).

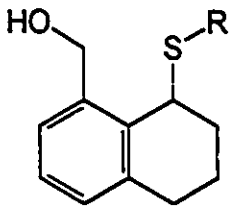
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.75 (m, 2H), 1.85 (m, 1H), 2.05 (m, 1H), 2.65 (m, 1H), 2.80 (m, 1H), 3.58 (br, 2H), 4.42 (d, 1H, J=12.2 Hz), 4.90 (d, 1H, J=12.2 Hz), 5.00 (t, 1H, J=4.0 Hz), 7.10 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.18, 30.04, 31.57, 36.73, 64.15, 64.18, 127.80, 127.85, 129.83, 136.87, 138.01, 139.86 ppm.

IR (CH_2Cl_2): 3597, 3402 cm^{-1}.

mp: 74 °C.

General Procedure for the preparation of 1-Thioalkyl-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene (8).



8a; R=Bn
8b; R=PMB
8c; R=tBu

ZnI_2 (180 mg, 0.56 mmol) was added in one portion to a solution of diol 9 (100 mg, 0.56 mmol) and one equivalent of the appropriate thiol in CH_2Cl_2 (20 mL). The resulting mixture was stirred at RT for 2 h, after which time it was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (20 mL). The combined organic extract were combined and subjected to standard work up. The resulting cloudy oil was chromatographed (3:1 Hex:EtOAc) affording the final product.

1-Thiobenzyl-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene (8a) (pale yellow oil).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.80 (m, 2H), 2.25 (m, 2H), 2.80 (m, 2H), 3.75 (d, 1H, J=13.3 Hz), 3.85 (d, 1H, J=13.3 Hz), 4.30 (m, 3H), 4.49 (d, 1H, J=12.4 Hz), 7.0-7.5 (m, 8H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.47, 27.19, 29.32, 36.67, 39.73, 62.33, 127.19, 127.32, 127.52, 128.57, 128.97, 129.13, 133.45, 137.62, 137.65, 139.68 ppm.

IR (CH_2Cl_2): 3599 cm^{-1}.

CI-MS (iso): 285 [(M^{+*}+1), 2.8].

1-Thio(p-methoxybenzyl)-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene (8b) (white solid).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.80 (m, 2H), 2.20 (m, 2H), 2.80 (m, 3H), 3.70 (d, 1H, J=13.2 Hz), 3.78 (s, 3H), 3.80 (d, 1H, J=13.2 Hz), 4.20 (m, 2H), 4.53 (d, 1H, J=12.0 Hz), 6.85 (d, 1H, J=7.0 Hz), 6.9-7.2 (m, 3H), 7.28 (d, 2H, J=7.0 Hz) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.42, 27.20, 29.27, 36.02, 39.71, 55.19, 62.24, 113.87, 127.19, 127.38, 129.01, 129.41, 129.98, 133.46, 137.48, 139.68, 158.64 ppm.

IR (CH_2Cl_2): 3328 cm^{-1}.

CA: For $C_{19}H_{22}SO_2$; Calc: C (72.58), H (7.05); Found: C (72.62), Found (7.17).

mp: 75 °C.

1-Thio(t-butyl)-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene (8c) (white solid).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.55 (s, 9H), 1.85 (m, 1H), 2.10 (m, 1H), 2.30 (m, 1H), 2.50 (m, 1H), 2.90 (m, 2H), 3.40 (d, 1H, J=8.6 Hz), 4.70 (m, 2H), 5.00 (d, 1H, J=12.0 Hz), 7.08 (d, 1H, J=8.0 Hz), 7.20 (m, 2H) ppm.

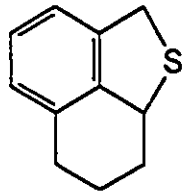
^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.89, 29.10, 29.65, 31.85, 39.21, 45.41, 62.92, 127.26, 127.86, 129.46, 134.72, 137.83, 139.22 ppm.

IR (CH_2Cl_2): 3341 cm^{-1}.

CI-MS (iso): 251 [(M^{+}+1), 1.8].

mp: 140 °C.

Tricyclic Sulfide 13.



13

To a solution of hydroxy-sulfide **8b** (100 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) was added TsOH (90.8 mg, 0.48 mol) and NaI (72 mg, 0.48 mmol). The resulting solution was stirred at RT for 10 h, poured into H_2O (50 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were worked up in the usual manner, and the dark oily residue chromatographed (20:1 Hex:EtOAc). The title compound was isolated as a slightly green oil (45 mg, 80%).

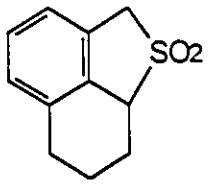
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.60 (m, 1H), 1.80 (m, 1H), 2.10 (m 1H), 2.30 (m, 1H), 2.80 (m, 2H), 3.85 (d, 1H, J=16.0 Hz), 4.32 (dd, 1H, J=16.0, 1.0 Hz), 4.50 (d, 1H, J=12.0 Hz), 6.9-7.1 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 23.35, 26.24, 29.93, 26.44, 48.79, 121.42, 126.12, 127.02, 134.59, 140.73, 141.64 ppm.

EI-MS(m/z, %): 176 ($M^{+\cdot}$, 61.8), 148 (100).

HRMS: Calc. for $C_{11}H_{12}S$: 176.06597, 176.06317.

Tricyclic Sulfone 6



6

A mixture of sulfide **11** (140 mg, 0.80 mmol) and H_5IO_6 (400 mg, 1.75 mmol) in CH_3CN (1 mL), CCl_4 (1 mL) and H_2O (1.5 mL) was stirred until it became homogenous. $RuCl_3 \bullet xH_2O$ (cat) was added and the resulting black reaction mixture stirred at RT for 3 h, after which time it was poured into Et_2O (50 mL). The organic phase was separated. Usual work up afforded sulfone **6** as a pale yellow solid (121 mg, 73%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.85 (m, 2H), 2.15 (m, 1H), 2.35 (m, 1H), 2.70 (m, 1H), 2.85 (m, 1H), 4.09 (d, 1H, J=15.4 Hz), 4.15 (dd, 1H, J=10.2, 1.0 Hz), 4.27 (d, 1H, J=15.4 Hz), 7.10 (m, 2H), 7.40 (m, 1H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.41, 21.20, 26.07, 55.55, 61.47, 123.03, 128.20, 128.40, 130.20, 131.41, 136.03 ppm.

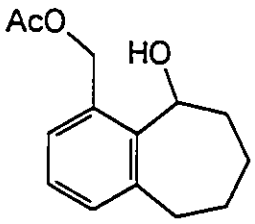
IR (CH_2Cl_2): 1317, 1133 cm^{-1}

CI-MS (iso): 209 [($M^{+\bullet}$+1), 100].

HRMS: Calc. for $C_{11}H_{12}$ ($M^{+\bullet}$-SO_2): 144.09390; Found: 144.09357.

mp: 130 °C.

10-Acetoxymethyl-1-hydroxy-benzosuberane.



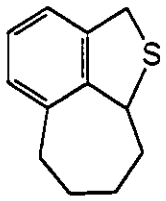
A solution of Ac_2O (265 mg, 2.60 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a cooled (0°C) solution of 10-hydroxymethyl-1-hydroxy-benzosuberane (500 mg, 2.60 mmol), triethylamine (312 mg, 3.09 mmol) and DMAP (50 mg) in CH_2Cl_2 (30 mL). The resulting solution was stirred at 0 °C for 30 min, then poured into H_2O (50 mL). Separation of the organic solution and usual workup afforded a clear oil. Chromatography afforded the title compound **14** as a clear oil (470 mg, 77%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (m, 1H), 1.65 (m, 2H), 1.90 (m, 2H), 2.05 (s, 3H), 2.15 (m, 2H), 2.65 (dd, 1H, J=16.0, 8.0 Hz), 3.35 (dt, 1H, J=8.0, 1.0 Hz), 5.13 (d, 1H, J=14.0 Hz), 5.19 (dd, 1H, J=14.0 Hz), 5.15 (dd, J=8.0, 2.5 Hz)7.10 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.00, 24.63, 28.17, 32.81, 35.75, 65.48, 69.12, 127.65, 128.61, 131.64, 133.05, 142.08, 144.29, 170.64 ppm.

IR (CH_2Cl_2): 3200, 1710 cm^{-1}.

Tricyclic Sulfide 16



16

To a solution of mono-acetate **14** (200 mg, 0.85 mmol) in CH_2Cl_2 (20 mL) was added sequentially 4-methoxy-α-toluenethiol (158 mg, 1.02 mmol) and ZnI_2 (327 mg, 1.02 mmol). The resulting cloudy solution was stirred at RT for 10 h, after which time it was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were subjected to normal workup. Chromatography with hexanes afforded the title compound as a yellow oil (80 mg, 50%).

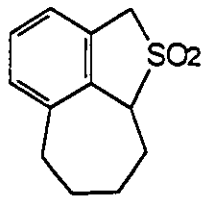
^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.20 (m, 1H), 1.80 (m, 2H), 2.05 (m, 3H), 2.80 (m, 2H), 4.21 (d, 1H, J=12.5 Hz), 4.38 (dd, 1H, J=12.5, 3.0 Hz), 4.74 (dd, 1H, J=11.0, 3.0 Hz), 6.90 (d, 1H, J=7.5 Hz), 7.00 (d, 1H, J=7.5 Hz), 7.20 (t, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 27.56, 31.27, 36.73, 37.66, 39.17, 55.00, 122.57, 126.94, 127.22, 139.76, 140.47, 144.29 ppm.

EI-MS (m/z, %): 190 ($M^{+\cdot}$, 100).

HRMS: Calc. for $C_{12}H_{14}S$: 190.08162; Found: 190.08107.

Tricyclic Sulfone 7



7

Sulfone 7 was prepared from sulfide 14 (75 mg, 0.39 mmol) in a manner identical to that described for sulfone 6. The title compound was isolated as a white solid (76 mg, 87%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (m, 1H), 1.55 (m, 1H), 1.75 (m, 1H), 2.00 (m, 1H), 2.20 (m, 1H), 2.42 (m, 1H), 2.75 (m, 1H), 4.27 (dd, 1H, J=12.0, 2.0 Hz), 4.32 (d, 1H, J=15.9 Hz), 4.36 (d, 1H, J=15.9 Hz), 7.06 (d, 1H, J=7.5 Hz), 7.09 (d, 1H, J=7.5 Hz), 7.18 (t, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 27.37, 27.81, 29.64, 35.91, 56.31, 66.97, 123.31, 128.50, 129.00, 129.17, 136.74, 141.56 ppm.

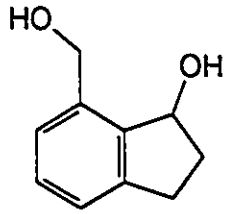
IR (CH_2Cl_2): 1312, 1118 cm^{-1}.

CI-MS(iso): 223 ($M^{+\bullet}$+1, 100).

HRMS: Calc. for $C_{12}H_{14}$ ($M^{+\bullet}$-SO_2): 158.10955; Found: 158.11004.

mp: 135 °C.

1(H)-2,3-dihydro-3-hydroxy-4-hydroxymethylindene (5).



5

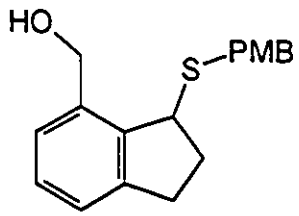
A solution of hydroxy-acid 17 (2.50 g, 14.0 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (533 mg, 14.0 mmol) in THF (25 mL). The resulting mixture was refluxed for 3 h, cooled to RT and poured *carefully* into a solution of potassium sodium tartrate (10%, 200 mL) and EtOAc (100 mL). The resulting mixture was stirred at RT for 10 h. Separation of the organic layer and usual workup followed by column chromatography (2:1 Hex:EtOAc) afforded the title compound as a clear oil (1.60 g, 70%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.95 (m, 1H), 2.35 (m, 1H), 2.80 (m, 1H), 3.05 (m, 1H), 4.00 (br, 2H), 4.46 (d, 1H, J=12.2 Hz), 4.79 (d, 1H, J=12.2 Hz), 5.31 (dd, 1H, J=7.0, 3.5 Hz), 7.05 (m, 1H), 7.20 (m, 2H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 30.36, 34.05, 64.05, 75.13, 124.73, 126.44, 128.75, 137.37, 143.39, 144.54 ppm.

IR (CH_2Cl_2): 3590, 3382 cm^{-1}.

1(H)-2,3-dihydro-3-thio-(p-methoxybenzyl)-4-hydroxymethyl-indene (4).



4

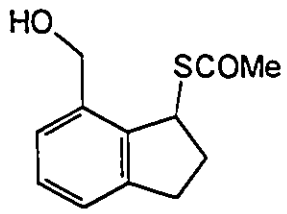
The title compound was prepared in a manner identical to that described for the preparation of **8b**. In this was, diol **5** (250 mg, 1.52 mmol) was converted into the title compound **4** (375 mg, 82%), which was isolated as a white solid after purification via column chromatography (5:1 Hex:EtOAc).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.20 (m, 2H), 2.80 (m, 2H), 3.10 (m, 1H), 3.70 (d, 1H, J=12.5 Hz), 3.72 (d, 1H, J=12.5 Hz), 3.78 (s, 3H), 4.30 (d, 1H, J=12.0 Hz), 4.50 (d, 1H, J=12.0 Hz), 4.63 (dd, 1H, J=12.0, 2.0 Hz), 6.83 (d, 2H, J=7.5 Hz), 7.20 (m, 5H) ppm.

CA: Calc. for $C_{18}H_{20}SO_2$: C (71.97), H (6.72); Found: C (71.80), H (6.82).

mp: 130 °C.

1-(H)-2,3-dihydro-3-thioacetyl-4-hydroxymethyl-indene (19).



19

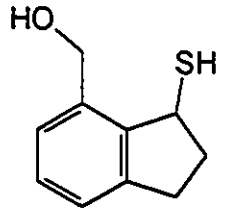
To a solution of diol 5 (250 mg, 1.52 mmol) and thiolacetic acid (118 mg, 1.55 mmol) in CH_2Cl_2 (50 mL) was added ZnI_2 (485 mg, 1.55 mmol). The cloudy solution was stirred at RT for 10, and was poured into H_2O (50 mL). The organic layer was separated, the aqueous phase extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic extracts were subjected to normal workup, followed by purification via column chromatography (10:1 Hex:EtOAc), affording the title compound **19** as a pale yellow oil (264 mg, 78%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.20 (m, 1H), 2.35 (s, 3H), 2.65 (m, 1H), 2.90 (m, 1H), 3.00 (m, 1H), 3.50 (br, 1H), 4.30 (d, 1H, J=10.0 Hz), 4.55 (d, 1H, J=10.0 Hz), 5.18 (d, 1H, J=7.5 Hz), 7.20 (m, 2H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 30.59, 30.85, 35.15, 46.64, 68.73, 124.51, 124.60, 128.13, 128.91, 135.76, 145.62, 195.93 ppm.

IR (CH_2Cl_2): 3355, 1688 cm^{-1}.

1(H)-2,3-dihydro-3-mercapto-4-hydroxymethylindene (20).



20

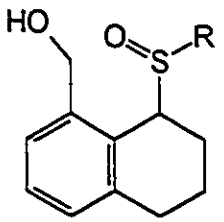
A solution of KOH (40%, 2 mL) was added to a solution of thioacetate **19** (250 mg, 1.13 mmol) in THF (20 mL). The resulting homogenous solution was stirred at RT for 2 h, after which time it was acidified with HCl (10%) and extracted with EtOAc (4 x 20 mL). The combined organic extracts were worked up in the usual manner affording, after column chromatography (5:1 Hex:EtOAc), the title compound as a green oil (200 mg, >95%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.20 (m, 1H), 2.60 (m, 1H), 2.80 (m, 1H), 3.20 (m, 1H), 4.61 (td, 1H, J=7.5, 1.0 Hz), 4.71 (d, 1H, J=13.0 Hz), 4.84 (d, 1H, J=13.0 Hz), 7.20 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 30.07, 37.48, 41.60, 63.12, 124.35, 126.66, 128.35, 136.33, 143.11, 143.89 ppm.

IR (CH_2Cl_2): 3602, 2592 cm^{-1}.

General Procedure for the preparation of 1-Thioalkyl-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene-S-oxide (24).



24a; R=Bn
24b; R=PMB
24c; R=tBu

A solution of $NaIO_4$ (1.2 equivalents) in H_2O was added to a solution of the appropriate sulfide (**8 a-c**) in MeOH. The resulting solution was stirred at RT overnight. The MeOH was then evaporated under reduced pressure, and to the remaining residue was added H_2O (10 mL). The solution was extracted with CH_2Cl_2 (4 x 10 mL). The sulfoxides were usually isolated as solids after typical workup.

1-Thiobenzyl-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene-S-oxide (24a).

White solid (82% yield).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.65 (m, 2H), 2.05 (m, 2H), 2.75 (m, 2H), 3.40 (d ,1H, J=5.0 Hz), 4.20 (m, 4H), 4.70 (d, 1H, J=3.0 Hz), 7.0-7.4 (m, 8H) ppm.

IR (CH_2Cl_2): 3683, 1053 cm^{-1}.

CI-MS(iso): 301 (M^{++}+1, 5.1).

mp: 95 °C.

1-Thio(4-methoxybenzyl)-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene-S-oxide (24b).

White solid (85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.80 (m, 2H), 2.15 (m, 1H), 2.60 (m, 1H), 2.83 (t, 2H, J=5.0 Hz), 3.40 (br, 1H), 3.80 (s, 3H), 4.10 (m, 1H), 4.50 (m, 3H), 6.85 (d, 2H, J=7.5 Hz), 7.05-7.45 (m, 6H) ppm.

IR (CH_2Cl_2): 3330, 1033 cm^{-1}.

CA: Calc. for $C_{19}H_{22}SO_3$: C (69.06), H (6.71); Found: C (69.40), H (6.90).

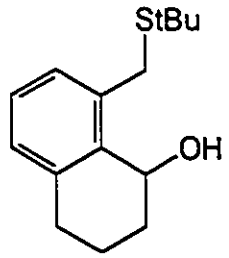
mp: 134 °C.

1-Thio(tert-butyl)-9-hydroxymethyl-1,2,3,4-tetrahydronapthalene-S-oxide (24c).

pale yellow oil (65%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.50 (s, 9H), 2.20 (m, 3H), 2.80 (m, 3H), 4.50 (br, 1H), 4.70 (m, 3H), 7.20 (m, 3H) ppm.

1-Hydroxy-9-thio(tert-butyl)-1,2,3,4-tetrahydronapthalene (32).



32

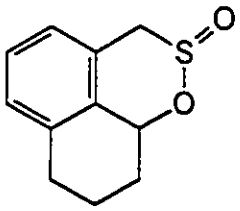
A solution of $POCl_3$ (265 mg, 1.73 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a cooled (-78 °C) solution of diol 9 (300 mg, 1.68 mmol) in CH_2Cl_2 (20 mL) containing pyridine (140 mg, 1.77 mmol). The resulting solution was slowly allowed to warm to RT over 4 h, after which time it was poured in H_2O (20 mL). The organic layer was separated and subjected to normal work up. The crude material was dissolved in THF (20 mL) and sodium t-butylmercaptide (282 mg, 2.52 mmol) was added. The resulting solution was stirred at RT for 10 h, evaporated to dryness and the residue partitioned over H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were worked up in the normal way, and chromatographed (10:1 Hex:EtOAc). The title compound was isolated as a clear oil (239 mg, 55% from diol 9).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.75 (m, 2H), 2.00 (m, 1H), 2.15 (m, 1H), 2.80 (m, 1H), 2.90 (m, 1H), 3.20 (br, 1H), 3.89 (d, 1H, J=10.5 Hz), 3.95 (d, 1H, J=10.5 Hz), 5.08 (t, 1H, J=3.2 Hz), 6.90 (d, 1H, J=7.5 Hz), 7.20 (m, 2H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.91, 29.96, 30.14, 30.64, 31.19, 43.69, 63.63, 127.64, 128.67, 128.93, 136.16, 136.92, 138.06 ppm.

IR (CH_2Cl_2): 3600 cm^{-1}.

Sultine 34



34

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.80 (m, 1H), 2.20 (m, 2H), 2.40 (m, 1H), 2.80 (m, 1H), 2.95 (m, 1H), 4.84 (d, 1H, J=14.0 Hz), 5.56 (d, 1H, J=14.0 Hz), 5.64 (t, 1H, J=4.3 Hz), 7.20 (m, 3H) ppm.

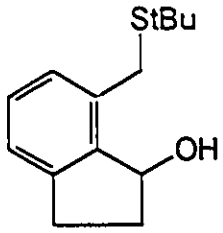
^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.88, 29.06, 31.98, 55.27, 68.00, 118.87, 125.35, 128.78, 131.40, 132.25, 136.22 ppm.

IR (CH_2Cl_2): 1116 cm^{-1}.

CI-MS (isobutane): 209 ($M^{+\cdot}$+1, 76.3).

EI-MS (m/z, %): 144 ($M^{+\cdot}$-SO_2, 45.8).

1(H)-2,3-dihydro-3-hydroxy-4-(t-butylthio)methyl-indene (35).



35

Hydroxy-sulfide **35** was prepared from diol **5** in an overall yield of 65% in a manner identical to that described for the preparation of **32**. Hydroxy-sulfide **35** was isolated as a clear oil after chromatography (5:1 Hex:EtOAc).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.05 (m, 1H), 2.30 (m, 1H), 2.75 (m, 1H), 3.20 (m, 1H), 3.25 (m, 1H), 3.86 (d, 1H, J=11.0 Hz), 3.93 (d, 1H, J=11.0 Hz), 5.39 (d, 1H, J=6.4 Hz) 7.20 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 24..21, 30.68, 32.29, 34.29, 43.70, 74.46, 124.74, 127.77, 128.74, 133.91, 144.10, 145.15 ppm.

IR (CH_2Cl_2): 3591, 2942 cm^{-1}.

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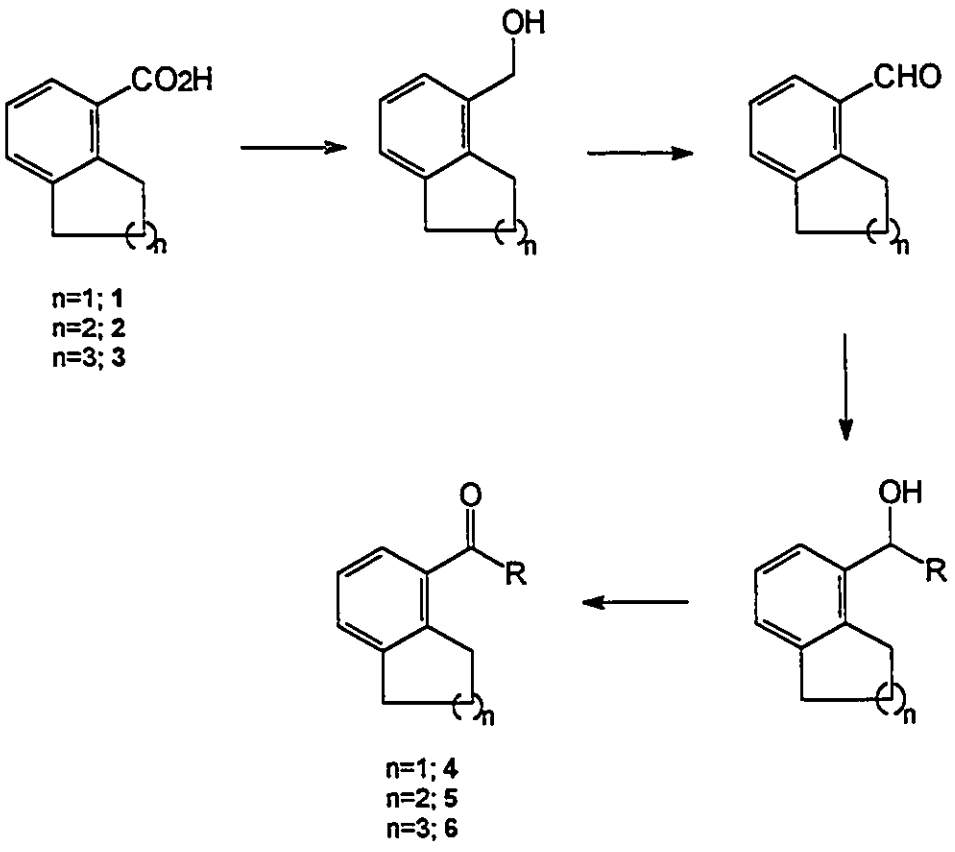
Chapter 11

Solid State NMR Study of a Weinreb Amide

11.1 Introduction

In chapter 9, the synthesis of a number of carboxaldehydes was described. In connection with a laser flash photolysis study, it was desirable to prepare a number of ketone derivatives. The strategy discussed in Chapter 9 involved reduction of the carboxylic acid to a benzylic alcohol, followed by oxidation of the alcohol to an aldehyde, addition of an organometallic reagent and another oxidation. This strategy is summarized in Scheme 11.1

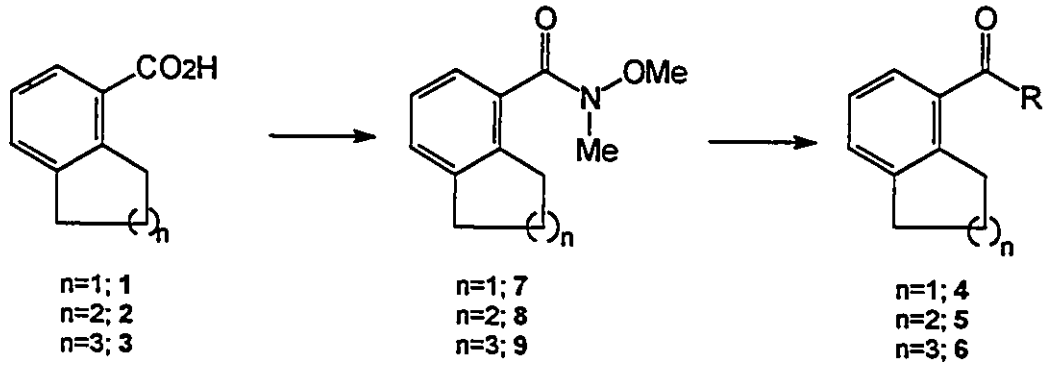


Scheme 11.1 - Initial Route to Ketones 4-6

Although the chemistry worked well, the strategy was lengthy, and required adjusting the oxidation state of the oxygen three times. This seemed wasteful, especially since the oxidation state of the starting acids (1-3) was at the same state as the products (4-6) so an alternative route was desired. The next section outlines the results of a different route that relies on the use of Weinreb's methodology[1] as a key step.

11.2 Synthesis of Weinreb Amides 7, 8 and 9

Considerable research has been done on the acylation of organometallic and Grignard reagents[2], and notable achievements have been made by the Weinreb group[1]. In particular, they have shown that N-methoxy-N-methylamides are very efficient acyl transfer reagents that do not suffer from the over-addition of organometallics to the acyl transfer reagent. Use of this methodology would shorten the route to ketones 4-6 from acids 1-3. This revised methodology is shown in Scheme 11.2.



Scheme 11.2 - Weinreb Amide Route to Ketones 4-6.

Activation of the carboxylic acids 1-3 with $SOCl_2$ provided the intermediate acid chlorides in near quantitative yields. Addition of the acid chlorides to a solution of N-methoxy-N-methylamide hydrochloride and triethylamine afforded amides 7, 8 and 9 in yields of 88, 86 and 83% respectively. Amides 7-9 all displayed very broad signals in the ^{1}H-NMR spectra (Fig 11.1-11.3 respectively). Complete characterization of the amides was complicated by inadequate responses of the carbon nuclei at

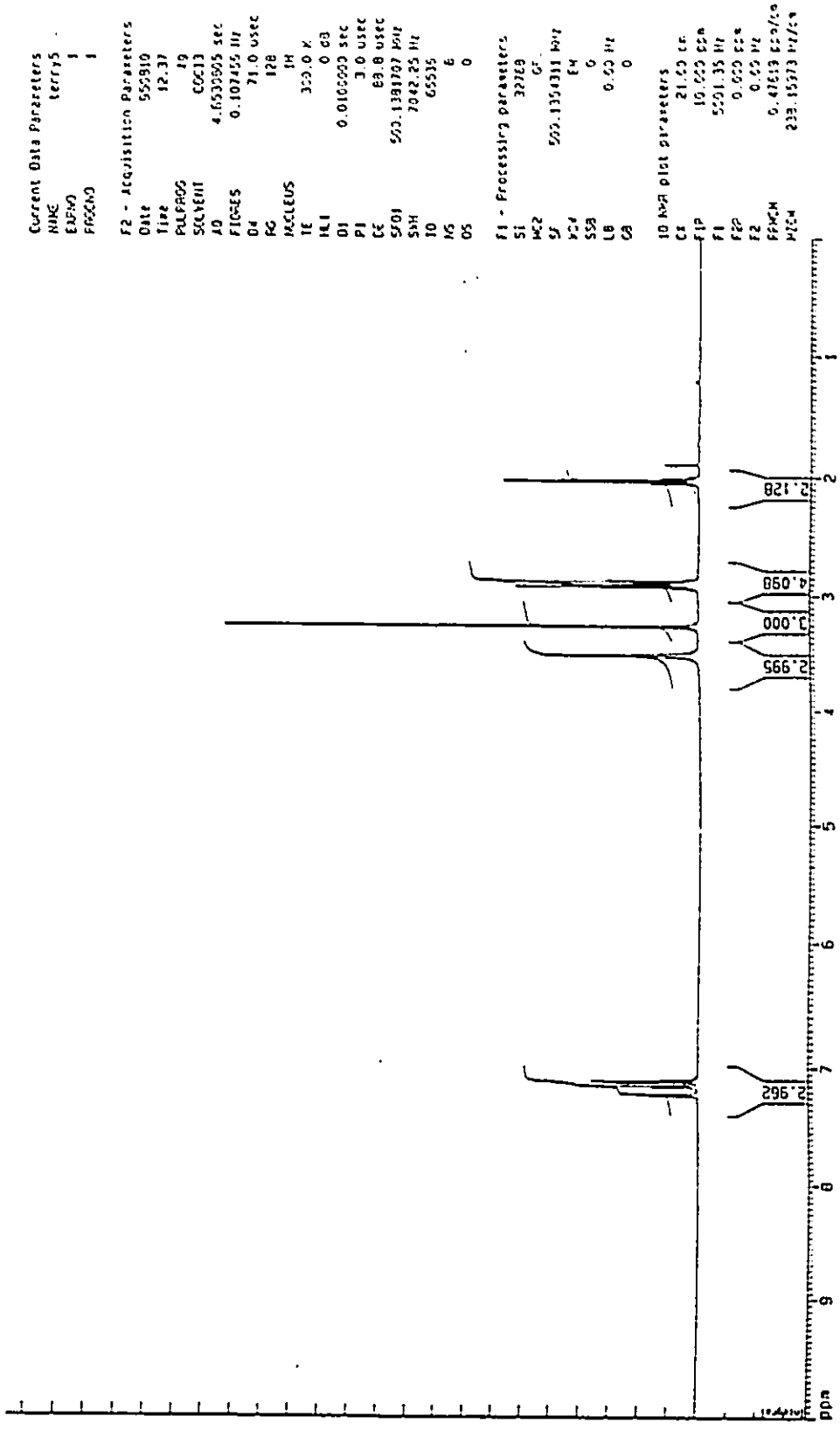


Figure 11.1 500 MHz ^{1}H-NMR Spectrum of Amide 7 in $CDCl_3$

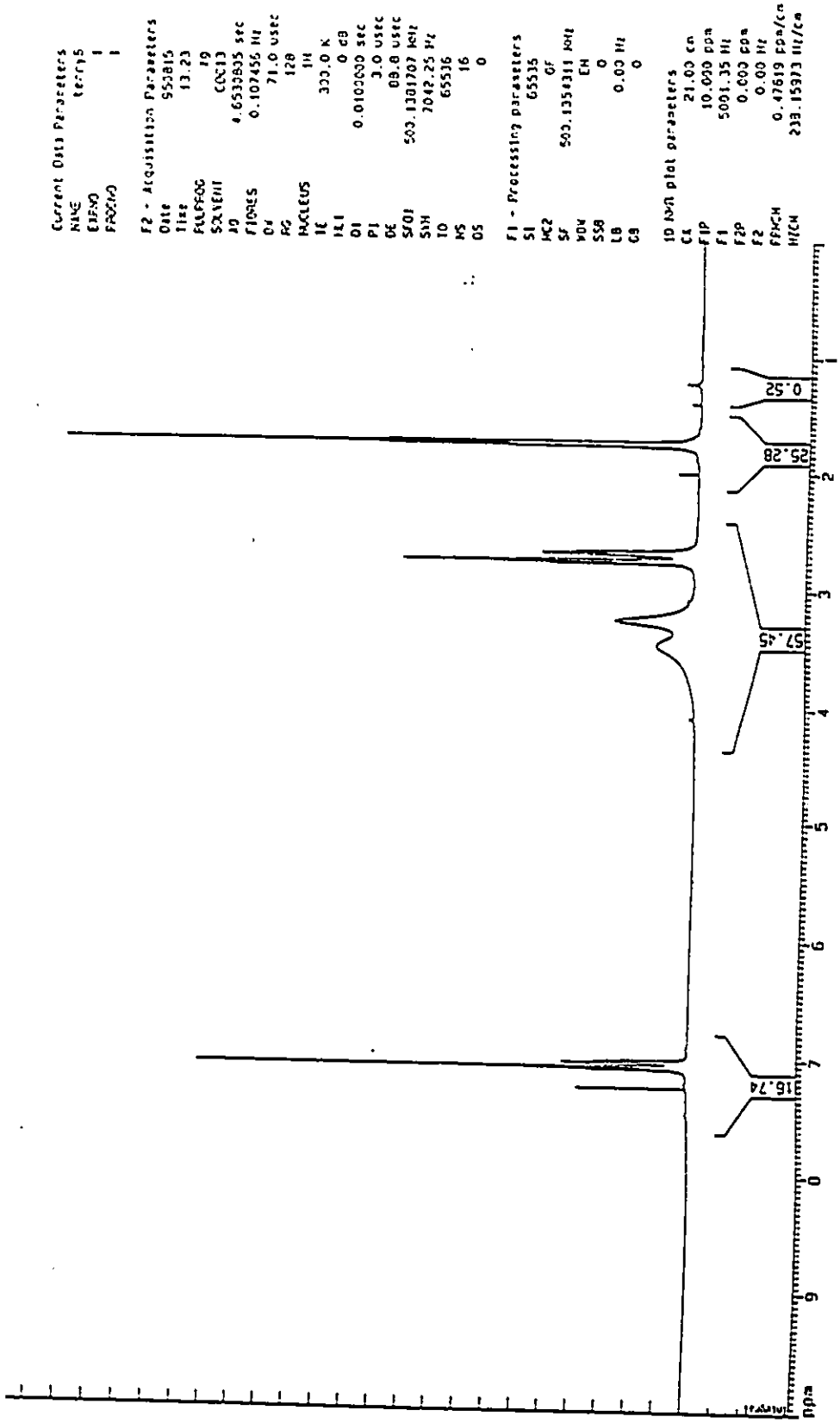


Figure 11.2 500 MHz ^{1}H-NMR Spectrum of Amide 8 in $CDCl_3$

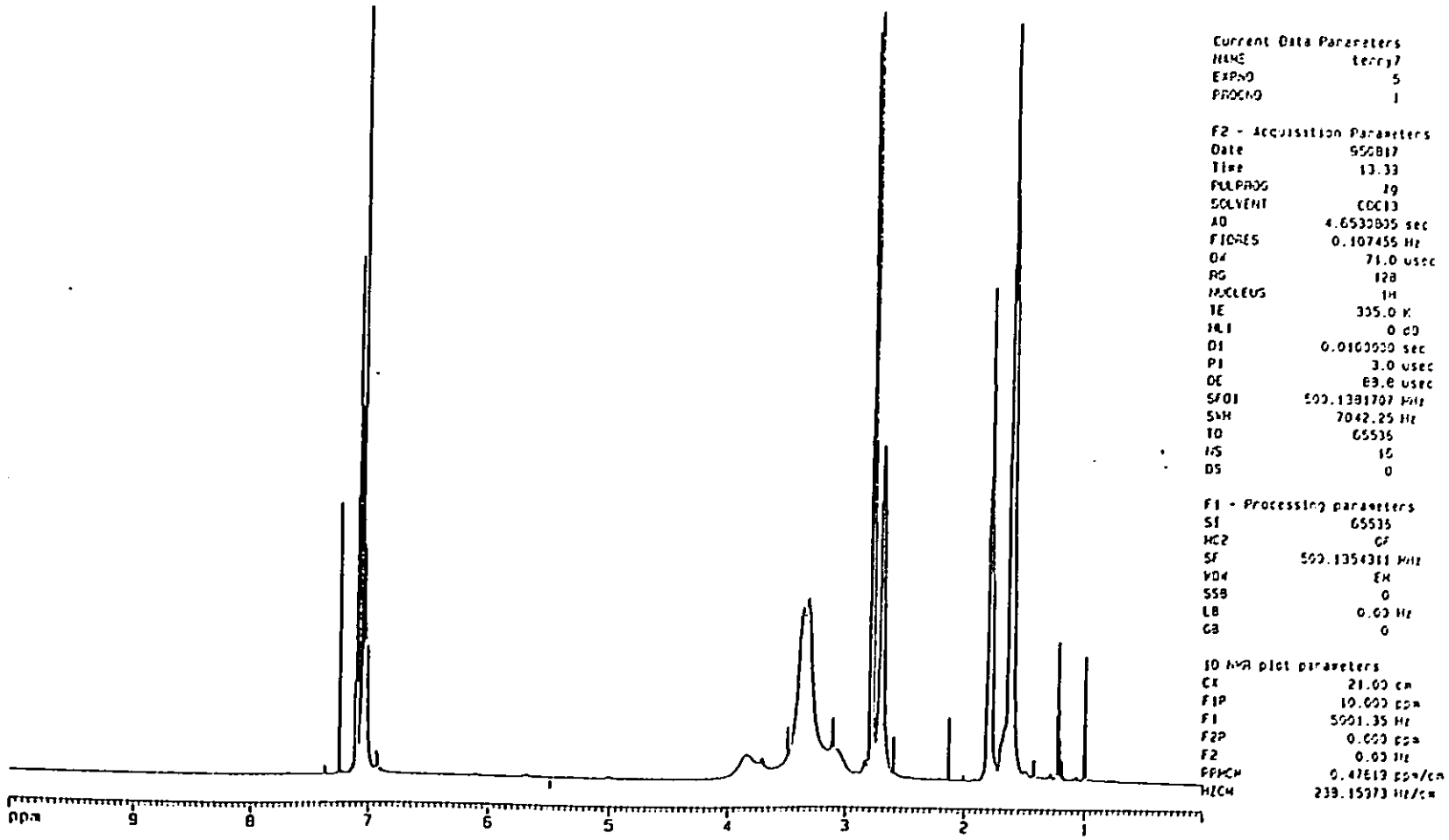


Figure 11.3 500 MHz ^{1}H-NMR Spectrum of Amide 9 in $CDCl_3$

50 MHz. Increasing the applied magnetic field strength to 125 MHz did not alleviate this problem. In order to assign all of the carbons, it was necessary to perform the HMQC experiment. In this way, a correlation between the visible protons and the broadened carbon lines could be found. The HMQC spectrum of amide 8 is shown in Fig 11.4 as a representative example.

The broadened lines for the N-methyl and N-methoxy groups indicated that the amides coalesced at temperatures close to room temperature. A dynamic NMR study was performed, but the results are not discussed in this thesis. It was found over the temperature range studied, the amides existed as a 2:1 ratio of rotomers. Amides 7 and 9 were oils, but amide 8 was highly crystalline solid. It was decided to probe the solid state using the recently acquired solid state NMR instrument. The initial expectation was that there may be two rotomers detectable in the solid state as well. The results of this solid state study are presented in the next section.

11.3 ^{13}C CP/MAS Study of Amide 8

All of the solid state spectra were acquired by Dr. Glenn Facey. Shown in Fig. 11.5 are two solid state spectra. The spectrum at the top is the CP/MAS spectrum of amide 8. The interpretation of the spectrum is quite straightforward. The are six aromatic carbons resonating between 120 and 140 ppm. The carbonyl carbon resonates downfield at 170 ppm. The high field region of the spectrum shows signals at 62 ppm (MeO-), a broadened signal at 34 ppm (N-Me) and three lines between 20 and 30 ppm, accounting for the methylene groups. Although only three lines appear, the highest field signal is twice as high as the other methylene signals. This line accounts for the methylene groups not attached to the benzene ring. This straightforward spectrum shows that only one rotomer exists in the solid state. A much more interesting result was obtained when Facey recorded the dipolar-dephased spectrum which is the lower spectrum in Fig. 11.5. This experiment is supposed to cancel out all protonated carbons except for methyl groups[3]. Inspection of the spectrum shows that the carbonyl and three quaternary carbons remained, as did the methoxy and n-methyl carbons. However, the signal which was assigned to the

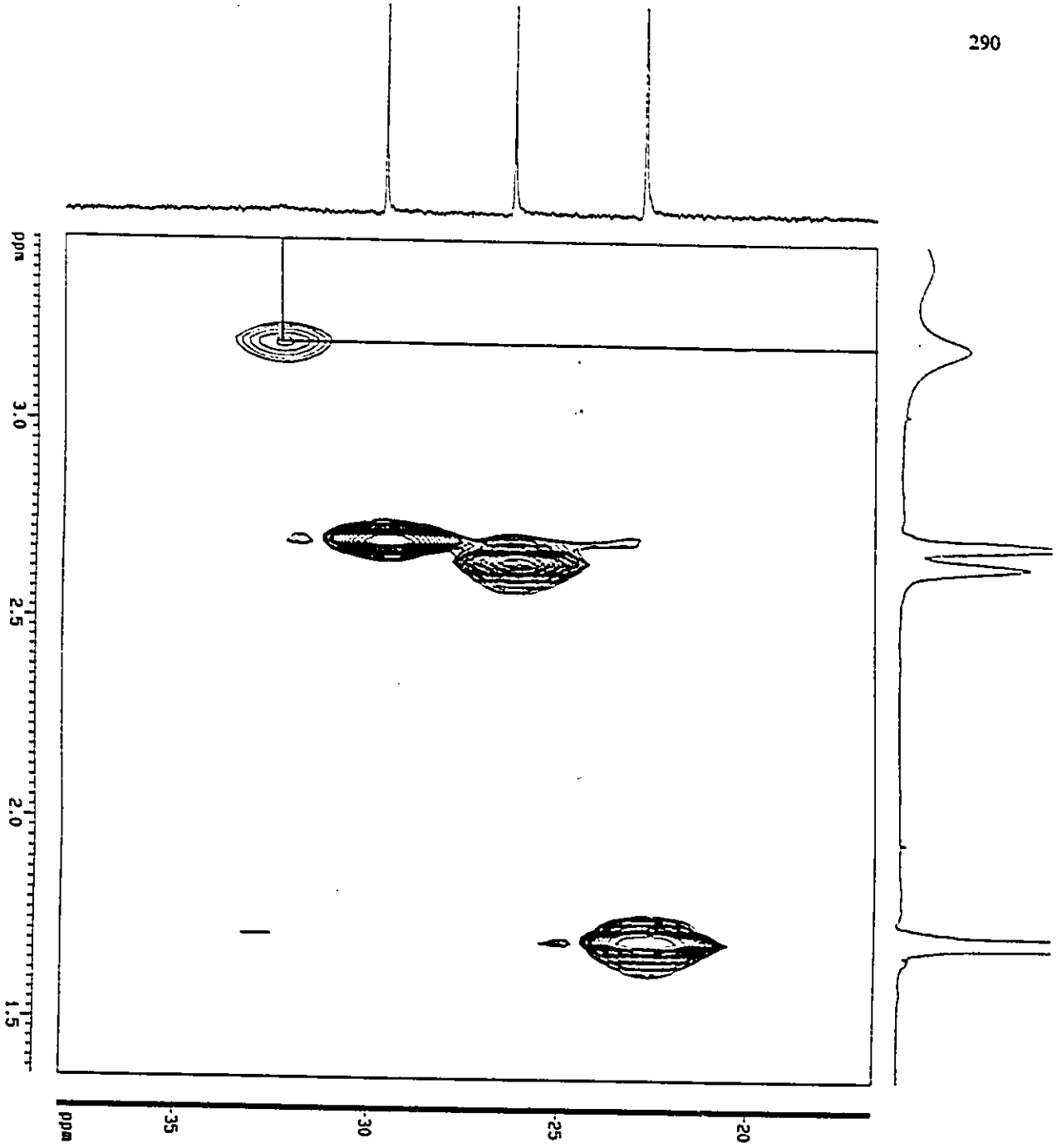


Figure 11.4 . 500 MHz HMQC Spectrum of Amide 8 in $CDCl_3$

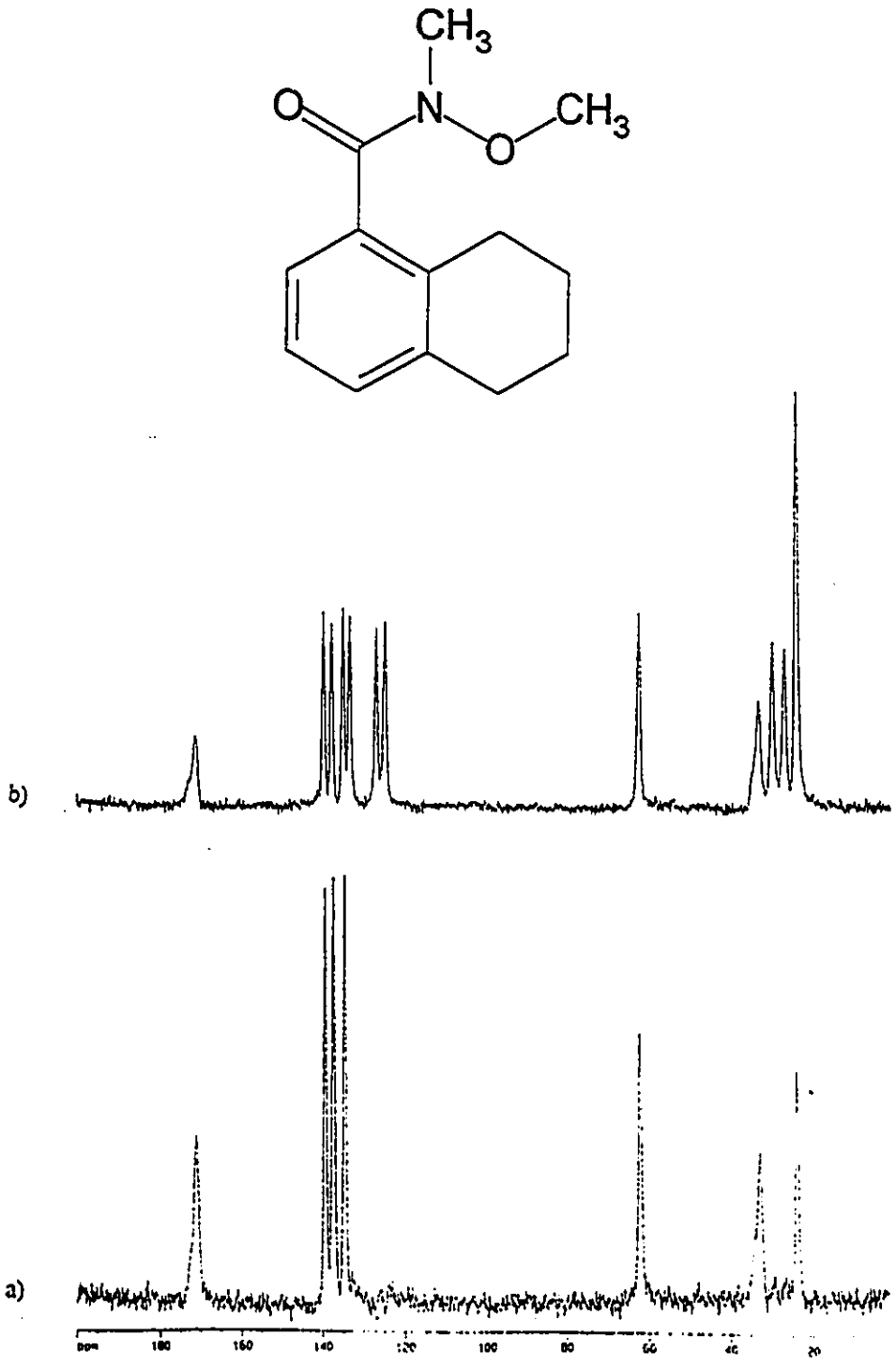
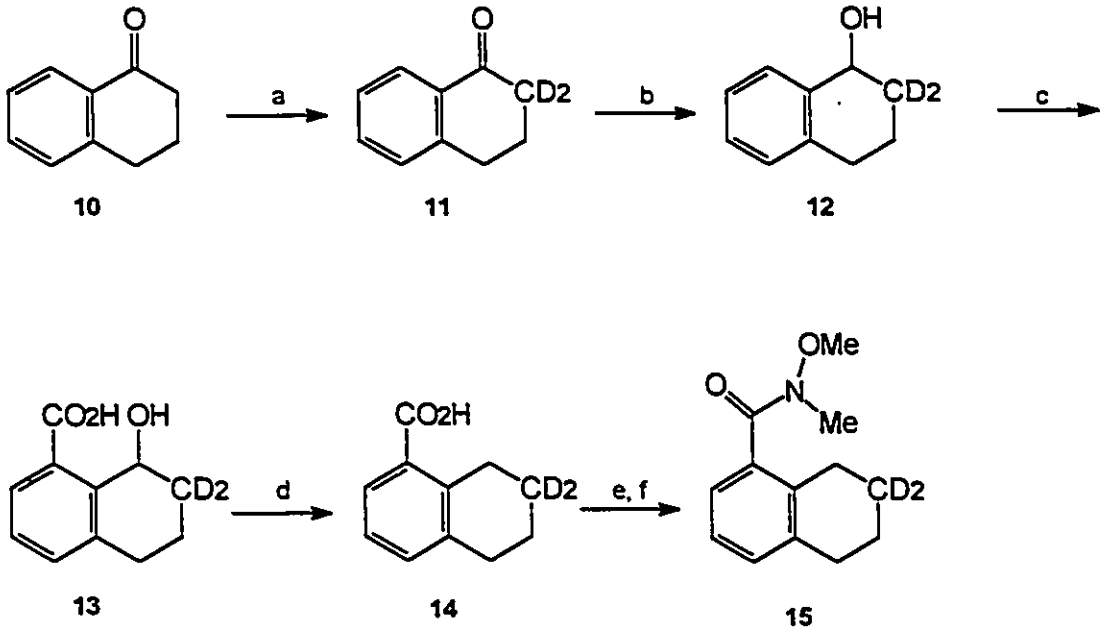


Figure 11.5 a) 50 MHz ^{13}C Dipolar Dephased Spectrum of Amide 8
b) 50 MHz ^{13}C CP/MAS Spectrum of Amide 8

overlapping methylene group remained! This is usually indicative of a high degree of molecular motion[3]. Facey suggested that if one of the methylene group β to the aromatic ring of amide 8 could be labeled with deuterium, then the degree of mobility in the solid state could be more accurately accessed. The synthesis of the deuterium labeled material is shown in Scheme 11.3.



Reagents: a) K_2CO_3, THF-D_2O (90%); b) $LiAlH_4$, THF (>95%); c) (i) nBuLi, TMEDA, pentane; (ii) CO_2; (iii) HCl (70%); d) H_2, Pd/C, HOAc (80%); e) $SOCl_2$, CH_2Cl_2, Δ; f) $H_2N^+(Me)(OMe)\ Cl^-$, CH_2Cl_2, TEA (78 % from 14).

Scheme 11.3 - Synthesis of Deuterium Labeled Amide 15

Starting with α-tetralone 10, the protons α to the carbonyl group were exchanged by allowing 10 to enolize in D_2O. After 24 h, deuterium incorporation was 70% as judged by ^{1}H-NMR. Adding fresh D_2O and allowing the reaction to continue for another 24 h led to complete exchange of the protons for deuterium, as judged by ^{1}H-NMR and a recovered mass balance of 90%. Reduction of the carbonyl group of 11 was accomplished in near quantitative yields with $LiAlH_4$ in THF, affording 12 as a clear oil. Ortho-metallation and carboxylation of alcohol 12 under the conditions described by Seebach[4] led to hydroxy-acid 13 in 70% yield. Hydrogenolysis of the benzylic alcohol with H_2 and 10% Pd/C in glacial

acetic acid afforded acid **14** as a white crystalline solid. Finally, conversion of the acid to an acid chloride, followed by addition of N-methoxy-N-methylamine hydrochloride led to amide **15** as a white crystalline solid (mp 76 °C) in 70% yield from acid **14**. All intermediates displayed spectroscopic properties consistent with their structures (see experimental section, this chapter).

Figure 11.6 shows the broad-line ^{2}H-NMR solid state spectrum of amide **15**. At 300 K, the line shape is indicative of a deuterium undergoing a two-site exchange, with the angle between the two sites being 109 °.[3] As the temperature is lowered, the line shape changes. This change in line shape was interpreted by Facey as meaning that the population of the two sites is no longer equal. To rule out the possibility of another dynamic process causing the change in line shape, a plot of the splitting of the broad-line pattern vs temperature was recorded (Fig. 11.7). The resulting plot shows that the slope of the top and bottom lines is approximately equal, and the slope of the center line is zero, indicative on only one dynamic process occurring.

Facey then determined the barrier to inversion of the cyclohexene ring to be approximately 12.3 kJ/mol from the relaxation times from the initial slope of the Arrehenius plot (Fig. 11.8). The only value which may be comparable to this is the solution phase barrier to inversion of cyclohexene determined by Anet[5] to be 6 kcal/mol (24 kJ/mol).

A crystal of amide **8** suitable for X-Ray diffraction was grown. Single crystal diffraction also provided evidence for this high degree of molecular motion, as evident from the disorder of the methylene groups β to the aromatic ring. The sizes of the thermal ellipsoid are also different, providing addition evidence for the unequal population of the two states at lower temperatures. The ORTEP of **8** is shown in Fig. 11.9.

This high degree of motion of the tetrahydronapthalene ring is particular only to the Weinreb amide. The ^{13}C CP/MAS spectrum of carboxylic acid **2**, a precursor to the amide, was also examined (Fig. 11.10). The solid state spectrum shows a carbonyl at 175 ppm, six aromatic carbons between 120 and 140 ppm, and four aliphatic carbons between 15 and 30 ppm. The lines between 40 and 50 ppm are spinning sidebands of the aromatic carbons. Unlike amide **8**, the methylene signals do disappear in the dipolar-dephased spectrum of acid **2**, shown as the lower spectrum of Fig. 11.10. This is indicative of a

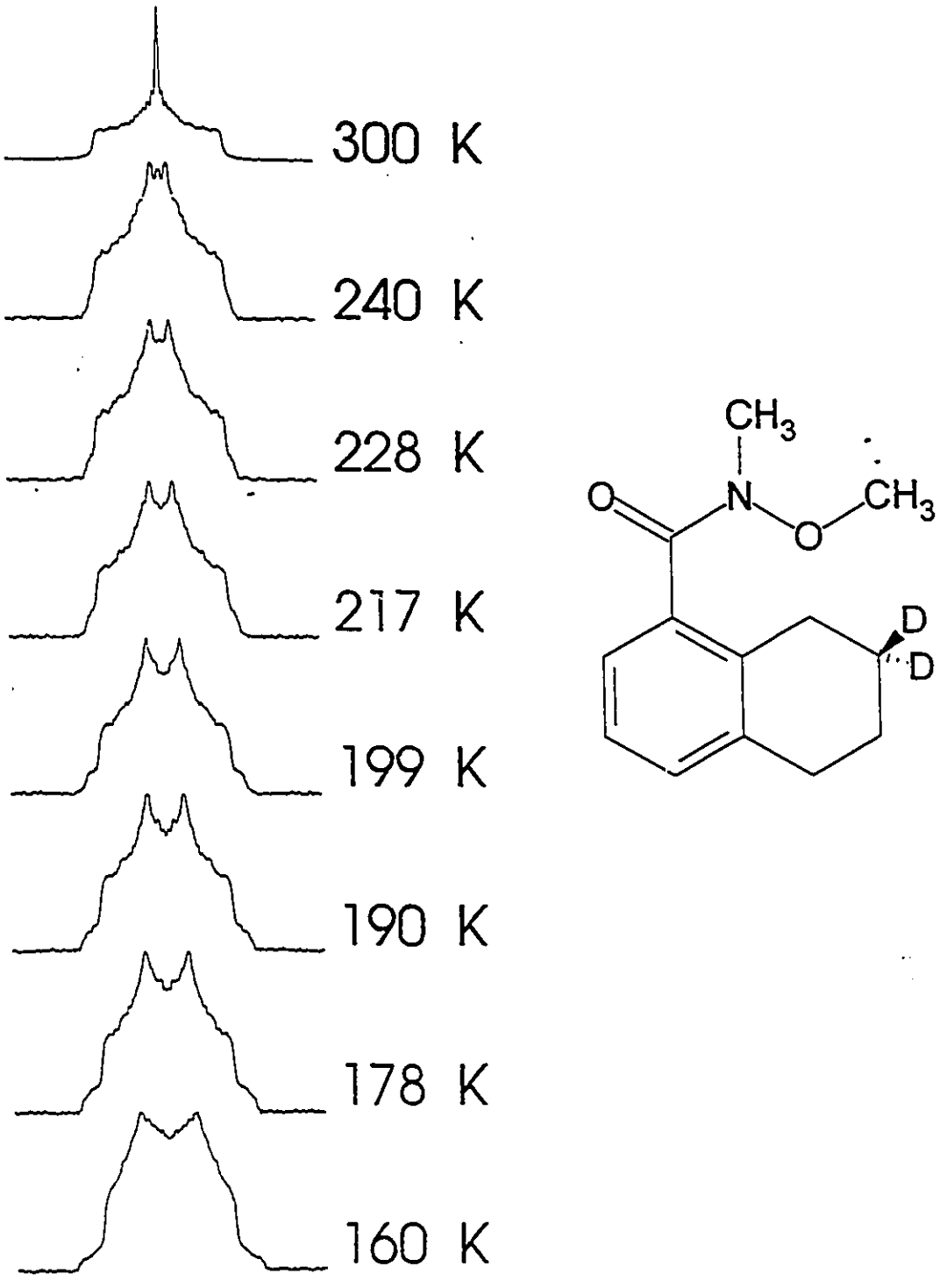


Figure 11.6 31 MHz ^{2}H-NMR Spectrum of Amide 15 at Various Temperatures

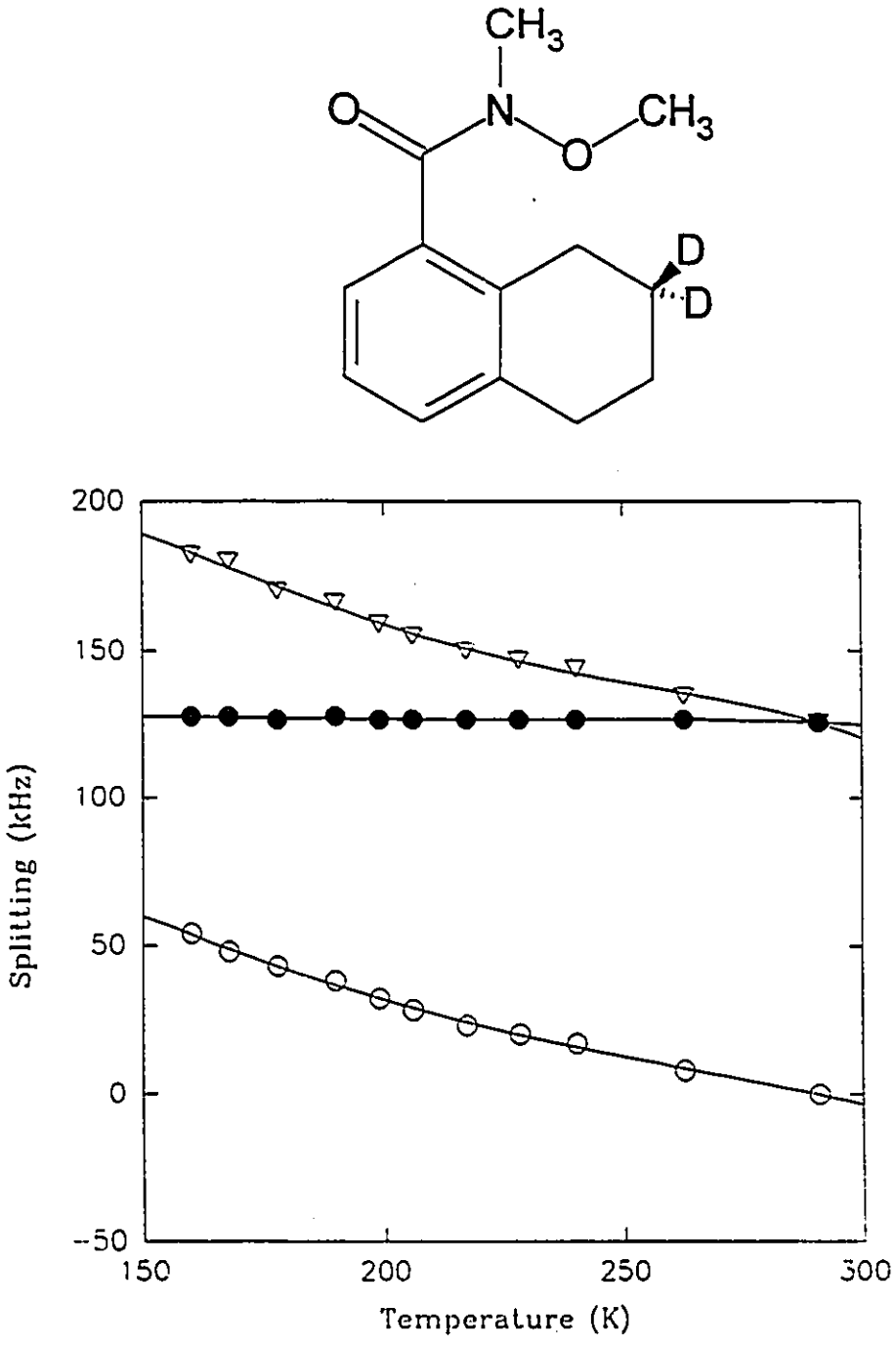
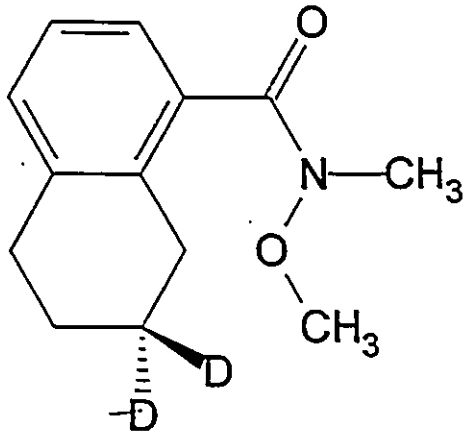


Figure 11.7 Plot of Signal Splitting vs Temperature



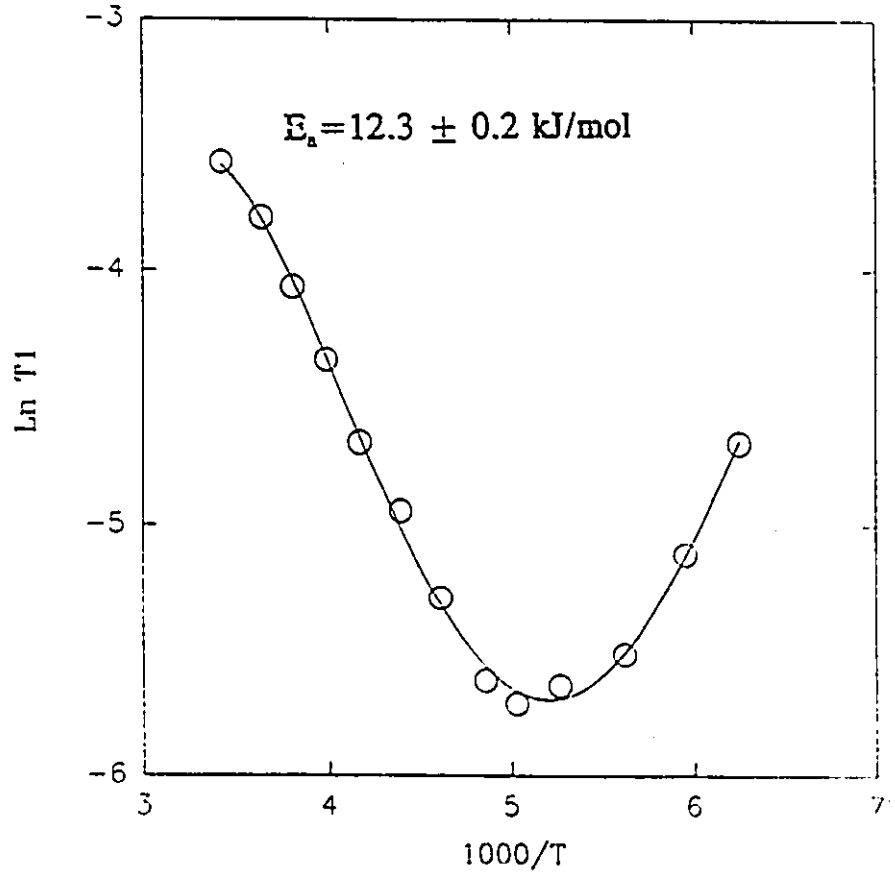
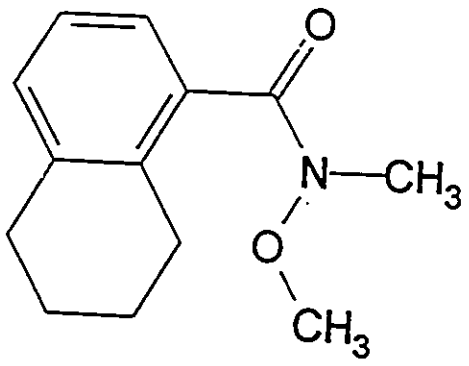


Figure 11.8 Plot of Ln T_1 vs 1000/T for Amide 8



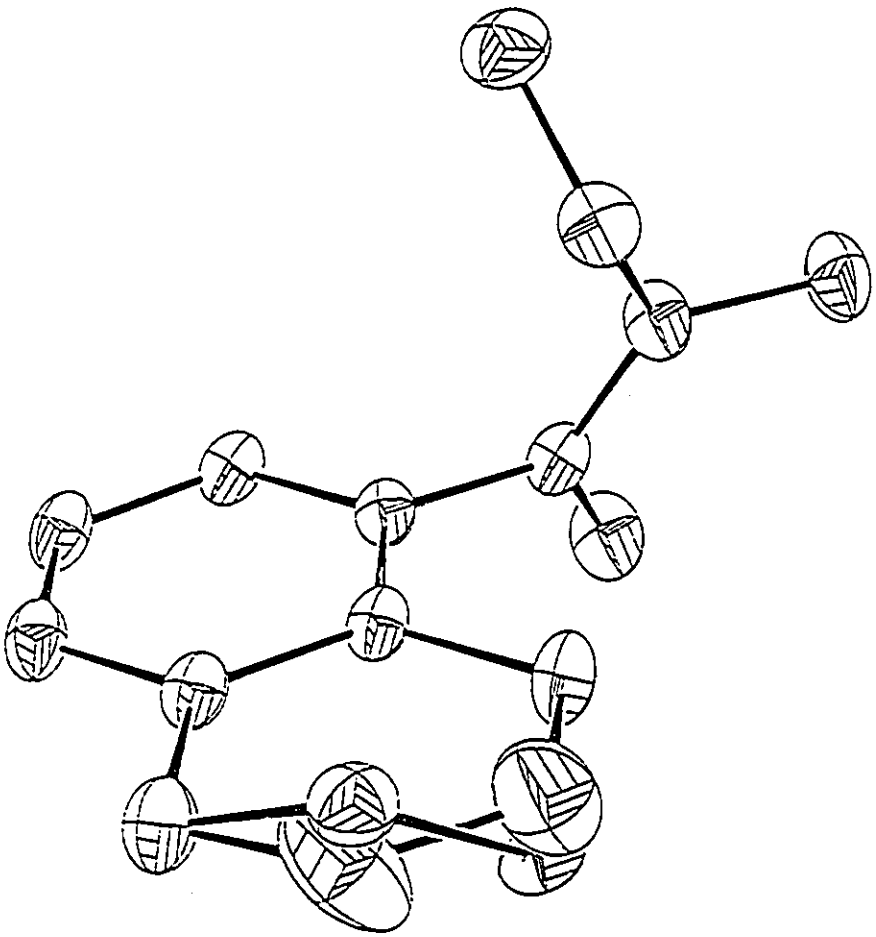
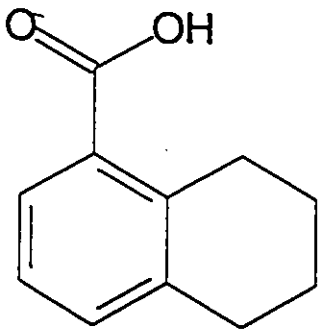


Figure 11.9 ORTEP of Amide 8



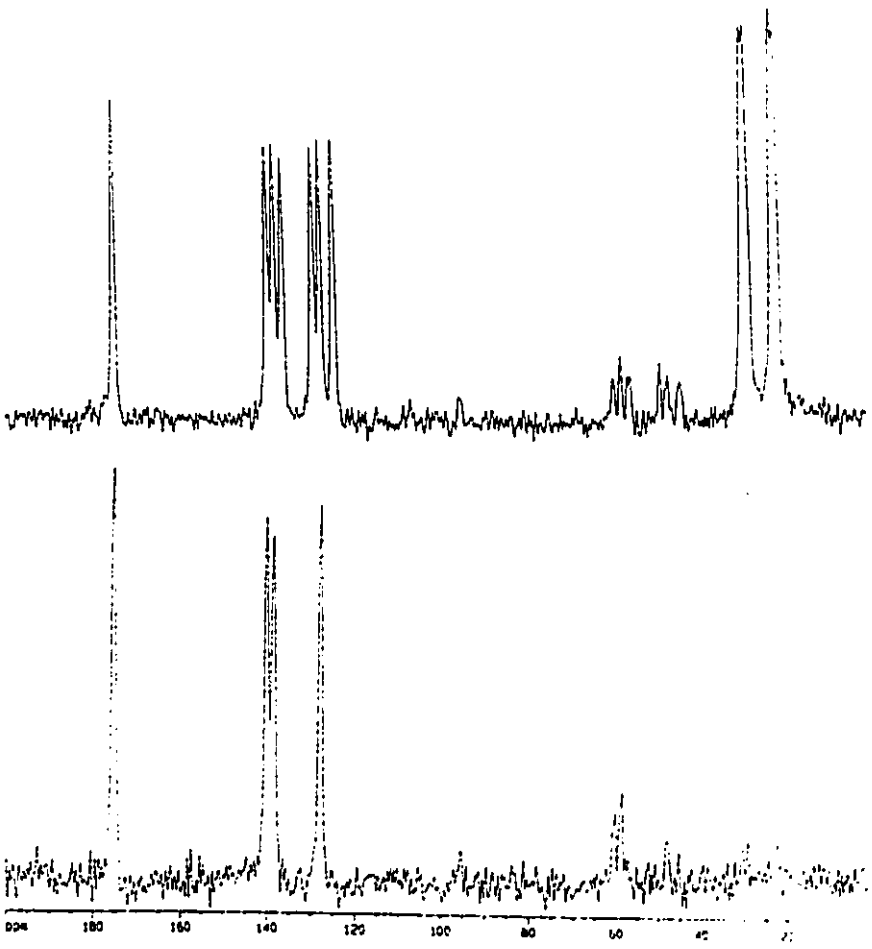


Figure 11.10 50 MHz ^{13}C CP/MAS Spectrum of Acid 2

rigid solid[3]. The ^{2}H-NMR spectrum of acid **14** (Fig. 11.11) also supports this rigid acid model, as evident by the line shape at ambient temperatures. However, increasing the temperature past 350 K shows that a new line is growing out of the center of the spectrum. This change in line shape was taken as evidence that the tetrahydronapthalene inversion was occurring, but the motion of the solid was attenuated as compared to the motion of amide **8** or **15**. It is believed that the difference in crystal packing of the amide and acid may account for this difference in motion. The carboxylic acid presumably crystallizes as a highly hydrogen bonded dimeric structure. Although the amide also crystallizes as a dimer, the presence of the two substituents on the nitrogen cause the carbonyl group to tip out of the plane of the benzene ring. This results in more of a void space between the two molecules of the unit cell. This increase in space between the two molecules is believed to be responsible for the facile inversion of the cyclohexene ring.

11.4 Conclusion

For the first time, a cyclohexene-type inversion has been detected in the solid state. This inversion of the tetrahydronapthalene ring system of a N-methoxy-N-methylcarboxamide was measured to have an activation energy of 12.3 kJ/mol by measuring the ^{13}C relaxation times at various temperatures. The mobility of this solid is believed to be due to the packing of the unit cell, which is believed to have large empty spaces present due to the conformation of the amide function.

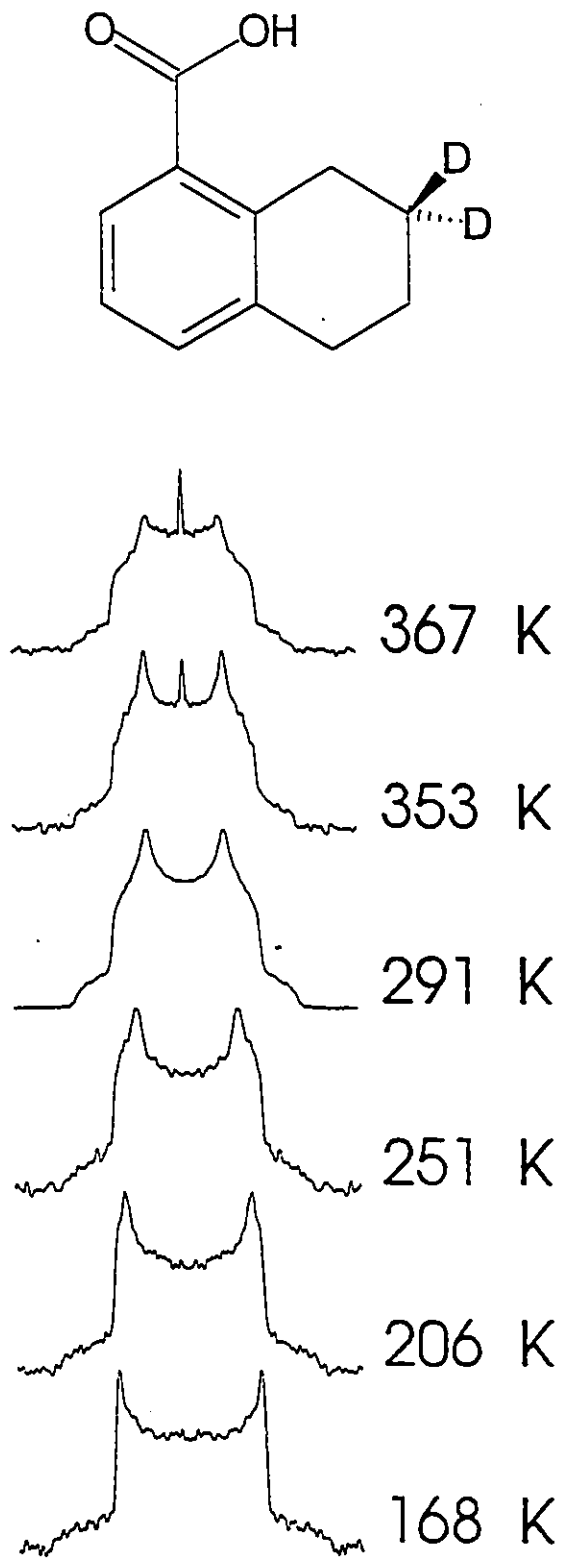
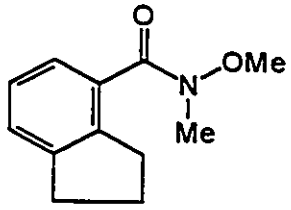


Figure 11.11 31 MHz ^{2}H-NMR Spectrum of Acid 14 at Various Temperatures

11.5 Experimental

For general experimental comments, see chapter 3. In addition, ^{2}H-NMR spectra were measured on a Bruker AMX-500 at a frequency of 77 MHz in CH_2Cl_2 and are referenced to CD_2Cl_2 (5.20 ppm). Solid state spectra were recorded with a Bruker ASX 200 spectrometer. Carboxylic acids 1 and 2 were prepared as reported in Chapter 9.

N-Methoxy-N-Methyl-1(H)-2,3-dihydroindene-4-carboxamide (7).



7

A solution of carboxylic acid 1 (1.00 g, 6.2 mmol) and $SOCl_2$ (1.84 g, 15.4 mmol) in CH_2Cl_2 (50 mL) was heated as reflux for 8 h. The solvent was evaporated, and the slightly yellow oil was dissolved in CH_2Cl_2 (20 mL) and added dropwise to a solution of N,O-dimethylhydroxylamine hydrochloride (0.73 g, 7.5 mmol), triethylamine (1.37 g, 13.6 mmol) and DMAP (100 mg) in CH_2Cl_2 (50 mL). The resulting solution was stirred at RT for 14 h, poured into H_2O (50 mL), and worked up in the usual way. The slightly brownish oil was chromatographed (3:1 Hex:EtOAc) affording the title compound as a clear oil (1.12 g, 88%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.08 (quintet, 2H, J=7.5 Hz), 2.93 (t, 2H, J=7.5 Hz), 2.97 (t, 2H, J=7.5 Hz), 3.31 (s, 3H), 3.55 (s, 3H), 7.20 (m, 3H) ppm.

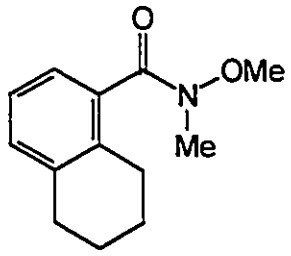
^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.05, 31.59, 32.71, 33.53, 61.03, 124.28, 125.64, 125.82, 131.16, 142.05, 144.90, 170.11 ppm.

IR (CH_2Cl_2): 1646 cm^{-1}.

EI-MS (m/z, %): 205 ($M^{+\cdot}$, 2.4), 145 (100)117 (34.2).

HRMS: For $C_{12}H_{15}NO_2$; Calc: 205.11028; Found: 205.10974.

N-Methoxy-N-Methyl-1,2,3,4,-Tetrahydronapthyl-5-carboxamide (8).



8

The title compound was prepared in a manner identical to 7. In this way, acid 2 (1.50 g, 9.4 mmol) was converted to the title compound (1.75 g, 86%). Amide 8 was isolated as a white crystalline solid.

^{1}H-NMR (500 MHz, $CDCl_3$): 1.80 (m, 4 H), 2.62 (t, 2H, J=7.0 Hz), 2.80 (t, 2H, J=7.0 Hz), 3.20 (bs, 3H), 3.45 (bs, 3H), 6.90 (m, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 22.76, 22.76, 26.26, 29.65, 31.08, 61.02, 123.20, 125.02, 130.01, 133.72, 135.43, 137.64, 170.00 ppm.

IR (CH_2Cl_2): 1647 cm^{-1}.

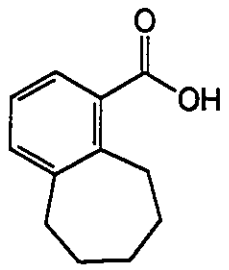
EI-MS (m/z, %): 219 (1.4, $M^{+\cdot}$), 159 (100), 131 (31.8), 91 (22.5).

HRMS for $C_{13}H_{17}NO_2$: 219.12593; Calc: 219.12617.

CA Calc: C (71.21), H (7.81), N (6.39); Found: C (72.18), H (7.97), N (6.26).

mp: 77 °C.

Benzosuberane-8-carboxylic acid (3).



3

A solution of Jones reagent (10 mL) was added dropwise to a solution of the benzylic alcohol precursor (250 mg, 1.42 mmol) in Et_2O (20 mL). The resulting solution was stirred at RT for 16 h, the phases separated and the aqueous phase extracted with Et_2O (4 x 15 mL). The combined organic extracts were subjected to normal work up, affording the title compound as a white crystalline solid (230 mg, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.60 (m, 4H), 1.80 (m, 2H), 2.85 (m, 2H), 3.20 (m, 2H), 7.10 (t, 1H, J=7.5 Hz), 7.25 (d, 1H, J=7.5 Hz), 7.65 (d, 1H, J=7.5 Hz) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ 27.16, 27.84, 30.56, 31.99, 125.38, 128.13, 129.62, 132.82, 144.55, 145.25, 175.16 ppm

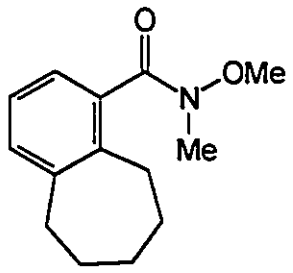
IR (CH_2Cl_2): 3500, 1690 cm^{-1}.

EI-MS (m/z, %): 190 ($M^{+\cdot}$, 100), 172 (90.6), 145 (83.1).

HRMS: For $C_{12}H_{14}O_2$: 190.09938; Found: 190.09832.

mp: 105 °C.

N-Methoxy-N-methyl-benzosuberane-8-carboxamide (9).



9

The title compound was prepared in a manner identical to that described for the preparation of 7. In this way, acid 3 (220 mg, 1.16 mmol) was converted to the title compound (225 mg, 83%), which was isolated as a clear oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.60 (m, 4H), 1.80 (m, 2H), 2.70 (m, 2H), 2.85 (m, 2H), 3.20 (bs, 3H), 3.50 (bs, 3H), 7.10 (m, 3H) ppm.

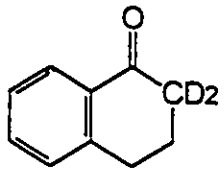
^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.05, 28.55, 29.95, 32.15, 32.75, 38.06, 60.05, 122.63, 126.54, 130.05, 138.06, 139.95, 143.27 ppm.

IR (CH_2Cl_2): 1650 cm^{-1}.

CI-MS (iso, m/z, %): 234 ($M^{+\bullet}$+1, 100).

HRMS: Calc. for $C_{12}H_{13}O$ [$M^{+\bullet}$-N(OMe)(Me)]: 173.09664; Found: 173.09782.

3,4-dihydro-1(2H)-napthalenone-2,2-d_2 (11).



11

A solution of α-tetralone (8.00 g, 54.8 mmol) in D_2O:THF (100 mL, 9:1) containing potassium carbonate (1.00 g, 7.25 mmol) was refluxed for 12 hours after which time, ^{1}H-NMR analysis indicated ca. 70% deuterium incorporation. The solution was extracted with Et_2O (4 × 50 mL), the combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. The resulting residue was re-dissolved in a freshly prepared solution of D_2O:THF (9:1, 100 mL) and refluxed for another 12 hours after which time, ^{1}H-NMR analysis of an aliquot indicated complete exchange. Work up as above afforded the title compound as a slightly yellow liquid (7.51 g, 94% recovery).

^{1}H-NMR (500 MHz, $CDCl_3$): 2.10 (t, 2H), 2.94 (t, 2H), 7.20 (d, 1H, J=8.0 Hz), 7.25 (t, 1H, J=8.0 Hz), 7.45 (t, 1H, J=8.0 Hz), 8.00 (d, 1H, J=8.0 Hz) ppm.

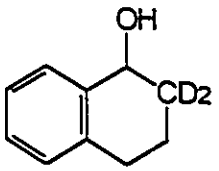
^{2}H-NMR (77 MHz, CH_2Cl_2): 2.59 ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 23.09, 29.61, 38.44 (quintet), 126.57, 127.08, 128.77, 132.61, 133.36, 144.49, 198.25 ppm.

EI-MS (m/z, %): 148 (75.0, $M^{+\cdot}$), 131 (11.5), 118 (100).

HRMS: Calc. for $C_{10}H_8D_2O$: 148.08572; Found: 148.08524.

1,2,3,4-tetrahydro-1-napthol-2,2-d_2 (12).



12

To a suspension of $LiAlH_4$ (1.28 g, 33.8 mmol) in THF (20 mL) was added dropwise with stirring a solution of tetralone 1 (5.00 g, 33.8 mmol) in THF (50 mL) the resulting gray solution was allowed to stir at room temperature for 1 h, then quenched by the slow careful dropwise addition of a solution of potassium sodium tartrate (saturated, 100 mL) followed by the addition of EtOAc (50 mL). Stirring was continued at room temperature for 2 h, the organic phase was separated and subjected to standard work up affording the title compound as a thick, slightly yellow oil (5.00 g, >95%).

^{1}H-NMR (200 MHz, $CDCl_3$): 1.70 (m, 1H), 1.90 (m, 1H), 2.75 (m, 2H), 4.80 (s, 1H), 7.00-7.20 (m, 3H), 7.40 (dd, 1H, J=8.0, 1.0 Hz) ppm.

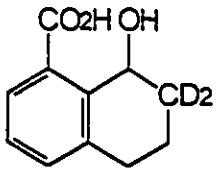
^{2}H-NMR (77 MHz, CH_2Cl_2): 1.78, 2.16 ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): 19.27, 29.82, 32.00 (quintet), 68.58, 126.75, 128.13, 129.30, 129.58, 137.73, 139.45 ppm.

EI-MS (m/z, %): 150 (46.3, $M^{+\bullet}$), 132 (100), 122 (86.4), 91 (57.5).

HRMS: Calc. for $C_{10}H_{10}D_2O$: 150.10136; Found: 150. 09943.

1,2,3,4-Tetrahydro-4-hydroxy-5-napthoic acid-3,3-d_2 (13).



13

The title compound was prepared using the procedure of Seebach[4] except that napthol 12 was used as the starting material. The material prepared in this way had the following spectroscopic properties:

^{1}H-NMR (500 MHz, $CDCl_3$): 1.80 (m, 1H), 2.10 (m, 1H)< 2.75 (m, 1H), 2.90 (m, 1H), 5.10 (s, 2H), 7.20 (t, 1H, J=8.0 Hz), 7.40 (d, 1H, J=8.0 Hz), 7.85 (d, 1H, J=8.0 Hz) ppm.

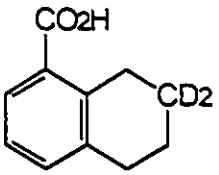
^{2}H-NMR (77 MHz, CH_2Cl_2): 1.76, 2.14 ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 16.77, 30.08, 63.63, 127.32, 129.44, 129.62, 134.95, 138.52, 139.64, 172.30 ppm.

EI-MS (m/z, %): 194 (24.6, $M^{+\cdot}$), 176 (70.3), 148 (50.3), 118 (100).

HRMS for $C_{11}H_{10}D_2O_3$; Calc: 194.09120; Found: 194.08990.

1,2,3,4-Tetrahydro-5-napthoic acid-3,3-d_2 (14)



14

To a suspension of Pd/C (10%, 100 mg) in glacial acetic acid (5 mL) was added dropwise a solution of hydroxy acid **13** (500 mg, 2.58 mmol) in glacial HOAc (15 mL). The resulting solution was stirred at room temperature while hydrogen was continuously bubbled through the solution for 4 h. The solution was then filtered trough Celite™, the filter cake was washed with Et_2O, and the resulting solution was evaporated to dryness, affording the title compound as a white solid. Recrystallization from EtOAc/Hex afforded white prisms (365 mg, 80%).

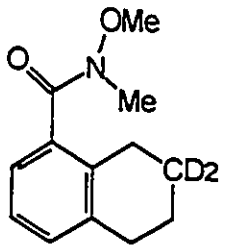
^{1}H-NMR (500 MHz, $CDCl_3$): 1.75 (t, 2H, J=7.5 Hz), 2.80 (t, 2H, J=7.5 Hz), 3.10 (s, 2H), 7.15 (t, 1H, J=8.0 Hz), 7.25 (d, 1H, J=8.0 Hz), 7.85 (d, 1H, J=8.0 Hz) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 22.13, 27.76, 30.23, 125.02, 128.75, 129.07, 134.17, 138.58, 139.88, 173.62 ppm.

EI-MS (m/z, %): 178 (79.0, $M^{+\cdot}$), 160 (82.8), 133 (100).

HRMS for $C_{11}H_{10}D_2O_2$: Calc. 178.09628; Found: 178.09625.

N-Methyl-N-methoxy-1,2,3,4-tetrahydro-5-napthamide-3,3-d_2 (15)



15

The title compound was prepared in a manned identical to that described for 7 except that carboxylic acid 14 (200 mg, 1.12 mmol) was used as the starting material. The product, isolated as a white solid (195 mg, 78%) had the following spectroscopic data:

^{1}H-NMR (500 MHz, $CDCl_3$): 1.73 (t, 2H, J=7.5 Hz), 2.00 (s, 2H), 2.73 (t, 2H, J=7.5 Hz), 3.15 (bs, 3H), 3.50 (bs, 3H), 7.00 (m, 3H) ppm.

^{2}H-NMR (77 MHz, CH_2Cl_2): 1.75 ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): 22.00 (quintet), 22.55, 26.07, 29.61, 32.16, 61.03, 123.21, 125.02, 130.01, 133.74, 135.45, 137.67, 165.10 ppm.

EI-MS (m/z, %): 221 ($M^{+\cdot}$, 1.3), 161 (100), 133 (34.5).

HRMS for $C_{13}H_{15}D_2NO_2$: Calc: 221.14158; Found: 221.14101.

mp: 76 °C.

References

1) Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.*, **1981**, *22*, 3815.

2) O'Neill, B.T. in *Comprehensive Organic Synthesis*, Vol. 1, p. 397, Permagon, New York, Eds. B.M. Trost and I. Fleming (1991).

3) Facey, G.A. Private Communication.

4) a) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Eng.*, **1978**, *17*, 521.
b) Meyer, N.; Seebach, D. *Helv. Chim. Acta.*, **1980**, *113*, 1304.

5) Anet, F.A.L.; Haq, M.Z. *J. Amer. Chem. Soc.*, **1965**, *87*, 3147.

Appendix I

X-Ray Data for 4-Pentafluorobenzoyl-1(H)-2,3-dihydroindene

```
   Space Group and Cell Dimensions    Monoclinic,    P 21
a   8.099(3)    b   8.314(4)    c   9.550(4)
beta  91.95(4)
        Volume    642.7(5)A**3

Empirical formula : F5 O C16 H9

Cell dimensions were obtained from  25 reflections with 2Theta angle
in the range  80.00 - 100.00 degrees.

Crystal dimensions :  0.20  X  0.20  X  0.20  mm

FW =    312.24      Z =    2      F(000) =      317.33

Dcalc  1.613Mg.m-3, mu   1.14mm-1, lambda 1.54056A, 2Theta(max) 100.0

The intensity data were collected on a Rigaku   diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max   -8    8;  Kmin,max     0    8;  Lmin,max   0    9
No. of reflections measured                          781
No. of unique reflections                            720
No. of reflections with Inet > 2.5sigma(Inet)        715
Merging R-value on intensities  0.113
No correction was made for absorption


The last least squares cycle was calculated with
 31 atoms, 199 parameters and  715 out of  720 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000200

The residuals are as follows :--
For significant reflections,  RF 0.036, Rw 0.051 GoF  3.49
For all reflections,          RF 0.036, Rw 0.051.
where RF = Sum(Fo-Fc)/Sum(Fo),
      Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
     GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was  0.077.

In the last D-map, the deepest hole was  -0.220e/A**3,
and the highest peak   0.170e/A**3.

Secondary ext. coeff.    1.019092      sigma    0.082736
```

The following references are relevant to the NRCVAX System.

1. Full System Reference :
   Gabe, E.J., Le Page, Y., Charland,.J.-P., Lee, F.L. and White, P.S.
   (1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :

International Tables for X-ray Crystallography, Vol. IV, (1974) Kynoch Press, Birmingham, England.

The following references may also be relevant.

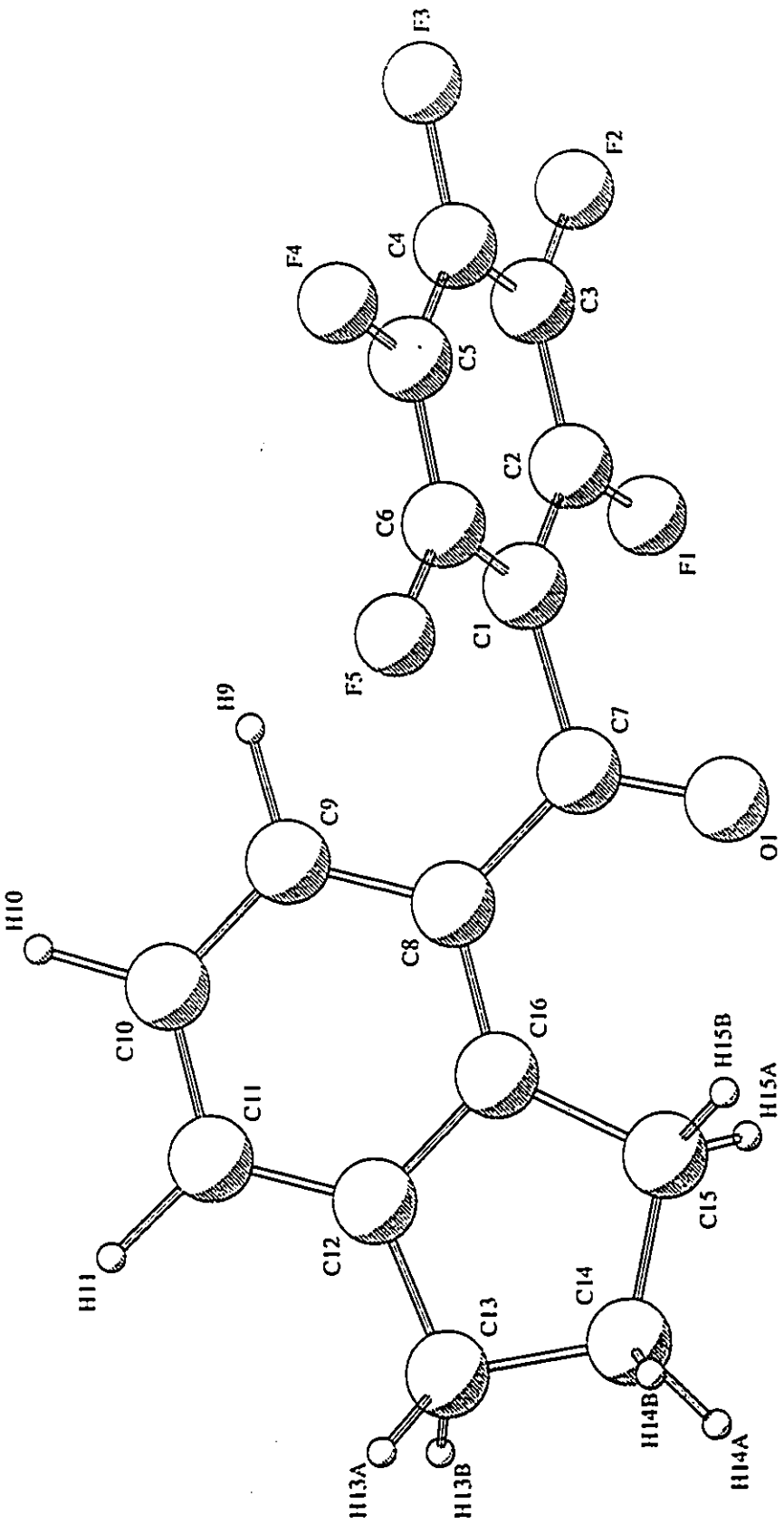
3. ORTEP Plotting :
Johnson, C.K., (1976) ORTEP - A Fortran Thermal Ellipsoid Plot Program, Technical Report ORNL-5138, Oak Ridge

4. Pluto Plotting :
S. Motherwell, University Chemical Laboratory, Cambridge, 1978

5. Missing Symmetry Treatment by MISSYM :
Le Page, Y., (1988) J. Appl. Cryst., 21, 983-984.

6. Grouping of Equivalent Reflections in DATRD2 :
Le Page, Y. and Gabe, E.J., (1979) J. Appl. Cryst., 12, 464-466.

7. Extinction Treatment :
Larson, A.C., (1970) p.293, Crystallographic Computing, Munksgaard, Copenhagen.


F3
F2
F4
C4
C3
C5
C2
C6
F1
C1
F5
H9
C7
C9
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H10
C8
C10
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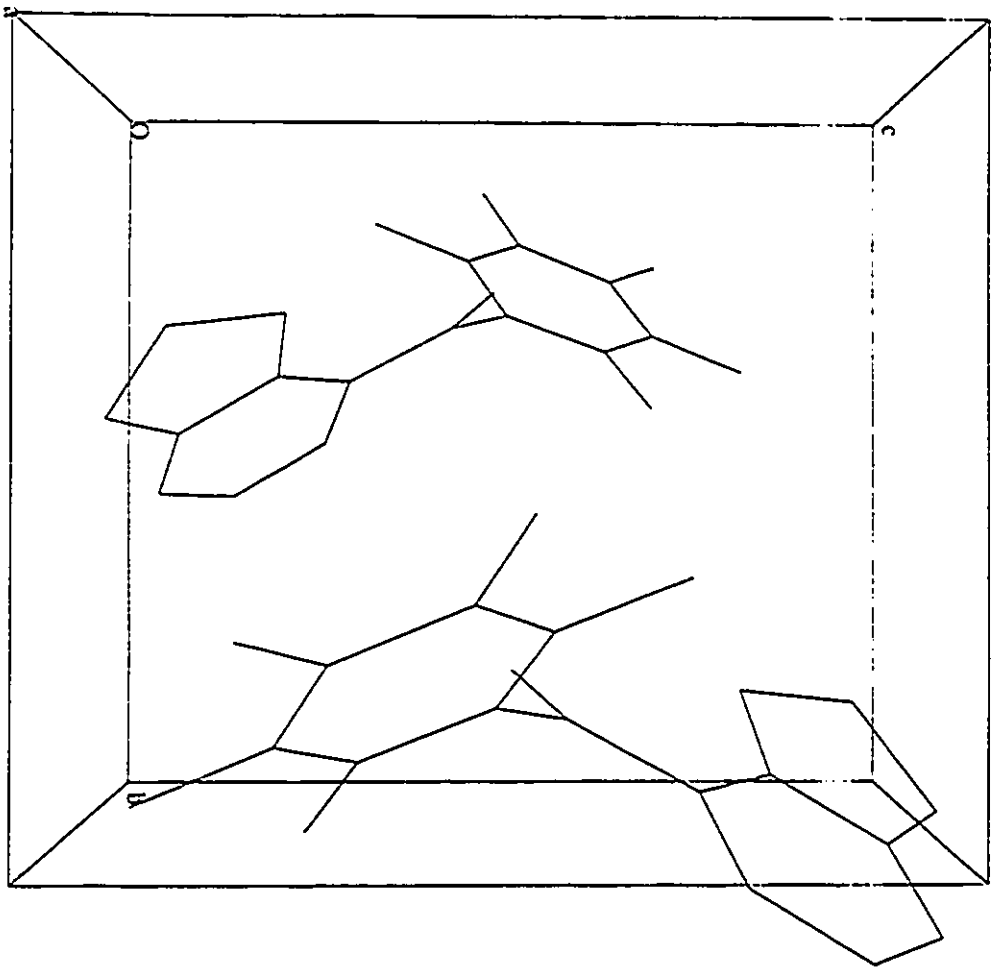
C14
C13
H14B
H13A
H13B
H14A


O
C

Appendix II

X-Ray Data for N-Methoxy-N-methyl-1,2,3,4-tetrahydronapthylcarboxamide

```
   Space Group and Cell Dimensions    Monoclinic,    P 21/a
a   8.6171(12)   b  12.2350(19)   c  11.2223(24)
beta 102.937(13)
        Volume  1153.1(3)A**3

Empirical formula : O2 N C13 H17

Cell dimensions were obtained from  24 reflections with 2Theta angle
in the range  80.00 - 100.00 degrees.

Crystal dimensions :  0.20  X  0.20  X  0.20  mm

FW =    219.28     Z =    4     F(000) =     473.38

Dcalc  1.263Mg.m-3, mu   0.85mm-1, lambda 1.54056A, 2Theta(max) 100.0

The intensity data were collected on a Rigaku   diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max   -8   8;  Kmin,max    0  12;  Lmin,max   0  11
No. of reflections measured                      1297
No. of unique reflections                        1195
No. of reflections with Inet > 2.5sigma(Inet)    1155
Merging R-value on intensities  0.050
No correction was made for absorption


The last least squares cycle was calculated with
 39 atoms, 164 parameters and 1155 out of 1195 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000250

The residuals are as follows :--
For significant reflections,  RF 0.066, Rw 0.138 GoF  8.13
For all reflections,          RF 0.067, Rw 0.138.
where RF = Sum(Fo-Fc)/Sum(Fo),
      Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
     GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was  0.183.

In the last D-map, the deepest hole was  -0.440e/A**3,
and the highest peak   0.460e/A**3.

Secondary ext. coeff.    9.989143      sigma    0.220005

      The following references are relevant to the NRCVAX System.

1. Full System Reference :
   Gabe, E.J., Le Page, Y., Charland,.J.-P., Lee, F.L. and White, P.S.
   (1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :
```

International Tables for X-ray Crystallography, Vol. IV, (1974) Kynoch Press, Birmingham, England.

The following references may also be relevant.

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4. Pluto Plotting :
S. Motherwell, University Chemical Laboratory, Cambridge, 1978

5. Missing Symmetry Treatment by MISSYM :
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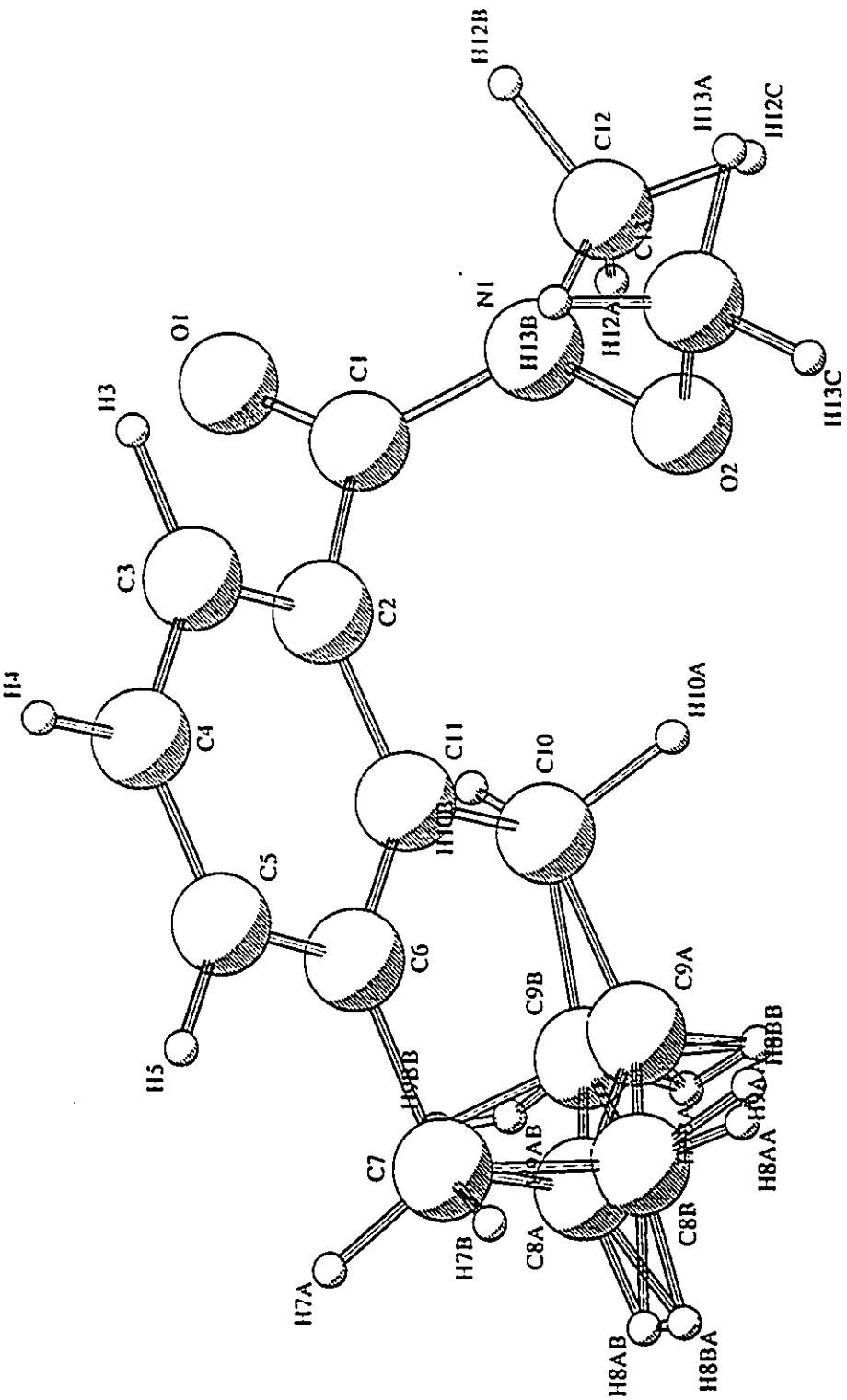
6. Grouping of Equivalent Reflections in DATRD2 :
Le Page, Y. and Gabe, E.J., (1979) J. Appl. Cryst., 12, 464-466.

7. Extinction Treatment :
Larson, A.C., (1970) p.293, Crystallographic Computing, Munksgaard, Copenhagen.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C12
H13A
H12C
C13
N1
H13B
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O1
C1
H3
O2
H13C
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H4
C4
C11
C10
H10A
H10B
C5
C6
C9B
C9A
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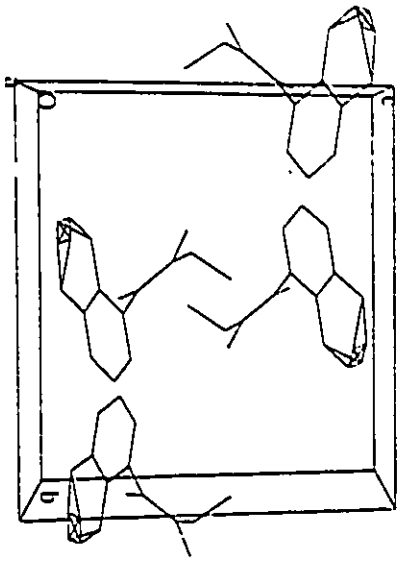
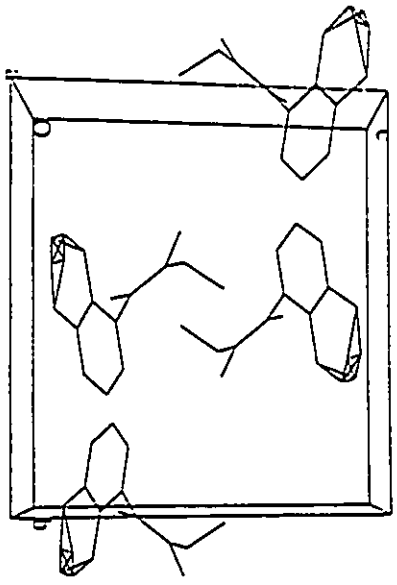
C8A
H7B
H7A
C7
H9BB
H5





CLAIMS TO ORIGINAL RESEARCH

1) The regioselectivity of 3-nitro-ortho-quinodimethane was probed using a sultine as the diene precursor. Use of methyl acrylate, vinyl acetate and butyl vinyl ether as representative dienophiles showed there to be no regioselectivity. Evaluation of the PM3 calculated HOMO supports these results, which shows the coefficients on the terminal ends of the diene to be almost equal in magnitude.

2) Two new tricyclic sulfones and two new tricyclic sultines were prepared. Preparation of sulfones derived from tetrahydronapthalene and benzosuberane was accomplished through the intermediacy of a sulfonium salt. This strategy failed when the substrate was derived from indane or indole. The sultines were derived from tetrahydronapthalene and indane. Cyclization of hydroxy sulfoxides was not as general a route to sultines as previously believed. The success of the reaction depended highly on the regiochemistry of the hydroxy sulfoxide.

3) A mechanistic investigation of the factors influencing the results of metal hydride mediated reduction of 3-thioalkl-2-oxindoles was completed. A proton α to the oxindole carbonyl protects this group from reduction. The C3 anion generated under the reaction conditions has a profound effect on the ease of reduction of a pendant carboxylic ester. When in a position ortho or para to the ester carbonyl, there is a low tendency for initial addition of hydride, and a subsequent high propensity for over-reduction. This result is best understood with resonance forms. The N1 anion does not interfere with the reduction of attached esters, even when ortho to this group.

4) A non-reductive method for the desulfenation and desulfination of 3-thioalkyl and 3-thioalkyl-S-oxides was developed. Use of a proton source (TsOH) and a thiophile (PPh_3) results in smooth removal of the sulfur substituent. The reaction is tolerant to a range of functional groups, including nitro, bromo and isolated double bonds (allyl and propargyl).

5) A series of bicyclic aldehydes and ketones were prepared. These compounds were found to undergo facile photoenolization, and the intermediates were readily trapped with added

dienophiles. The only anomaly was indane-6-carboxaldehyde. However, this is believed to be the result of rapid auto-oxidation of the aldehyde to the carboxylic acid.

6) The solid state mobility of a tetrahydronapthalene derivative was studied for the first time. This Weinreb amide was found to undergo a cyclohexene type inversion with an apparent activation energy of 12.3 kJ/mol as calculated from T_1 measurements.