The Use of Rhodium Carbenoid Insertion Reactions in Organic Synthesis

Michael Dean Hrytsak, MSc

A thesis submitted to the

School of Graduate Studies and Research

University of Ottawa

in

partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

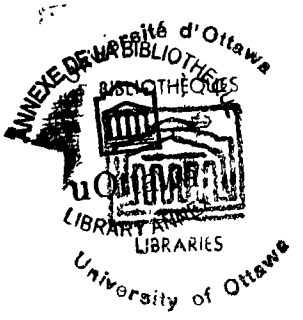
in the

Department of Chemistry

October, 1987

Candidate — Michael D. Hrytsak

Supervisor — Professor T. Durst



For Melanie, Kira, and Tatiana

ABSTRACT

CHAPTER 1

A brief overview of aliphatic diazo chemistry is presented.

CHAPTER 2

The synthesis of O-2-isocephems, a novel class of β-lactam antibiotics, is reported. The synthesis is performed in a highly convergent manner by coupling two key fragments (a pre-formed β-lactam, complete with amide side chain, and an α-diazo-β-ketoester bearing the eventual C-3 side chain) via an intermolecular rhodium carbenoid insertion reaction. The monocyclic β-lactams thus obtained are cyclized to the corresponding O-2-isocephems esters; three of which are deprotected to the respective acids. One of these was tested for antibacterial activity. The scope and limitations of this method is investigated, and a number of novel compounds are isolated and characterized.

CHAPTER 3

A conceptually new route to 1,3-dihydro-benzo[c]thiophene-2,2-dioxides from α-diazo-β-sulfonyl esters via a rhodium carbenoid insertion into aromatic C-H bonds is reported. The reaction is found to give products arising from attack at the position *para* to existing alkoxy susbstituents. Several examples are reported.

The aromatic C-H insertion reaction described above is extended to include α-diazo-β-keto aryl and naphthyl esters. This results in the formation of 3-acetylbenzofuran-2(3H)-ones and 3-acetylnaphthylfuran-2(3H)-ones respectively.

The mechanism of the benzofuran forming reaction is investigated by kinetic isotope effect. A rather large isotope effect is observed, most probably indicative of an insertion mechanism.

CHAPTER 4

The Ramberg-Backlund reaction is investigated as a possible route to carbapenems by ring contraction of a 3-sulfonyl cepham. The appropriate 3-sulfonyl cepham is prepared, however the Ramberg-Backlund reaction fails.

The 2-thiomethylethyl ester group is investigated as a possible protective group for the carbapenem carboxylate. It is possible to prepare the appropriate ester but the deprotection requires conditions that results in the destruction of the carbapenem.

A synthesis of 1-β-methylcarbapenems is attempted via a "3+2" cycloaddition reaction. The β-lactam precursor is prepared by displacement of the 4-acetoxy group of a chiral β-lactam with the anion of nitroethane followed by elaboration of the nitro group to a mesylate. The cycloaddition reaction using this substrate fails.

The use of camphor as a chiral auxiliary in the Staudinger (ketene-imine) reaction is investigated. The camphoryl-imido lactam is formed, but it is not possible to determine if the reaction favored the formation of one enantiomer.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Professor Tony Durst for his expert guidance, endless patience and mostly for being as good a listener as he is an instructor; his always open door was most appreciated.

I would also like to thank Raj Capoor for the many nmr spectra he recorded, and especially thank Dr. Clem Kazakoff for recording the 241 mass spectra (he counted them!) during my studies. Dr. John Krause is thanked for many helpful discussions.

I would like to thank my friends M.K. Sharma and Bill Brown for countless favors and consultations over the past four years.

I would finally like to thank my family Melanie, Kira and Tatiana for their patience and understanding during the preparation of this thesis. I would also like to thank them for the confidence they showed in me and the constant support that they gave me.

PREFACE

The use of aliphatic diazo compounds in synthesis is well known. Many synthetic transformations of diazo compounds involve the use of transition metal catalysts, historically the metal of choice being copper in various oxidation states. In the mid-seventies the discovery was made that rhodium(II) carboxylates were far superior catalysts than copper for most reactions, and since that time the use of aliphatic diazo compounds in synthesis has undergone a renaissance as witnessed by the large number of recent research and review articles dealing with the subject.

This thesis is largely concerned with exploring the use of aliphatic diazo compounds (as carbenoid precursors) in the synthesis of a novel class of β-lactam antibiotics and with the development of synthetic methodology featuring insertion reactions of rhodium carbenoids into aryl C-H bonds.

Chapter 1 is devoted to giving the reader a brief overview of the history and recent developments in the areas of aliphatic diazo chemistry and metal catalyzed decomposition reactions of these compounds.

Chapter 2 describes our preparation of O-2-isocephems (a synthetic class of β-lactam antibiotics) by utilizing an intermolecular rhodium carbenoid N-H insertion reaction to assemble the molecule in a convergent manner.

Chapter 3 deals with our efforts in the area of rhodium carbenoid insertions into aromatic C-H bonds. The preparation of various benzfused heterocycles via this methodology as well as some mechanistic information is presented.

Chapter 4 is a summary of the results of a series of smaller projects aimed at improving various aspects of carbapenem syntheses. Some of these results may lay the foundation for further studies; none of these projects were carried to a fully successful completion.

TABLE of CONTENTS

ACKNOWLEDGEMENTS i

PREFACE ii

TABLE OF CONTENTS iv

LIST of FIGURES vii

LIST of ABBREVIATIONS viii

LIST of SPECTRA xi

LIST of TABLES xiii

CHAPTER 1 1

The Chemistry of Aliphatic Diazo Compounds 1

General 1

Preparation 2

Metal Catalyzed Reactions 8

Interaction of Metal Catalysts and Diazo Compounds 15

REFERENCES 19

CHAPTER 2 22

Intermolecular Rhodium Carbenoid Insertions into the N-H Bond of β-Lactams 22

O-2-Isocephems 22

Retrosynthesis and Our Approach 24

Results and Discussion 27

Conclusions 59

Experimental 60

General 60

Preparation of Starting Materials.....61
β-Lactams 61
α-Diazo-β-ketoesters.....67
Carbenoid Insertion Reactions 74
Cyclization Reactions 80
Carboxylate Deprotection Reactions 83
Appendix 1.....85
Appendix 2.....86
Appendix 3.....87
REFERENCES.....88
CHAPTER 3.....90
Intramolecular Rhodium Carbenoid Insertions into Aromatic C-H Bonds 90
Preparation of 1,3-Dihydrobenzo[c]thiophene-2,2-dioxides.....90
Description of the Project.....90
Results and Discussion.....94
Preparation of 3-Acetylbenzofuranones and 3-Acetylnaphthofuranones.....103
Introduction.....103
Results and Discussion.....104
Mechanistic Considerations 123
Experimental 133
Appendix 1 152
REFERENCES.....154
CHAPTER 4.....157
Studies on Various Aspects of Carbapenem Synthesis 157

Carbapenems via a Ramberg-Backlund Approach.....157
2-Methylthioethyl ester as a Carbapenem Protective Group.....164
1-β-Methylcarbapenems via Nitroethane.....171
Camphor as a Chiral Auxiliary in the Staudinger Reaction.....176
Experimental.....183
REFERENCES.....195
CLAIMS to ORIGINAL RESEARCH.....197
PUBLICATIONS from this THESIS.....198

LIST of FIGURES

CHAPTER 1

FIGURE 1 Preparation of Diazo Compounds.....4

FIGURE 2 Metal Salt Catalyzed Reactions of Diazo Compounds.....9

LIST of ABBREVIATIONS

Ac.....acetyl

Ar.....aryl

aq.....aqueous

b.p.....boiling point

Bu.....butyl

°C.....degrees Celsius

CAN.....ceric ammonium nitrate

ci.....chemical ionization

cm.....centimeter

dec.....decomposition

d.....doublet

DMS.....dimethyl sulfide

ei.....electron impact

eq.....equivalents

Et.....ethyl

EtOAc.....ethyl acetate

ev.....electron volts

g.....gram

gc.....gas chromatograph

h.....hours

HOAc.....acetic acid

HOMCOR.....homonuclear correlation

HPLC....high performance liquid chromatography

Hz.....Hertz

ir.....infrared

L.....leaving group

LDA.....lithium diisopropylamide

L_n....."n"-ligands

M.....molar

M^+.....parent molecular ion

MCPBA.....*meta*-chloroperoxybenzoic acid

Me.....methyl

mm.....millimole

mp.....melting point

Ms.....mesyl

ms.....mass spectrum

NCS.....N-chlorosuccinimide

nmr.....nuclear magnetic resonance

OAc.....acetate

OMe.....methoxy

OtBDMS.....O-*tert*-butyldimethylsilyl

p.....page

PG.....protective group

ppm.....parts per million

Pr.....propyl

PMP.....*para*-methoxyphenyl

R.....typical alkyl group

tBu.....*tert*-butyl

tBuO.....*tert*-butoxide

tert.....tertiary

Tf.....trifluoromethanesulfonate

TFA.....trifluoroacetic acid

THF.....tetrahydrofuran

Tos.....tosylate

TMS.....trimethylsilyl

Z.....typical electron withdrawing group

LIST of SPECTRA

CHAPTER 2

^{1}H NMR Spectrum of Compound **13**.....29
^{1}H NMR Spectrum of Compound **15**.....31
^{1}H NMR Spectrum of Compound **17**.....33
^{1}H NMR Spectrum of Compound **20**.....36
^{1}H NMR Spectrum of Compound **25**.....38
^{1}H NMR Spectrum of Compound **28**.....40
^{1}H NMR Spectrum of Compound **31a**.....43
^{1}H NMR Spectrum of Compound **31e**.....44
^{1}H NMR Spectrum of Compound **33b**.....48
^{1}H NMR Spectrum of Compound **33e**.....49
^{1}H NMR Spectrum of Compound **40**.....57
^{13}C NMR Spectrum of Compound **40**.....57

CHAPTER 3

^{1}H NMR Spectrum of Entry **5**, Table 1.....99
^{1}H NMR Spectrum of Compound **28a**(CCl_4).....108
^{1}H NMR Spectrum of Compound **28a**(acetone d_6).....109
^{13}C NMR Spectrum of Compound **28a**.....111
^{1}H NMR Spectrum of Compound **28d**.....115
^{1}H NMR Spectrum of Compound **43**.....120
^{1}H NMR Spectrum of Compounds **44** & **45**.....122
Mass Spectra of Deuteroester & Product.....128

CHAPTER 4

^{1}H NMR Spectrum of Compound **10** 162

^{1}H NMR Spectrum of Compound **23** 167

^{1}H NMR Spectrum of Compound **25**.....168

^{1}H NMR Spectrum of Compound **34** 174

^{1}H NMR Spectrum of Compound **41** 179

^{1}H HOMCOR NMR Spectrum of Compound **43** 182

LIST of TABLES

CHAPTER 2

Table 1 Yields of the Insertion Reactions.....47

Table 2 Antibacterial Activity of O-2-Isocephems.....50

CHAPTER 3

Table 1 Products of the Diazosulfone Insertion Reactions.....97

Table 2 Products of the Diazoarylester Insertion Reactions.....113

Table 3 Benzylic Sulfides.....135

Table 4 Benzylic Sulfones.....137

Table 5 Benzylic Diazosulfones.....140

Table 6 1-Carboalkoxy-1,3-dihydrobenzo[c]-thiophene-2,2-dioxides.....142

Table 7 Aryldiazoesters.....145,146

Table 8 3-Acetylbenzofuran-2(3H)-ones and 3-Acetylnaphthofuran2(3H)-ones.....148,149

CHAPTER 4

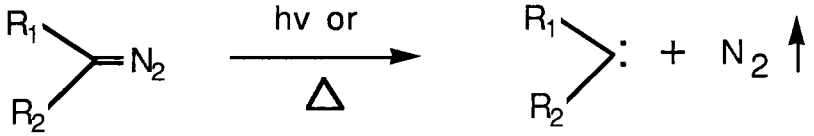
Table 1 Deprotection of 2-Thiomethylethyl cinnamate 169

CHAPTER 1

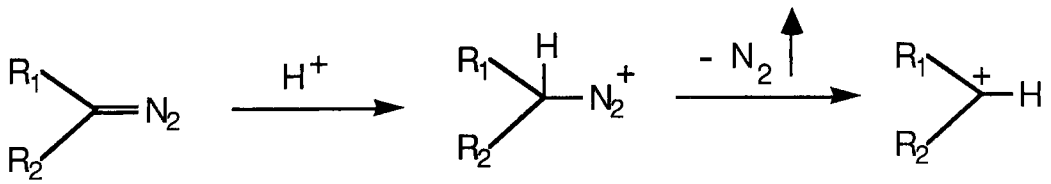
The Chemistry of Aliphatic Diazo Compounds

General

Aliphatic diazo compounds were first described in 1883 by Curtius,[1] and since that time their main use has been as precursors to carbenes (and carbenoids) which are formed by their decomposition. In fact, their value as "carbenic" precursors has provided much of the impetus for the development of the chemistry of diazoalkanes. The decomposition may occur photolytically or thermally and may be catalyzed by transition metals.



Diazoalkanes are also carbocation precursors since protonation of the diazo group's carbon followed by loss of N_2 produces a variety of results by way of an intermediate carbocation.



Many diazo compounds are explosive, especially those without electron withdrawing groups (Z groups) and are readily decomposed by heating or by contact with traces of metallic impurities. Most are also poisons, therefore caution must be exercised when working with these compounds particularly on a preparative scale. Distillation is not recommended for the higher molecular weight diazo compounds. Their stability is greatly enhanced by the presence of at least one electron withdrawing group such as carbonyl, sulfonyl or phosphoryl in the position α to the diazo function.[2] The carbon atom of the diazo group is not as easily protonated as non-stabilized diazo compounds and therefore their acid stability is much better.

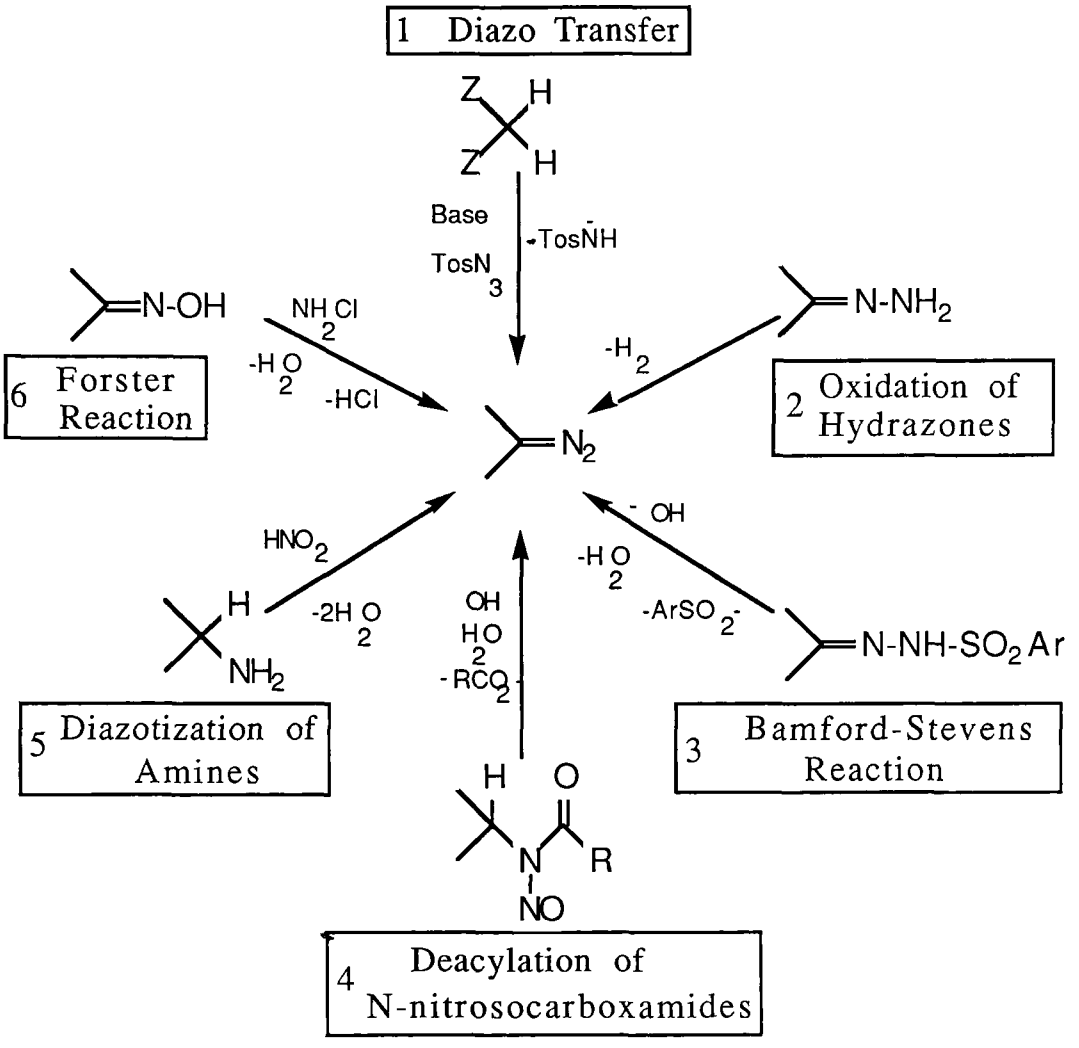
Preparation

There are at present six useful methods for the preparation of aliphatic diazo compounds.[3] The method of preparation is of course dependent on the substrate one chooses to diazotize. These reactions are diazo transfer, oxidation of hydrazones, Bamford-Stevens reaction, deacylation of N-nitrosocarboxamides, diazotization of amines and the Forster reaction (Figure 1) These may be broadly categorized in three groups; transfer of a diazo group from a donor to an active methylene compound (reaction 1), conversion of an existing N-N linkage into the diazo group (reactions 2, 3 and 4), and reaction of two N containing molecules resulting in diazotization (reactions 5 and 6). Thus the diazo function may be introduced directly, built up sequentially or prepared from existing N-N functionalities.

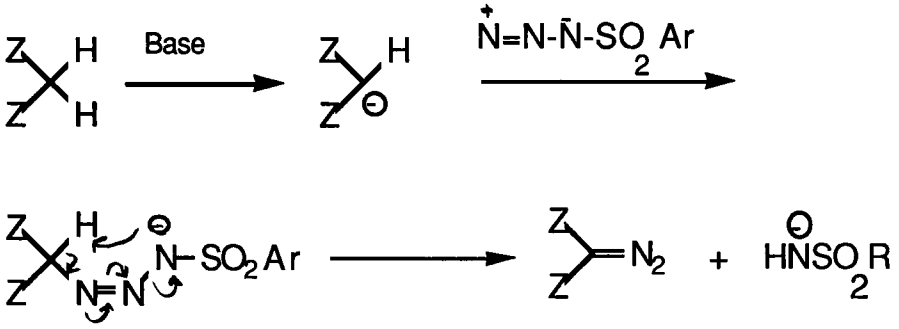
Since all of the diazo compounds used in this thesis were prepared by diazo transfer, this method of diazotization will be focused on. For detailed information on the remaining methods the reader is encouraged to consult the review articles cited in references 2,3 and 4.

The diazo transfer reaction[4,5] is the method of choice for preparing diazo compounds from active methylene compounds, and has virtually replaced all other methods. The reaction involves the transfer of two nitrogen atoms as the diazo group from a donor molecule (usually an azide) to the active methylene compound. The donor molecule is typically p-toluenesulfonyl azide,[6,7] however other sulfonyl azides have been used as well. These include p-carboxy,[8] p-dodecyl,[9] and polymeric benzenesulfonyl azides.[10] Recently methanesulfonyl azide[11] has been demonstrated to be an excellent diazo transfer reagent. For base sensitive substrates 2-azido-3-ethyl-1,3-thiazolinium tetrafluoroborate[12] has proven to be an efficient agent particularly in the pH 0-8 range.

FIGURE 1

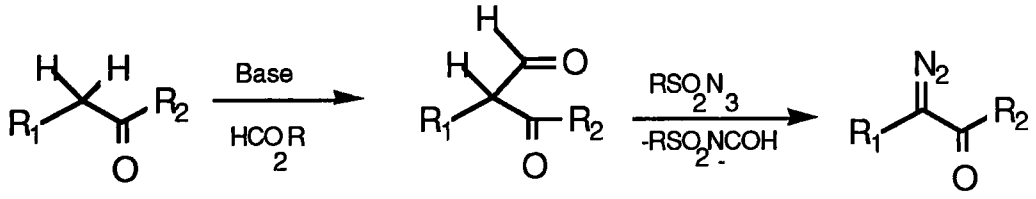


The diazo transfer reaction is thought to proceed via a triazene intermediate that decomposes to the diazo compound and a sulfonamide.

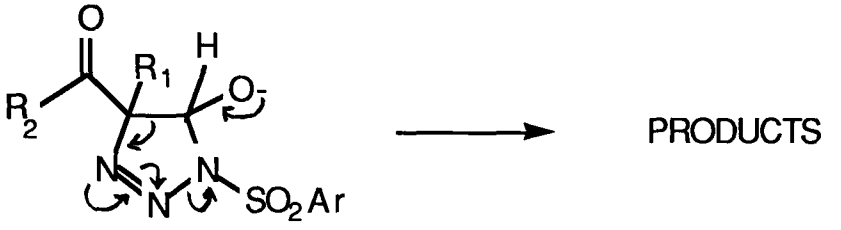


The strength of the base used is determined by the electron withdrawing groups Z. In the cases of β-ketoesters (Z_1=RCO, Z_2=CO_2R) triethylamine or piperidine is sufficient, however for substrates such as β-sulfonylamides[13](Z_1=RSO_2,Z_2=$CONR_2$) or disulfones[14](Z_1,Z_2=RSO_2) a strong base such as sodium or potassium hydroxide or hydride may be required. Yields vary according to substrate, but are typically in the 70-90% range; best yields are obtained for the more acidic methylene compounds.

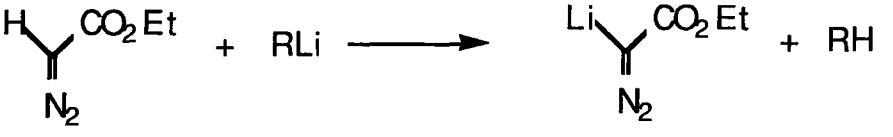
When monoactivated methylene compounds are subjected to diazo transfer, yields are generally very poor due to the low acidity of the methylene hydrogens compared to the diactivated compounds. This problem may be alleviated by use of the "deformylative" diazo transfer reaction.[15] The monoactivated substrate (cyclohexanone for example) is first formylated by reaction with base and a formate ester (Claisen reaction) followed by addition of the sulfonyl azide.



The reaction proceeds via a triazoline salt that undergoes decomposition. The initial formylated compound may be isolated, but a one-pot procedure is more commonly used.

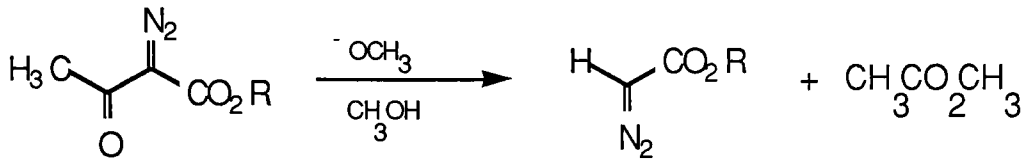


While the chemistry of diazo compounds is greatly dominated by reactions involving their decomposition, there do exist reactions in which the diazo moiety is retained. Primary diazo compounds ($RCHN_2$) possess an acidic hydrogen that is capable of undergoing exchange with metals such as lithium,[16] mercury[17] and silver[18] from an organolithium or, in the latter



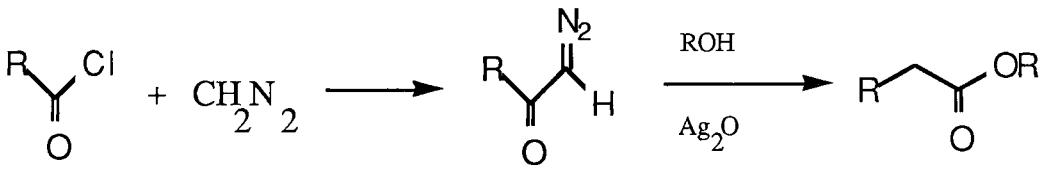
two cases, the metal oxides. The metallated compounds undergo a variety of reactions such as C-alkylation, acylation and aldol reaction. Primary diazo compounds may also be acylated by reaction with anhydrides.

A most useful reaction of diazo compounds derived from β-diketones, β-ketoesters, β-ketoamides and β-ketosulfones is the acyl cleavage reaction. The acylated diazo compound is simply stirred with a solution of sodium hydroxide or methoxide to afford the primary diazo compound as a result of deacylation.[19]



The yields for this reaction are in the order of 50-90%. This reaction represents one of the best preparative methods for esters of diazoacetic acid, in fact it is often an annoying side reaction observed in diazo transfer reactions of compounds requiring strong base for deprotonation.

Perhaps the best known reaction of diazo compounds in which the diazo function is retained is the reaction between acyl halides and diazomethane that results in the formation of a diazo ketone.[20] In this reaction diazomethane is used in excess, one full equivalent is



taken up in scavenging the acid by-product produced in the reaction. This reaction is the first step in the Arndt-Eistert synthesis[21] where an acyl halide is converted to a carboxylic acid (or derivative) whose chain length has been increased by one carbon. The second step is the Wolff rearrangement and is usually catalyzed by silver(I) oxide but it can also be accomplished photochemically.

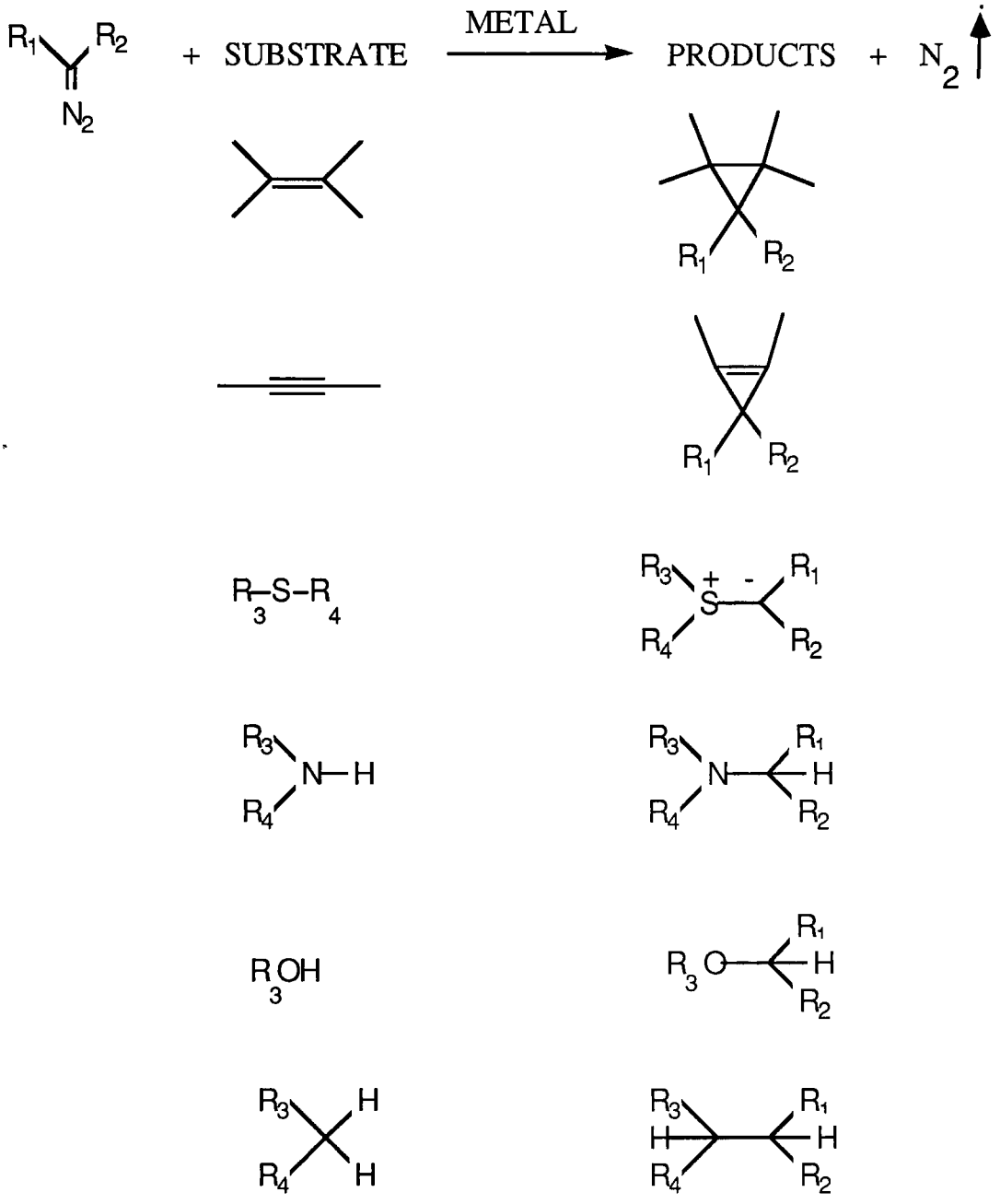
Metal Catalyzed Reactions

The use of transition metal catalyzed reactions of diazo compounds in synthesis has enjoyed a resurgence with the discovery of rhodium(II) carboxylates as efficient catalysts.[22] Prior to the late seventies, the chemistry of metal catalyzed diazo reactions was dominated by copper.[23] Many copper compounds have found use in these catalytic reactions including copper metal, copper bronze, copper(II) sulfate and copper(I) halides. Some of the other metal salts that have been employed are palladium(II) acetate, zinc(II) halides and silver(I) oxide, the latter being a particularly good catalyst for promoting the Wolff rearrangement.[24]

Metal catalyzed reactions of diazo compounds may be classified as to the substrate the diazo compound is reacted with. The general types of the most common reactions are summarized in Figure 2.

Entry 1 illustrates the cyclopropanation reaction. This reaction is very well known and is the most studied of all metal catalyzed reactions of diazo compounds. The cyclopropanation reaction occurs both intramolecularly and intermolecularly with a wide variety of olefinic substrates. There has been an enormous amount of work published in this area, particularly by the groups of Doyle[25] and Noels,[26] who have systematically examined the effects of various catalysts (metals, ligands) and diazo compounds on the cyclopropanation of substituted alkenes. From this huge body of work the following observations may be made.

ENTRY FIGURE 2



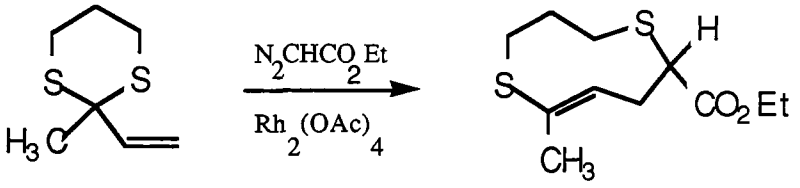
Rhodium(II) carboxylates are the most efficient catalysts, being generally superior to palladium(II) acetate or copper(I) triflate. The regiochemistry and stereochemistry of cyclopropanation may be controlled by judicious choice of catalyst. There appear to be two

modes of reaction, a carbenoid mode and a coordination mode. In the former a metal-carbene (or diazo compound-metal complex) attacks the olefin whereas in the latter an intramolecular reaction occurs between the metal-carbene and the olefin that are both coordinated to the same metal. It is expected that for rhodium(II) carboxylates the carbenoid mode is most likely since they possess only one coordination site per metal whereas palladium compounds are known to complex olefins and may be expected to react by coordinating both the diazo compound and the olefin. In most cases it is desirable to add the diazo compound to a solution (or suspension) of the olefin and catalyst in an inert solvent in order to minimize the amount of product formed by formal coupling of carbenes ("carbene dimers"). Yields of cyclopropane vary with the three variables mentioned above, but are usually high, and in general are best for electron rich sterically unhindered alkenes, since most metal-carbenes are electrophilic.

Entry 2 is the cyclopropenation reaction. This reaction has been studied far less than cyclopropanation, but again rhodium(II) carboxylates have proven to be the best catalysts.[27]

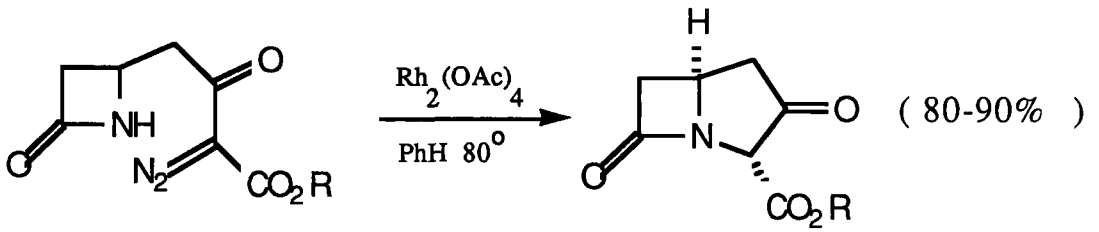
Entry 3 represents the reaction between diazo compounds and sulfides resulting in sulfonium ylides.[28] This reaction (ylide formation) is also observed with ethers, the products isolated depend on the substituents present on the diazo function. In the case of sulfides and diazoketones it is often possible to isolate the ylide, but in the case of ethers the product is usually the result of a 1,2 carbon shift (Stevens rearrangement) of the intermediate ylide giving a formal C-O insertion product.[29,30] Recently, Davies has prepared

stable cyclic sulfonium ylides by intramolecular reaction of α-diazo-β-ketoesters bearing a pendant sulfide functionality.[31] Epoxides are deoxygenated by metallocarbenes to give alkenes.[32] The 1,2 carbon shift can also be observed in the sulfonium ylide case, and this reaction has been used to expand sulfur heterocycles by one carbon.[33] Rhodium carbenoids have been used to form intermediate sulfonium ylides capable of undergoing [2,3] sigmatropic rearrangement. Thus cyclic allylic sulfides give ring expanded products on exposure to ethyl diazoacetate and rhodium(II) acetate.[29]



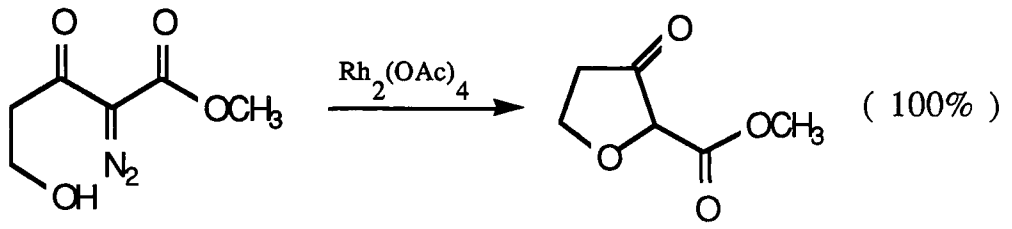
Pirrung has recently extended this reaction to include allylic ethers.[34]

Entry 4 illustrates the formal insertion of a carbene into an N-H bond resulting in alkylation at nitrogen. Ylide formation is often observed with tertiary amines. This reaction has been used most often in the intramolecular sense. The significance of these insertion reactions is best demonstrated by the intramolecular ring closure of β-lactams bearing an α-diazo-β-ketoester side chain at C-4 to the carbapenem skeleton.[35] The reaction is equally effective in the



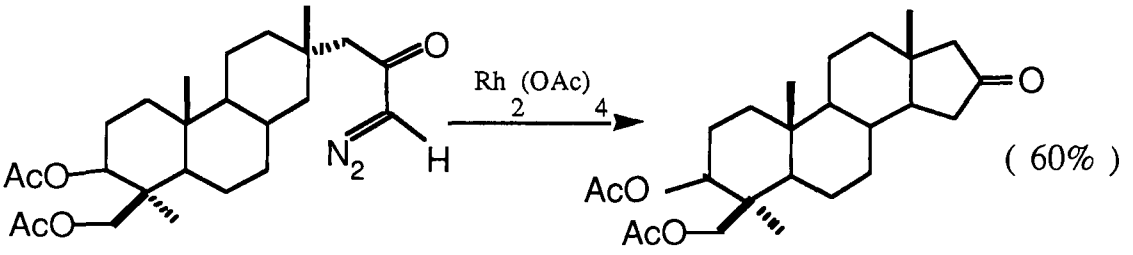
preparation of the oxapenem,[36] carbacephem,[37] and oxacephem[38] ring systems.

Entry 5 refers to the analogous O-H insertion reaction. Teyssie discovered in 1973 that rhodium(II) carboxylates are very useful for catalyzing insertions into the O-H bond.[39] Recently the reaction has found use in the synthesis of oxygen heterocycles

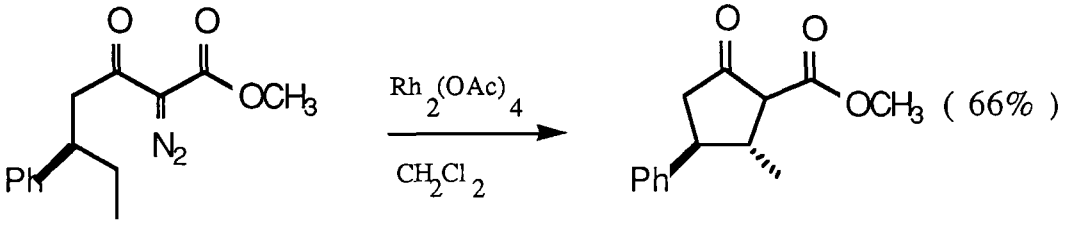


as reported by Rapoport in 1985.[40] The best yields were obtained in the formation of four to six membered rings.

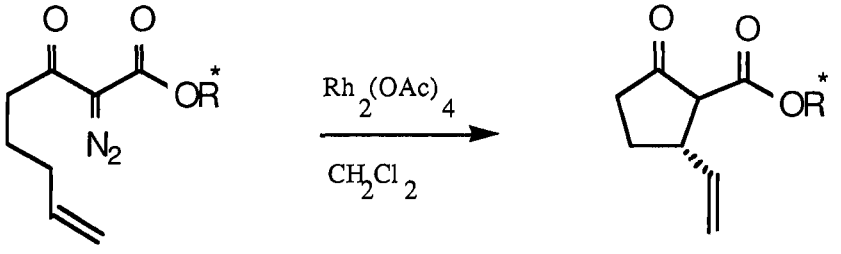
Entry 6 represents the aliphatic C-H insertion reaction. It is this reaction that has perhaps seen the most dramatic improvement by rhodium(II) carboxylate catalysis. Wenkert was the first to report on the use of rhodium(II) acetate in the synthesis of carbocycles via carbenoid insertion in 1982.[41] This was demonstrated by the synthesis of the D ring of the steroid skeleton.



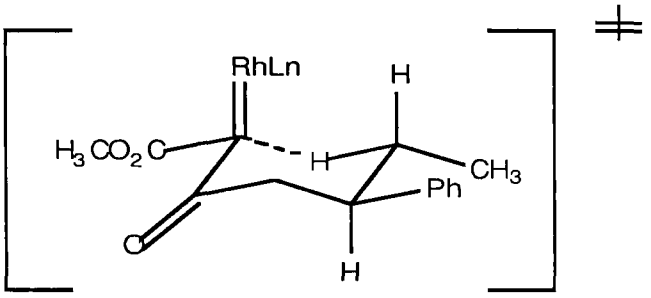
The majority of the recent work in this area has been reported by Taber, who has prepared cyclopentanones by intramolecular insertion of rhodium carbenoids derived from acyclic α-diazo-β-ketoesters.[42] The following example shows a C-H insertion that demonstrates high diastereoselectivity.[43]



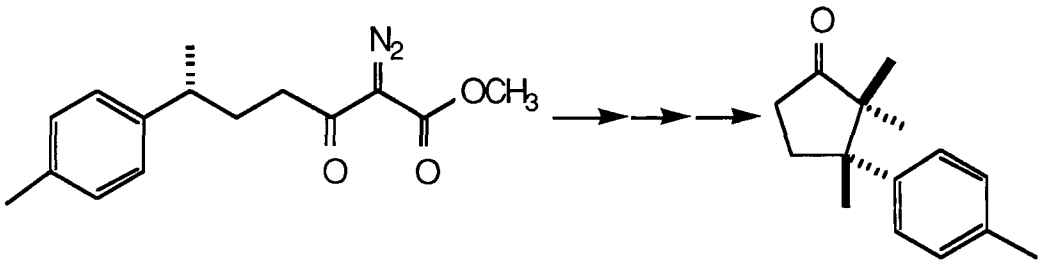
When a bulky, chiral ester group is present the reaction gives substituted cyclopentenones in high optical yield.This technique has been used to synthesize (+)-estrone methyl ether in 91%e.e.[44]



Acyclic systems display a preference for five membered ring formation, possibly via a chair-like transition state.



Taber has also demonstrated that rhodium carbenoid insertions proceed with retention of configuration.[45]



(+)-alpha-cuparenone

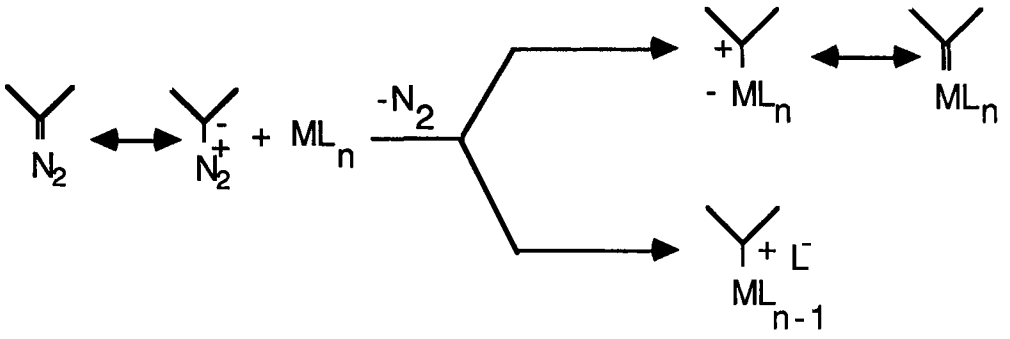
The intermolecular version of the C-H insertion reaction using rhodium(II) carboxylates has been investigated by Teyssie who found that diazoacetic esters would insert into aliphatic C-H bonds using rhodium(II) trifluoroacetate.[46] The hydrocarbon is present in excess, and good yields of insertion products based on diazoacetate were realized. The order of reactivity noted was secondary> tertiary> primary C-H bonds.

Interaction of Metal Catalysts and Diazo Compounds

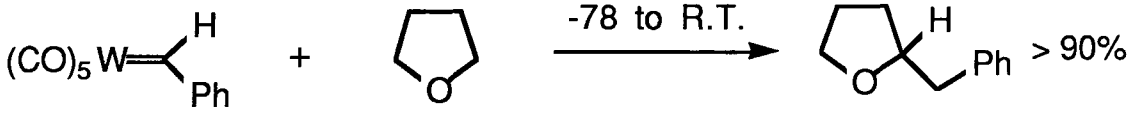
For the most part, transition metals are used in carbenoid reactions in a catalytic manner. The metal reacts with the diazo compound (especially diazo carbonyl compounds) to form the metal-carbene, bearing an electrophilic carbenic carbon, whereupon the carbenic moiety is transferred to an electron rich substrate (alkene, sulfur, oxygen) releasing the metal to react with another diazo compound completing the cycle.

The term "carbenoid" was first used by Nozaki in 1966 to describe that which is neither a free carbene nor an activated diazo compound. Since that time the term has been used freely to describe a transient electrophilic species resulting from the reaction between a diazo compound and a suitable transition metal. As early as 1952 Yates[47] had suggested that copper reacted with diazo carbonyl compounds to liberate N_2 and generate a metal-bound carbene as an intermediate. The question of what is the structure of the actual metal containing intermediate has remained unanswered since that time. To date no one has actually observed this intermediate so its nature remains the subject of speculation, much of it based on comparisons with similar model systems.

Currently it is thought that the transition metal (having an available coordination site) acts as an electrophile and attacks the diazo compound. This results in loss of N_2 and possible displacement of one of the metal's

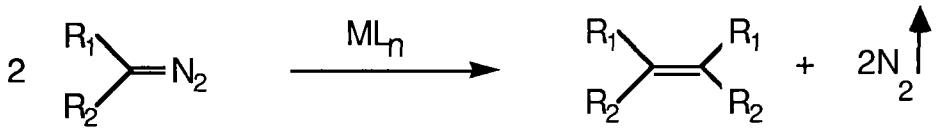


ligands as an anionic species. This gives rise to two possible intermediates, the metal-carbene or an ion pair. The latter may be considered as arising from carbene insertion into a metal-ligand bond. These insertions have been observed in the reaction between some transition metal halides and diazo compounds.[48] The former (metal-carbene) is analogous to stable metal-carbene complexes that have been known to undergo typical "carbenoid reactions", for example Fischer observed the C-H insertion reaction of a stable tungsten carbene into tetrahydrofuran.[49]

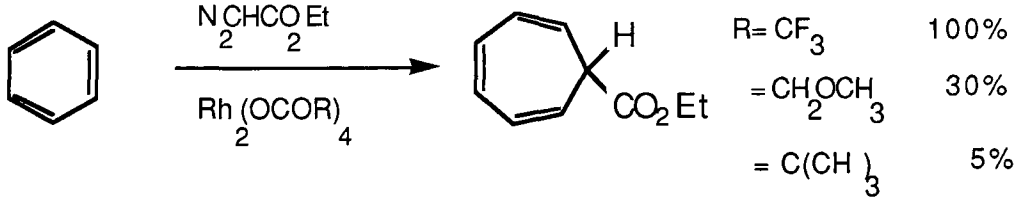


There are a number of observations that implicate metal-carbenes in carbenoid reactions. In 1975 Aratani[50] found that a copper chelate compound having chiral, bulky ligands was able to catalyze the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with ethyl diazoacetate. This suggests that the chiral ligands are in close proximity to the reaction center, hence a metal-carbene is more likely than a "free" carbene.

A reaction typical of carbenoids is the formation of "carbene dimers".[51] These are not normally observed in reactions involving

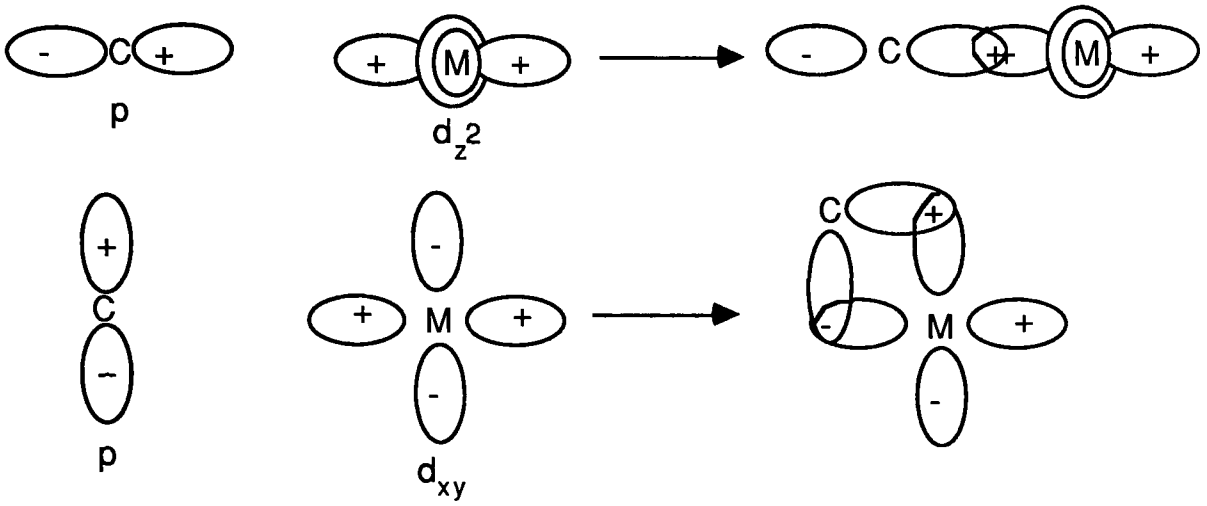


free carbenes, presumably due to the short life times of the highly reactive carbenes. The fact that changing the ligands of the transition metal catalyst can influence the reactivity of the carbenoid suggests that the electrophilic nature of the metal bound carbon is altered by the electron withdrawing nature of the ligands. For example, in the reaction between benzene and ethyl diazoacetate catalyzed by rhodium(II) carboxylates[52] it was found that the more strongly electron withdrawing ligands gave higher yields of cycloheptatrienes.



These observations are consistent with a bonding situation involving the p-orbitals of the carbene and two d-orbitals of the metal. The degree of backbonding would determine the polarization of the carbene-metal bond. Strong backbonding will favour $^{-}C \rightarrow M^{+}$

and weak will favour $^{+}C \rightarrow M^{-}$. There can also be a balance between the two where the bond is non-polar C=M or a diradical ·C—M·.



Wulfman discusses this and many more aspects of metal-salt-catalyzed reactions in a very in-depth manner focusing mainly on copper catalyzed systems in a 1980 review [23].

Finally, known stable metal complexes display the same selectivity with the same substrates as transient intermediates of assumed similar structure. The cyclopropanation of olefins with $(CO)_5W$=CHPh gives the same cis/trans ratios of products as the reaction of $Rh_2(OAc)_4/N_2$=CHPh.[53] Both metal carbenes are thought to have a metal atom surrounded by ligands with one coordination site occupied by the carbenic carbon and its substituents.

REFERENCES

[1] T. Curtius *Chem. Ber.* 1883, **16**, 2330.

[2] M. Regitz In " The Chemistry of Diazonium and Diazo Groups "; S. Patai Ed.; John Wiley and Sons: New York, 1978; p 751.

[3] M. Regitz In " The Chemistry of Diazonium and Diazo Groups "; S. Patai Ed.; John Wiley and Sons: New York, 1978; p 659.

[4] M. Regitz *Synthesis* 1972, 351.

[5] M. Regitz *Ang. Chem. Internat. Edit.* 1967, **6**, 733.

[6] M. Regitz, J. Hocker, A. Liedhegener " Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 197.

[7] J.E. Leffler, Y. Tsuno *J. Org. Chem.* 1963, **28**, 902.

[8] J.B. Hendrickson, W.A. Wolf *J. Org. Chem.* 1968, **33**, 3610.

[9] G.C. Hazen, L.M. Weinstock, R. Connell, F.W. Bollinger *Synth. Comm.* 1981, **12**, 947.

[10] W.R. Roush, D. Reitler, J. Rébek *Tetrahedron Lett.* 1974, 1391.

[11] D.F. Taber, R.E. Ruckle Jr., M.J. Hennessy *J. Org. Chem.* 1986, **51**, 4077.

[12] H. Balli, R. Low, V. Muller, H. Rempfler, G. Sezen-Gezgin *Helv. Chim. Acta.* 1978, **61**, 97.

[13] M. Regitz, W. Bartz *Chem. Ber.* 1970, **103**, 1477.

[14] F. Klages, K. Bott *Chem. Ber.* 1964, **97**, 735.

[15] M. Regitz, F. Menz *Chem. Ber* 1968, **101**, 2622.

[16] U. Schollkopf, H. Frasnelli *Ang. Chem. Internat. Edit.* 1970, 5237.

[17] T. Dominh, O.P. Strausz, H.E. Gunning *Tetrahedron Lett.* 1968, 5237.

[18] U. Schollkopf, N. Rieber *Chem. Ber.* 1969, **102**, 488.

[19] M. Regitz, J. Hocker *Org. Synth.* 1968, **48**, 36.

[20] W. Ried, H. Mengler *Fortschr. Chem. Forsch.* 1965, **5**, 1.

[21] H. Meier, K. Zeller *Ang. Chem. Internat. Edit.* 1975, **14**, 32.

[22] M.P. Doyle *Chem. Rev.* 1986, **86**, 919.

[23] D.S. Wulfman, B. Poling In " Reactive Intermediates "; R.A. Abramovitch Ed.; Plenum Press: New York, 1980; Vol. 1, p321.

[24] G. Maas In " Topics in Current Chemistry Organic Synthesis, Reactions and Mechanisms "; Springer-Verlag: New York, 1987; Vol. 137, p 75.

[25] M.P. Doyle *Acc. Chem. Res.* 1986, **19**, 348.

[26] A.J. Anciaux, A.J. Hubert, A.F. Noels, N. Petiniot, Ph. Teyssié *J. Org. Chem.* 1980, **45**, 695.

[27] W.A. Donaldson, R.P. Hughes *J. Am. Chem. Soc.* 1982, **104**, 4846.

[28] R.J. Gillespie, J. Murray-Rust, P. Murray-Rust, A.E.A. Porter *J. Chem. Soc. Chem. Commun.* 1978, 83.

[29] M.P. Doyle, J.H. Griffin, M.S. Chinn, D. van Leusen *J. Org. Chem* 1984, **49**, 1917.

[30] C.R. Johnson, E.J. Roskamp *J. Am. Chem. Soc.* 1986, **108**, 6062.

[31] H.M.L. Davies, L. Van. T. Crisco *Tetrahedron Lett.* 1987, **28**, 371.

[32] M.G. Martin, B. Ganem *Tetrahedron Lett*, 1984, **25**, 251.

[33] Y. Takamura, Y. Takebe, C. Mukai, M. Ikeda *Heterocycles* 1981, **15**, 875.

[34] M.C. Pirrung, J.A. Werner *J. Am. Chem. Soc.* 1986, **108**, 6060.

[35] R.W. Ratcliffe, T.N. Salzmann, B.G. Christensen *Tetrahedron Lett.* 1980, **21**, 31.

[36] L.D. Cama, B.G. Christensen *Tetrahedron Lett.* 1978, 4233.

[37] D.A. Evans, E.B. Sjogren *Tetrahedron Lett.* 1985, 26, 3787.

[38] D. Häbich, W. Hartwig *Tetrahedron* 1984, 40, 3667.

[39] R. Paulissen, H. Reimlinger, E. Hayez, A.J. Hubert, Ph. Teyssié *Tetrahedron Lett.* 1973, 2233.

[40] M.P. Moyer, P.L. Feldman, H. Rapoport *J. Org. Chem.* 1985, **50**, 5233.

[41] E. Wenkert, L.L. Davis, B.L. Mylari, M.F. Solomon, R.R. da Silva, S. Shulman, R.J. Warnet, P. Ceccherelli, M. Curini, R. Pellicciari *J. Org. Chem.* 1982, **47**, 3242.

[42] D.F. Taber, E.H. Petty *J. Org. Chem.* 1982, **47**, 4808.

[43] D.F. Taber, R.E. Ruckle Jr. *Tetrahedron Lett.* 1985, **26**, 3059.

[44] D.F. Taber, K. Raman, M.D. Gaul *J. Org. Chem.* 1987, **52**, 28.

[45] D.F. Taber, E.H. Petty, K. Raman *J. Am. Chem. Soc.* 1985, **107**, 196.

[46] A. Demonceau, A.F. Noels, A.J. Hubert, Ph. Teyssié *J. Chem. Soc. Chem. Commun.* 1981, 688.

[47] P. Yates *J. Am. Chem. Soc.* 1952, **74**, 5376.

[48] H.J. Callot, E. Schaeffer *Tetrahedron Lett.* 1977, 239.

[49] H. Fischer, J. Schmid, R.J. Märkl *J. Chem. Soc. Chem. Commun.* 1985, 572.

[50] T. Aratani, Y. Yoneyoshi, T. Nagase *Tetrahedron Lett.* 1975, 1707.

[51] B.K.R. Shankar, H. Shechter *Tetrahedron Lett.* 1982, **23**, 2277.

[52] A.J. Anciaux, A. Demonceau, A.J. Hubert, A.F. Noels, N. Petiniot,Ph. Teyssié *J. Chem. Soc. Chem. Commun.* 1980 765.

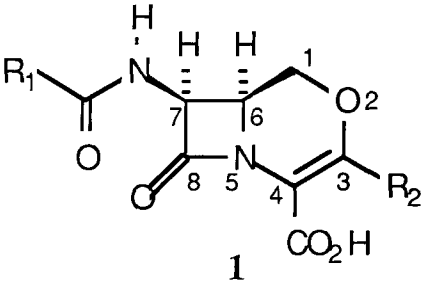
[53] M.P. Doyle, J.H. Griffin, V. Bagheri, R.L. Dorow *Organometallics* 1984, **3**, 53.

CHAPTER 2

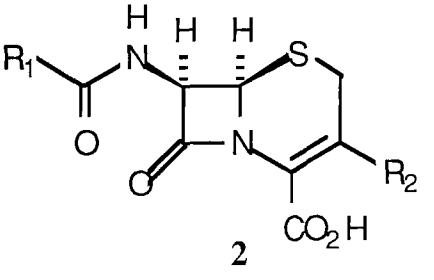
Intermolecular Rhodium Carbenoid Insertions into the N-H Bond of β-Lactams[1]

O-2-Isocephems

The O-2-isocephems **1** are a synthetic class of β-lactam antibiotics that are effective against a wide variety of pathogenic bacteria.[2] O-2-isocephems differ from their parent natural product cephalosporins **2** in that the six-membered ring contains an oxygen atom at the two position versus a sulfur atom at the one position.



1



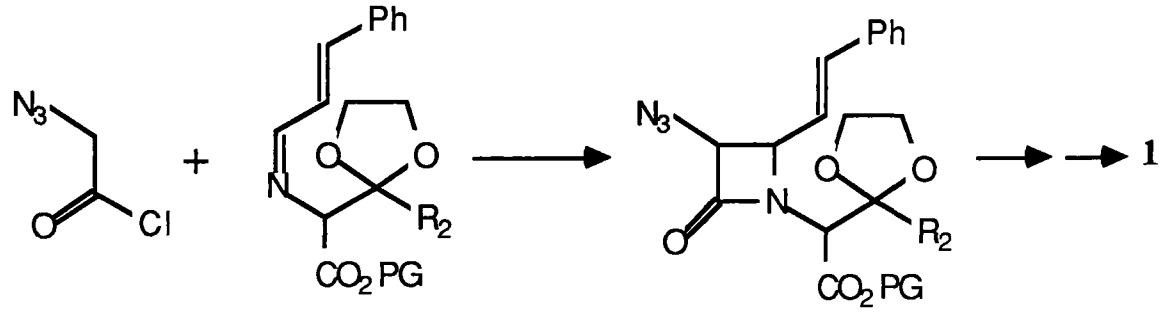
2

Hence, the structural difference is in the molecular "skeleton" or nucleus, and therefore O-2-isocephems are "nuclear" analogues of cephalosporins.

In the period from 1976 to 1980 there was a flurry of activity in the area of O-2-isocephems, mostly by the Bristol Canada group.[3] Chemists at Bristol published a series of articles that described their syntheses of many analogues (varying in R_1 and R_2) and reported

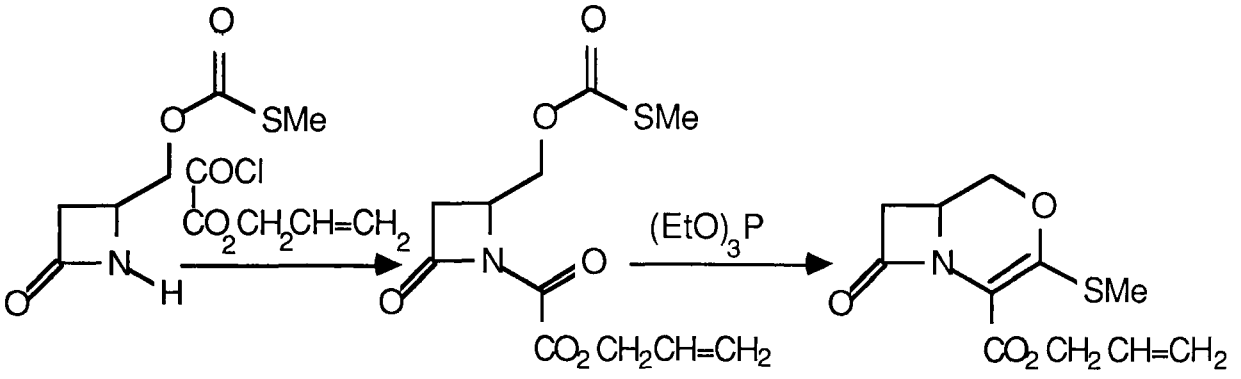
their findings on structure-activity relationships. For the most part antibacterial activities of the O-2-isocephems tested were comparable to their cephalosporin counterparts.

Recently, interest in these compounds was renewed with the observation that when R_2= $CH{=}CHCH_3$ (*cis*), the biological activity was appreciably increased.[4] We therefore became interested in developing a new general synthesis of O-2-isocephems. A survey of the literature, mostly Bristol work, showed that most previous syntheses were based on the formation of the β-lactam ring late in the synthesis by a ketene-imine approach.



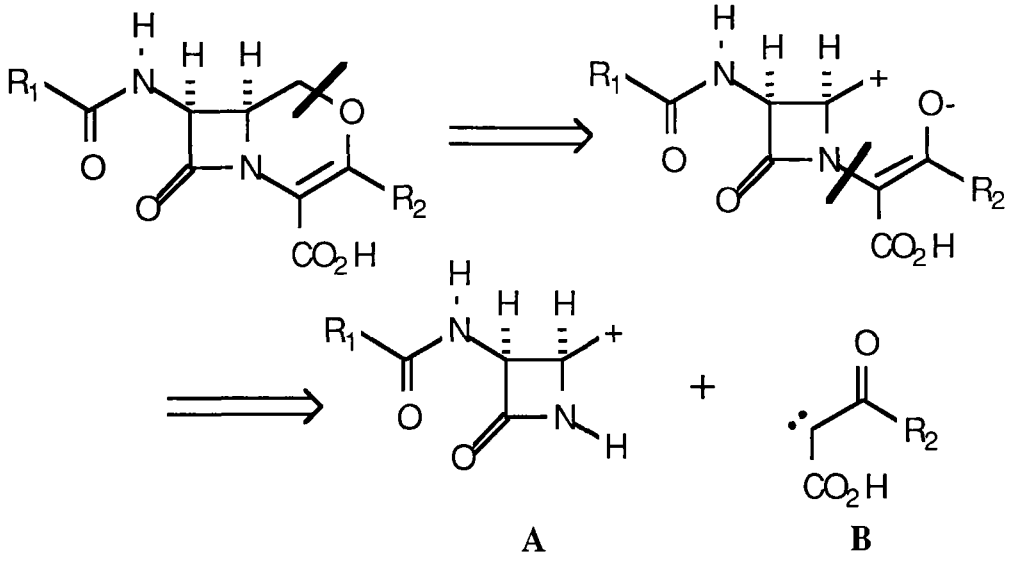
For each new analogue at C-3 (R_2 in **1**), a new Schiff base (imine) had to be prepared. Also, since the β-lactam forming reaction is not enantiospecific, no chiral products were obtained. One exception is found in the work of Tenneson and Belleau[5] who obtained a 90% optical yield of the desired *cis* lactam by utilizing an imine derived from D-threonine in the cycloaddition step.

While our work was in progress, McCombie[6] reported the following synthesis of the O-2-isocephem nucleus via triethyl phosphite induced cyclization methodology.



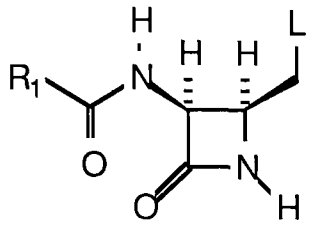
Retrosynthesis and Our Approach

On inspection of the O-2-isocephem system, one notices the presence of a "1,3 di-O" relationship. Disconnecting the indicated bonds gives us two idealized fragments "A" and "B".

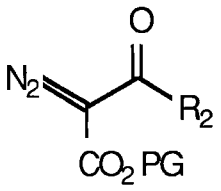


Fragment A is the β-lactam portion of the molecule, complete with the amide side chain. Fragment B could be a carbene derived from a β-keto acid. The actual compounds used in the synthesis would be "C"

and "D", where L is a suitable leaving group and PG is a suitable protecting group.

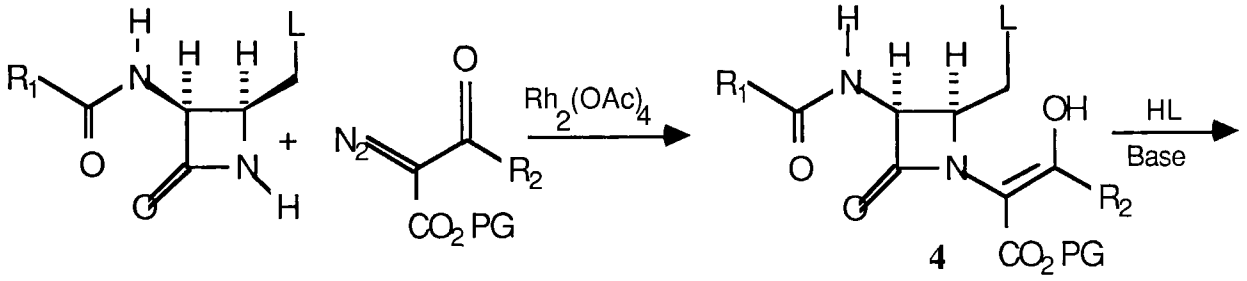


C

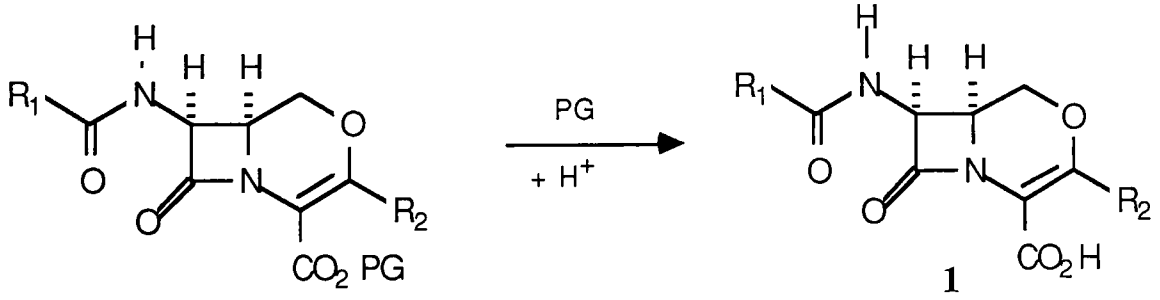


D

We envisioned the synthesis as proceeding as follows. Rhodium(II) acetate catalyzed insertion of the α-diazo-β-ketoester **3** into the N-H bond of the preformed β-lactam would result in the formation of enol **4.** The O-2-isocephem skeleton would be formed by displacement of the leaving group L



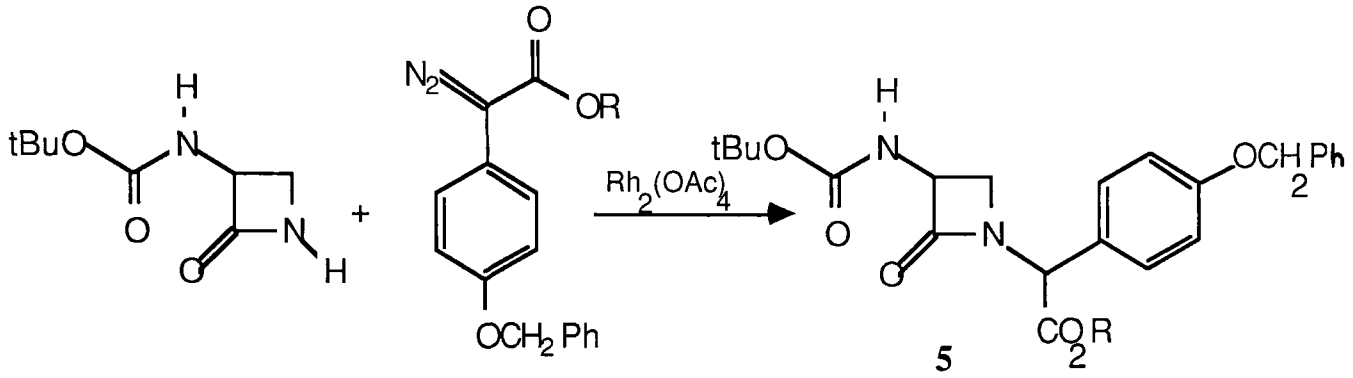
4



1

by the enolate of **4**; and final deprotection of the carboxylate should give the desired target antibiotic **1**.

We had reason to suspect that the "carbene" disconnection was a reasonable one since intramolecular rhodium carbenoid N-H insertion reaction is well known (see Chapter 1, page11) and Miller[7] had previously reported an intermolecular insertion into the β-lactam N-H bond in a novel preparation of nocardicins **5**.



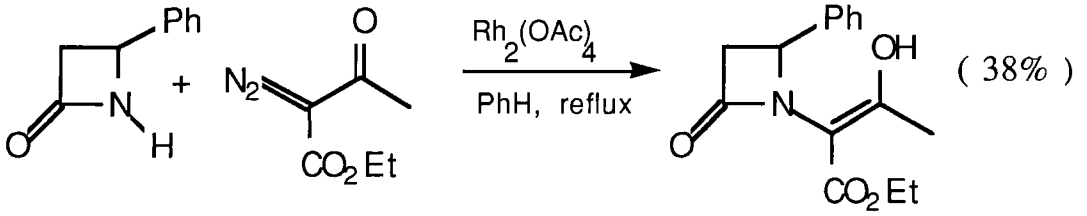
Potential advantages of this approach are; a) a wide variety of R_2 analogues could easily be prepared by acetoacetic ester dianion condensation prior to diazo transfer and insertion. b) the synthesis is highly convergent, requiring only cyclization and carboxylate deprotection after assembly of the two precursors by rhodium carbenoid insertion. c) if one begins with enantiomerically pure β-lactam[8] precursor, one would arrive at optically pure **1** since the two chiral centers of the β-lactam are fixed and would not be epimerized under the reaction conditions.

The questions that had to be answered were these: Would the selective N-H rhodium carbenoid insertion succeed in our hands? What would be the best leaving group to use in terms of leaving ability, lack of interference in the carbenoid reaction and general ease of use? Which carboxylic acid protecting group would be the

best in terms of ease of removal and compatability with the carbenoid reaction? What types of R_2 groups would be accessible by our technique? The following section attempts to answer these questions by presenting the results of our studies.

Results and Discussion

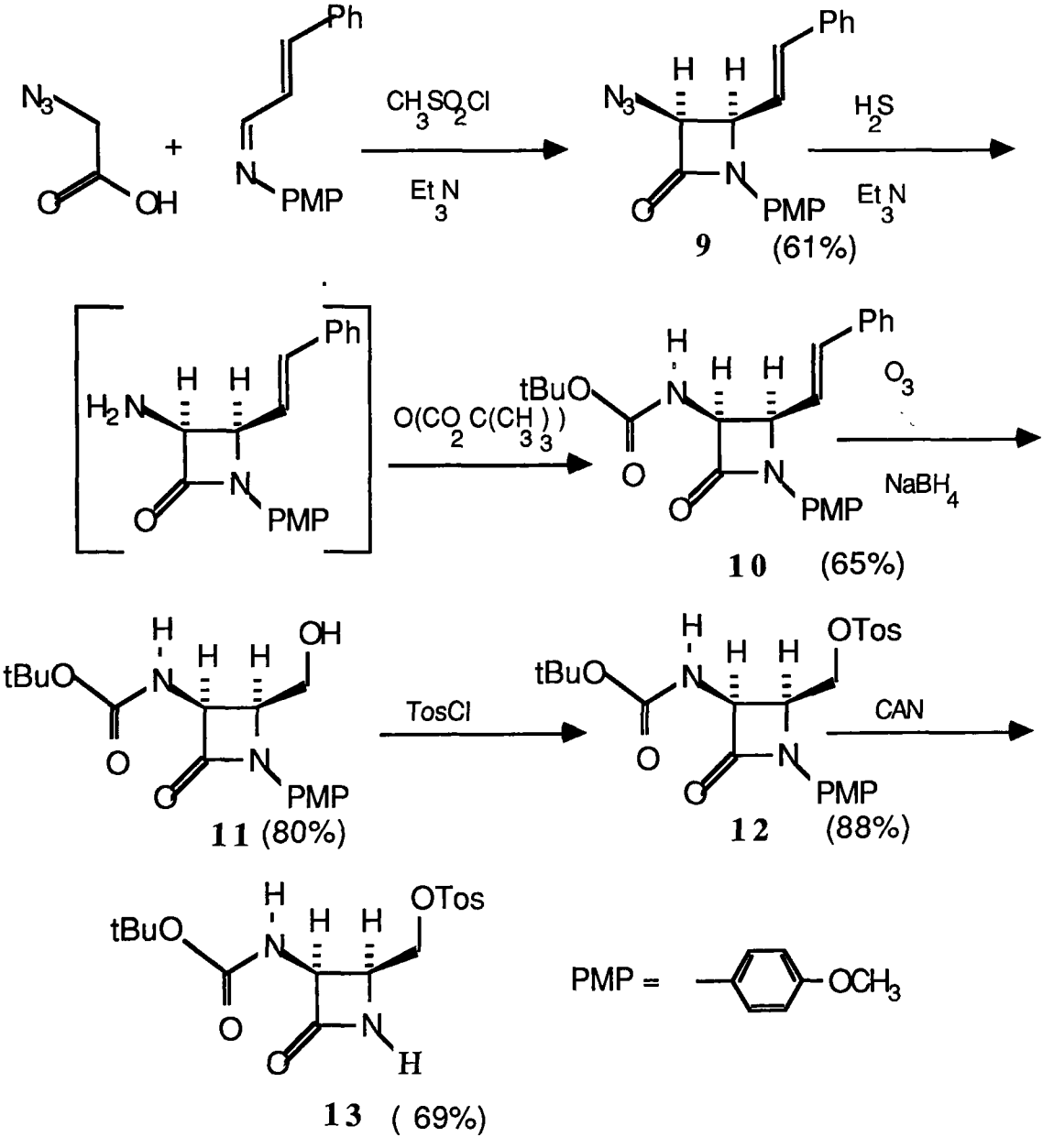
We chose to begin our study with a simple model system , one that would give useful results from easily obtainable starting materials. As our first attempt at the intermolecular insertion reaction, we reacted 4-phenylazetidin-2-one **6** with ethyl 3-oxo-2-diazobutyrate **7** by adding 5 mole% of $Rh_2(OAc)_4$ to a solution of **6** and **7** in refluxing benzene. After 1 hour at reflux the solution was eluted through a silica gel plug and the resulting solution was concentrated and subjected to flash chromatography. This resulted in a 38% yield of the desired insertion product **8** obtained as an oil.



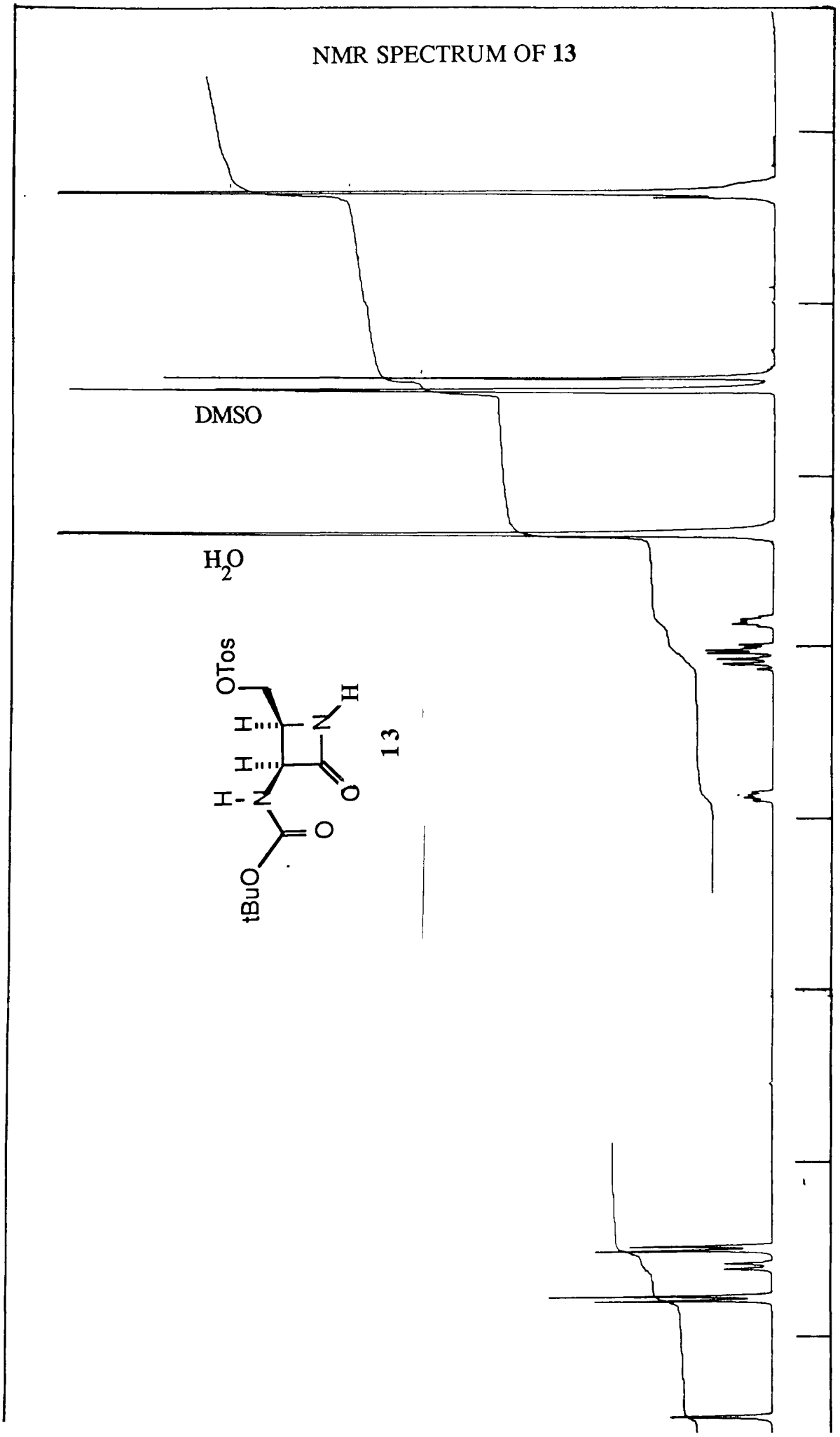
6 **7** **8**

Evidence that the insertion reaction had indeed taken place could be found in the ^1H nmr spectrum of **8** that showed an enolic resonance at δ=13.1 and in the ei-ms that featured peaks at m/z 275 (M^+, 2.9%), 233 (M^+-42, 27.8%), and a base peak at 104 (CH_2CHPh^+) due to a retro 2+2 cleavage of the β-lactam ring of the molecular ion.

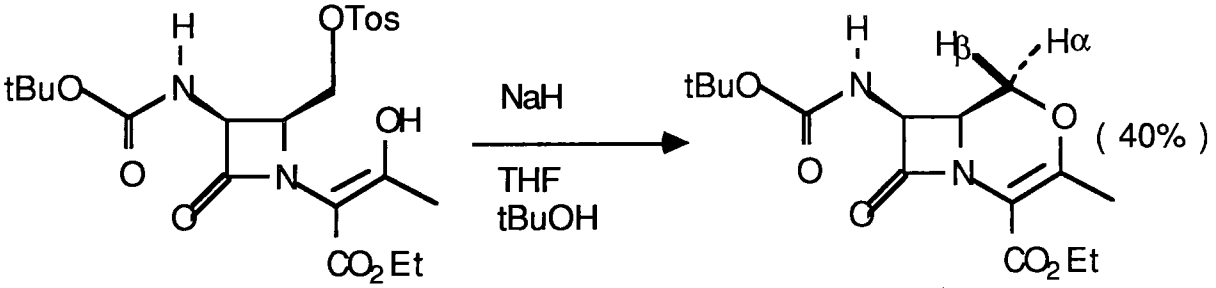
Encouraged by our initial test we proceeded to attempt the insertion reaction on a β-lactam bearing the required leaving group at the eventual C-1 carbon of the O-2-isocephem, as well as bearing a C-3 amide group. Thus, 3-(*tert*-butoxycarbonyl)-4 tosyloxymethylazetidin-2-one **13** was prepared by the following route (see Experimental section for details).



NMR SPECTRUM OF **13**



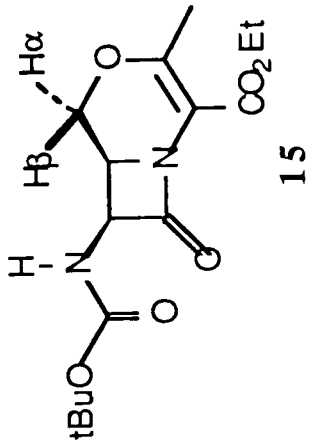
The first step is a ketene-imine cycloaddition reaction using methanesulfonyl chloride to activate azidoacetic acid that we developed in the course of this work. Its ease of use and cost efficiency makes it our method of choice for preparing *cis* β-lactams over other activating agents[9] such as tosyl chloride or trifluoroacetic anhydride. Note that **9** and compounds derived from it are all racemic and the stereochemistry depicted for them is relative (*cis*) and not absolute.When a mixture of **13** and **7** in dry refluxing $CHCl_3$ was treated with 5 mole% of $Rh_2(OAc)_4$, a disappointingly low 30% yield of insertion product **14** was realized. Compound **14** was dissolved in dry tetrahydrofuran containing a little *tert*-butanol and sodium hydride was added. This caused ring closure to the O-2-isocephem **15** which was isolated



14 **15**

as an oil in 40% yield following aqueous workup and thick layer chromatography. The bicyclic β-lactam **15** was characterized by ^1H nmr: δ= 1.30 (t, 3H, ester CH_3), 1.42 (s, 9H, tBu), 2.24 (s, 3H, =C-C$\underline{H}_3$), 3.77-3.80 (m, 2H, C6-H, C1β-H), 4.18-4.32 (m,2H, ester CH_2),

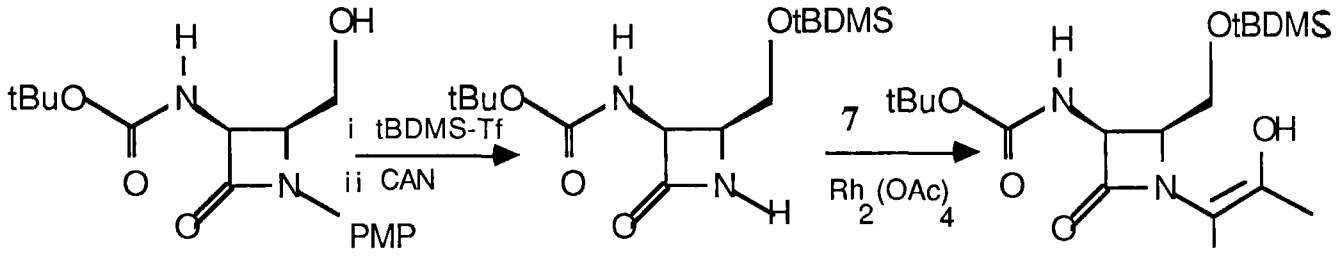
NMR SPECTRUM OF **15**



15

4.55 (m, 1H, C1α-H), 4.96 (m, 1H, C7-H), 5.28 (m, 1H, NH). The ci-ms featured peaks at m/z 327 (M^++1, 2.7%), 271 (M^++1-56, 20.7%) and 243 (100%). The infrared spectrum displayed bands corresponding to amide NH (3420), β-lactam (1772), ester (1720) and amide (1620 cm^{-1}).

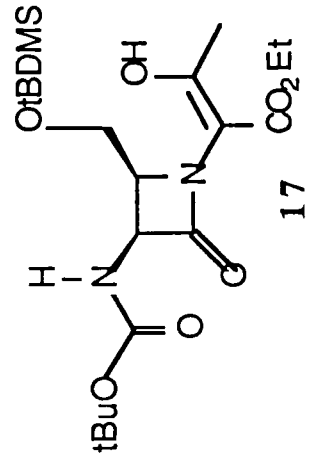
Since the tosylate gave a poor yield of insertion product, possibly due to solubility problems, and the cyclization reaction gave a low yield of bicyclic material we thought it would be advantageous to protect the alcohol as an O-*tert*-butyldimethylsilyl ether during the insertion reaction. The O-*tert*-butyldimethylsilyl group could be removed later and converted into a suitable leaving group. The β-lactam **16** was prepared by silylation of alcohol **11** .



11 **16** **17**

The insertion reaction of **16** with **7** in refluxing benzene proceeded much better, and a 59% yield of insertion product **17** was obtained. Compound **17** was identified by its ci-ms that showed peaks at m/z 459 (M^++1, 18.1%) and 403 (M^++1-56, 100%); its infrared spectrum displayed bands at 3430, 1760, and 1715 cm^{-1} corresponding to the NH of the amide, the β-lactam C=O and the ester functions respectively; the ^1H nmr spectrum featured resonances at

NMR SPECTRUM OF **17**

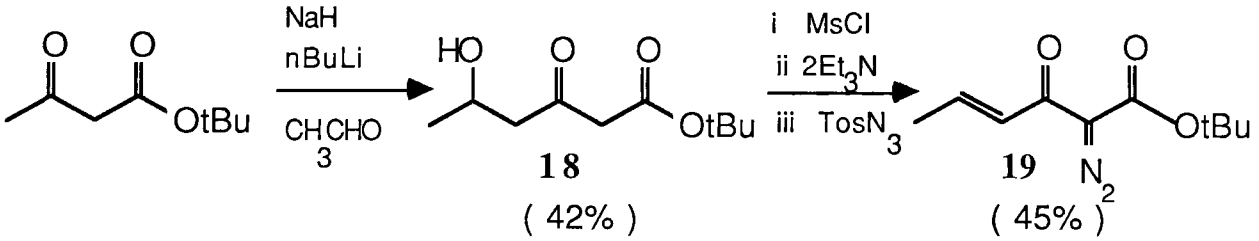


17

δ= 1.27 (t, ester CH_3), 2.14 (s, =C-C$\underline{H}_3$), 4.15 (m, ester CH_2) and an enolic resonance at 12.30.

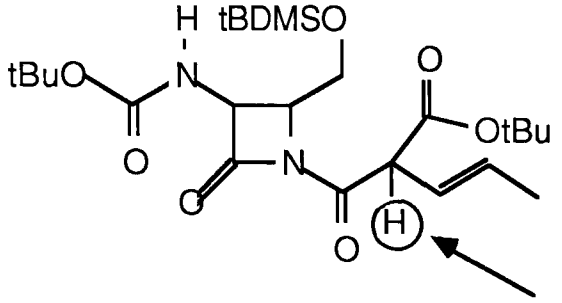
We decided that the *tert*-butyldimethylsilyl group[10] would be our choice to protect the OH group during the carbenoid insertion which would later be revealed and converted to a leaving group. These results also confirmed the expected selectivity of NH insertion (β-lactam over amide). We did not attempt to cyclize **17** to the corresponding O-2-isocephem since the resulting ethyl ester would not be easy to saponify without concomitant destruction of the β-lactam. In order to have a more easily removable carboxylate protecting group we chose the *tert*-butyl group[11] (removable with acid) since *tert*-butyl acetoacetate is commercially available.

At this point we decided to attempt the insertion reaction of **16** and a diazoester possessing a propenyl group. This was prepared by reaction of the dianion[12] of *tert*-butyl acetoacetate with acetaldehyde followed by mesylation and subsequent elimination of methane-

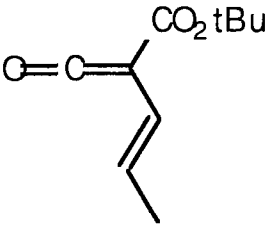


sulfonic acid.The product olefin **19** was shown to be *trans* by the presence of a 15.2 Hz coupling of the alkene hydrogens in its ^1H nmr spectrum. The reaction between **16** and **19** at first appeared normal, resulting in a 55% yield of the major insertion product **20**. However closer examination of its infrared spectrum revealed an unusually high frequency carbonyl band of 1800 cm^{-1}. The 300 MHz ^1H nmr

spectrum of **20** (2D-HOMCOR) showed the presence of a one-proton doublet coupled to one of the olefinic protons. This is consistent with the structure depicted below for **20**.

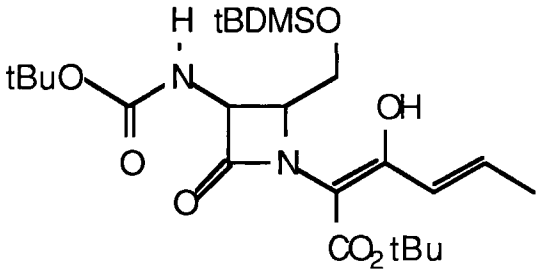


20



21

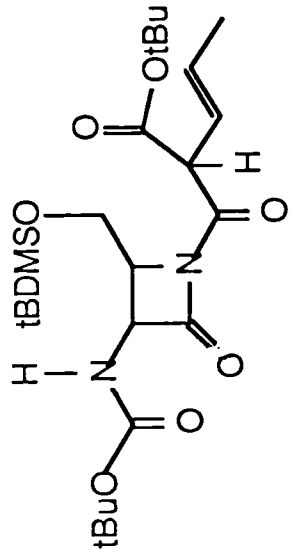
This product is thought to be formed by nucleophilic attack of the β-lactam nitrogen on the ketene[13] **21**, the product of a Wolff rearrangement of **19**. We did however isolate the desired isomer **22**, but in only 11% yield.



22

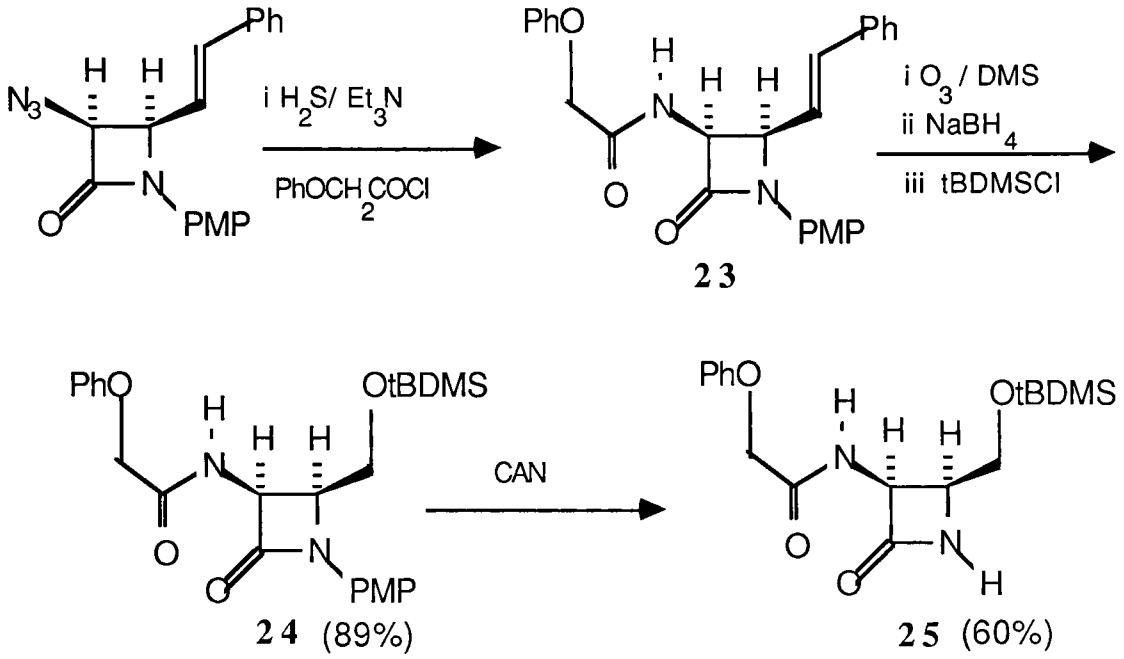
The migration of an allyl group under these conditions must be a very facile process. Predomination of the Wolff rearrangement product places the first restriction on our method; the desired double bond would have to be introduced after the insertion reaction.

NMR SPECTRUM OF **20**



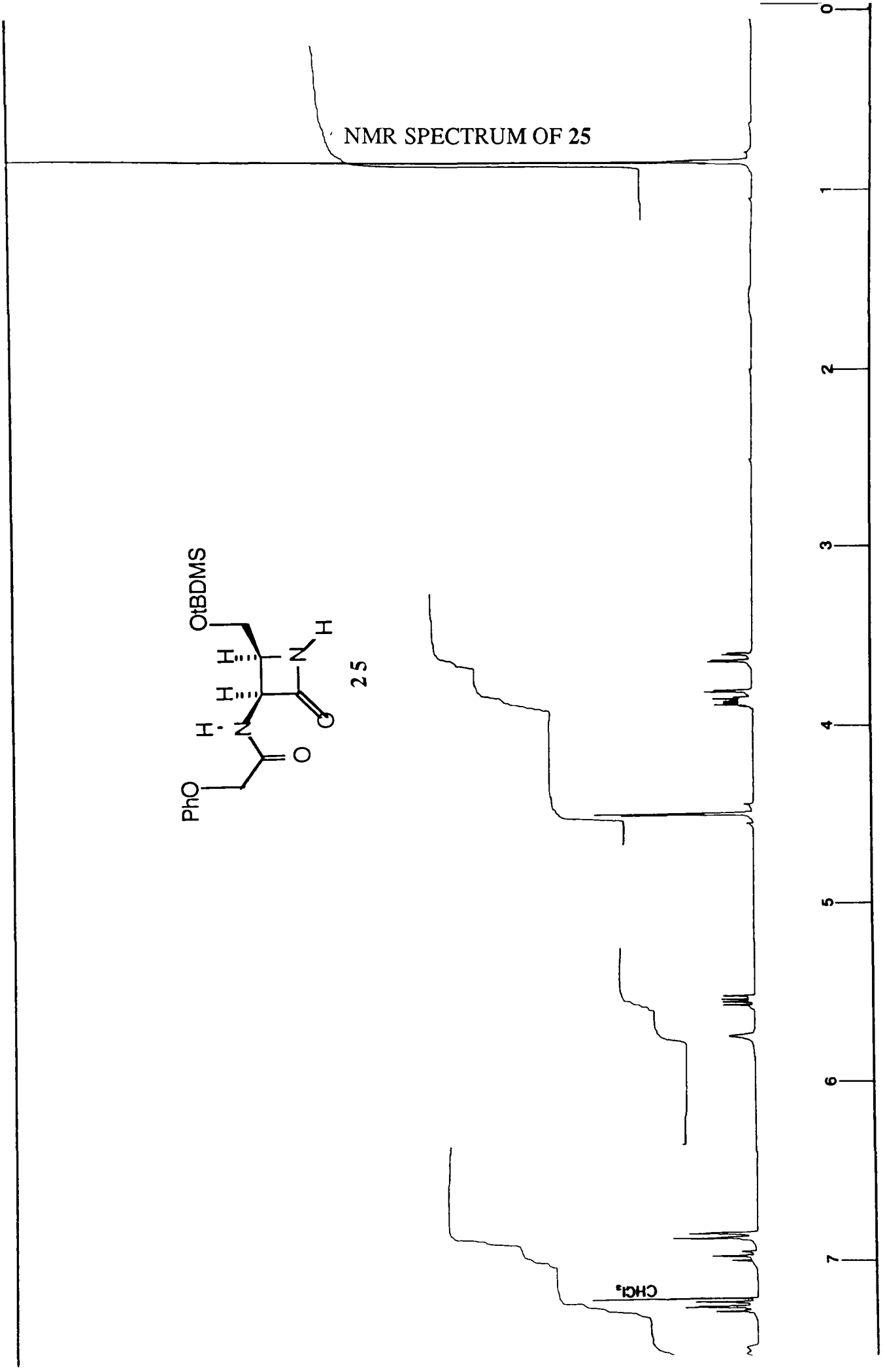
20

In order to determine if the *tert*-butyl ester group was implicated in the rearrangement problem, we reacted the parent diazo compound, *tert*-butyl 3-oxo-2-diazobutyrate **42** with β-lactam **25**. The 3-N-(*tert*-butoxycarbonyl) group was dispensed with as our amide side chain in favor of the 3-phenoxyacetamido group (the "Pen V" side chain), one that is known to be active in the O-2-isocephem series. It was prepared from **9** by the following sequence of reactions and was obtained as a white powder, mp 125-126 °C.



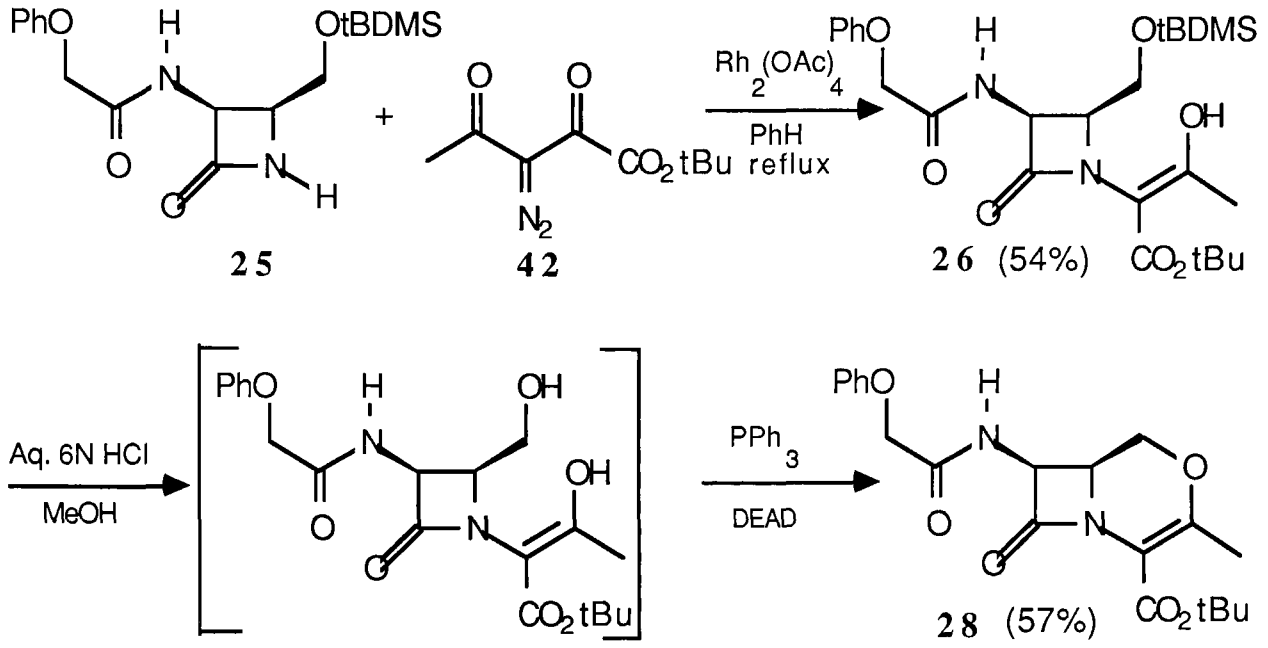
The β-lactam **25** (Scheme 1) was reacted with *tert*-butyl 3-oxo-2-diazobutyrate **42** in the usual manner and a 54% yield of the enol-lactam **26** was recovered. Compound **26** was identified as the insertion product by its ci-ms that featured ions at m/z 521 (M^++1, 21.3%), 465 (M^++1-56, 83%); its ei-ms showed ions at m/z 464 (M^+ 56) and 407 (M^+-56-57); the infrared spectrum of **26** showed bands at 3420, 2920, 1715, 1760 and 1685 cm^{-1}. The ^1H nmr spectrum of

NMR SPECTRUM OF **25**



26 featured resonances at δ= 1.48 (s, tBu), 2.12 (s, =C-C$\underline{H}_3$), as well as an enolic H at 12.2

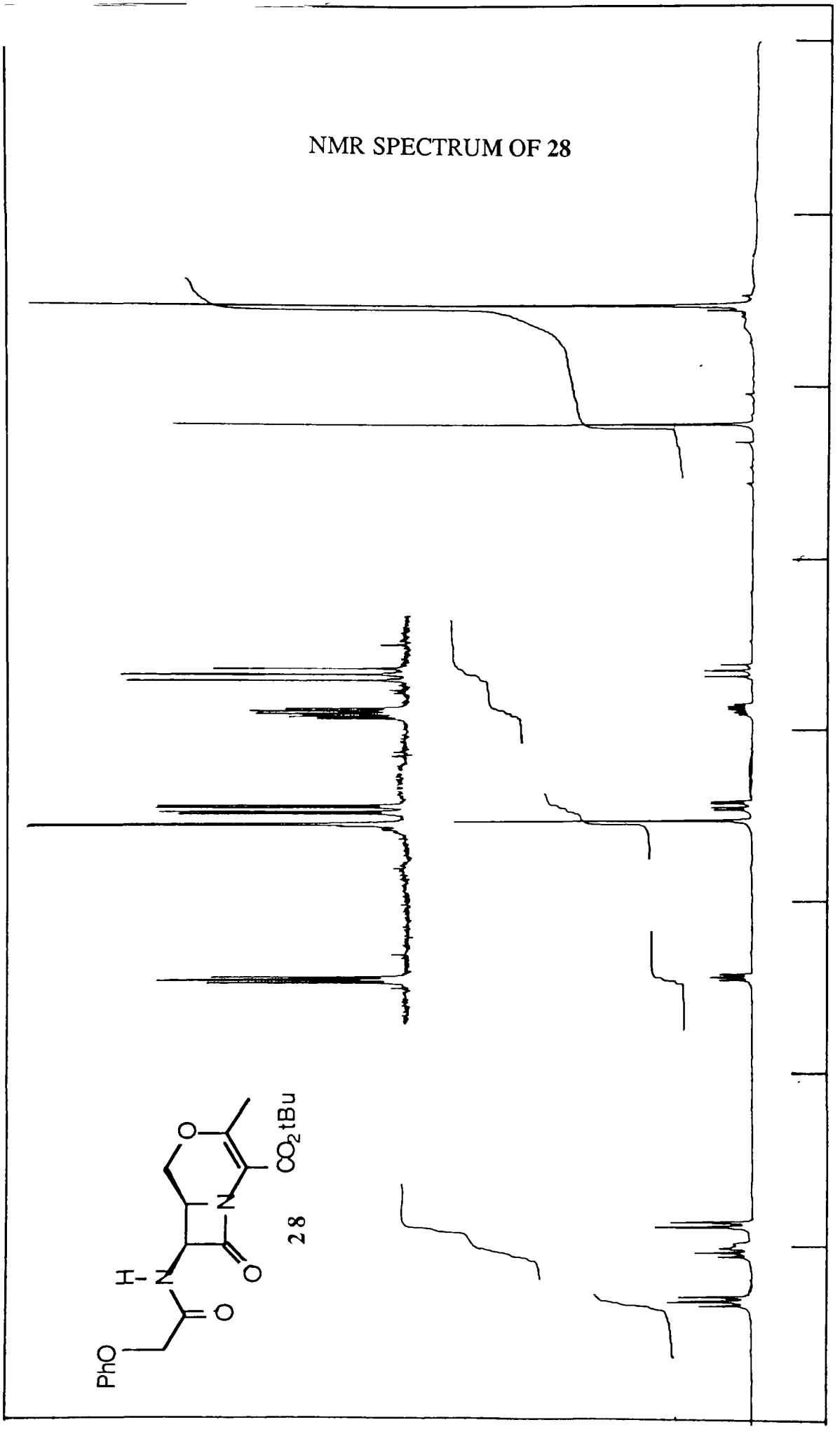
SCHEME 1



25 **42** **26** (54%) **28** (57%)

Satisfied that neither the *tert*-butyl ester nor the phenoxyacetamido groups posed any problems, we proceeded to cyclize **26** to the O-2-isocephem **28**. Lactam **26** was desilylated by treatment with three equivalents of 6N HCl in aqueous methanol in quantitative crude yield. The reaction was monitored by TLC which showed the higher R_f starting material give way to the much more polar desilylated material over a period of 3 hours. The crude enol-alcohol **27** was dissolved in dry tetrahydrofuran and treated with one equivalent each of triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD).[14]

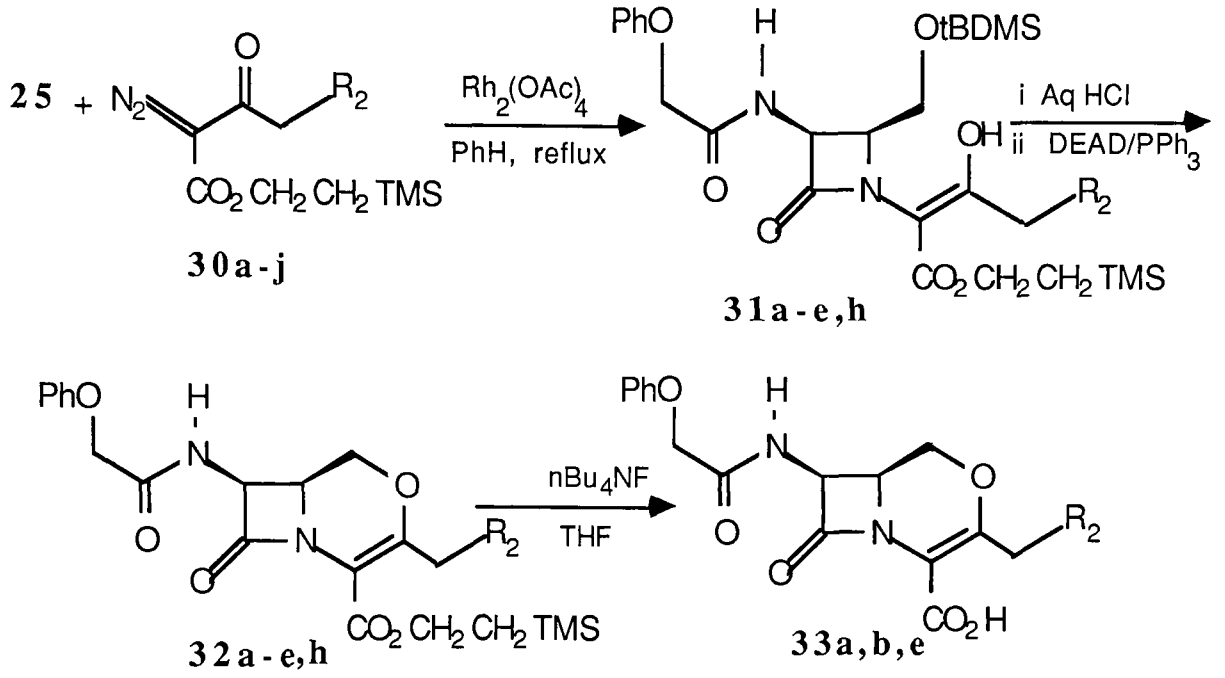
NMR SPECTRUM OF **28**



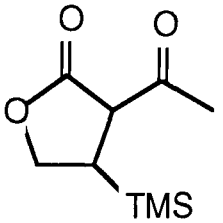
The desired O-2-isocephem **28** was isolated as a crystalline solid (mp 120-121 °C) in 57% yield (two steps) following column chromatography. The infrared spectrum of **28** showed an increased β-lactam C=O frequency of 1772cm^{-1}, as expected for the fused bicyclic ring system. The ^{1}H nmr spectrum of **28** indicated the loss of the *tert*-butyldimethylsilyl group and the enolic proton was no longer evident. The ci-ms of **28** displayed ions at m/z 389 (M^{+}+1, 14.0%), and 333 (M^{+}+1-56, 89.5%). Unfortunately, attempted deprotection of the carboxylate group with trifluoroacetic acid failed to give the the O-2-isocephem acid.

We now had a general method to assemble the two precursors and close the fused six-membered ring; all that remained to be found was a suitable protecting group for the carboxylate. The 2-(trimethylsilyl)ethyl group (-CH_2CH_2TMS) is a carboxylic acid protecting group that is removable with fluoride ion under mild conditions. In order to evaluate the effectiveness of the 2-(trimethylsilyl)ethyl group in our reaction scheme, we prepared 2-(trimethylsilyl)ethyl acetoacetate **29** by reaction of diketene with 2-(trimethylsilyl)ethanol. This was diazotized by diazo transfer reaction with triethylamine/tosyl azide, and the resulting diazoester **30a** was reacted with β-lactam **25** in the usual manner to give **31a** (R=CH_3) in 40% yield, 51% based on recovered β-lactam (Scheme 2).

SCHEME 2



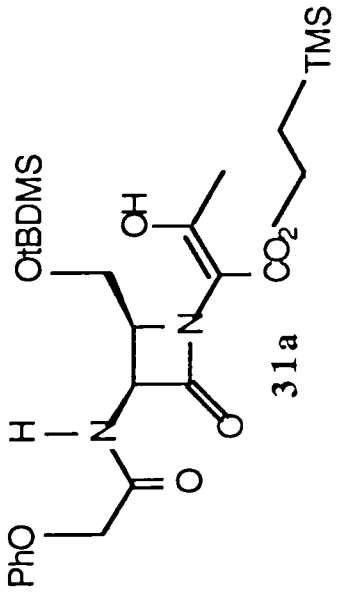
The desired product was accompanied by a 21% yield of γ-lactone **34** , the result of an intramolecular insertion into a C-H bond α to silicon; 21% of the starting β-lactam **25** was also recovered. Compound **34** was identified by it's infrared spectrum that showed a



34

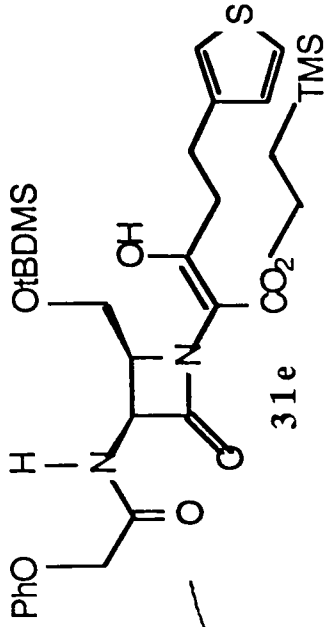
band at 1765 cm^{-1} (γ-lactone) and it's nmr spectrum that was in agreement with the assigned structure (see the Experimental section). This insertion reaction into an aliphatic C-H bond γ to the

NMR SPECTRUM OF **31a**



31a

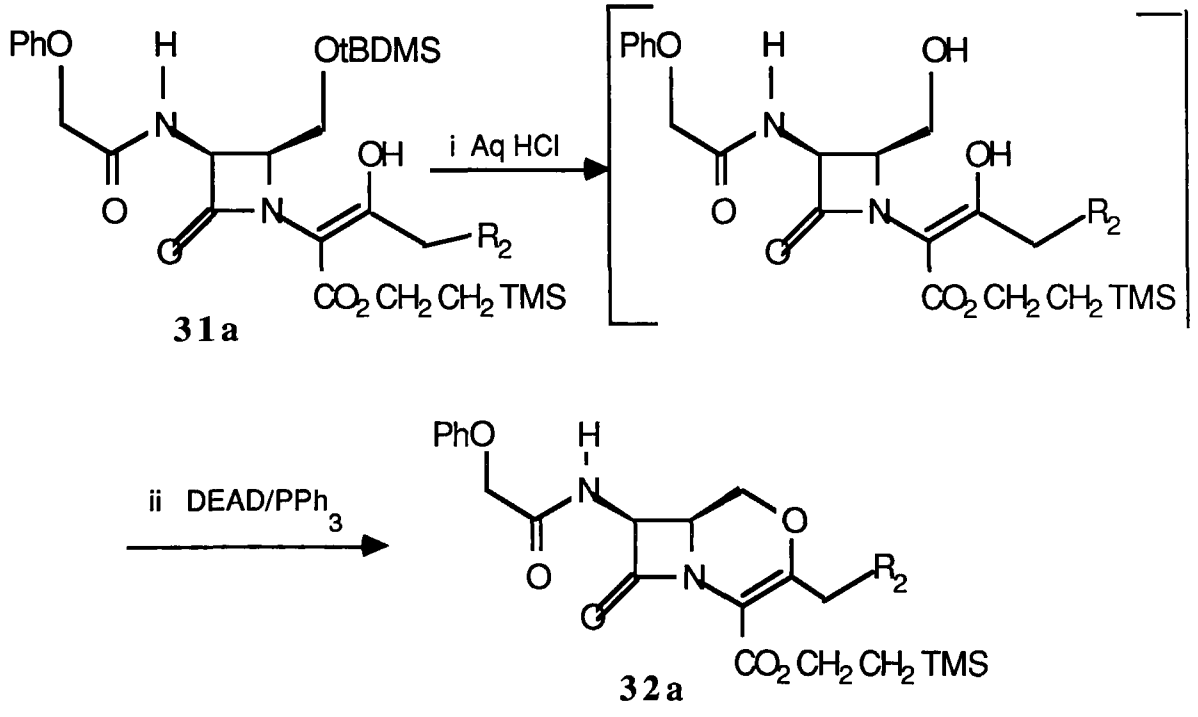
NMR SPECTRUM OF **31e**



31e

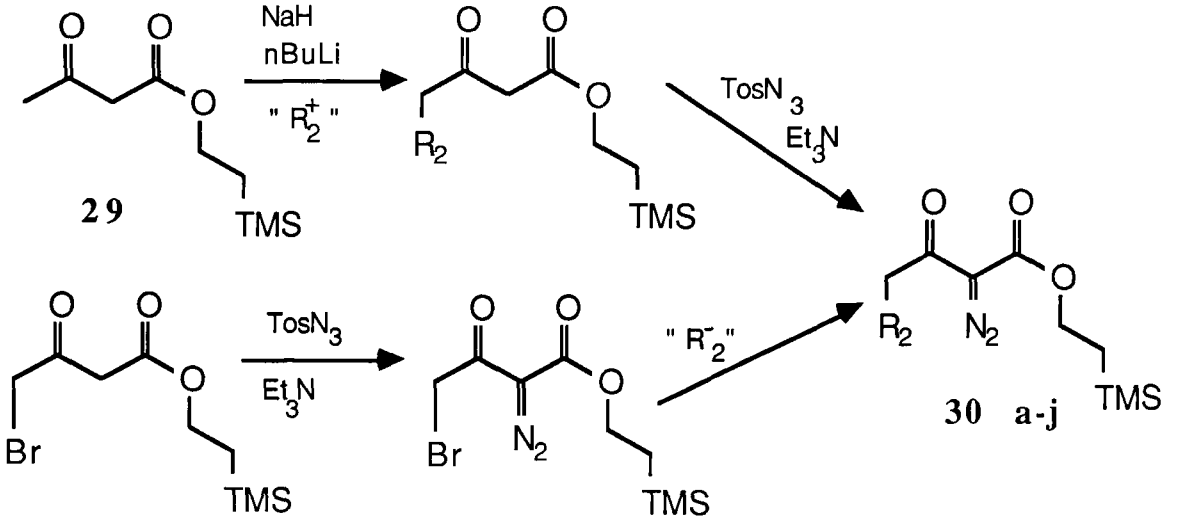
carbenoid center on the ester moiety represents a possible route to γ-lactones. Taber has reported many insertions on the "keto" side of α-diazo-β-ketoesters, but we believe this to be the first example of an insertion on the "ester" side. We would later decompose a bromo analogue of **30a** (**30h**) without the β-lactam being present to afford the corresponding γ-lactone in good yield (see page 54).

The desired adduct **31a** ($R_2=CH_3$) a clear colorless oil, was desilylated by stirring with methanolic HCl and cyclized as previously described (DEAD/PPh_3) to give **32a** ($R=CH_3$) in 61% yield (two steps) as a white powder, mp 169-170 °C (lit.[15] mp 171-172 °C).



We adopted this as our approach to O-2-isocephems. A number of α-diazo-β-ketoesters (**30 a-j**) were prepared in order to

test the scope of substituents that do not interfere with the insertion reaction. These esters were prepared by the reaction of the dianion of 2-(trimethylsilyl)ethyl acetoacetate **29** with the appropriate electrophile, or alternatively by reaction of the appropriate nucleophile with 2-(trimethylsilyl)ethyl 4-bromo-3-oxobutyrate followed by diazo transfer.



The results of these insertions and the subsequent elaborations to the bicyclic β-lactams are summarized in Table 1.

The bicyclic O-2-isocephems **32a**, **b** and **e** were deprotected to the O-2-isocephem acids **33a**, **b** and **e** by treatment with tetrabutylammonium fluoride in dry tetrahydrofuran at room temperature (followed by acidification with dilute sulfuric acid) in 98, 84 and 83% yield respectively. Compound **33e** was a new analogue, and was therefore submitted for antibacterial testing at Bristol Laboratories. The results appear in Table 2 with known antibiotics for comparison. The thiophene bearing O-2-isocephem

33e showed poor antibacterial properties compared with the propenyl bearing analogue. With most organisms tested, **33e** was as good as **33b** except against some Gram positive bacteria.

TABLE 1

30	**R_2**	**Yield[1] 31**	**Yield[2] 32**
a	-H	40(51)	61
b	$-CH_2Ph$	46(61)	42
c	$-CH(OAc)CH_3$	33(53)	64
d	-CH(OtBDMS)Ph	35(40)	20[6]
e	-3-thienylmethyl	17(37)[3]	68
f	$=CHCH_3$	0[4]	--
g	-CH(OtBDMS)-3-pyridinyl	0[5]	--
h	-Br	23(41)	19
i	-SPh	0[3]	--
j	$-SO_2Ph$	0	--

NOTES

1) Yields refer to isolated yields; yield based on recovered β-lactam in brackets.

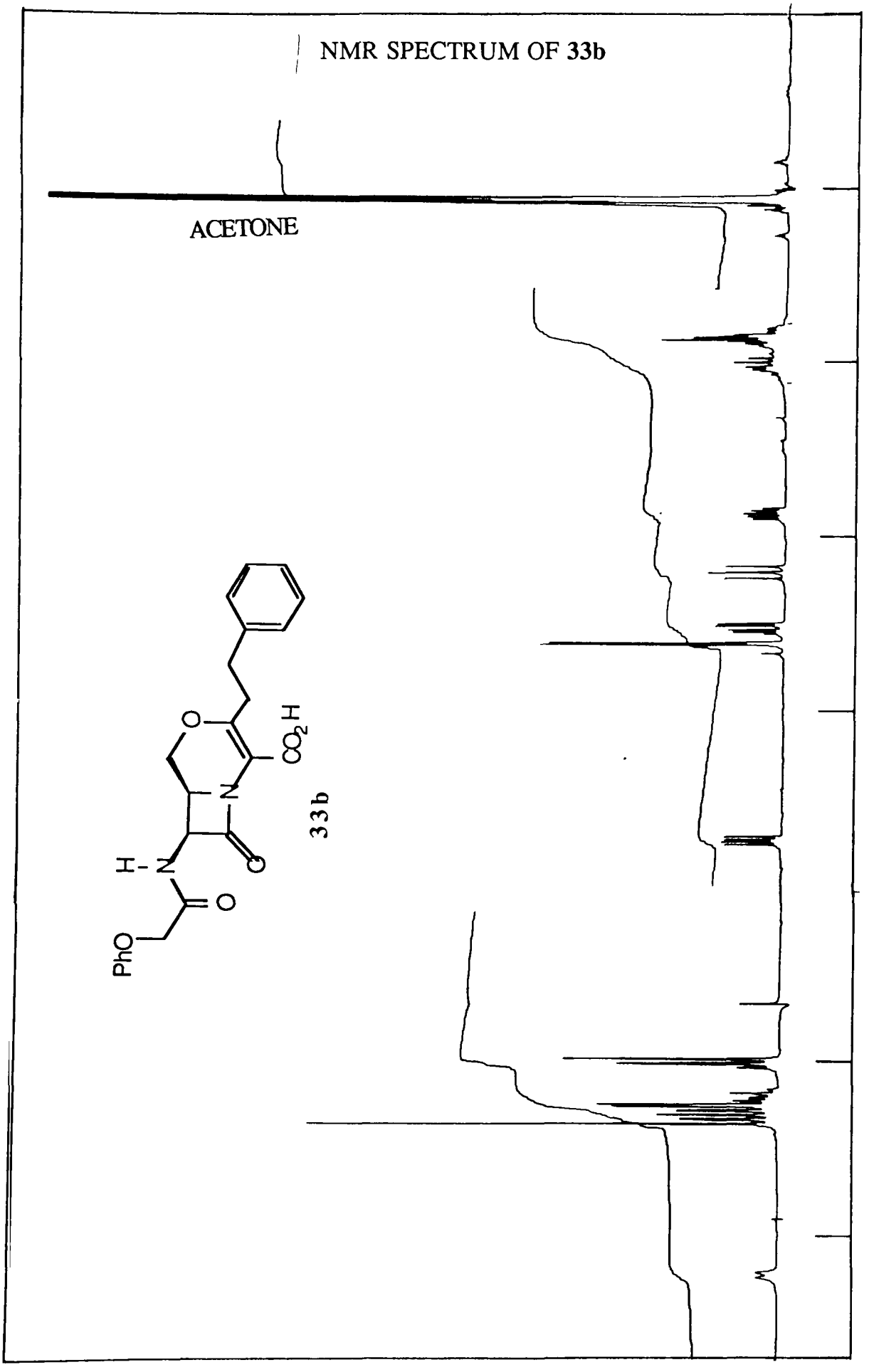
2) Yields are for 2-steps from **31** and are isolated.

3) Most diazo compound reacted intramolecularly, see text.

4) Only products derived from Wolff rearrangements were observed.

5) Starting α-diazo-β-ketoester was recovered.

6) O-desilylated product.


NMR SPECTRUM OF 33b
ACETONE
2
3
4
5
6
7
8
PhO
O
H-N
O
N
O
CO2H
33b

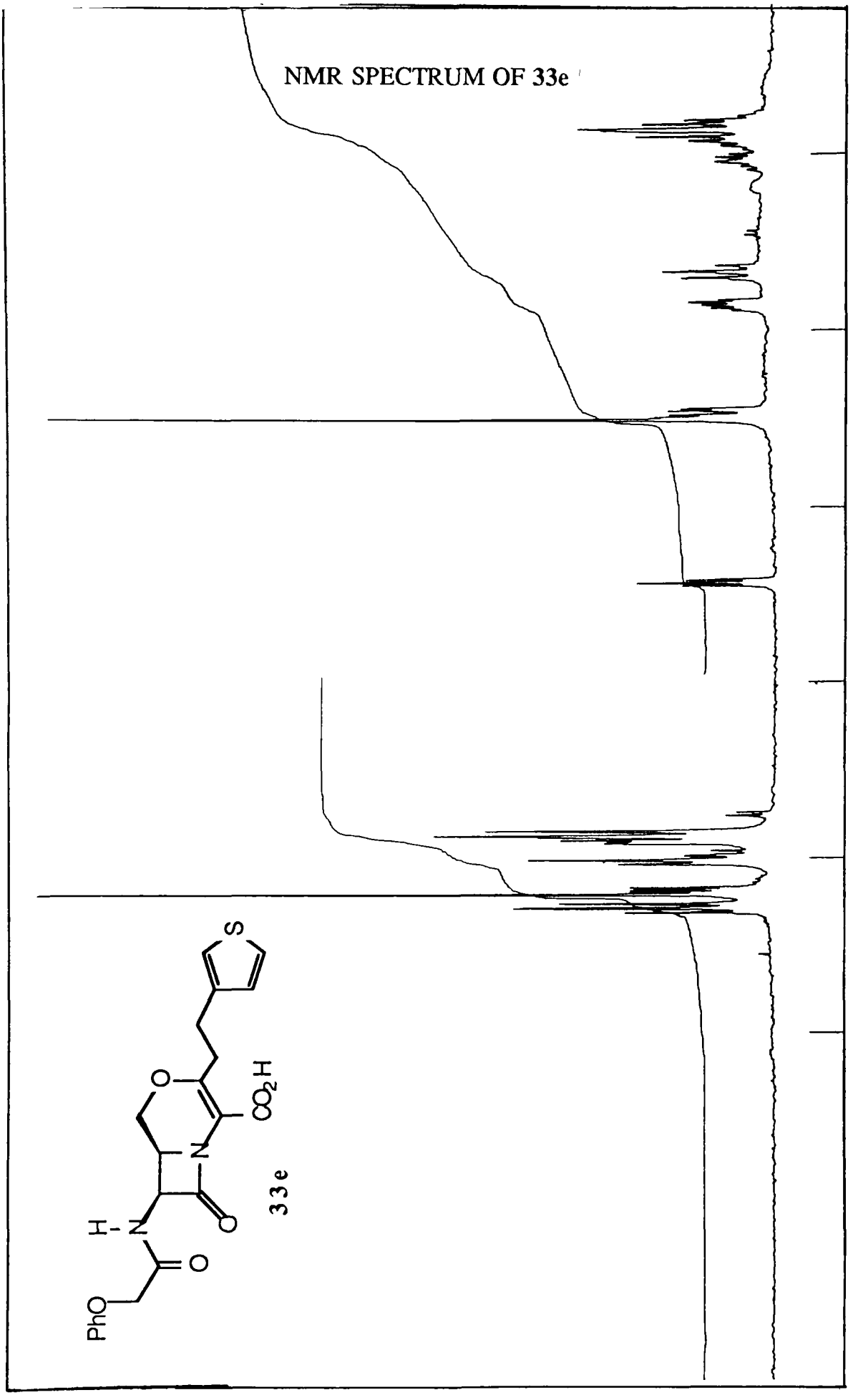
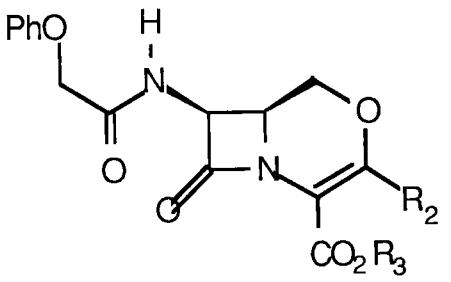
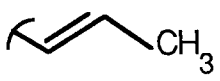
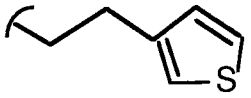

NMR SPECTRUM OF 33e
3
4
5
6
7
8
S
O
CO2H
N
H-N
O
O
PhO
33e

TABLE 2

ANTIBACTERIAL ACTIVITY OF O-2-ISOCEPHEMS*



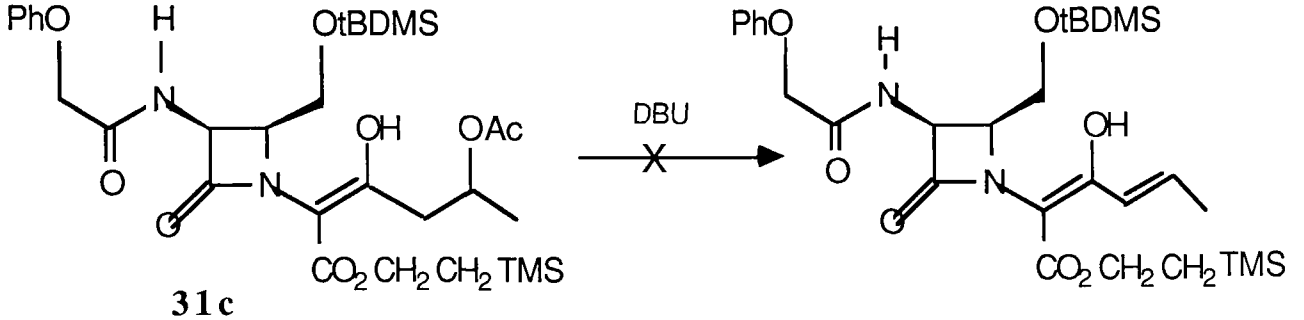
R_2 =   

R_3 = Na H H

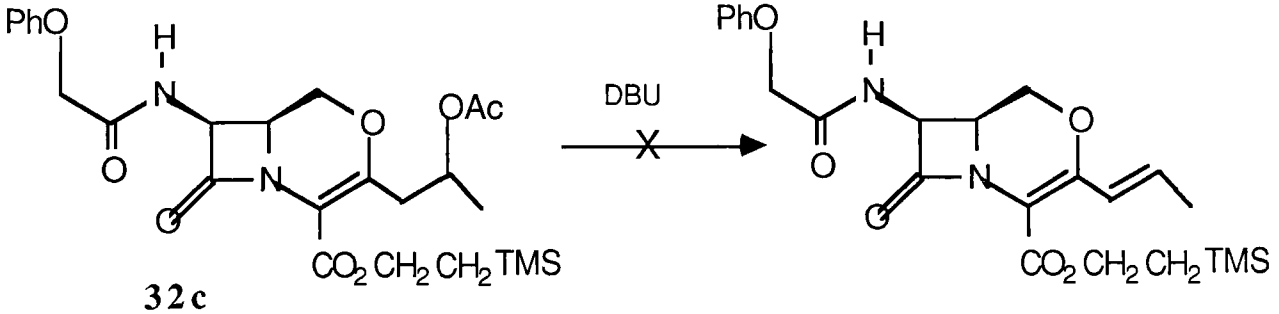
ORGANISM				
Gram +ve				
S. Pneumoniae	A9585	0.06	0.13	0.50
S. Pyogenes	A9604	0.06	0.13	0.50
S. Faecalis	A20688	16.	16.	32.
S Aureus	A20699	>125	>63.	>63.
Gram -ve				
E. Coli	A15119	32.	>63.	>63
K. Pneumoniae	A9664	125.	>63.	>63
E. Cloacae	A9659	>125.	>63.	>63
P. Mirabilis	A9900	4.	>63.	>63
P. Vulgaris	A21559	63.	>63.	>63

* Expressed as Minimum Inhibitory Concentration (M.I.C.) in μg/mL

The O-2-isocephems bearing an alkenyl side chain remained elusive to us, since at no stage were we able to effect elimination of elements of H_2O or HOAc from insertion products **31c** or **d**,or from bicyclic β-lactams **32c** or **d**. We attempted to eliminate HOAc from the insertion product **31c** (R_2= $CH(OAc)CH_3$) by stirring with 2 eq of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2, however after 2h t.l.c. analysis showed only the presence of starting material. Compound **31c** was cyclized to the O-2-isocephem **32c** in 64% yield, and again we attempted the elimination by stirring **32c** with 2 eq of DBU in CH_2Cl_2; the starting β-lactam was recovered unchanged. The experiment was repeated by refluxing **32c** with 2 eq of DBU in benzene, again only unchanged starting β-lactam was recovered.

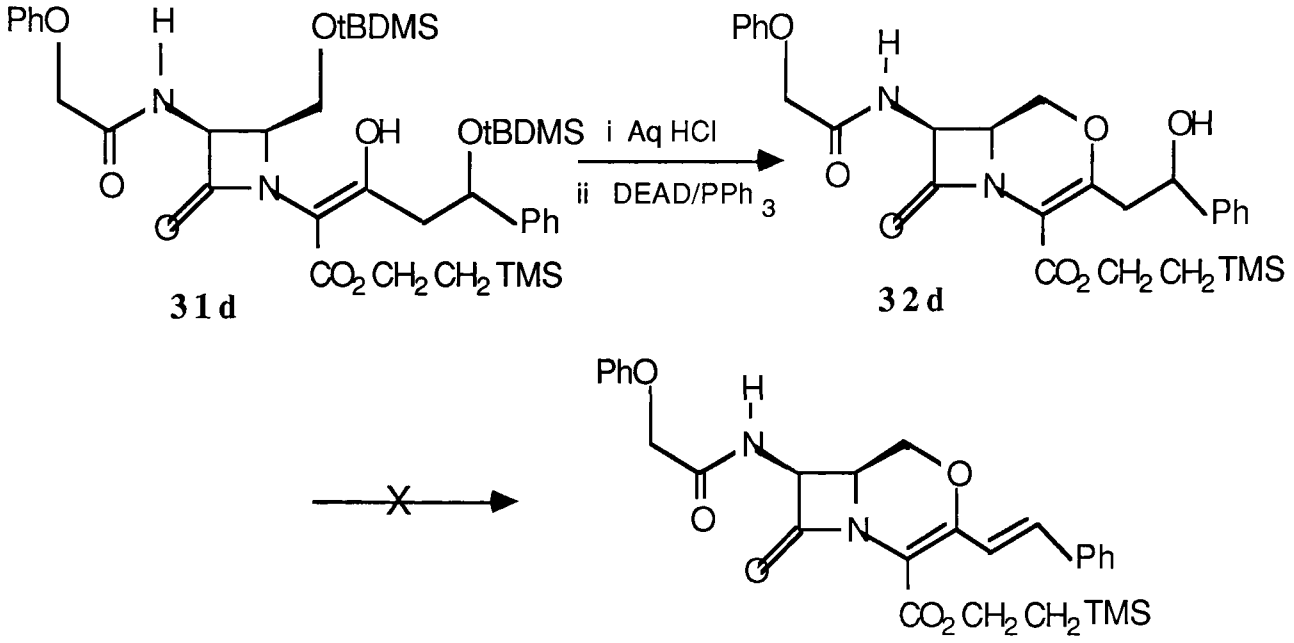


31c



32c

We anticipated that the insertion product **31d** would dehydrate to the olefin upon exposure to the dilute acid required for removal of the primary and secondary O-*tert*-butyldimethylsilyl groups prior to cyclization. Unfortunately, only the cyclized material **32d** bearing the deprotected secondary alcohol was isolated in 20% yield; no dehydrated product was recovered.

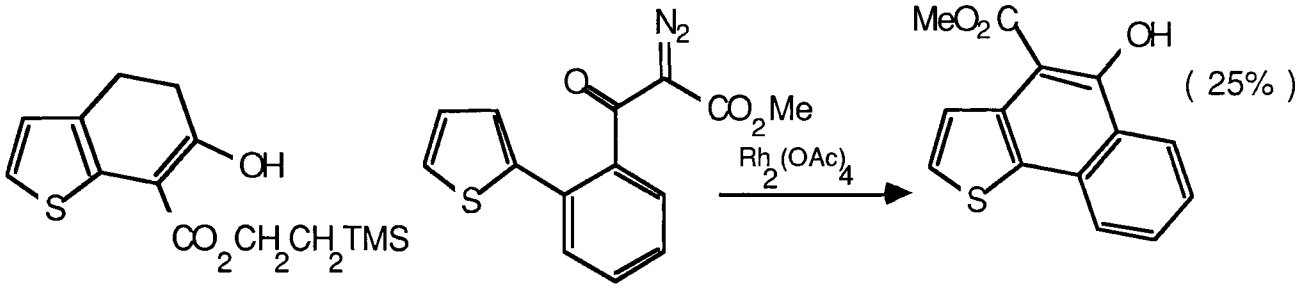


31d **32d**

Since the bicyclic β-lactams **32c** and **32d** would give rise to complex mixtures of diastereomeric O-2-isocephem acids they were not deprotected. The ^1H nmr data for all of the phenoxyacetamido β-lactams prepared is listed in Tables 2 , 3 and 4 in the Appendices.

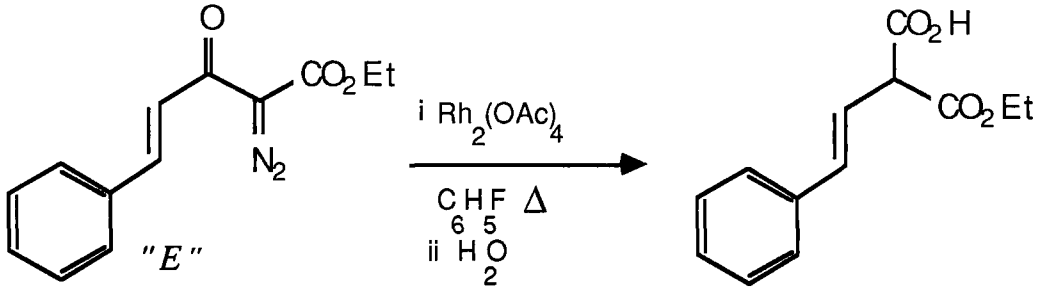
In many cases the desired insertion product was accompanied by products arising from an intramolecular reaction of the diazo ester, and in some cases these were the major products isolated. Diazo esters **30a-d** gave useful yields of insertion products. In the

case of **30e** the major product isolated in 53% yield was **43**, the result of a formal carbenoid insertion into the heteroaromatic C-H bond α to the sulfur atom of the thiophene moiety. This reaction is relatively rare with only a few reported examples (eg. **35--36**).[16] We would later explore aromatic C-H insertion reactions (see Chapter 3).



43 **35** **36**

Diazo ester **30f** gave a Wolff rearrangement product analogous to the *tert*-butyl ester case **20** previously mentioned. Davies[17] has reported a rhodium(II) acetate catalyzed Wolff rearrangement of **37** to give **38**.

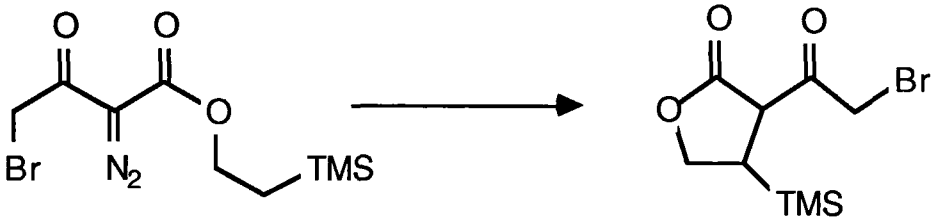


37 **38**

Diazo ester **30g**, possessing a pyridinyl moiety, gave a dark insoluble tar immediately upon addition of the catalyst. Much of the starting diazo ester **30g** was recovered unchanged. It is likely that the pyridine present acted as a ligand, binding strongly to the

rhodium tying up the available coordination sites thereby rendering the catalyst inactive. Teyssie[18] has noted the coordination of pyridine to rhodium(II) carboxylates in the presence of diazo esters, and Johnson[19] has actually prepared the pyridine adduct of rhodium(II) acetate.

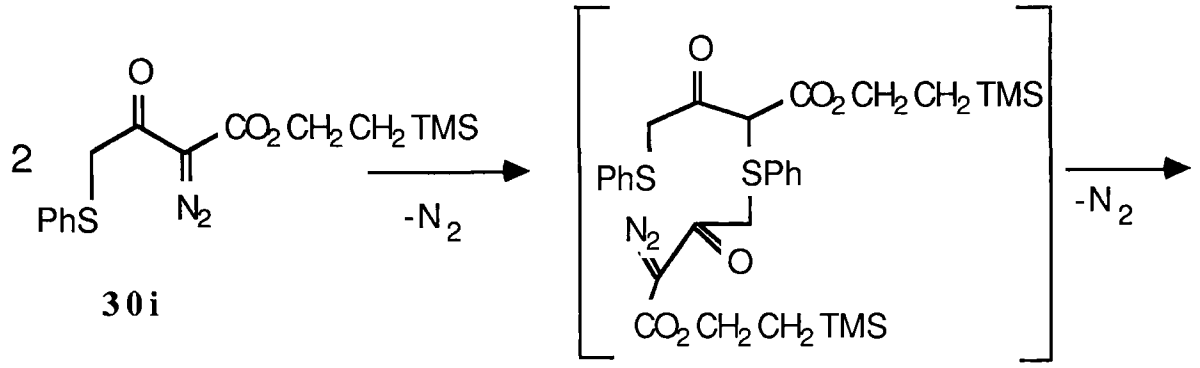
Diazo ester **30h** gave a low yield of insertion product and only a 19% yield of bicyclic material **32h**. This O-2-isocephem could in principle give rise to alkenyl lactams via Wittig elaboration, however we were not fully confident of the compound's identity and the small amount prepared precluded further investigation. When **30h** alone was stirred with 2 mole% of catalyst in CH_2Cl_2 a 60% yield of C-H insertion product γ-lactone **39** was obtained. The nmr data were in agreement with the assigned structure, and the infrared spectrum of **39** showed a strong band at 1760 cm^{-1} (see Experimental section).



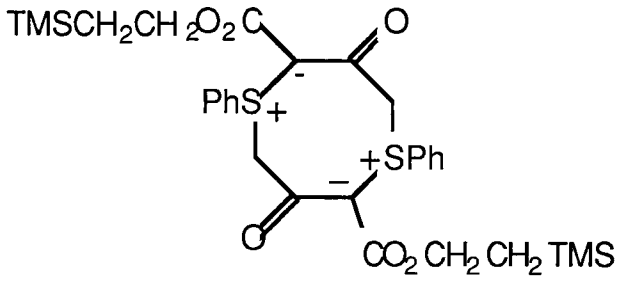
30h **39**

Diazo ester **30i** gave back 67% of the starting β-lactam **25**, and an 18% yield of di-ylide **40**, the result of intermolecular reaction between two molecules of **30i**. This compound, a white crystalline solid of mp 91-92 °C, gave satisfactory C, H and S analysis and an ^1H nmr spectrum that showed the -$C\underline{H_2}S$ methylene resonance at δ= 5.18 compared with δ= 4.05 in the starting diazo compound **30i**. The ci-ms of **40** featured ions at m/z 589 (M^++1- CH_2CH_2), 561 (M^++1-CH_2CH_2,-

CH_2CH_2), and 471(M^++1-TMS,-TMS). The infrared spectrum of **40** displayed a carbonyl band at 1700 cm^{-1}. The ^{13}C spectrum of **40** displayed the requisite eleven resonances (symmetrical molecule) including four singlets due to quaternary carbons and three triplets due to the methylenes

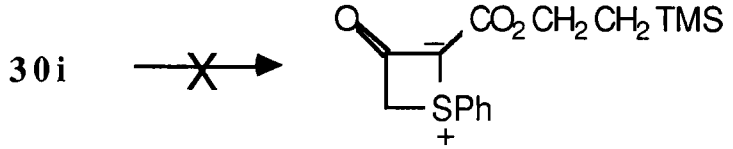


30i

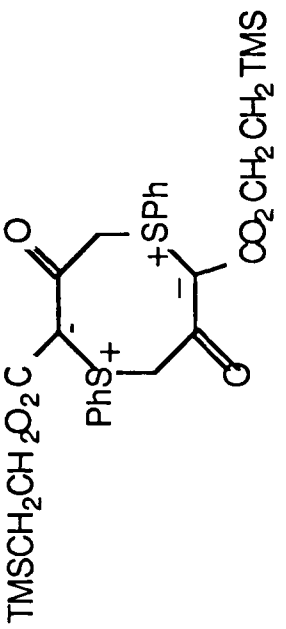


40

This was a most surprising result! The formation of eight-membered rings is not a favorable process. One would have expected to find a by-product formed by an intramolecular reaction of **30i** to give the ylide depicted below.

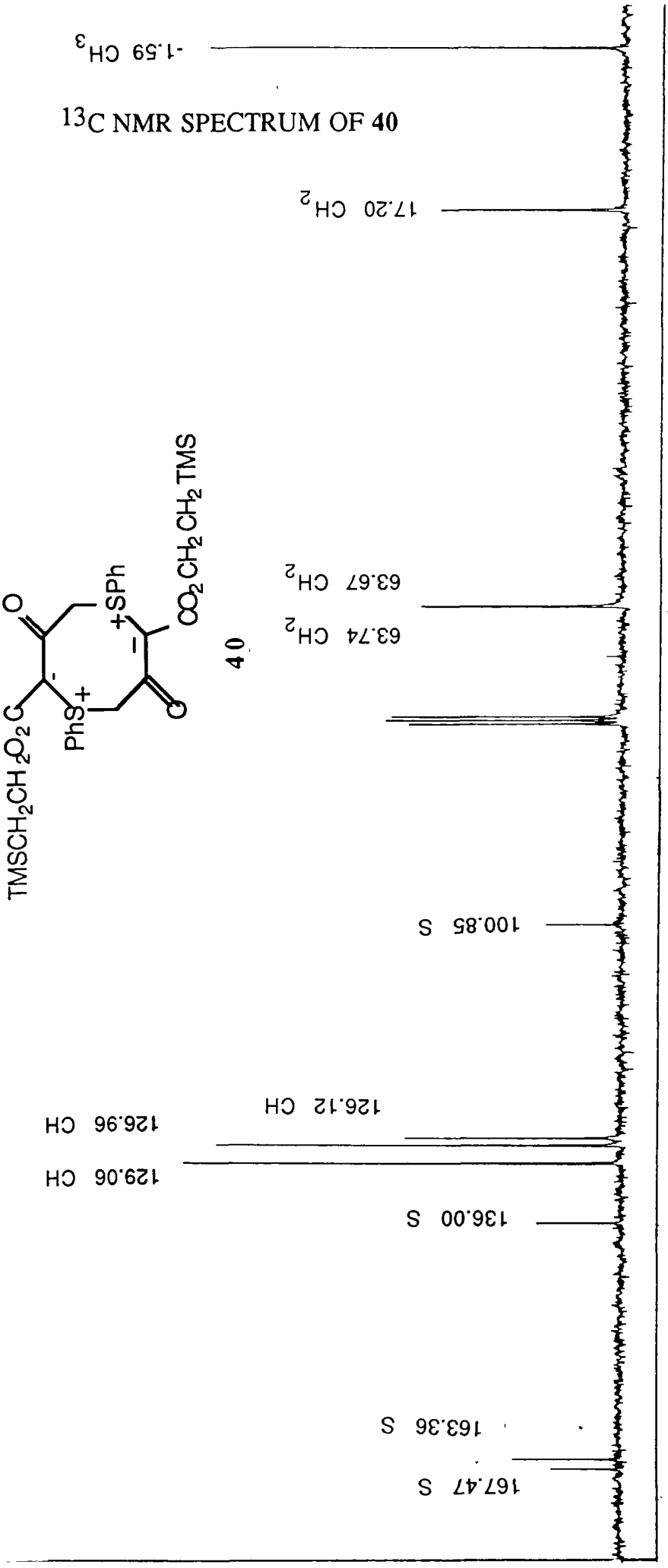


NMR SPECTRUM OF 40

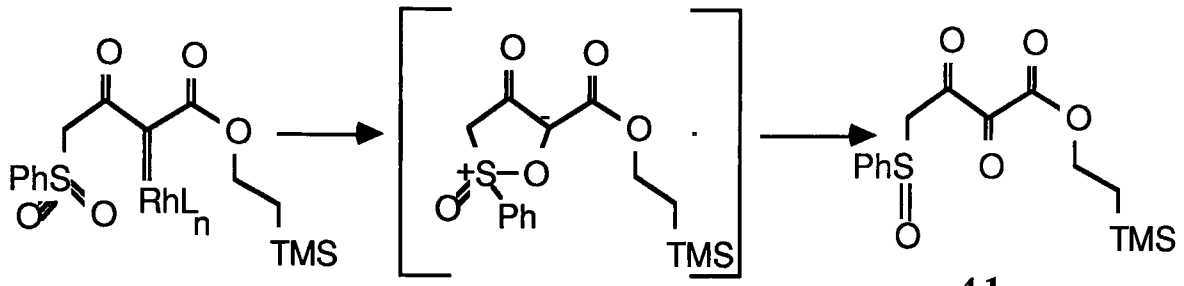


40

^{13}C NMR SPECTRUM OF **40**



Diazo ester **30j** gave one of the most intriguing results. The intermolecular reaction with β-lactam **25** gave a very complex reaction mixture, however when **30j** alone was treated with the catalyst (as in the case of **30h**) a yellow viscous oil was obtained in 73% yield tentatively assigned as the sulfoxide **41**!



41

The product was very polar (Rf=0.18, silica gel, EtOAc-hexane (1:1)) and in contrast to the starting diazo ester-sulfone did not display characteristic SO_2 infrared absorptions. The ^1H nmr spectrum showed a much simpler aromatic region (unlike the diazo ester-sulfone) and the methylene resonance $PhSO_2\underline{CH_2}C{=}O$ was no longer a sharp singlet. Unfortunately continued handling of this material resulted in its decomposition and attempts to fully characterize it failed. This reaction is now the subject of a new investigation currently underway in our laboratory. Compound **41** may be formed by attack of a sulfone oxygen on a rhodium carbenoid to give an intermediate ylide that rearranges to the sulfoxide. This is a very unusual result, since the sulfone oxygens are poor nucleophiles. This would represent a very mild one step method of deoxygenating sulfones to sulfoxides. Typically one has to reduce the sulfone to the

sulfide and re-oxidize to effect this transformation. Still[20] has deoxygenated sulfones by intermolecular reaction with aromatic diazonium compounds under high temperatures and vacuum, followed by reduction of the product (aryloxy)sulfoxonium salt with sodium borohydride.

Conclusions

The intermolecular rhodium carbenoid insertion approach to O-2-isocephems proved to be encumbered by many intramolecular interferences. These included competing aliphatic C-H insertion, aromatic C-H insertion, ylide formation, Wolff rearrangement and possibly sulfone deoxygenation. This was especially the case when it was possible to form a six-membered ring intermediate. These side reactions themselves may have proved more valuable than the original goal of preparing O-2-isocephems. The potential of the C-H insertion into the ester chain which yields 3-substituted γ-lactones has already been alluded to, and the insertion of rhodium carbenoids into aryl C-H bonds forms the basis for Chapter 3 of this thesis.

No competing side chain amide N-H insertion products were isolated, although their presence in the generally complex reaction product mixtures may have gone unnoticed.

In cases where the above interferences could not occur useful yields of O-2-isocephems were realized.

Experimental

General

Proton nmr spectra were recorded in $CDCl_3$ with a Varian XL 300 or EM 360 spectrometer (chemical shifts are given in ppm from tetramethylsilane) unless otherwise indicated, infrared spectra with a Perkin-Elmer 783 spectrophotometer, and mass spectra with a VG ANALYTICAL 7070E mass spectrometer (ei-ms 70ev; ci-ms 70ev ionizing potential, ether was used as reagent gas). Flash chromatography was performed with Merck 9385 silica gel; HPLC separations were performed with a Waters PREP LC/system 500 using a PrepPAK-500 silica column. Melting points were determined on a Gallenkamp apparatus, and are uncorrected. Solvents were dried prior to use; benzene and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl; methylene chloride from phosphorus pentoxide and stored over 4A° molecular sieves.

Preparation of Starting Materials

β-Lactams

cis-3-Azido-1-(4-methoxyphenyl)-4-(2-phenylethenyl)azetidin-2-one (**9**)

Freshly distilled methanesulfonyl chloride(4.35 g, 38 mmole) was added dropwise to a stirred solution of azidoacetic acid hemihydrate(4.18 g, 38 mmole) and triethylamine (3.85 g, 38 mmole) in 20 ml of dry CH_2Cl_2 at 0 °C. The mixed anhydride solution was stirred for 10 min and added to a stirred solution of N-(3-phenyl-2-propenylidene)-4-methoxyaniline (9.0 g, 38 mmole) and triethylamine (7.69 g, 76 mmole) in 100 ml of dry CH_2Cl_2 at 0 °C. The resulting solution was stirred for 18h at room temperature and washed successively with H_2O, 5% HCl, 5% $NaHCO_3$, then dried over $MgSO_4$ and evaporated to give 10.0 g of crude β-lactam. Recrystallization from warm EtOAc gave 7.44 g of **9** as a tan powder (61%); mp 116 °C (lit[21]. mp 116-117 °C).

cis-3-(*tert*-Butoxycarbonylamino)-1-(4-methoxyphenyl)-4-(2-phenyl-ethenyl)azetidin-2-one (**10**)

β-Lactam **9** (6.4 g, 20 mmole) was dissolved in 100 ml of dry CH_2Cl_2. Triethylamine (2.02 g, 20 mmole) was added and the mixture was stirred at 0 °C while H_2S was bubbled in at a fast rate for 10 min. The disappearance of the "azido" band in the infrared was noted after the solution was aged for 35 min following the H_2S treatment. The solution was then evaporated to dryness to give an orange solid

that was redissolved in 50 ml of CH_2Cl_2. The resulting solution was filtered and added dropwise to 25 ml of a stirred solution of di-*tert*-butyl dicarbonate (5.24 g, 24 mmole) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred at room temperature for 24 h, then refluxed an additional 1h, cooled to room temperature and washed with 1% HCl. The organic extracts were dried over $MgSO_4$ and evaporated to afford 10.0 g of crude acylated material. Trituration with ether followed by filtration yielded 5.08 g of pure **10** as a white powder; mp 203-204° C (dec.); ir (CH_2Cl_2) 3420, 1753, 1720 cm^{-1}; ei-ms m/z 394 (M^+, 1.4%), 338 (M^+-56, 2.6%), 294 (M^+-100, 23.5%), 277 (M^+ 117, 29.3%),171 (100%); nmr δ 1.36 (s,tBu), 3.75 (s,OCH_3), 4.86 (m,C4-H), 5.07 (m,C3-H), 5.20 (m, NH), 6.16 (dd,-CH=CH-Ph, J=7, 16 Hz), 6.70 (d, -CH=CH-Ph, J=16 Hz), 6.81-7.41 (m, aromatics).

cis-3-(*tert*-Butoxycarbonylamino)-1-(4-methoxyphenyl)-4-hydroxymethyl-azetidin-2-one (**11**)

A solution of **10** (1.47 g) in 100 ml of CH_2Cl_2-CH_3OH (10:1) was cooled to -78 °C under N_2, and ozonized until a blue colour persisted. The excess ozone was purged with N_2 and the solution was warmed to -30 °C (external bath temperature), whereupon $NaBH_4$ (350 mg) was added in 1 ml of EtOH, and the solution was allowed to warm up to room temperature. After 1 h at room temperature the pH of the solution was made slightly acidic (pH 5-6) with Amberlite IR-120 (H^+), followed by filtration and evaporation. The resulting milky oil (1.28 g) was triturated with hexane-ether (15:1) and filtered to extract the benzyl alcohol by-product. The solid obtained was triturated with cold EtOAc and filtered to afford **11** (960 mg) as a

white powder (80%); mp 162-163°C(dec.); ei-ms 322 (M^+, 2.9%), 266 (M^+-56, 8.7%), 248 (M^+-56-18, 9.0%), 149 (100%); ir (CH_2Cl_2) 3610, 3430, 1755, 1715, 1515, cm^{-1}; nmr δ 1.44 (s,tBu), 3.77 (s,OCH_3), 3.88 (dd, 1H, C$\underline{H_2}$OH, J= 12.7, 1.1 Hz), 4.18 (dd,1H, C$\underline{H_2}$OH, J=12.7, 3.5 Hz), 4.30 (m, C4-H), 5.22 (m, C3-H), 5.62 (br. d., N$\underline{H}$), 6.85 (d, 2H, J=8.9, aromatic), 7.52 (d, 2H, J=8.9, aromatic).

cis-3-(*tert*-Butoxycarbonylamino)-1-(4-methoxyphenyl)-4-tosyloxymethyl-azetidin-2-one (**12**)

The β-lactam **11** (880 mg, 2.73 mmole) was dissolved in 5 ml of pyridine, tosyl chloride (1.04 g, 5.46 mmole) was added and the resulting solution was stored at 0 °C overnight (18 h). The solution was then poured into 10 ml of H_2O and extracted with EtOAc (5 x 10 ml). The organic extracts were washed with 10% HCl, dried over $MgSO_4$ and evaporated to give **12** (1.145 g) as an off-white solid (88%). The material was shown to be pure by nmr. An analytical sample was recrystallized from warm ether;mp 146-147 °C(dec.); nmr δ 1.44 (s,tBu), 2.36 (s, $ArCH_3$), 3.77 (s,OCH_3), 4.24-4.42 (m,C$\underline{H_2}$O, C4-H), 5.19-5.21 (m, NH, C3-H) 6.73-7.58 (m, 8H, aromatics); ei-ms 476 (M^+, 9.0%), 420 (M^+-56, 75.0%), (M^+-100, 100.0%); ir (CH_2Cl_2) 3420, 1760, 1720, 1140 cm^{-1}.

cis -3-(*tert*-Butoxycarbonylamino)-4-tosyloxymethylazetidin-2-one (**13**)

The β-lactam **12** was N-dearylated by the method of Kronenthal.[21] A solution of **12** (1.1 g, 2.31 mmole) in 20 ml of CH_3CN was cooled to 0 C. A solution of ceric ammonium nitrate (3.8 g, 6.93 mmole, 3 eq) in 30 ml of H_2O was rapidly added in a dropwise

fashion to the stirred solution of **12**. Stirring was continued at 0 °C for 25 min. The mixture was diluted with 100 ml of H_2O and extracted with EtOAc (3 x 30 ml), the organic extracts were washed successively with saturated $NaHCO_3$, 10% Na_2SO_3 and brine followed by drying with $MgSO_4$, filtration and evaporation to give crude **13** (660 mg). The crude product was purified by trituration with ether followed by filtration to afford pure **13** (589 mg, 69%) as a white powder; mp 147-148 °C(dec.); nmr (DMSO d_6) δ 1.36 (s,tBu), 2.42 (s, $ArCH_3$), 3.80-4.16 (m,$C\underline{H}_2O$, C4-H), 4.88 (m, C3-H), 7.50 (d, 2H, J= 9.0, aromatics), 7.60 (br. d., NH amide), 7.78 (d, 2H, J= 9.0, aromatics), 8.46 (br. s, NH β-lactam); ei-ms 271 (M^+-99, 94.8%), 214 (M^+-156, 9.3%), 172 ($TosOH^+$, 16.4%), 56 (100%); ir (KBr) 3430, 3320, 1785, 1692, 1530, 1370, 1338, 1170 cm^{-1}.

cis-3-(*tert*-Butoxycarbonylamino)-4-*tert*-butyldimethylsilyloxymethyl-azetidin-2-one (**16**)

A solution of β-lactam **11** (322 mg, 1 mmole) in 4 ml of CH_2Cl_2 was cooled to -10 °C, *tert*-butyldimethylsilyl triflate (317 mg, 1.2 mmole) and 2,6 lutidine (161 mg, 1.5 mmole) were added and the resulting mixture was stirred for 30 min whereupon t.l.c analysis revealed that the starting alcohol was no longer present. At this point the reaction mixture was poured into ice cold 1% HCl, the organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give the crude silyl ether (337 mg) as a white powder. This material was N-dearylated as above (3 eq ceric ammonium nitrate in CH_3CN-H_2O(5:7), 25 min, 0°C) to give crude **16** (185 mg). Chromatography (silica gel, hexane-EtOAc (75:25)) afforded pure **16** (66.5 mg) as a

white powder (20%, 2 steps); mp °C; nmr δ 0.04 (s, $SiCH_3$), 0.06 (s, $SiCH_3$), 0.86 (s,SitBu), 1.38 (s, tBuO), 2.72-3.92 (m, $C\underline{H}_2O$, C4-H), 5.14 (m, C3-H), 5.54 (br. d., NH amide), 5.65 (br. s., NH β-lactam); ei-ms 257 (M^+-73, 8.2%), 217 (M^+-113, 25.9%), 57 (100%); ir ($CDCl_3$) 3420, 1770, 1618 cm^{-1}.

cis-3-Phenoxyacetamido-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-azetidin-2-one (**23**)

The azido β-lactam **9** (10.0 g) was reduced with H_2S in the presence of triethylamine (3.16 g, 1 eq) in 250 ml of dry CH_2Cl_2, as above (see compound **10**). The resulting orange solid was dissolved in 100 ml of dry CH_2Cl_2 containing 4-dimethylaminopyridine (381 mg, 0.1 eq) and triethylamine (3.16 g, 1 eq). The solution was cooled in an ice bath and phenoxyacetyl chloride (5.326 g, 1 eq) dissolved in 10 ml of dry CH_2Cl_2 was added over 20 min. The resulting thick white slurry was stirred for 3 h, then filtered to give 13.05 g of crude acylated material as a white powder (containing traces of sulfur) which was used without further purification. A small sample was recrystallized from CH_2Cl_2-hexane, mp 213-214 °C; ir (KBr) 3305, 1760, 1665, 1545 cm^{-1}; ei-ms m/z 428 (M^+, 18.5 %), 277 (M^+ 151, 87.0%), 236 (M^+-192, 100%); nmr δ 3.75 (s, OCH_3), 4.46 (ABq, $C\underline{H}_2O$, J= 15.0 Hz), 4.95 (m,C4-H), 5.54 (dd,-C$\underline{H}$=CH-Ph, J= 6.6, 16.2 Hz, and m, C3-H), 6.10 (dd,-CH=C$\underline{H}$-Ph, J= 6.6, 16.2 Hz), 6.70-7.40 (m, aromatics, NH amide).

cis-3-Phenoxyacetamido-1-(4-methoxyphenyl)-4-*tert*-butyldimethylsilyl-oxymethylazetidin-2-one (**24**)

The crude β-lactam **23** was dissolved in a mixture of 700 ml of CH_2Cl_2 and 150 ml of CH_3OH and was ozonized and reduced as above (excess O_3, 2.3 g $NaBH_4$) to give 9.93 g of pure β-lactam alcohol as a white powder(89%, 2 steps from **9**) following trituration with hexane-ether(15:1); mp 161-163 °C; ir ($CHCl_3$) 3610, 3400, 1755, 1690 cm^{-1}; ci-ms m/z 356 (M^+, 11.0 %), 338 (M^+-18, 9.2%), ; nmr (Acetone d_6) δ 3.74-3.79 (m, 4H, OCH_3, 1H of $C\underline{H}_2O$), 4.31 (dd, ABq, 1H of $C\underline{H}_2O$, J= 2.6, 12.7 Hz), 4.49 (m, C4-H), 4.60 (ABq, $PhOC\underline{H}_2$, J=15.0 Hz), 5.64 (dd, C3-H, J=5.6, 10.0 Hz), 6.92-7.48 (m, aromatics), 8.25 (br. d., NH, J=10.0 Hz).

The β-lactam alcohol was protected as a *tert*-butyldimethylsilyl ether by dissolution in 25 ml of dry N,N'-dimethylformamide followed by addition of imidazole (4.75 g, 2.5 eq) and *tert*-butyldimethylsilyl chloride (5.05 g, 1.2 eq). The solution was allowed to stand at room temperature for 12h, then poured into ether-water, separated, the organic layer dried over $MgSO_4$, filtered and evaporated to give the crude silyl ether (14.0 g). This was recrystallized from warm hexane-EtOAc (25:15) to give 11.56 g of pure **24** as a white powder (89%). mp 148-149 °C; nmr δ –0.33 (s, $SiCH_3$), -0.21 (s, $SiCH_3$), 0.75 (s,SitBu), 3.69 (d, $C\underline{H}OSi$, J= 12.0 Hz), 3.77 (s, OCH_3), 4.15 (d, $C\underline{H}OSi$, J= 12.0 Hz), 4.30 (m, C4-H), 4.55 (ABq, $PhOCH_2$, J=15.0 Hz), 5.73 (dd, C3-H, J=5.2, 10.8 Hz), 6.84-7.34 (m, aromatics), 7.63 (d, NH amide, J=10.8 Hz); ei-ms 470 (M^+, 18.0%), 413 (M^+-57, 9.2%), 280 (100%); ir ($CHCl_3$) 3400, 1755, 1680, 1512 cm^{-1}.

cis-3-Phenoxyacetamido-4-*tert*-butyldimethylsilyloxymethylazetidin-2-one (**25**)

The silyl ether **24** (11.56 g) was dissolved in 250 ml CH_3CN and N-dearylated as above with ceric ammonium nitrate (40.22 g, 3 eq in 365 ml of H_2O) to give 9.6 g of crude **25** as a brown solid. Trituration of this solid with cold ether followed by filtration gave 5.2 g of pure **25** as a white powder (60%). A small sample was recrystallized from warm hexane-EtOAc (3:1); mp 125-126 °C; nmr δ 0.10 (s, $SiCH_3$), 0.12 (s, $SiCH_3$), 0.90 (s,SitBu), 3.70-4.00 (m, $C\underline{H}_2OSi$, C4-H), 4.4 (s, $PhOCH_2$,), 5.5 (dd, C3-H, J=5, 7 Hz), 6.2 (br., lactam NH) 6.7-7.6 (m, aromatics, amide NH); ei-ms 307 (M^+-57, 29.2%), 264 (M^+-57-43, 41.6%), 116 (100%); ir (CH_2Cl_2) 3410, 1775, 1685 cm^{-1}.

α-Diazo-β-ketoesters

General Procedure for Diazo Transfer: Preparation of *tert*-Butyl 3-oxo-2-diazobutyrate **42**

A solution of *tert*-butyl acetoacetate (316.4 mg, 2 mmole) in 8 ml of CH_3CN was stirred at room temperature and triethylamine (202 mg, 2 mmole) was added, followed by addition of tosyl azide (394 mg, 2 mmole). The reaction mixture was stirred for 2h and the solvent was evaporated. The resulting residue was dissolved in 10 ml of ether, washed with 5 ml of 10% KOH, H_2O, dried over $MgSO_4$ and evaporated to give 318 mg of diazo ester (86%) as a yellow oil; ir (neat) 2120, 1712, 1655 cm^{-1}; nmr δ 1.5 (s,tBu), 2.43 (s, CH_3).

2-(Trimethylsilyl)ethyl Acetoacetate **29**

A mixture of 2-(trimethylsilyl)ethanol (4.0 g, 33.8 mmole) and 20 mg of NaOAc was heated to 80 °C, the heating bath was removed and diketene (3.0 g, 1.06 eq) was added dropwise with stirring. The stirring was continued for 30 min after addition, and the resulting brown solution was distilled under vacuum to give 5.94 g (87%)of **29** as a pale yellow oil (bp 74 °C/ 0.15 mm); ir (neat) 2960, 1740, 1650 cm^{-1}; nmr δ 0.1 (s,SitBu), 0.96 (dd, CH_2Si), 2.23 (s, $COCH_3$), 3.33 (s, CH_2CO), 4.13 (dd, OCH_2).

tert-Butyl 5-Hydroxy-3-oxohexanoate **18**

A solution of *tert*-butyl acetoacetate (3.16 g, 20 mmole) in 20 ml of dry tetrahydrofuran was added dropwise with stirring under nitrogen to a suspension of NaH (960 mg of a 50% w/w oil dispersion, 20 mmole) in 20 ml of dry tetrahydrofuran at O °C. After stirring the suspension for 10 min, a solution of nBuLi in hexane (2.83M, 7.42 ml, 21 mmole) was added in a dropwise fashion, followed by addition of acetaldehyde (4.5 ml, 80 mmole). The resulting mixture was stirred and allowed to come to room temperature, whereupon it was quenched with saturated NH_4Cl and extracted with ether. The ethereal extracts were dried over $MgSO_4$ and evaporated to give 4.94 g of crude alcohol that was purified by preparative HPLC to afford 1.7 g of pure alcohol **18** (42%) as a yellow oil. ir (neat) 3450, 2980, 1740-1700, 1650 cm^{-1}; nmr δ 1.20 (d, CH_3, J=7 Hz), 1.47 (s, tBu), 2.43-2.73 (m, -C<u>H</u>(OH)C<u>H</u>$_2$-), 3.30 (s, $COCH_2CO$), 4.10 (br., O<u>H</u>).

tert-Butyl 3-oxo-2-diazo-4-hexenoate **19**

A 404 mg sample of **18** was subjected to diazo transfer as above to give 266 mg of pure diazo alcohol (58%) as an orange oil; ir (neat) 3450, 2980, 2118, 1710, 1650 cm^{-1}; nmr δ 1.20 (d, CH_3, J=7 Hz), 1.47 (s, tBu), 2.83-3.26 (m, -C<u>H</u>(OH)C<u>H</u>$_2$-), 4.20 (br., O<u>H</u>); ei-ms m/z 184 (M^+-44, 2.5%), (M^+-73, 11.3%), 57 (100%). This material was dissolved in 5 ml of dry CH_2Cl_2 at O °C containing triethylamine (237 mg, 2 eq) and methanesulfonyl chloride (134 mg, 1 eq) was added dropwise. The resulting solution was allowed to come to room temperature and stirring was continued for 3h. The reaction mixture was then washed with 10% HCl, dried over $MgSO_4$ and evaporated to give 243 mg of orange oil that was purified by flash chromatography with hexane-EtOAc (9:1) to afford 191 mg of pure 19 (78%) as a colourless oil; ir (neat) 2980, 2122, 1710, 1655, 1610 cm^{-1}; nmr δ 1.51 (s, tBu), 1.90 (dd, CH_3, J= 6.6, 1.5 Hz), 6.96-7.10 (m, CH=C<u>H</u>-CH_3), 7.15 (dd, COC<u>H</u>=CH, J= 15.2, 1.5 Hz); ei-ms m/z 154 (M^+-56, 23.2%), 57 (100%).

Preparation of α-Diazo-β-ketoesters **30a-j**

The dianion of **29** was generated according to the method of Weiler[12] (NaH, nBuLi), and was alkylated with the appropriate electrophiles:

Compound **30a** (R_2=H) was prepared by diazo transfer reaction of 2-(trimethylsilyl)ethyl acetoacetate (**29**) in 68% yield after purification by flash chromatography as a yellow oil; ir (neat) 2955, 2120, 1715, 1660 cm^{-1}; nmr δ 0.1 (s,$SiCH_3$), 0.95 (dd, CH_2Si), 2.46 (s, $COCH_3$), 4.20 (dd, OCH_2).

Compound **30b** (R_2=CH_2Ph) was prepared by reaction of 8 mmole of dianion of **29** with 12 mmole of $PhCH_2Cl$ for 30 min: yield 1.82 g as a clear oil (78%); bp 160-163 °C/ 0.2 mm; ir (neat) 2950, 1740, 1715, 1645 cm^{-1}; nmr δ 0.1 (s,$SiCH_3$), 0.96 (dd, CH_2Si), 2.90 (s, $PhCH_2CH_2$), 3.40 (s, CH_2CO), 4.20 (dd, CH_2O), 7.2 (s, Ph). Diazo transfer gave **30b** in 96% crude yield which was used without further purification; ir (neat) 2950, 2115, 1655 cm^{-1}; nmr δ 0.1 (s,$SiCH_3$), 0.96 (dd, CH_2Si), 2.6-3.2 (m, $PhCH_2CH_2$), 4.20 (dd, CH_2O), 7.2 (s, Ph).

Compound **30c** (R_2=$CH(OAc)CH_3$) was prepared by reaction of 15 mmole of dianion of **29** with 60 mmole of acetaldehyde for 40 min: yield 2.13 g as a clear oil (58%) of alcohol isolated by preparative HPLC (2 hexane:1 EtOAc); ir (neat) 3410, 2930, 1735, 1710 cm^{-1}; nmr δ 0.1 (s,$SiCH_3$), 0.96 (dd, CH_2Si), 1.2 (d, CH_3, J=7 Hz), 2.1-2.8 (m, $-CH_2CH(OH)$), 3.4 (s, CH_2CO), 4.2 (dd, CH_2O). Diazo transfer was accomplished in 95% crude yield, the product was used as such: ir (neat) 3450, 2120, 1710, 1650 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.95 (dd, $SiCH_2$), 1.2 (d, CH_3, J= 7Hz), 2.6-3.0 (m, $-CH_2OH$), 4.2 (dd, CH2O), 4.0 (br., CH). A 1.09 g sample was acetylated by addition of 2 eq of acetyl chloride to a stirred solution of the alcohol and 1 eq of pyridine in 15 ml of CH_2Cl_2. The solution was stirred for 15 min, poured into 15 ml of water, separated and the organic extracts were dried over $MgSO_4$ and evaporated. Chromatography with hexane-EtOAc (9:1) gave 1.04 g of protected diazo alcohol **30c** as a clear colourless oil (83%): ir (neat) 2950, 2120, 1740, 1710, 1655 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.96 (dd, $SiCH_2$), 1.2 (d, CH_3, J=7 Hz), 4.2 (dd, CH_2O), 5.2 (dd, CH).

Compound **30d** (R_2=CH(OtBDMS)Ph) was prepared by reaction of 5 mmole of the dianion of **29** with 5.5 mmole of PhCHO for 30 min: yield 972 mg (63%) of alcohol as a clear oil, isolated by chromatography (5 hexane: 1 EtOAc): ir (neat) 3350-3600, 2950, 1740, 1700 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.96 (dd, $SiCH_2$), 2.8 (d, $CHCH_2$, J=7 Hz), 3.3 (s, CH_2CO) 4.2 (dd, CH_2O), 5.2 (br. t, CH), 7.2 (s, Ph). Diazo transfer was performed on 700 mg of the above alcohol to give 695 mg of crude diazo compound (91%) subsequently used as such: ir (neat) 3350-3600, 2950, 2120, 1710, 1650 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.96 (dd, $SiCH_2$), 3.2 (d, $CHCH_2$, J=7 Hz), 3.5 (br., OH) 4.3 (dd, CH_2O), 5.2 (br. t, CH), 7.2 (s, Ph). A 673 mg sample was O-*tert*-butyldimethylsilylated by dissolution in 8 ml of CH_2Cl_2 at 0 °C followed by treatment with 2 eq of 2,6 lutidine and 1.2 eq of *tert*-butyldimethylsilyl triflate for 30 min. The mixture was poured into 10 ml of cold 1% HCl, separated, the organic layer over $MgSO_4$ and evaporated. Column chromatography with hexane-EtOAc (95:5) gave 735 mg (81%) of pure protected diazo compound **30d** as a yellow oil: ir (neat) 2950, 2120, 1710, 1650 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$, $Si(CH_3)_2$), 0.90 (s, $Si(CH_3)_3$) 0.96 (dd, $SiCH_2$), 2.8 (dd, 1H, CH_2CO, J=14, 4 Hz), 3.6 (dd, 1H, CH_2CO, J=14, 8 Hz), 4.3 (dd, CH_2O), 5.2 (dd, CH, J= 8, 4 Hz), 7.2 (s, Ph).

Compound **30e** (R_2=3-thienylmethyl) was prepared by reaction of 4 mmole of the dianion of **29** with 4.4 mmole of 3-bromomethylthiophene for 30 min: yield 490 mg of yellow oil (41%) isolated by column chromatography with hexane-EtOAc (9:1); ir (neat) 2950, 1740, 1715 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.9 (dd, $SiCH_2$), 2.8 (s, $ThCH_2CH_2$-), 3.3 (s, CH_2CO), 4.1 (dd, CH_2O), 6.8 (br. s., 2H), 7.1

(br. s, 1H). Diazo transfer was effected in 79% yield after column chromatography with hexane-EtOAc (9:1); ir (neat) 2950, 2115, 1710, 1655 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.95 (dd, $SiCH_2$), 2.8-3.2 (s, Th-$C\underline{H}_2C\underline{H}_2$-), 4.3 (dd, CH_2O), 6.9 (br. s., 2H), 7.2 (br. s, 1H).

Compound **30f** (R_2= =$CHCH_3$) was prepared by dehydration of of the precursor of **30c**. Thus 3.4 mmole of diazo alcohol in 10 ml of dry CH_2Cl_2 was stirred at at 0 °C with 2 eq of triethylamine and 1 eq of methanesulfonyl chloride was added. The mixture was stirred at room temperature for 18h, washed with 10% HCl, water, and dried over $MgSO_4$ then evaporated to give 780 mg of orange oil. This was chromatographed with hexane-EtOAc (95:5) to give 640 mg of pure olefin **30f** as a yellow oil; ir (neat) 2950, 2118, 1715, 1660, 1615 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.95 (dd, $SiCH_2$), 1.9 (d, $CHC\underline{H}_3$, J= 8.3 Hz), 4.2 (dd, CH_2O), 7.1 (s, CHCO), 6.9-7.3 (m, $C\underline{H}CH_3$).

Compound **30g** (R_2=CH(OtBDMS)-3-pyridinyl) was prepared by reaction of 4.5 mmole of the dianion of **29** with 5 mmole of pyridine-3-carboxaldehyde for 1h: yield 775 mg of alcohol as a yellow oil (50%). ir ($CHCl_3$) 3400, 2950, 1740-1700 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.96 (dd, $SiCH_2$), 2.9 (d, $COC\underline{H}_2$), 3.4 (d, $COCH_2CO$), 4.2 (dd, CH_2O), 5.2 (t, CH), 7.0-8.5 (m, pyridinyl). Diazo transfer afforded the diazo alcohol in 78% yield as a yellow oil; ir (neat) 3400-3500, 2120, 1705, 1640 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.96 (dd, $SiCH_2$), 3.2 (d, $COC\underline{H}_2$), 4.2 (dd, CH_2O), 5.2 (t, CH), 7.0-8.5 (m, pyridinyl). This diazo alcohol was O-*tert*-butyldimethylsilylated (by the same procedure as for **30d**) to give **30g** as a yellow oil in 38% yield: ir (neat) 2950, 2120, 1710, 1650 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$, $Si(CH_3)_2$), 0.90 (s, $Si(CH_3)_3$) 0.96 (dd, $SiCH_2$), 3.1 (dd, 1H, $COC\underline{H}_2$, J= 14, 4 Hz), 3.6 (dd,

1H, $COCH_2$, J= 14, 8 Hz), 4.2 (dd, CH_2O), 5.3 (dd, CH, J= 8, 4 Hz), 7.0-8.7 (m, pyridinyl).

Compound **30h** (R_2=Br)[22] was prepared by reaction of **30 a** (1mmole) in 8 ml of CCl_4 at 0°C with 1.2 eq of triethylamine and 1.1 eq of trimethylsilyl triflate, followed by stirring at room temperature for 30 min, after which a floating layer of triethylamine triflate was removed by pipette. A solution of 1 mmole of bromine in 3 ml of CCl_4 was added dropwise with stirring to the solution of enol silyl ether and the resulting mixture was evaporated. The crude product was eluted through a short plug of silica gel with hexane-EtOAc (95:5) to give 310 mg of pure bromo compound **30h** as a light yellow oil (100%); ir (neat) 2950, 2120, 1710, 1655 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$, $Si(CH_3)_2$), 1.08 (dd, $SiCH_2$), 4.38 (dd, CH_2O), 4.42 (s, CH_2Br); ci-ms m/z 307, 309 (M^++1, 13.1%, 13.7%), 279,281 (M^++1-28, 31.1%, 32.8%), 147 (100%).

Compound **30i** (R_2=SPh) was prepared by reaction of **30h** (480 mg, 1.56 mmole) in 4 ml of CH_2Cl_2 with thiophenol (165 mg, 1.5 mmole) in the presence of triethylamine (152 mg, 1.5 mmole) for 3h. The reaction mixture was poured into water, the organic layer was separated and washed with 10% HCl,dried over $MgSO_4$ and evaporated to give 416 mg of crude **30i** as a yellow solid. Recrystallization from hot hexane with a trace of ether gave 315 mg of pure **30i** (63%) as white needles; mp 62-63 °C; ir ($CHCl_3$) 3010, 2122, 1708, 1650, 1328, 1200 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 0.95 (dd, $SiCH_2$), 4.05 (s, CH_2SPh), 4.20 (dd, CH_2O), 7.0-7.5 (m, SPh).

Compound **30j** (R2=SO_2Ph) was prepared by dissolution of 524 mg of crude **30i** (≈ 1.56 mmole) in 10 ml of CH_2Cl_2 at 0 °C followed

by addition with stirring of 675 mg of 3-chloroperoxybenzoic acid. The reaction mixture was stirred at room temperature for 45 min, the solid 3-chlorobenzoic acid by-product was filtered off and the filtrate was washed successively with 10% Na_2SO_3 and 5% $NaHCO_3$. The organic extracts were dried over $MgSO_4$ and evaporated to give 630 mg of yellow solid. This was chromatographed on silica gel with hexane-EtOAc (7:3) to afford 490 mg of pure **30j** (85%) as a pale yellow waxy solid; ir ($CDCl_3$) 2960, 2120, 1710, 1650, 1328, 1162 cm^{-1}; nmr δ 0.1 (s, $SiCH_3$), 1.03 (dd, $SiCH_2$), 4.20 (dd, CH_2O), 4.80 (s, $C\underline{H_2}SO_2$), 7.33-8.06 (m, SO_2Ph); ci-ms m/z 341 (M^++1-28, 96.8%), 313 (M^++1-28-28, 100%).

Carbenoid Insertion Reactions

General Procedure for Diazo Insertion Reactions: **31a** (Insertion of **30a** into **25**)

A solution of 0.824 mmole of **25** in 7 ml of dry benzene was warmed to effect dissolution. Diazo compound **30a** (0.99 mmole, 1.2 eq) was added and the solution was brought to reflux, allowing some benzene vapors to escape (in an effort to remove possible traces of water) and $Rh_2(OAc)_4$ (18 mg, 5 mole % based on β-lactam) was added in one portion. The solution was refluxed for 1h. Vigorous gas evolution occurred during the initial stages of the reaction. The reaction mixture was cooled, filtered and evaporated to give 525 mg of green oil. The oil was dissolved in 4 ml of warm hexane-EtOAc (3:1) and allowed to cool, 65 mg of pure **25** was recovered by filtration. The mother liquor was evaporated and subjected to column

chromatography with hexane-EtOAc (2:1). Two fractions were recovered, R_f= 0.41 (187 mg) β-lactam **31a** (40%). This compound crystallized on standing; mp 98-100 °C; ir ($CHCl_3$) 3418, 2960, 1760, 1685 cm^{-1}; ci-ms m/z 565 (M^++1, 44.1%), 537 (M^++1-28, 100%), and R_f= 0.62 (41 mg) of γ-lactone **34** (21%); ir (neat) 2960, 1765, 1720 cm^{-1}; ei-ms m/z 200 (M^+, 2.1%), 185 (M^+-15, 13.5%), 157 (M^+-43, 68.3%), 142 (M^+-43-15, 91.0%), 68 (100%); nmr δ 0.02 (s, $SiCH_3$), 2.42 (s, CH_3), 2.42 (dd, CHSi, J=11,9), 3.43 (d, $COCHCO_2$, J=11), 4.07 (dd, 1H, $C\underline{H_2}CHSi$, J=11,9), 4.45 (dd, 1H, $C\underline{H_2}CHSi$, J=11,9).

Compound **31b** (R_2=CH_2Ph) (Insertion of **30b** into **25**) Treatment of 0.824 mmole of **25** with 0.99 mmole of **30b** as above gave 71 mg of **25** (23%) and 250 mg of **31b** (46%) as a yellow oil after chromatography; ir ($CHCl_3$) 3420, 2960, 1760, 1685 cm^{-1}; ci-ms m/z 655 (M^++1, 53.1%), 627 (M^++1-28, 56.9%)

Compound **31c** (R_2=CH(OAc)CH_3) (Insertion of **30c** into **25**) Treatment of 1.86 mmole of **25** with 2.33 mmole of **30c** as above gave 254 mg of **25** (38%) and 400 mg of **31c** (33%) as a yellow oil after chromatography; ir ($CHCl_3$) 3400, 2950, 1760, 1675, 1650 cm^{-1}; ci-ms m/z 651 (M^++1, 89.4%), 623 (M^++1-28, 58.7%), 264 (100%).

Compound **31d** (R_2=CH(OtBDMS)Ph) (Insertion of **30d** into **25**) Treatment of 1.25 mmole of **25** with 1.5 mmole of **30d** as above gave 60 mg of **25** (13%) and 340 mg of **31d** (35%) as a white foam after chromatography; ir ($CHCl_3$) 3420, 2960, 1765, 1685, 1600 cm^{-1}; ci-ms m/z 785 (M^++1, 12.3%), 757 (M^++1-28, 3.8%), 625 (24.2%).

Compound **31e** (R_2=3-thienylmethyl) (Insertion of **30e** into **25**) Treatment of 0.775 mmole of **25** with 0.93 mmole of **30e** as above gave 152 mg of **25** (54%) and 89 mg of **31e** (17%) as an

orange gum after chromatography- ; ir ($CHCl_3$) 3420, 2950, 1760, 1685, 1600 cm^{-1}; ci-ms 661 (M^++1, 13.9%), 633 (M^++1-28, 27.5%). Also isolated was 145 mg (53%) of heteroaromatic insertion product **43** as a greenish oil; ir ($CHCl_3$) 1640, 1593 cm^{-1}, nmr δ 0.9 ($SiCH_3$), 1.1 (dd, CH_2Si), 4.2 (dd, CH_2O), 6.6 (d, 1H), 6.9 (d, 1H), 12.8 (br. s., enolic H); ci-ms m/z 297 (M^++1, 7.0%), 269 (M^++1-28, 100%), 253 (33%), 179 (94.9%).

Compound **31f** (R_2= =$CHCH_3$) (Insertion of **30f** into **25**) Treatment of 1.90 mmole of **25** with 2.28 mmole of **30f** as above gave only 472 mg of a product derived from a Wolff rearrangement analogous to **22** (42%) as a yellow oil after chromatography, identified by ir ($CHCl_3$) 3400, 2925, 2960, *1800*, 1735, 1690, 1600 cm^{-1}; ci-ms m/z 591 (M^++1, 26.4%), 563 (M^++1-28, 48.4%). No "normal" insertion product **31f** was recovered.

Compound **31g** (R_2=CH(OtBDMS)-3-pyridinyl) (Insertion of **30g** into **25**) Treatment of 0.55 mmole of **25** with 0.66 mmole of **30g** as above gave back mostly unchanged starting materials, no insertion products were observed.

Compound **31h** (R_2=Br) (Insertion of **30h** into **25**) Treatment of 0.168 mmole of **25** with 0.20 mmole of **30h** as above gave 117 mg of green oil from which no identifiable products could be obtained. However, dropwise addition of a solution of 0.275 mmole of **25** and 0.33 mmole of **30h** in 5 ml of dry CH_2Cl_2 to 7 mg (5 mole%) of $Rh_2(OAc)_4$ in 1 ml of dry CH_2Cl_2 over 15 min followed by filtration and evaporation after 1.5h gave 200 mg of brown oil. Trituration with hexane-EtOAc (2:1) gave 45 mg of **25** (45%). Column chromatography of the mother liquor gave 40 mg of **31h** (23%) as a

light-brown oil; R_f= 0.24; ir ($CHCl_3$) 3418, 3000, 1760, 1685, 1655 cm^{-1}; ci-ms m/z 563 (M^++1-80, 9.9%), 535 (M^++1-80-28, 6.3%), 463 (M^++1-80-101, 36.0%), 348 (M^++1-80-101-115, 32.7%). Also isolated was 10 mg of γ-lactone **39** (11%) as a clear colourless oil; R_f= 0.67; ir (neat) 2950, 1760, 1730-1710 cm^{-1}; ei-ms m/z 263, 265 (M^+ 15, 1.6%, 1.7%), 199 (M^+-79, 3.0%), 171 (199-28, 5.8%), 157 (M^+-$COCH_2Br$, 39.7%), 73 (100%); nmr δ 0.06 (s,$SiCH_3$), 2.50 (m, C<u>H</u>Si), 4.02 (dd, CH_2Br, J= 7.8,11.5 Hz), 4.10 (dd, 1H, C<u>H</u>$_2$CHSi, J= 9, 11.5 Hz), 4.47 (d, $COCHCO_2$, J= 11.5 Hz), 4.50 (t, J= 9 Hz). When 110 mg of **30h** in 10 ml of dry CH_2Cl_2 was added dropwise to a stirred slurry of 3 mg of $Rh_2(OAc)_4$ in 5 ml of CH_2Cl_2, the mixture stirred for 40 min, filtered , evaporated and chromatographed as above, 60 mg of **39** (60%) was recovered.

<u>Compound **31i** (R_2=SPh) (Insertion of **30i** into **25**)</u> Treatment of 0.81 mmole of **25** with 0.89 mmole of **30i** as above gave 615 mg of a green solid. Trituration of this material with warm hexane-EtOAc (3:1) gave back 200 mg of **25** (67%) after filtration. The filtrate was chromatographed with hexane-EtOAc (3:1) to give 105 mg of **40** (18%) as a pale yellow waxy solid. Recrystallization from hexane-ether yielded **40** as white needles; mp 91-92 °C; Analysis Calculated for $C_{30}H_{40}O_6Si_2S_2$: C 58.44, H 6.49, S 10.39: Found C 57.90, H 6.42, S 10.77; ir ($CDCl_3$) 2960, 1700, 1600, 1580 sh., 1490, 1440, 1305, 1210-1120 cm^{-1}; ^1H nmr δ 0.01 (s, $SiCH_3$), 0.86 (dd, CH_2Si), 4.08 (dd, CH_2O), 5.18 (s, C<u>H</u>$_2$SPh), 6.45-7.26 (aromatics); ^{13}C nmr δ -1.59, 17.20, 63.67, 63.74, 100.85, 126.12, 126.96, 129.06, 136.00, 163.36, 164.47; ci-ms m/z 589 (M^++1-28, 1.7%), 561 (M^++1-28-28, 12.1%),

471 (M^++1-73-73, 10.5%). Compound **31i** was not detected in the complex product mixture.

Compound **31j** (R_2=SO_2Ph) (Insertion of **30j** into **25**) Treatment of 0.82 mmole of **25** with 0.98 mmole of **30j** as above gave back 80 mg of **25** (26%) and 490 mg of a red-brown oil containing a complex mixture of products from which no identifiable compounds could be isolated. When a solution of 110 mg of **30j** (0.3 mmole) in 8 ml of dry CH_2Cl_2 was added dropwise to a stirred suspension of 3 mg of $Rh_2(OAc)_4$ in 1 ml of CH_2Cl_2, TLC analysis (hexane-EtOAc 1:1) revealed the diazo compound (R_f= 0.66) had given way to a much more polar compound (R_f= 0.18). The reaction was complete in 2.5 h. Filtration and evaporation of the reaction mixture gave 100 mg of a greenish oil. Chromatography with hexane-EtOAc (1:1) afforded 74 mg of a yellow viscous oil (73%) tentatively identified as **41**; ir (neat) 2950, 1735, 1445w, 1250, 1030 br. cm^{-1}; nmr (poorly resolved) δ 0.01 (s, $SiCH_3$), 0.95 (dd, CH_2Si), 4.1 (dd, CH_2O), 5.7 (br., $C\underline{H}_2SO$), 7.4 (br. s., aromatics); ci-ms m/z 341 (M^++1, 6.4%), 313 (M^++1-28, 100%).

Compound **8** (Insertion of **7** into **6**) Treatment of 2.0 mmole of **6** with 2.4 mmole of **7** as above gave 207 mg of **8** (38%) as a red-brown oil after chromatography; ei-ms m/z 275 (M^+, 2.9%), 233 (M^+-42, 27.8%), 232 (M^+-43, 9.7%), 190 (22.2%), 104 ($CH_2CH_2Ph^+$, 100%); nmr δ 1.30 (t, CH_3), 1.94 (s, CH_3), 3.26 (dd, C3-H's), 4.20(q, CH_2O), 4.80 (m, C4-H), 7.26 (aromatics), 13.1 (s, enolic H); ir ($CHCl_3$) cm^{-1}.

Compound **14** (Insertion of **7** into **13**) A mixture of 75 mg of β-lactam **13** (0.2 mmole) and 37 mg of diazoester **7** (0.24 mmole, 1.2 eq) in dry $CHCl_3$ was brought to reflux and $Rh_2(OAc)_4$ (4 mg, 5

mole%) was added in one portion. Vigorous gas evolution occurred, and the mixture was allowed to reflux for 1h. The mixture was cooled, filtered and evaporated to give 104 mg of crude as a burgundy oil. Chromatography with hexane-EtOAc (7:3) afforded 30 mg of insertion product **14** (30%) as an oil (contained trace of impurity, not fully characterized); ir ($CHCl_3$) 3420, 3000, 1760, 1715,1510, 1360, 1170 cm^{-1}; nmr δ 1.20 (t, CH_3),1.45 (s, tBu), 2.3 (s, CH_3), 2.4 (s, CH_3), 4.0-4.3 (m, C4-H, CH_2O, OCH_2), 5.2 (m, C3-H), 7.2-7.7 (aromatics), 12.3 (enolic H).

Compound **17** (Insertion of **7** into **16**) Treatment of 0.17 mmole of **16** with 0.20 mmole of **7** as above gave 46 mg of **17** (59%) after chromatography as a white solid; mp 114-116 °C; ir ($CDCl_3$) 3430, 1760, 1715,1660, 1620, 1510 cm^{-1}; nmr δ 0.06 (s, $SiCH_3$), 0.09 (s, $SiCH_3$), 0.90 (s, SitBu),1.42 (s, CO_2tBu), 2.14 (s, CH_3), 3.84 (dd, CH_2OSi, J=12,2 Hz), 4.03 (m, C4-H), 4.20 (m, CH_2O), 5.22 (dd, C3-H, J=10,6 Hz), 5.55 (br. d., NH), 12.30 (s, enolic H); ci-ms m/z 459 (M^++1, 18.1%), 403 (M^++1-56, 100%).

Compound **22** (Insertion of **19** into **16**) Reaction of 0.2 mmole of **16** with 0.24 mmole of **19** as above gave 108 mg of crude as a greenish oil. Chromatography with hexane-EtOAc (4:1) yielded two fractions, both were colourless oils: 56 mg (55%) of the major product of R_f= 0.49, identified as **20** (Wolff rearrangement product); ir ($CDCl_3$) 3420, 2980, *1800*, 1740-1700, 1510 cm^{-1}; ci-ms m/z 401 (M^++1-tBu-tBu, 100%); ei-ms m/z 388 (M^+-56-56-17, 12.9%), 343 (M^+-56-56-57, 52.9%), 57 (100%); nmr (diastereomeric pair, complex spectrum, structure assignments aided by HOMCOR) δ 0.05 (s, $SiCH_3$), 0.88, 0.84[(s, SitBu)], 1.39 (s, CO_2tBu), 1.42 (s, CO_2tBu), 1.74 (dd,

$CHC\underline{H}_3$), 3.68 (m, C4-H), 4.34 (m, CH_2OSi), 4.56, 4.72 [(d, $COCHCO_2$)], 5.30 (m, C3-H), 5.6-5.9 (m, $C\underline{H}=C\underline{H}-CH_3$, NH); and a minor product of R_f= 0.40, identified as the desired product **22**; ir ($CHCl_3$) 3420, 1755, 1712,1660, 1510 cm^{-1}; ei-ms m/z 400 (M^+-56-56, 9.8%), 343 (400-57, 16.3%), 300 (400-CO_2tBu, 37.8%), 57 (100%); nmr δ 0.03 (s, $SiCH_3$), 0.04 (s, $SiCH_3$), 0.86 (s, SitBu), 1.37 (s, CO_2tBu), 1.43 (s, CO_2tBu), 1.82 (dd, $CHC\underline{H}_3$, J=6.9,1.7), 3.96 (m, C4-H), 5.15 (dd, C3-H), 5.48 (br. d., NH), 6.30 (m, $CH=C\underline{H}-CH_3$), 6.68-6.76 (m, $C\underline{H}=CH-CH_3$).

Compound **26** (Insertion of **42** into **25**) Treatment of 0.17 mmole of **25** with 0.20 mmole of **42** as above gave 104 mg of crude as a greenish oil. Chromatography afforded 47 mg of **26** (54%) as a clear colourless oil; ir ($CHCl_3$) 3420, 2920, 1760, 1685 cm^{-1}; ci-ms m/z 521 (M^++1, 60.8%), 465 (M^++1-56, 83.0%), 421 (M^++1-56-44, 44.6%); nmr δ 0.02 (s, $SiCH_3$), 0.82 (s, SitBu), 1.48 (s, CO_2tBu), 2.12 (s, $C\underline{H}_3$), 3.73,3.85 (AB, CH_2OSi, J=12,4 Hz), 4.10 (m, C4-H), 5.44 (dd, C3-H, J=6,5 Hz), 6.88-7.30 (m, Ph, NH), 12.23 (s, enolic H).

Cyclization Reactions

General Procedure for Desilylation-Cyclization Sequence: Preparation of **28**.

A 43 µl aliquot of 6N HCl (0.26 mmole, 3 eq) was added to a stirred solution of 45 mg of β-lactam **26** (0.087 mmole) in 2 ml of methanol at room temperature, and stirred until TLC analysis revealed that the starting material was no longer present (≈ 3h). Powdered $NaHCO_3$ (3.5 eq) was added in one portion and the mixture was evaporated to dryness. The residue was taken up in CH_2Cl_2,

filtered and evaporated to give the crude enol-alcohol in near quantitative yield which was used as such in the following step. The crude enol-alcohol was dissolved in 1 ml of dry tetrahydrofuran and stirred at room temperature. Solid triphenylphosphine 1eq was added to the above stirred solution followed by diethyl azodicarboxylate, and the reaction mixture was stirred for 30 min, then evaporated to give 79 mg of brown foam. Column chromatography with hexane-EtOAc (2:1) gave 19 mg of pure **28** as a white powder; mp 120-121 °C; ir ($CHCl_3$) 3405, 1772, 1700 cm^{-1}; ci-ms m/z 389 (M^++1, 14.0%), 333 (M^++1-56, 89.5%), 142 (100%).

Preparation of **32a** (R_2=H) Treatment of 164 mg of **31a** as above gave 131 mg of crude enol-alcohol, cyclization gave 260 mg of brown foam. Chromatography with hexane-EtOAc (2:1) afforded 77 mg of pure **32a** (61%) as a clear colourless oil; ir ($CHCl_3$) 3400, 1775, 1710 cm^{-1}; ei-ms m/z 432 (M^+, 6.5%), 389 (M^+-28-15, 7.0%), 214 (49.1%), 124 (100%).

Preparation of **32b** (R_2=CH_2Ph) Desilylation of 191 mg of **31b** gave 220 mg of crude enol-alcohol. This was purified by chromatography to give 92 mg of pure enol-alcohol (58%) as a clear colourless oil which was cyclized as above to afford 65 mg of pure **32b** (73%) as a clear colourless oil; ir ($CHCl_3$) 3405, 1773, 1698, 1610, 1600 cm^{-1}; ci-ms m/z 523 (M^++1, 8.4%), 495 (M^++1-28, 24.5%).

Preparation of **32c** (R_2=$CH(OAc)CH_3$) Treatment of 385 mg of **31c** as above gave 620 mg of crude cyclic material as a pink oil. Chromatography with hexane-EtOAc (2:1) yielded 172 mg of pure **32c** (56%) as a clear colourless oil; ir ($CHCl_3$) 3405, 1763, 1730,

1690, 1615, 1600 cm^{-1}; ci-ms m/z 519 (M^++1, 5.2%), 491 (M^++1-28, 18.7%), 300 (100%).

Preparation of **32d** (R_2=CH(OH)Ph) Desilylation of 326 mg of **31d** with 6 eq of 6N HCl gave 285 mg of of pink foam which was a mixture of products. This was purified by chromatography with hexane-EtOAc (2:1) to give 86 mg of pure enol-diol (37%) as a white foam, which was cyclized as above to afford 43 mg of pure **32d** (52%) as a clear colourless oil; ir ($CHCl_3$) 3500-3300 br., 3000, 2950, 1775, 1685, 1610, 1600 cm^{-1}; ci-ms m/z 539 (M^++1, 7.1%), 521 (M^++1-18, 8.5%), 511 (M^++1-28, 39.6%), 493 (M^++1-18-28, 100%).

Preparation of **32e** (R_2=3-thienylmethyl) Treatment of 83 mg of **31e** as above gave 73 mg of crude enol-alcohol, which was purified by column chromatography with hexane-EtOAc (1:1) to afford 55 mg of pure enol-alcohol (80%) as a clear oil. This was cyclized to give 45 mg of pure **32e** as a clear colourless oil after chromatography with hexane-EtOAc (2:1); ir ($CHCl_3$) 3405, 3000, 2960, 1775, 1700, 1610, 1600 cm^{-1}; ci-ms m/z 529 (M^++1, 1.1%), 501 (M^++1-28, 3.4%), 310 (22.5%).

Preparation of **32h** (R_2=Br) Desilylation of 40 mg of **31h** as above gave 32 mg of crude enol-alcohol as a red-brown oil. Cyclization afforded 6 mg (19%) of a clear oil tentatively identified as **32h**; ir ($CHCl_3$) 3420, 3000, 2950, 1765, 1680, 1520 cm^{-1}; ci-ms m/z 431 (M^++1-80, 5.4%), 403 (M^++1-80-28, 8.9%), 191 ($PhOCH_2CONHCH{=}C{=}O^+$,46.9%).

Preparation of **15** The β-lactam **14** (29 mg, 0.058 mmole) was dissolved in 1 ml of tetrahydrofuran containing 8 drops of *tert*-butanol. This was added to a slurry of 4 mg of sodium hydride (0.087

mmole, 1.5 eq) in dry tetrahydrofuran at 0 °C. The reaction mixture was stirred at room temperature for 22h and then poured into water layered over with ether. The ethereal layer was washed with 10% HCl, dried over $MgSO_4$ and evaporated to give 15 mg of crude bicyclic material as an orange oil. Preparative layer chromatography afforded 8 mg of pure **15** as a clear colourless oil; ir ($CDCl_3$) 3420, 3150, 1772, 1720, 1620 cm^{-1}; ci-ms m/z 327 (M^++1, 2.7%), 271 (M^++1-56, 20.7%), 243 (100%); nmr δ 1.30 (t, CH_3), 1.42 (s, tBu), 2.24 (s, CH_3), 3.77-3.80 (m, C1-βH, C6-H), 4.18-4.32 (m, CH_2O), 4.55 (m, C1-αH), 4.96 (m, C7-H), 5.28 (m, NH).

Carboxylate Deprotection Reactions

General Procedure for Removal of the 2-(Trimethylsilyl)ethyl Protecting Groups: Preparation of **33a** (R_2=H).

A 72 µl aliquot (1.1 eq) of 1.0 M tetrabutylammonium fluoride in tetrahydrofuran was added to a stirred solution of 24 mg of **32a** in 1 ml of dry tetrahydrofuran. After 5h TLC analysis revealed the presence of some starting material, therefore another 0.5 eq of tetrabutylammonium fluoride in tetrahydrofuran were added. The deprotection was completed in 30 min. The reaction mixture was poured into 4 ml of EtOAc and washed with 2 ml of 0.3 M H_2SO_4. The organic layer was dried over $MgSO_4$ and evaporated, leaving an off-white powder. Recrystallization from acetone-ether gave 18 mg of **33a** (98%) as a white powder; mp 169-170 °C (lit. 171-172°C); ir (nujol) 3420, 1750, 1650, 1600 cm^{-1}; ei-ms 288 (M^+-44).

Preparation of **33b** (R_2=CH_2Ph) Deprotection of 68.5 mg of **32b** gave 46 mg (84%) of pure **33b** as a white powder from acetone-ether; mp 161-163 °C; (lit. 162-163 °C); ir ($CHCl_3$) 3400, 1775, 1690, 1600 cm^{-1}; ci-ms 423 (M^++1), 379 (M^++1-44), 329 (M+-93).

Preparation of **33e** (R_2=3-thienylmethyl) Deprotection of 45 mg of **32e** gave 30 mg (83%) of pure **33e** as tan crystals from acetone-ether; mp 152-153 °C; (dec.); ir ($CHCl_3$) 3400, 3010, 1773, 1690, 1600 cm^{-1}; ci-ms 429 (M^++1), 385 (M^++1-44), 335 (M+-93).

Nuclear Magnetic Resonance Data for Monocyclic Phenoxyacetamido β-Lactams

COMPOUND	AROMATIC	C3-H	$PhOC\underline{H}_2$	C4-H	$C\underline{H}_2OtBDMS$	OTHER
26	6.88-7.33 (m,6H)[1]	5.44 (dd,J=6,5)	4.51 (AB,J=14)	4.10 (m)	3.73, 3.85 (dd,J=12.4)	0.02(s,6H), 0.82(s,9H), 1.48(s,9H) 2.12 (s,3H),12.23(s,1H)
31a	6.86-7.34 (m,6H)[1]	5.50 (dd,J=9,5)	4.51 (AB,J=14)	4.15 (m)	3.73,3.85 (dd,J=12.4)	0.02(s,6H), 0.03(s,9H),1.04(m,2H) 2.14(s,3H), 4.24(m,2H), 12.2(s,1H)
31b	6.88-7.34 (m,11H)[1]	5.54 (dd,J=9,5)	4.51 (AB,J=14)	4.12 (m)	3.69,3.82 (dd,J=12.4)	0.02(s,6H), 0.03(s,9H),0.73(s,9H), 1.07(t,2H,J=8.8), 2.86-3.20(m,4H), 4.30(m,2H), 12.56(s,1H).
31c[2]	6.89-7.33 (m,5H)	5.53 (dd,J=8,5)	4.55 (s)	4.13 (m)	3.75-3.90 (m,2H)	0.02(s,6H), 0.03(s,9H), 0.79(s,9H), 1.05(m,2H), 1.32(d,3H,J=7), 2.00 (s,3H), 2.9-3.25(m,2H), 4.27(m,2H), 5.10(m,1H), 7.8(d,J=8,NH), 12.19 (s,1H)
31d[2,3]	6.95-7.42 (m,10H)	5.48 (dd,J=8,5)	4.56 (AB,J=14)	4.28 (m)	3.73,4.03 (dd,J=12.4)	0.03(s,9H), 2.51(dd,1H,J=14,4),3.16 (dd,1H,J=14,4), 4.38(m,2H), 5.20(dd, J=11,4), 8.32(d,J=8,NH)
31e	6.86-7.34 (m,9H)[1]	5.48 (dd,J=9,5)	4.51 (AB,J=14)	4.09 (m)	3.67-3.79 (dd,J=12.4)	0.02(s,6H), 0.03(s,9H), 0.76(s,9H), 1.04(m,2H), 2.84-3.08(m,2H),12.4 (s,1H)
31h	7.03-7.34 (m,6H)	5.44 (dd,J=8,5)	4.52 (AB,J=14)	4.15 (m)	3.76-3.90 (m,2H)	0.05(s,6H), 0.85(s,9H),1.04(m,2H) 4.20-4.36(m,4H), 7.20(br.d, NH)

1 includes NH of amide
2 mixture of diastereomers
3 O-desilylated, recorded in acetone d_6

Nuclear Magnetic Resonance Data for Bicyclic Phenoxyacetamido β-Lactams

COMPOUND	AROMATIC	C7-H	$PhOC\underline{H}_2$	C1-α	C1-β	C6-H	OTHER
28	6.88-7.34 (m,6H)[1]	5.45 (t,J=5)	4.52 (s)	4.45 (dd,J=11,4)	3.68 (t,J=11)	3.90 (m)	1.50(s,9H), 2.20(s,3H)
32a	6.86-7.34 (m,5H)	5.44 (dd,J=5,6)	4.51 (s)	4.44 (dd,J=11,4)	3.67 (dd,J=11,10)	3.86 (m)	0.03(s,9H), 1.07(t,2H,J=8.8), 2.23(s,3H), 4.20(m,2H), 6.96 (d,J=6, NH)
32b	6.87-7.35 (m,11H)[1]	5.44 (dd,J=5,6)	4.52 (s)	4.45 (dd,J=11,4)	3.62 (dd,J=11,10)	3.84 (m)	0.03(s,9H), 1.06(t,2H,J=8.4), 2.77-3.10(m,4H),4.30(m,2H)
32c[2]	6.87-7.34 (m,6H)[1]	5.45 (t,J=5)	4.51 (s)	4.45 (m)	3.61 (m)	3.85 (m)	0.03(s,9H), 1.07(t,2H,J=8.8), 1.24(d,3H,J=7),1.96,1.99(s,3H), 2.78-3.10(m,2H),4.28(m,2H), 5.17(m,1H)
32d[2]	6.88-7.40 (m,11H)[1]	5.52 (t,J=5)	4.52 (s)	4.51 (m)	3.78 (t,J=10)	3.93 (m)	0.03(s,9H), 1.07(t,2H,J=8.8), 2.65(dd,1H,J=14,4),3.26(dd, 1H,J=14,10),4.90(dd,1H,J=10,4)
32e	6.90-7.35 (m,9H)[1]	5.44 (t,J=5)	4.52 (s)	4.45 (dd,J=11,4)	3.60 (t,J=11)	3.78 (m)	0.03(s,9H), 1.06(t,2H,J=8.8), 2.7-3.0(m,4H),4.30(m,2H)
32h	6.86-7.34 (m,5H)	5.48 (dd,J=5,6)	4.52 (s)	4.47 (m)	3.72 (t,J=11)	3.92 (m)	0.03(s,9H), 1.09(t,2H,J=8.8), 4.20-4.52(m,4H),6.98 (d,J=6,NH)

1 includes NH of amide
2 mixture of diastereomers
3 recorded in acetone d_6

Nuclear Magnetic Resonance Data for Bicyclic Phenoxyacetamido β-Lactam Acids

COMPOUND	AROMATIC	C7-H	$PhOCH_2$	C1-α	C1-β	C6-H	OTHER
33a[1]	7.00-7.40 (m,5H)	5.74 (dd,J=5,8)	4.62 (AB,J=14)	4.48 (dd,J=11,4)	4.20 (dd,J=11,10)	3.88 (m)	2.20(s,3H),8.22(d,J=8,NH)
32b[1]	7.00-7.35 (m,10H)	5.72 (dd,J=5,8)	4.60 (AB,J=14)	4.51 (dd,J=11,4)	4.12 (dd,J=11,10)	3.85 (m)	2.78-3.10(m,4H),8.22 (d,J=8,NH)
32e	6.80-7.35 (m,9H)[2]	5.23 (t,J=5)	4.48 (s)	4.46 (dd,J=11,4)	3.66 (dd,J=11,10)	3.86 (m)	2.76-3.10(m,4H)

1 recorded in acetone d_6
2 includes NH of amide

REFERENCES

[1] This work has appeared in part as "Intramolecular Rhodium Carbenoid Insertions into the N-H Bond of β Lactams. Synthesis of O-2-Isocephems", M. Hrytsak, T. Durst *Heterocycles* 1987, **26,** 2393.

[2] T.W. Doyle, J.L. Douglas, B. Belleau, T.T. Conway, C.F. Ferrari, D.E. Horning, G. Lim, B.Y. Luh, A. Martel, M. Menard, L.R. Morris, M. Misiek, *Can. J. Chem.* 1980, **58**, 2508.

[3] For a compilation of references to this work see reference 1 in S.M. Tenneson and B. Belleau, *Can. J. Chem.* 1980, **58**, 1605.

[4] W. Dürkheimer, J. Blumbach, R. Lattrell, K.H. Scheunemann *Ang. Chem. Int. Ed.* 1985, **24**, 180.

[5] S.M. Tenneson and B. Belleau, *Can. J. Chem.* 1980, **58**, 1605.

[6] S.W. McCombie, W.A. Metz, A. Afonso *Tetrahedron Lett.* 1986, **27**, 305.

[7] P.G Mattingly, M.J. Miller *J. Org. Chem.* 1981, **46**, 1557.

[8] R. Labia, C. Morin *J. Antibiotics* 1984, **37**, 1103; C. Hubschwerlen, G. Schmid *Helv. Chim. Acta* 1983, **66**, 2206.

[9] G.A. Koppel "The Synthesis of the β-Lactam Function"; A. Hassner, Ed.; John Wiley and Sons: New York, 1983; p 219.

[10] E.J. Corey, A. Venkateswarlu *J. Am. Chem. Soc.* 1972, **94**, 6190.

[11] D.B. Bryan, R.F. Hall, K.G. Holden, W.F. Huffman, J.G. Gleason *J. Am. Chem. Soc.* 1977, **99**, 2353.

[12] S.N. Huckin, L. Weiler *J. Am. Chem. Soc.* 1974, **96**, 1082.

[13] For an intramolecular example of ketene trapping by a β-lactam N-H see R.W. Ratcliffe, T.N. Salzmann, B.G. Christensen *Tetrahedron Lett.* 1980, **21**, 31.

---

[14] O. Mitsunobu *Synthesis* 1981, 1.

[15] T.W. Doyle, B. Belleau, B.Y. Luh, T.T. Conway, M. Menard, J.L. Douglas, D.T. Chu, G. Lim, L.R. Morris, P. Rivest, M. Casey *Can. J. Chem* 1977, **55**, 484.

[16] H. Storflor, J. Skramstad, S. Nordenson *J. Chem. Soc. Chem. Commun.* 1984, 208.

[17] E.C Taylor, H.M.L. Davies *Tetrahedron Lett.* 1983, **24**, 5453.

[18] A.J. Anciaux, A. Demonceau, A.J. Hubert, A.F. Noels, N. Petiniot,Ph. Teyssié *J. Chem. Soc. Chem. Commun.* 1980 765.

[19] S.A. Johnson, H.R. Hunt, H.M. Neumann *Inorg. Chem.* 1963, **2**, 960.

[20] I.W.J. Still, F.J. Ablenas *J. Org. Chem.* 1983, **48**, 1617.

[21] D.R. Kronenthal, C.Y. Han, M.K. Taylor *J. Org. Chem.* 1982, **47**, 2765.

[22] This method of preparing the enol silyl ether was communicated to us by H. Masterlerz, Bristol Laboratories of Canada, Candiac, Quebec.

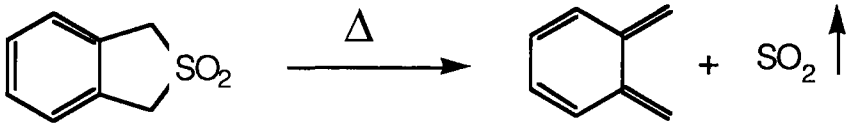
CHAPTER 3

Intramolecular Rhodium Carbenoid Insertions into Aromatic C-H Bonds[1]

Preparation of 1,3-Dihydrobenzo[c]thiophene-2,2-dioxides

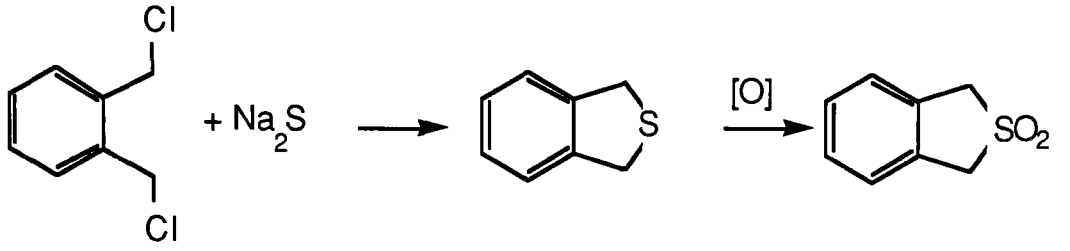
Description of the Project

1,3-Dihydrobenzo[c]thiophene-2,2-dioxides **1** are valuable precursors to transient *ortho*-quinodimethanes **2** which are important as the diene component in both inter and intramolecular Diels-Alder reactions.

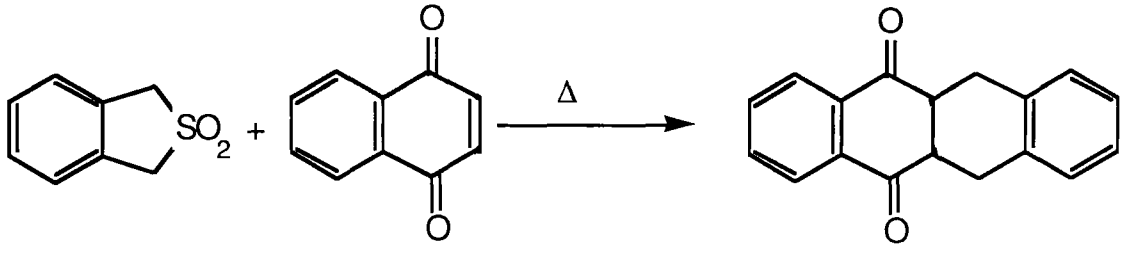


1 **2**

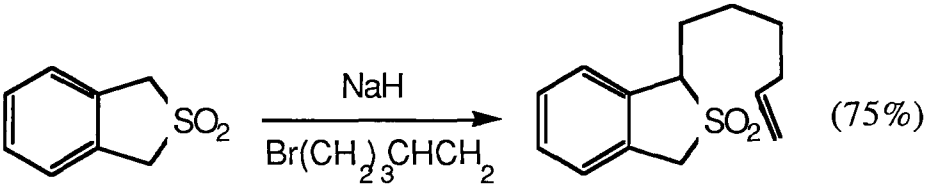
The use of these reactions for the efficient synthesis of polycyclic compounds is well documented,[2] the pioneering work in this area being performed by Cava in the 1950's.[3] Cava prepared the parent compound **1** in the series by reaction of 1,2-dihalomethyl benzenes with sodium sulfide to give the bicyclic sulfide which was then oxidized to **1**.



Cava proceeded to demonstrate the thermal extrusion of sulfur dioxide (cheletropic elimination) to generate an intermediate *ortho*-quinodimethane by trapping with 1,4-naphthoquinone.[4]

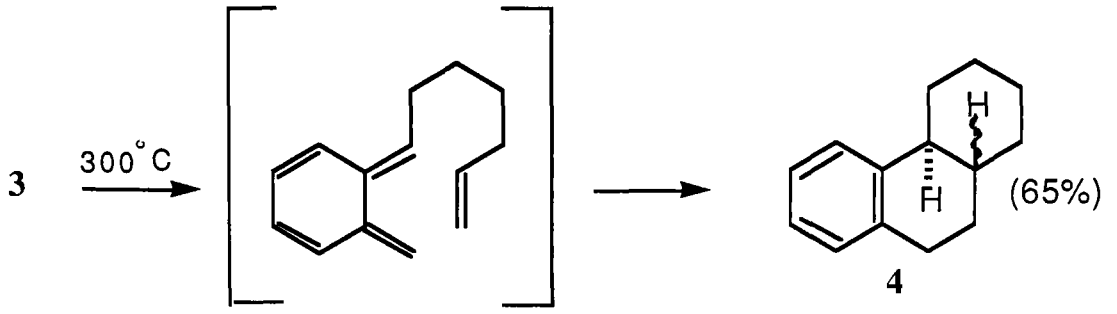


In 1980, Nicolaou[5] and Oppolzer[6] independently reported on the alkylation of **1** by the action of a strong base (KH, NaH, or L.D.A.) to form an α-sulfonyl anion followed by quenching with various electrophiles to give 1-substituted sulfones such as **3**.

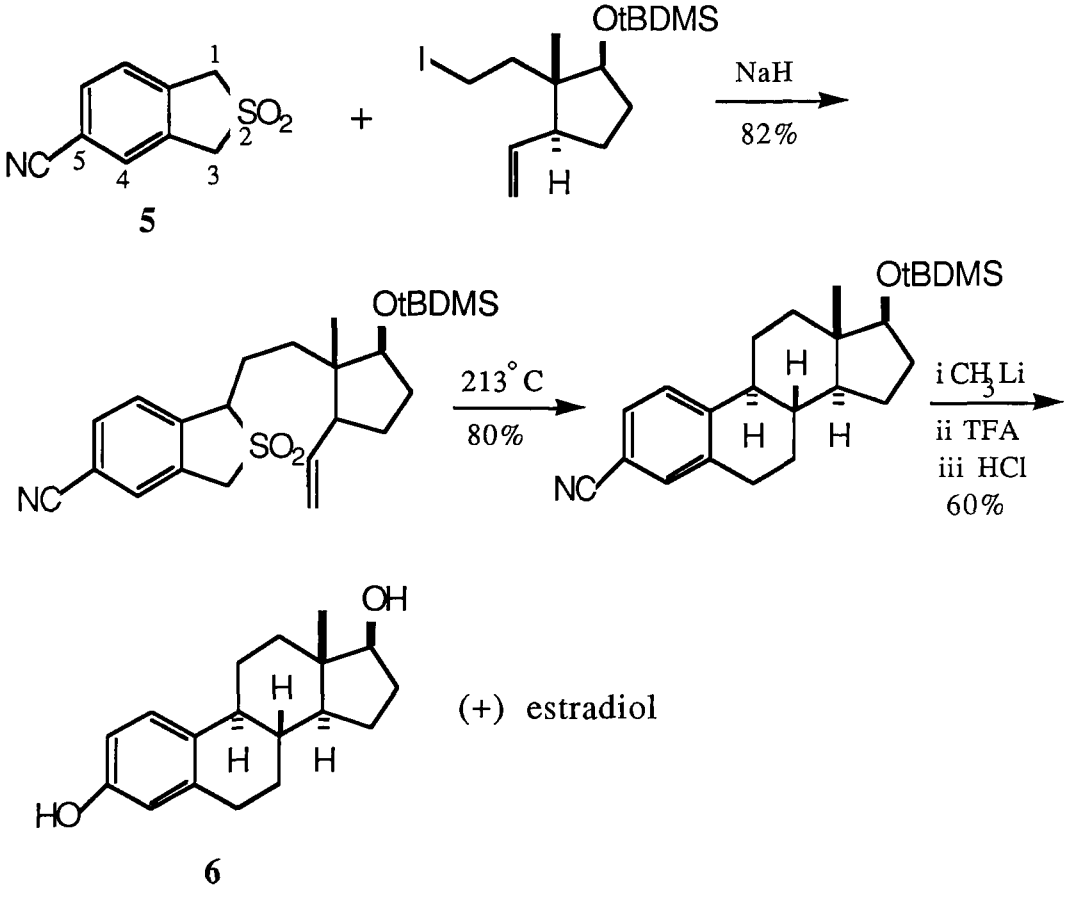


3

Thermolysis of **3** leads to the polycycle **4** via an intramolecular Diels-Alder reaction.

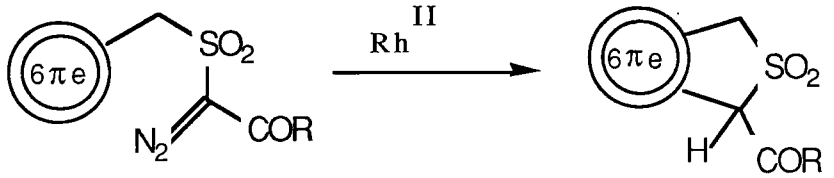


Using this approach, Oppolzer[7] synthesized (+)-estradiol **6** by the following route:



Crucial to this approach was the regiochemically controlled alkylation of the cyano sulfone **5** . The cyano group at C-5 acidifies the protons at C-1 more than C-3, thus controlling the site of deprotonation and alkylation.

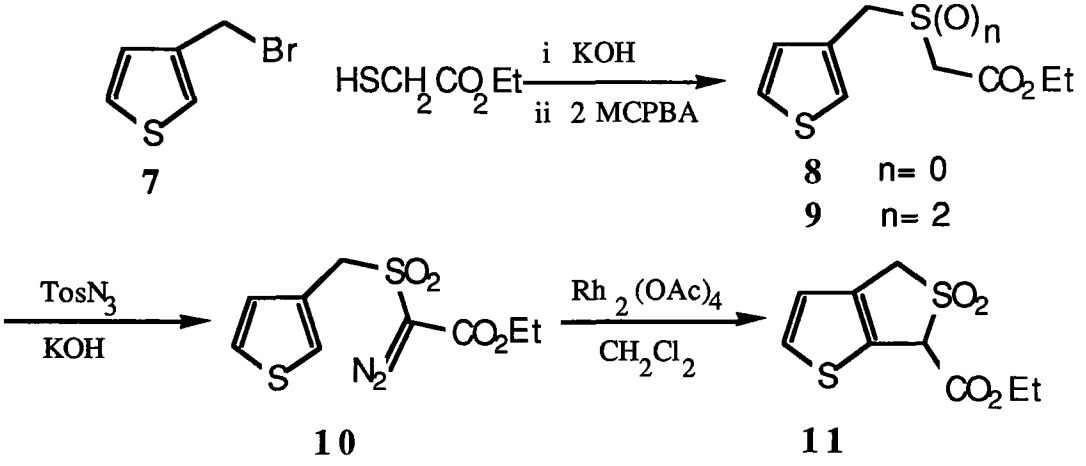
In forming a synthetic strategy for the preparation of 1,3-dihydrobenzo[c]thiophene-2,2-dioxides that require substitution "*meta*" rather than "*para*" (as in **5**) controlling the site of alkylation could be a problem. We envisioned a new synthesis of these sulfones, based on the following observations. During the preparation of an O-2-isocephem possessing a C-3 side chain (compound **33e**, Chapter 2, page 49) we isolated a product arising from the formal insertion of a rhodium carbenoid carbon into a heteroaromatic C-H bond(compound **43**, Chapter 2, page 53). Also known was the fact that β-sulfonyl esters undergo the diazo transfer reaction with tosyl azide to give α-diazo-β-sulfonyl esters (see Chapter 4, page 163). We reasoned that if the carbenoid insertion into aromatic C-H bonds was general, and if no interference from the neighboring sulfone occurred (Wolff rearrangement to a highly reactive sulfene) then we should be able to form the five-membered sulfur heterocyclic ring by a rhodium carbenoid insertion route.



Recall from Chapter 1 (page 11) that Taber has postulated that rhodium carbenoids insert into aliphatic C-H bonds via a six-membered ring transition state, hence formation of a five membered ring should be a favorable process here as well.

Results and Discussion

To test our hypothesis, we looked at a system analogous to the previously mentioned thiophene insertion. We reacted 3-bromomethyl thiophene **7** with ethyl thioglycolate in the presence of potassium hydroxide to give the sulfide **8**. This was oxidized to the sulfone **9** by treatment with 2 eq of *meta*-chloroperoxybenzoic acid in CH_2Cl_2. The sulfone was subjected to diazo transfer with tosyl azide, furnishing the diazo ester **10** in 37% yield.

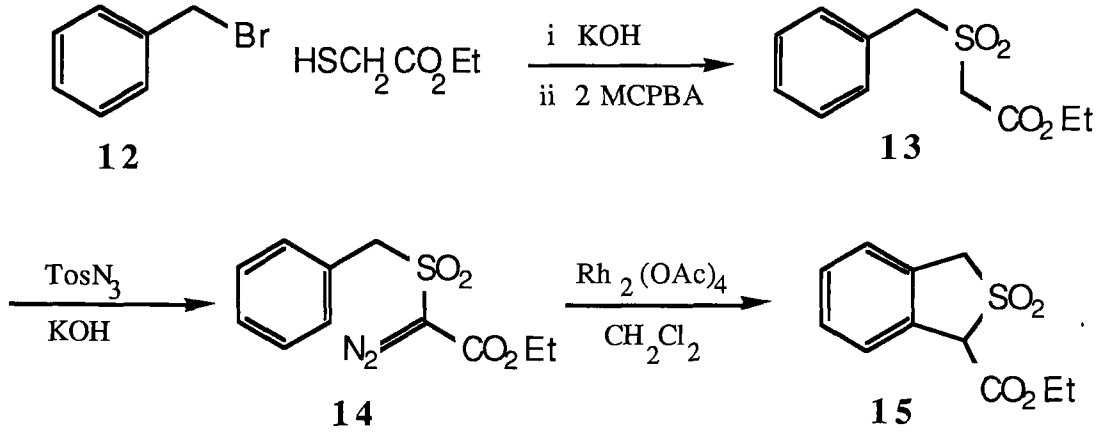


7 **8** n= 0 **9** n= 2 **10** **11**

The diazo ester **10** was stirred in CH_2Cl_2 (≈ 0.2 M) at room temperature in the presence of 5 mole% of rhodium(II) acetate for 18h. Filtration and evaporation of the solvent gave a yellow oil. This oil was chromatographed on silica gel to give a 49% yield of insertion product **11** as light brown crystals, mp 83-84 °C from hexane-EtOAc. This confirmed our expectations that the α-sulfonyl carbenoid would insert into the C(2)-H bond of thiophene analogous to the α-keto carbenoid.

Next we focused our attention on preparing the 1,3-dihydro-benzo[c]thiophene-2,2-dioxide system by this approach. Benzyl bromide **12** was treated in the same manner as 3-bromomethyl

thiophene to give the sulfone **13** as an off-white powder, mp 48-49 °C. Diazo transfer was accomplished in 40% yield using potassium hydroxide/tosyl azide in methanol to give **14** as a yellow oil.



12 **13** **14** **15**

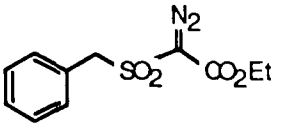
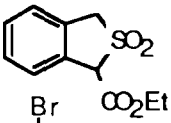
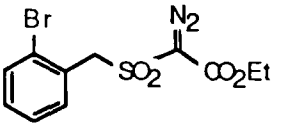
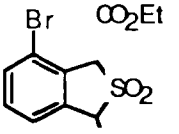
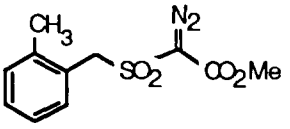
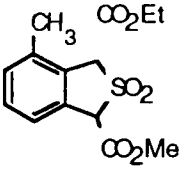
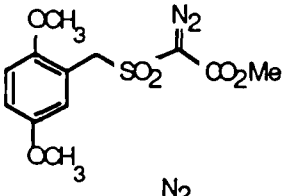
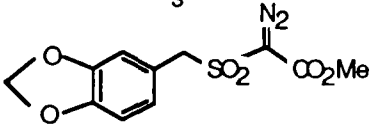
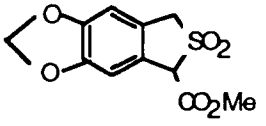
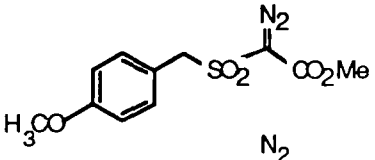
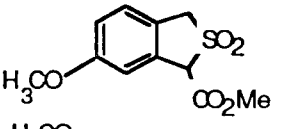
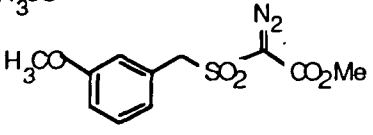
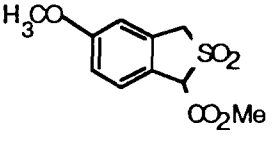
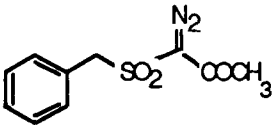
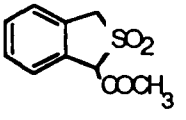
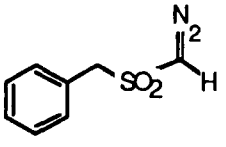
When the diazo sulfone **14** was stirred in CH_2Cl_2 in the presence of 5 mole% of rhodium(II) acetate for 2h followed by filtration, evaporation and chromatography on silica gel, a 46% yield of bicyclic sulfone **15** was isolated as a clear colourless oil. The product was identified by its ^1H nmr spectrum that displayed resonances at δ= 1.30 (t, CH_3), 4.27 (q, CH_2), 4.43 (dd, CH_2SO_2), 5.0 (s, O_2SCHCO_2), 7.33 (s, aromatics); its infrared spectrum featured bands at 1740 and 1335 cm^{-1}, and its ei-ms that showed ions at m/z 240 (M^+), 176 (M^+-SO_2), and a base peak of 148 (M^+-C_2H_4, -SO_2).

A series of diazo sulfones were prepared in order to test the scope and limitations of this method. All sulfones were prepared from readily available benzylic alcohols and $HSCH_2CO_2R/ZnI_2$ or benzylic halides and $HSCH_2CO_2R$/base followed by oxidation with *meta*-chloroperoxybenzoic acid or hydrogen peroxide / acetic acid and subsequent diazo transfer with tosyl azide/base. All intermediates and products in these series were characterized by

their nmr and infrared data (Tables 2, 3 and 4 of the Experimental section). In particular the final diazo sulfones all showed the expected diazo absorption at ≈2120 cm^{-1}.

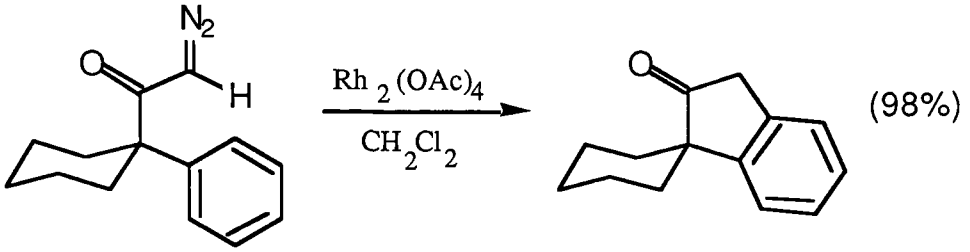
The results of the reaction of these diazo sulfones with catalytic amounts of rhodium(II) acetate are summarized in Table1. All of the products were fully characterized by ^1H nmr, infrared and high resolution mass spectral analysis. Most of these sulfones displayed a significant molecular ion in their ei-ms. The molecular ion is normally not observed with dihydro-benzo[c]thiophene-2,2-dioxides unless an electron withdrawing group is present at the 1 position. In other cases an M^+-64 (due to facile loss of SO_2) ion is the highest mass observed. This suggests that the 1-carboalkoxy-dihydrobenzo[c]thiophene-2,2-dioxides would require a higher temperature for the cheletropic elimination of SO_2 than the 1-methoxy analog.[8]

TABLE 1

ENTRY	DIAZOSULFONE	PRODUCT	YIELD [a]	NMR [b] CH	NMR [b] CH_2
1			46	5.00	4.43
2			48	5.10	4.43
3			14	5.16	4.42
4		——	——	——	——
5			47	4.90	4.26
6			45	4.96	4.33
7			42	4.90	4.30
8			56 [c]	5.25	4.44
9		——	——	——	——

a) isolated yields, following column chromatography
b) PPM from TMS in $CDCl_3$,60 MHz
c) using $Rh_2(OCOCF_3)_4$ as catalyst

Inspecting Table 1 we note the following. Entries 2 and 3 possessing *ortho* substituents still gave aromatic insertion products; no other insertion products were isolated from the generally complex mixtures. Insertion into the benzylic C-H bond of the *ortho*-methyl group might have been a reasonable expectation. Such an insertion would require a seven-membered ring transition state.[9] This process is not competitive with the aryl C-H insertion generating a five-membered ring (six-membered ring transition state). Following publication of our results Nakatani[10] has reported that the α-diazoketone **16** gave the aromatic C-H insertion product 2-indanone **17** in preference to an aliphatic C-H insertion.

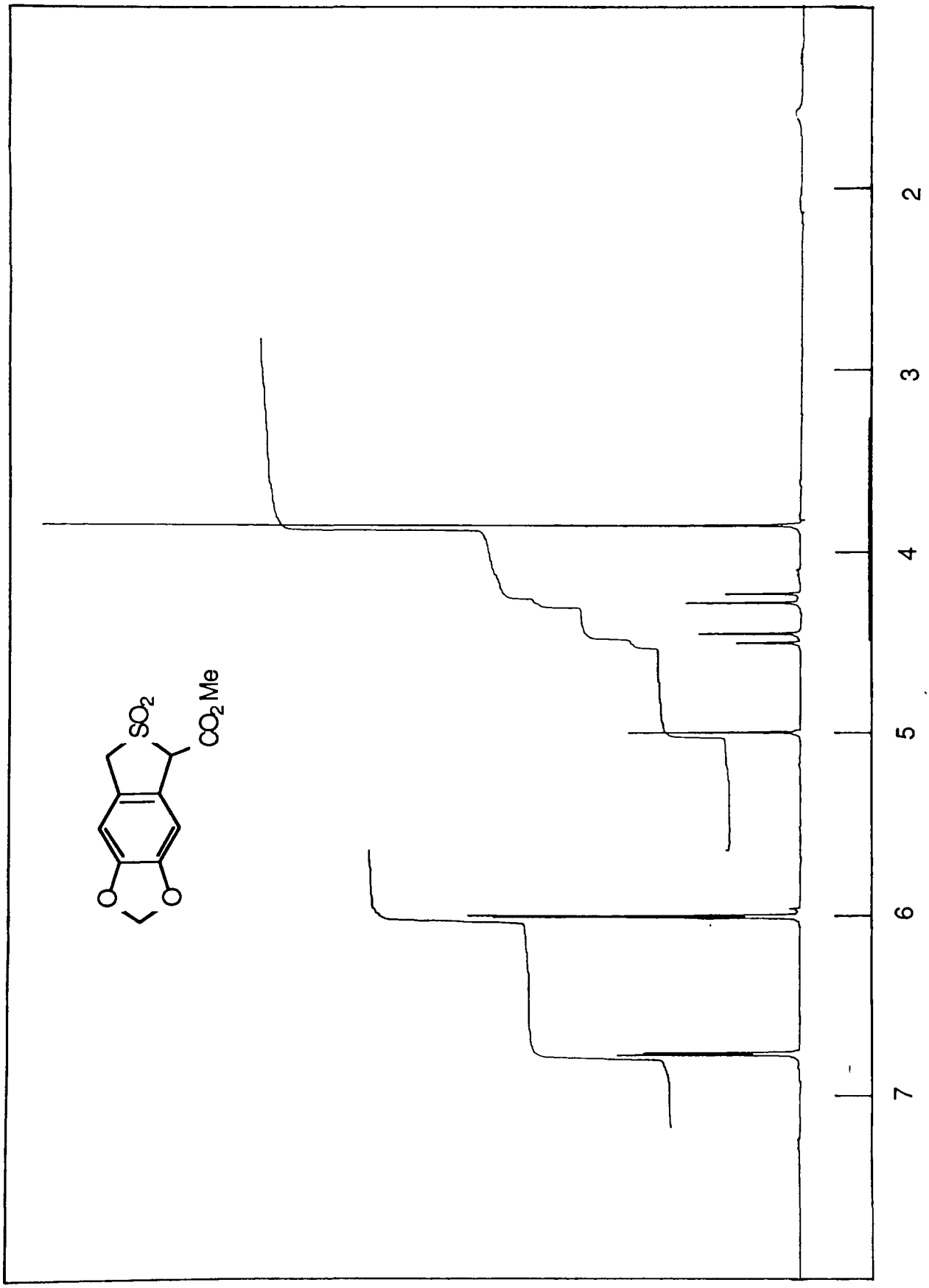


16 **17**

No insertion product was isolated from the *ortho*-methoxy substituted sulfone (entry 4), possibly due to oxygen ylide formation followed by decomposition.[11] Thin layer chromatography of the crude product indicated a complicated mixture from which no pure substance could be isolated.

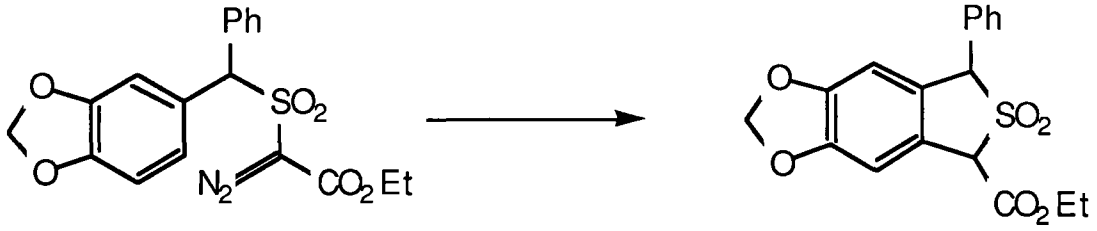
The reaction has a propensity to give products arising from insertion into the C-H bond *para* to existing alkoxy substitution (entries 5,7) and no isomeric by-products were recovered. The yields in these reactions (entries 5,7) were not significantly higher than in the case of entry 6 where insertion occurs *meta* to an alkoxy

NMR SPECTRUM OF THE PRODUCT OF ENTRY 5



group. If the insertion were an electrophilic phenomenon one would expect that the favorable attack in the *para* example would be reflected in better yields.

The diazo ketone (entry 8, prepared from benzyl mercaptan and chloroacetone followed by diazo transfer) gave only an intractable tar with rhodium(II) acetate, however when rhodium(II) trifluoroacetate (prepared by boiling the acetate in TFA followed by evaporation) was used as the catalyst a 56% yield of bicyclic sulfone resulted. The beneficial effect of the trifluoroacetate ligand may be due to the increased reactivity of the carbenoid when the rhodium bears a more electron withdrawing ligand. This was later confirmed in our laboratories by S. Babu who noted a marked increase in the yield of insertion product recovered in the reaction of **18** to give **19** when rhodium(II) trifluoroacetate was used in place of rhodium(II) acetate (52%vs.72%). It is reasonable to assume that similar increases in the yield of the insertion products listed in Table 1 would be observed if rhodium(II) trifluoroacetate was substituted for rhodium(II) acetate.

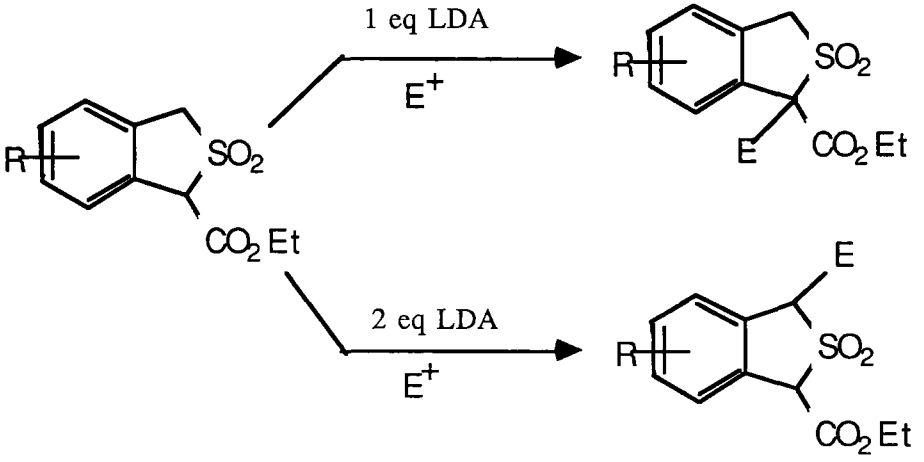


18 **19**

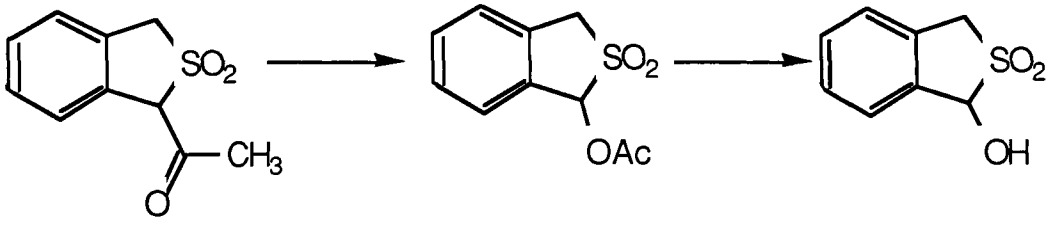
The sulfonyl diazomethane depicted in entry 9 (prepared by acyl cleavage of the diazo ketone) gave a complex mixture of products on exposure to rhodium(II) acetate; none were identified.

The use of rhodium(II) trifluoroacetate might also be beneficial for this substrate.

The products obtained by this route should be useful for a wide variety of transformations. The presence of the carboalkoxy or acyl group on the sulfone bearing ring brings an element of control to alkylation reactions. It should be possible to alkylate regiospecifically at the methine or methylene carbon via a mono or dianion intermediate. Such control has been demonstrated in our laboratories by S. Babu utilizing the thiophene sulfone **11**.

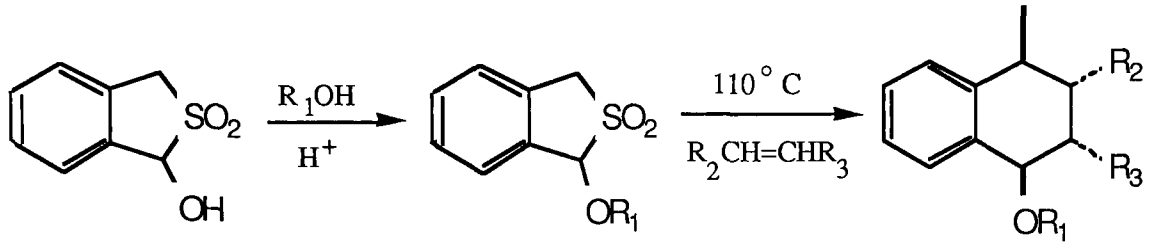


In the case of the product of entry 9, one may perform a Baeyer-Villiger oxidation, followed by saponification of the resulting ester to arrive at 1-hydroxybenzo[c]thiophene-2,2-dioxides.



These compounds have been used by Charlton and Durst[12] to prepare 1-carboalkoxy substituted *ortho*-quinodimethanes via facile exchange with alcohols followed by cheletropic elimination of SO_2.

The intermediate diene has been trapped by dienophiles to give tetrahydronaphthalenes, which have considerable potential in the synthesis of lignans.

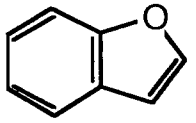


In conclusion, the rhodium carbenoid insertion route presents an easy access to 1,3-dihydrobenzo[c]thiophene-2,2-dioxides specifically substituted in both rings from readily available starting materials. It is conceptually different from the previously known methods of constructing this ring system and should find use in the synthesis of complex polycyclic molecules.

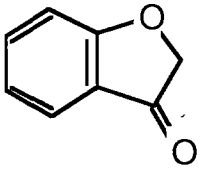
Preparation of 3-Acetylbenzofuranones and 3-Acetylnaphthofuranones

Introduction

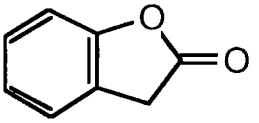
Oxidation of the furan ring of benzofuran **20** can lead to the two isomeric benzofuranones **21** and **22**.



20



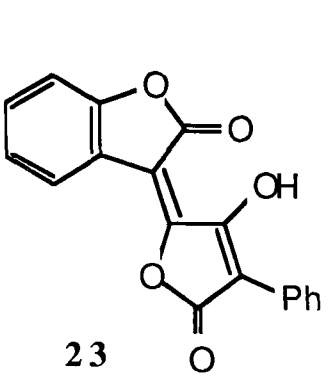
21



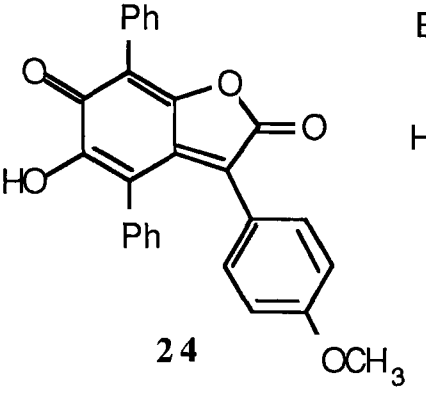
22

The parent member of the series **22** is the lactone of *ortho*-hydroxyphenylacetic acid, and is also known as α-coumaranone, coumaran-2-one and isocoumaranone. These compounds have been prepared by thermal[13] or acid catalyzed[14] cyclization of substituted *ortho*-hydroxyphenylacetic acids. There have also been a number of novel routes to 2(3H)-benzofuranones; these preparations as well as their miscellaneous reactions have been reviewed by Mustafa.[15] In contrast to the benzofuran **20** and the 3(2H)-benzofuranones **21**, the 2(3H)-benzofuranone ring system **22** is a type of benzfused heterocycle that is rarely found in nature.

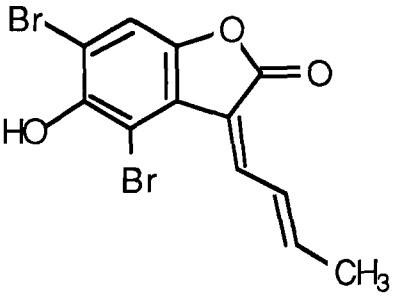
Three noteworthy examples of natural products containing this ring system are calycin **23**,[16] a pigment isolated from the lichen *Sticta xantholeucum* ; xylerythrin **24**,[17] a pigment found in decaying wood that has been attacked by the fungus *Corticuim sanguinaum* Fr.; and **25**[18] a bromophenolic metabolite that was very recently isolated from the sponge *Aplysina aerophoba*.



23

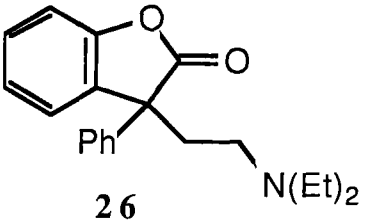


24



25

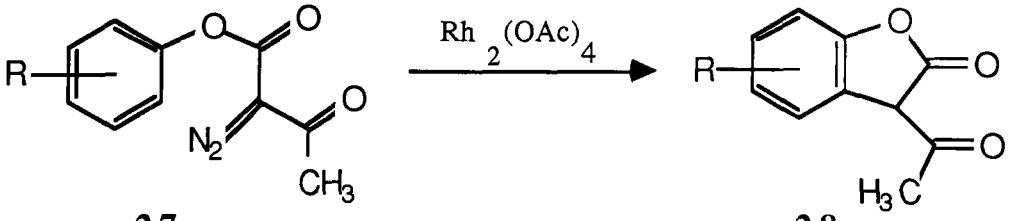
A series of 3-alkyl(aminoalkyl) substituted 2(3H)-benzofuranones[19] have been prepared and investigated for their antispasmodic properties, the most promising of these being Amethone **26**.



26

Results and Discussion

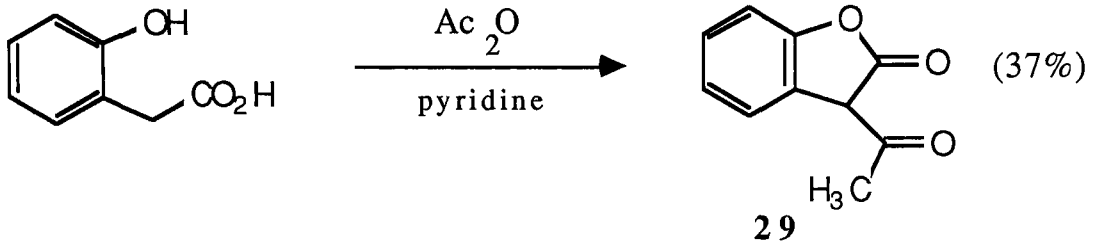
Based on the results described in the previous section it was expected that the rhodium(II) acetate catalyzed decomposition of the α-diazo-β-keto phenyl esters **27** should give 3-acetyl-2(3H)-benzofuranones **28**.



27 **28**

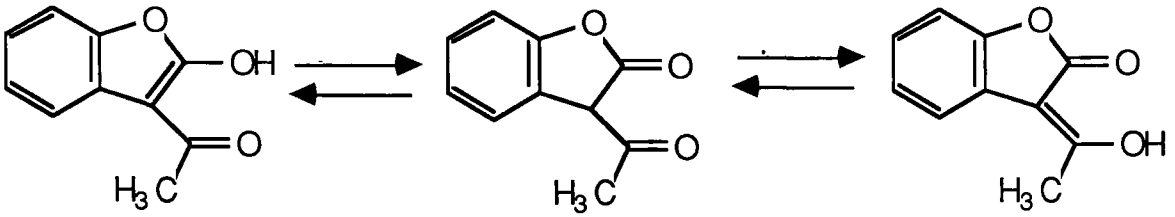
The parent 3-acetyl lactone **29** had been previously prepared by Geissman[20] in 37% yield by heating *ortho*-hydroxyphenylacetic

acid in pyridine containing acetic anhydride. This compound was of considerable



29

interest, because of its existence as a keto **29** or two possible enolic forms **30**, **31**.

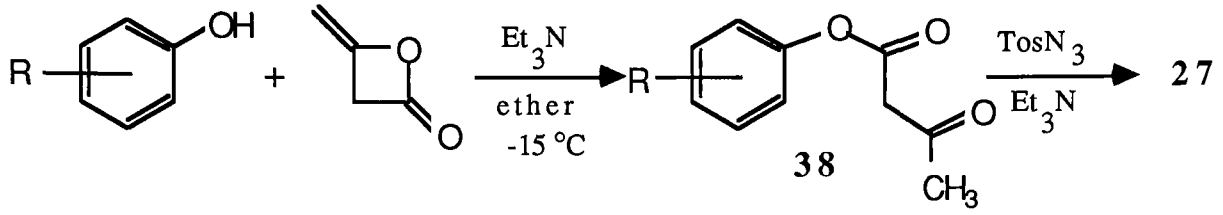


30 **29** **31**

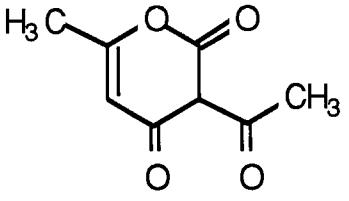
It was generally accepted that **29** was responsible for its ketonic behavior[21] (formation of an oxime and a 2,4-dinitrophenylhydrazone), while **31** was responsible for the enolic behavior (blue colored Fe^{+3} chelate, enol ether and acetate formation).[17] Elix[22] suggested that "**29**" existed as a mixture of the enols **30** and **31** based on the observation that reaction of **29** with ethereal diazomethane gave essentially a 1:1 mixture of the enol methyl ethers formally derived from **30** and **31** respectively (overall 86% yield of enol methyl ethers).

We prepared the known **29** by the rhodium carbenoid route. The required α-diazo-β-ketoester **27a** (R=H) was obtained from the reaction of phenol with diketene, followed by diazo transfer. The

addition of phenols to diketene[23] is usually carried out at 70-80 °C in the presence of base,



however under these conditions we noted that large amounts of dehydroacetic acid (DHA) **32** were being formed. We therefore modified our



32

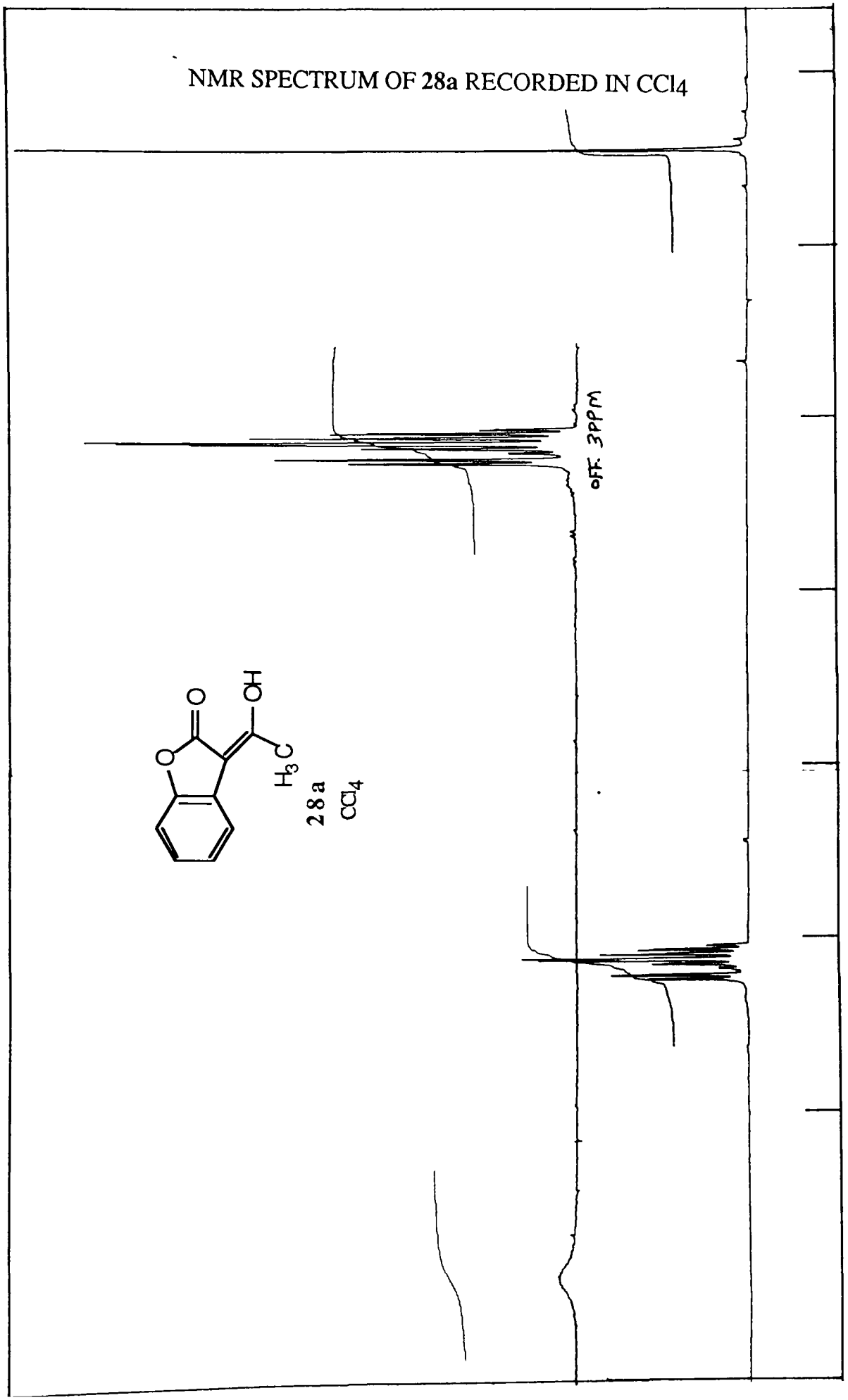
procedure to minimize this side reaction and found that we could suppress the formation of DHA by performing the reaction in ether at -15 °C with a catalytic amount of triethylamine. A number of substituted aryl acetoacetates **38** were prepared in this manner in high yield. It was generally possible to perform the addition of the various phenols to diketene

and carry out the diazo transfer without extensive purification of the intermediate aryl ester (other than a simple acid base extraction of unwanted by-products and reagents that remained). The α-diazo-β-keto arylesters were characterized by nmr and ci-ms analysis and all showed an absorption of ≈2120 cm^{-1} in the infrared confirming the presence of the diazo function (see Table 6 in the Experimental section).

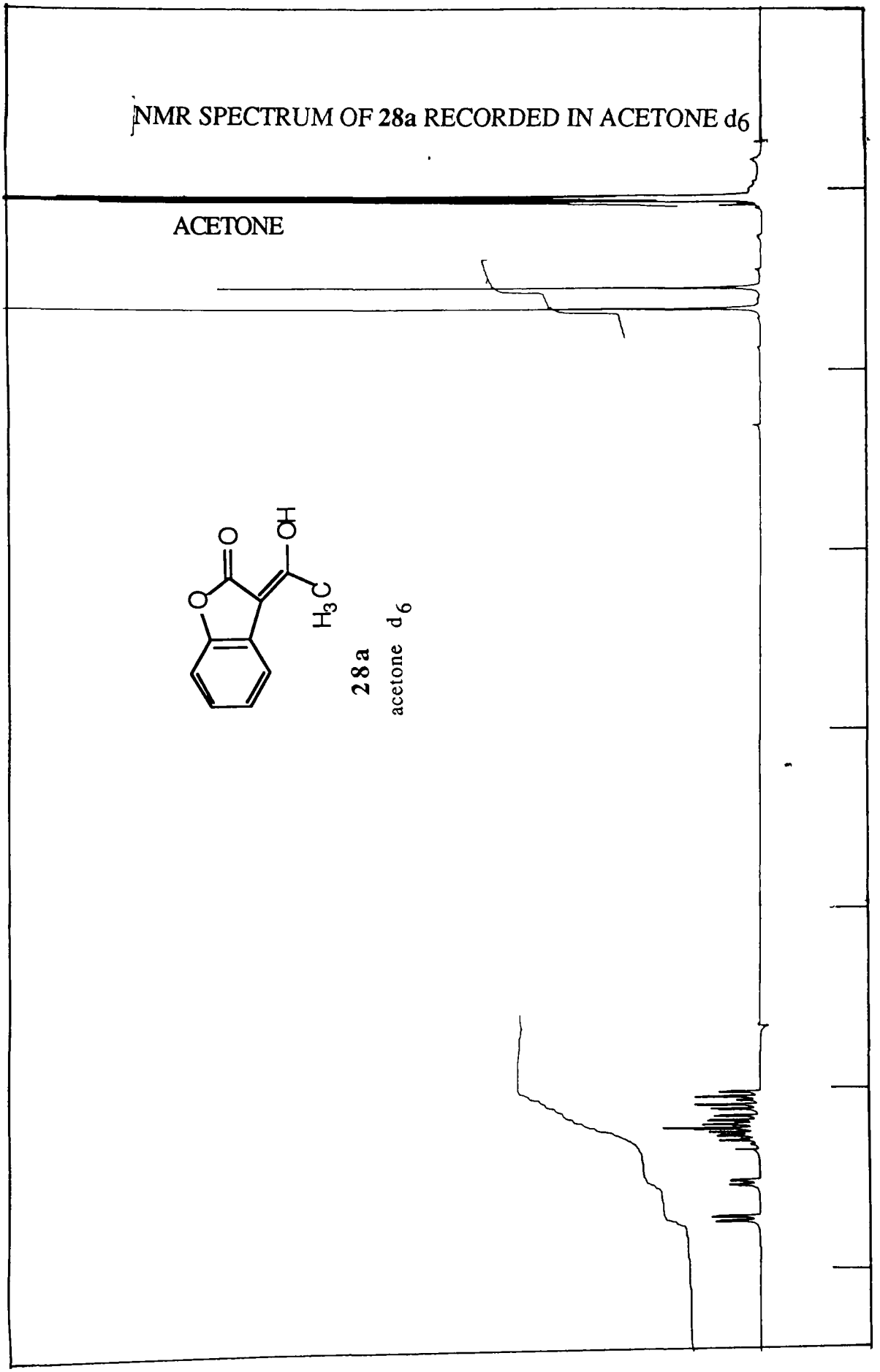
The α-diazo-β-ketoester **27a** (R=H) was dissolved in dry CH_2Cl_2 and 5 mole% of rhodium(II) acetate was added in one portion. The diazoester solution began to evolve N_2 vigorously and much of the catalyst dissolved, resulting in a greenish colored solution. The progress of the reaction was monitored by t.l.c. (silica gel, hexane-EtOAc 7:3) which revealed that after 1h the less polar diazoester (R_f= 0.38) was completely and cleanly replaced by a much more polar compound (R_f= 0.10). The solution was filtered through a cotton plug and evaporated to give a 98% yield of 3-acetyl-2(3H)-benzofuranone **28a** (R=H) as a pale green powder. Attempted chromatographic separation of this material gave a 90% yield of dark blue colored crystals whose nmr, ir and ms were identical to the crude material. The nature of the blue coloration was never determined, although Chatterjea[18] has reported that this compound turns blue on treatment with acid or Fe^{+3}. An analytical sample was recrystallized from the crude using ether-hexane to give a white powder identical in all respects (mp, ir, nmr, ms) to an authentic sample prepared according to Geissman (from *ortho*-hydroxyphenylacetic acid and Ac_2O/ pyridine). When $Pd(OAc)_2$ or $Cu(Tf)_2$ were substituted for $Rh_2(OAc)_4$, no products were detected by t.l.c. after 3h, only the starting diazoester was evident.

The spectral data for **28a** (R=H) have not been reported. The 300 MHz ^1H nmr spectrum was recorded in CCl_4 and showed the following resonances; δ= 2.23 (s,$COCH_3$), 7.04-7.20(m, 3H, aromatics), 7.24 (d, J= 8.3 Hz, C-4), 11.96 (br. s.,enolic H). When the spectrum was recorded in acetone-d_6, all of the signals were doubled in a

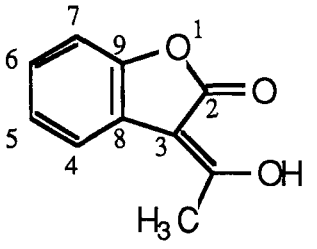
NMR SPECTRUM OF 28a RECORDED IN CCl_4



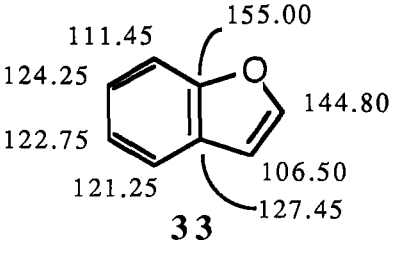
NMR SPECTRUM OF **28a** RECORDED IN ACETONE d_6



28a
acetone d_6

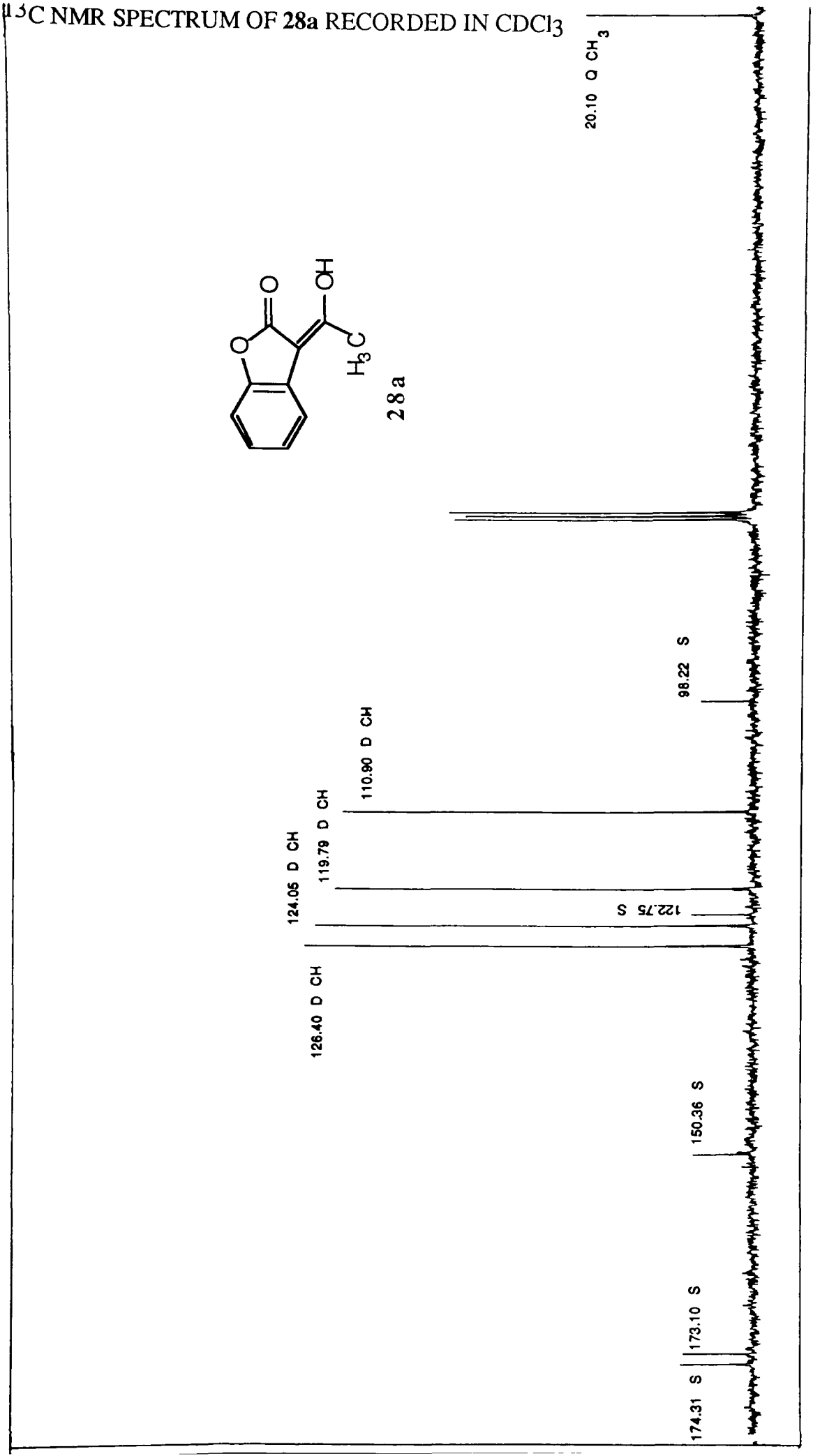


2:1 ratio, suggestive of the presence of a keto and enol or more likely two enolic forms since the C3(H) proton was never observed in this solvent. The ^{13}C nmr spectrum, recorded in $CDCl_3$, confirmed the existence of **28a** (R=H) as an enol in non polar solvents, with five quaternary carbon resonances being present δ= 174.31 (C-2), 173.08 (C-10), 150.36 (C-9), 122.75 (C-8) and 98.22 (C-3). These assignments were made by comparison with the data reported for benzofuran, **33**.[24]



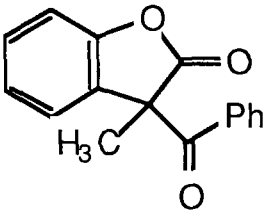
33

^{13}C NMR SPECTRUM OF **28a** RECORDED IN $CDCl_3$

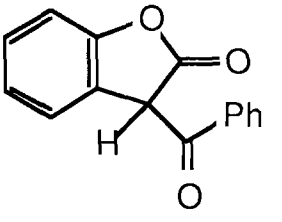


28a

The infrared spectrum of **28a** (R=H), recorded in $CHCl_3$, displayed bands at 3020, 1725, 1710 and 1637 cm^{-1}. Typically, one expects the C=O absorption at 1800-1810 cm^{-1} of benzofuranones as found in the parent **22** or 3,3-disubstituted (non-enolizable) benzofuranones such as **34**,[25] (1810 cm^{-1}). Enolizable compounds such as **35**[26] show a much lower frequency band, 1686 cm^{-1}.



34



35

The ei-ms of **28a** (R=H) gave a molecular ion at m/z 176 that was also the base peak. Other significant ions were observed at 134 (M^+-42, 60.7%, loss of ketene), 106 (M^+-42-28, 40.7%, loss CO), 43 (96.3%, $COCH_3^+$). The accurate mass-ms found 176.0492 compared to a calculated value of 176.0473 mass units.

The series of α-diazo-β-ketoesters **27b-d** were decomposed with rhodium(II) acetate in the same manner as **27a**; all gave similar results that are tabulated below.

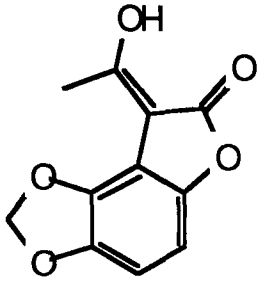
TABLE 2

DIAZOESTER **27**	PRODUCT **28**	YIELD	mp(°C)
27a R= H	**28a** R= H	98	133-134
b 2-Me	**b** 7-Me	98	112-113
c 2-Br	**c** 7-Br	92	164-166
d 3,4-OCH_2O-	**d** 5,6-OCH_2O-	91	211-212
e 3-Me	**e** 6-Me	93	133-135
f 3-OMe	**f** 6-OMe	95	142-144

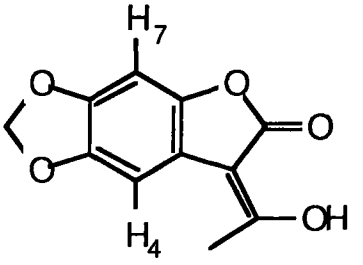
It is interesting to note that the reaction of the *ortho*-substituted derivatives **27b** and **27c** gave only aromatic insertion and no evidence of any C-Br or benzylic C-H insertion products. Analogous results were obtained with the corresponding α-diazo-β-carboalkoxysulfones (page 97).

In the case of **27d** (*para* substituted) the linear product **28d** was obtained rather than the angular product **28d'**. This product, **28d**, was identified by its 300 MHz ^1H nmr spectrum, recorded in

acetone d_6, that showed the presence of H-4 as singlets at δ= 7.21 and 7.05 and H-7 as singlets at δ= 6.88 and 6.71.



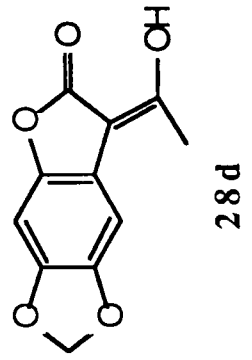
28d



28d

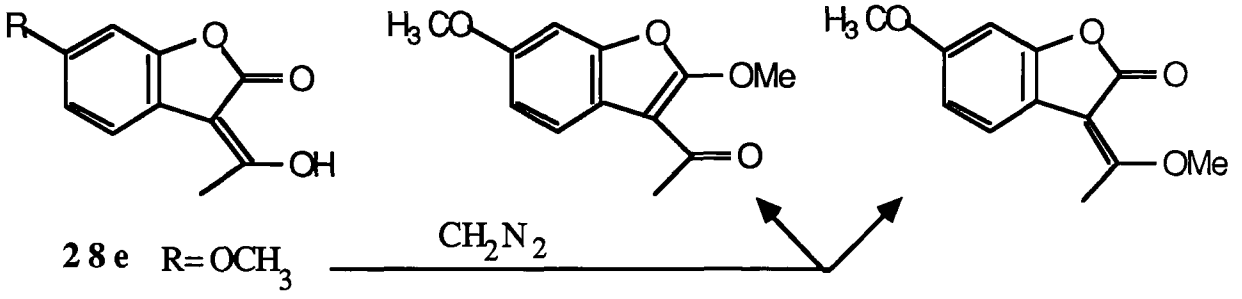
The assignment of these resonances as singlets due to a set of enols was corroborated by the addition of triethylamine that caused both sets of singlets to collapse to single resonances, H-4 at δ= 7.38 and H-7 at δ= 6.49 respectively. Recall that **28a** (R=H) also existed as a mixture of enols in acetone d_6. The spectrum of **28d** could not be recorded in CCl_4 due to solubility problems.

NMR SPECTRUM OF **28d**



28d

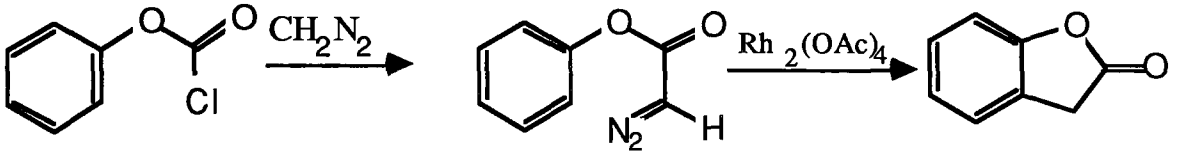
Diazoesters **27e** and **f** both gave exclusively the *para* substituted isomer **28e** [^{1}H nmr aromatic region in CCl_4- δ= 7.19 (d, H-4, J=8.2Hz), 6.99 (s, H-7), 6.97 (d, H-5, J=8.2Hz)] and **28f**. The latter product was identified as its methyl enol ethers, obtained by reacting a sample of **28f** with ethereal diazomethane. The reaction gave a major and a minor enol methyl ether [^{1}H nmr aromatic region in CCl_4- major enol δ= 7.93 (d, H-4, J=8.6Hz), 6.46 (d, H-5, J=8.6Hz), 6.51 (s, H-7)].



28e R=OCH_3

28f R=CH_3

The parent benzofuranone **22** (non-acylated) was obtained by the following route;

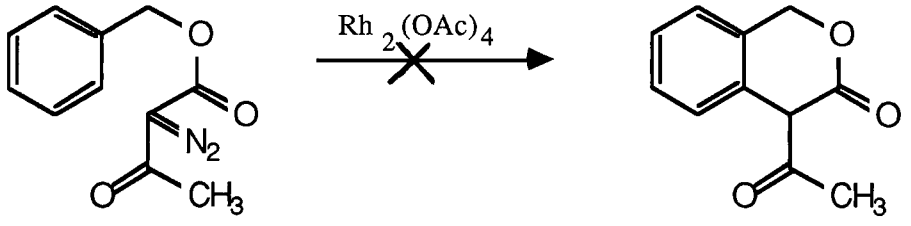


36 **37** **22**

Phenyl chloroformate **36** was dissolved in a large excess of ethereal diazomethane at 0 °C, and was allowed to stand for 48h at 0 °C. The resulting solution was evaporated and chromatographed to give pure **37** as a yellow oil in 81% yield. When **37** was dissolved in CH_2Cl_2 and 5 mole% of rhodium(II) acetate was added an extremely

vigorous efflux of N_2 was noted, and after stirring for 1h followed by filtration and evaporation, an orange solid was recovered that contained mainly diphenyl fumarate by nmr and ei-ms. The experiment was repeated, by adding a 0.1M solution of the diazo ester **37** in CH_2Cl_2 to a stirred suspension of the catalyst (0.5 mole%) in CH_2Cl_2 over a period of 30 min. After 1h the solution was worked up as above. Nmr and gc-ms analysis revealed that the mixture consisted mostly of the desired benzofuranone **22** [nmr δ= 3.7(s, $ArCH_2CO$), and gc-ei-ms (m/z 134 (M^+, 86.2%), 106 (M^+-CO, 49.1%) and 78 (M^+-CO-CO, 100%)] by comparison with literature data.[27] We were unable to obtain **22** in a pure form.

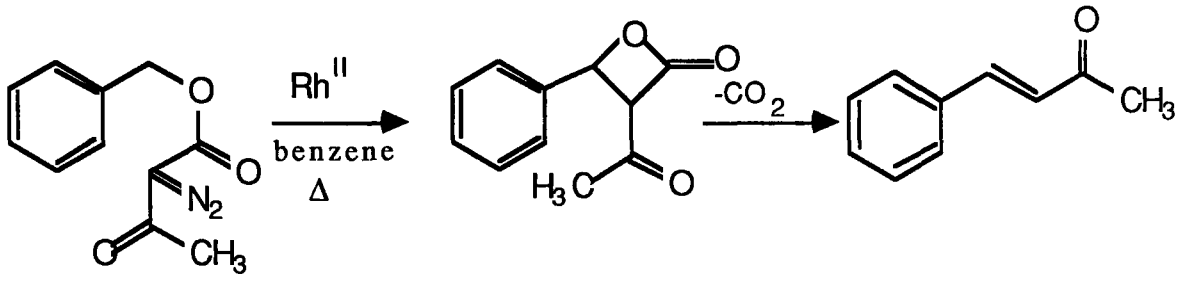
In an effort to prepare six-membered ring benzfused heterocycles, compound **39** was prepared from benzyl alcohol and diketene followed by diazo transfer. Its structure follows from the method of synthesis and spectroscopic properties (infrared 2120 cm^{-1}, nmr δ= 2.3 (s, 3H), 5.2 (s, 2H)). Reaction of **39** with rhodium(II) acetate or trifluoroacetate failed to



39

give any identifiable compounds, even under high dilution conditions. When **39** was refluxed in benzene with rhodium(II) acetate, a small amount (≈13%) of benzalacetone was recovered. This

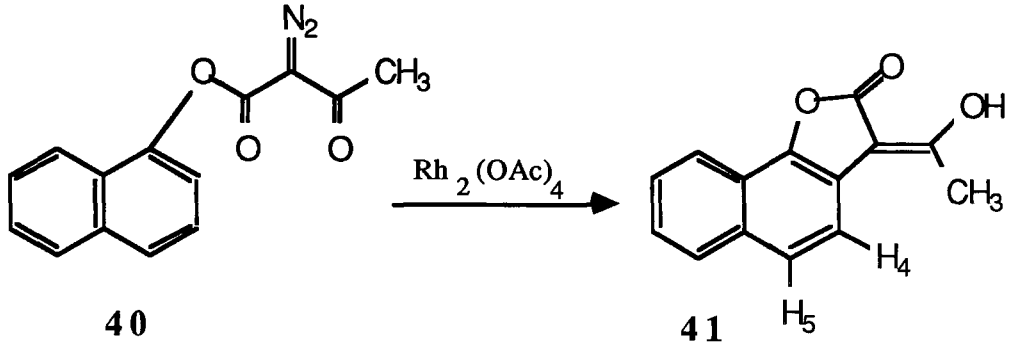
product most likely arises from insertion of the carbenoid into the benzylic C-H bond followed by thermal extrusion of CO_2.



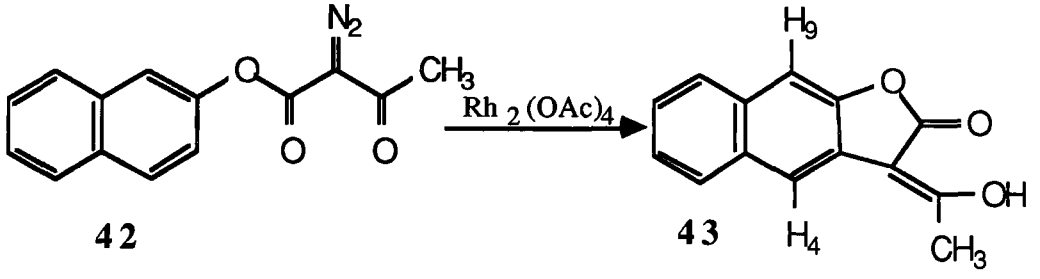
39

Southgate[28] has observed the formation of a four membered ring via rhodium carbenoid insertion in the preparation of β-lactams.

The α-diazo-β-keto naphthyl esters **40** and **42**, prepared by reaction of diketene with α and β-naphthol respectively, were reacted with rhodium(II) acetate as above.



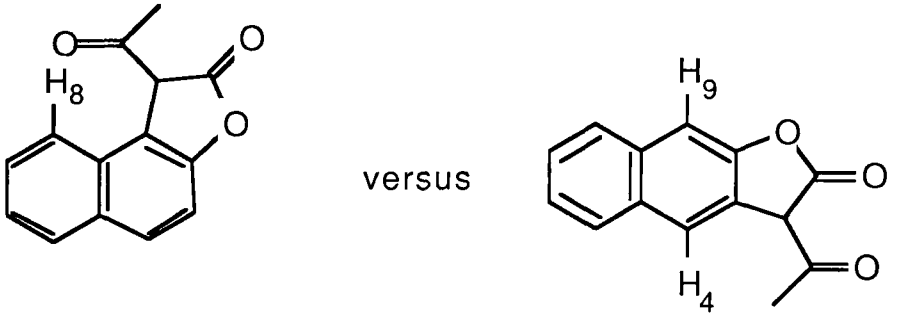
40 **41**



42 **43**

They were cleanly converted into their respective insertion products **41** and **43**. The α-naphthylester **40** gave the β-insertion product **41** rather than the peri-product, and most surprisingly the β-

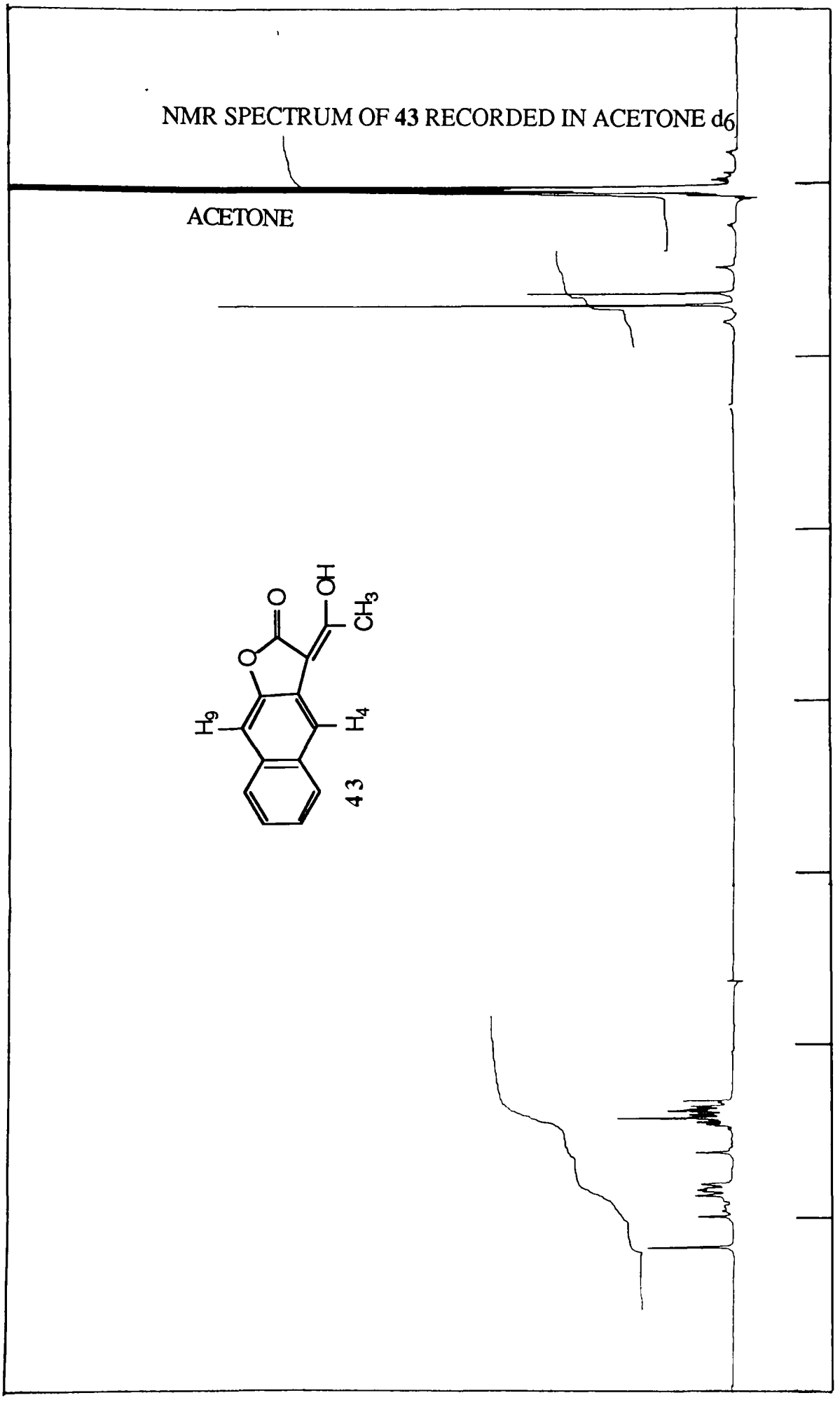
naphthylester gave the linear, rather than the angular product. The isolation of only **43** from **41** has important mechanistic implications since β-naphthols have a marked propensity for electrophilic aromatic substitution at the α position. Compound **41** was easily identified as 3-acetyl-2(3H)-naphtho[1,2-b]furanone by its ^1H 300 MHz nmr spectrum, recorded in CCl_4, that clearly displayed H-5 and H-4 as doublets (J= 8.3 Hz) at δ= 7.77 and 8.06 respectively. The insertion product **43,** 3-acetyl-2(3H)-naphtho[2,3-b]furanone, was not as easily identified due to its lack of solubility in non polar solvents. When the ^1H nmr spectrum was recorded in acetone d_6, the usual complication due to the presence of enols was obtained. However the aromatic region did not display any obviously *ortho*-coupled doublets (as would be expected for any α-insertion product);



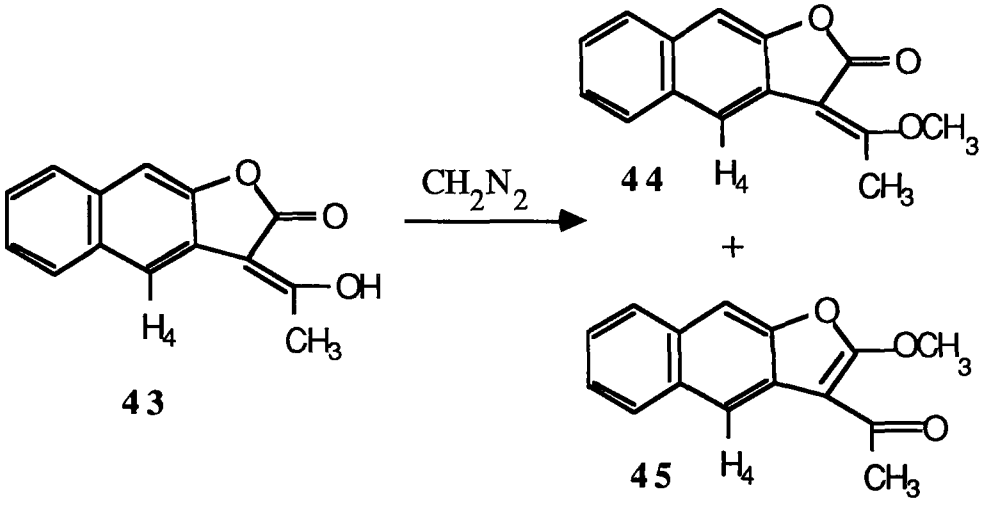
α insertion γ insertion

H-9 and H-4 could be visible as singlets at δ= 7,46, 7.66 and 8.03, 8.21 respectively. The α-insertion product has been previously reported[29] to have a melting point of 207-209 °C (light grey plates from HOAc). Our product melted at 214-216 °C (white needles from methanol).

NMR SPECTRUM OF 43 RECORDED IN ACETONE d6



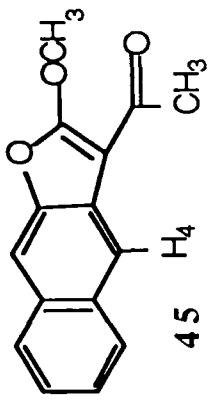
Final structure proof was obtained when **43** was reacted with an excess of ethereal diazomethane to give a mixture of the enol methyl ethers **44** and **45** in a ratio of 7:3 by nmr.



The ^{1}H 300 MHz nmr spectrum of the **44/45** mixture showed H-4 as a singlet at δ= 7.88 (**45**) and at δ= 8.54 (**44**), due to deshielding by the acetyl carbonyl. For the α-insertion product one would have expected a doublet for H-8 of J≈ 8 Hz, at a lower field than the other aromatic resonances; this is not the case.

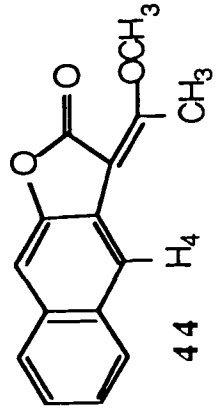
NMR SPECTRUM OF ENOL METHYL ETHERS **44** and **45**

RECORDED IN CCl_4

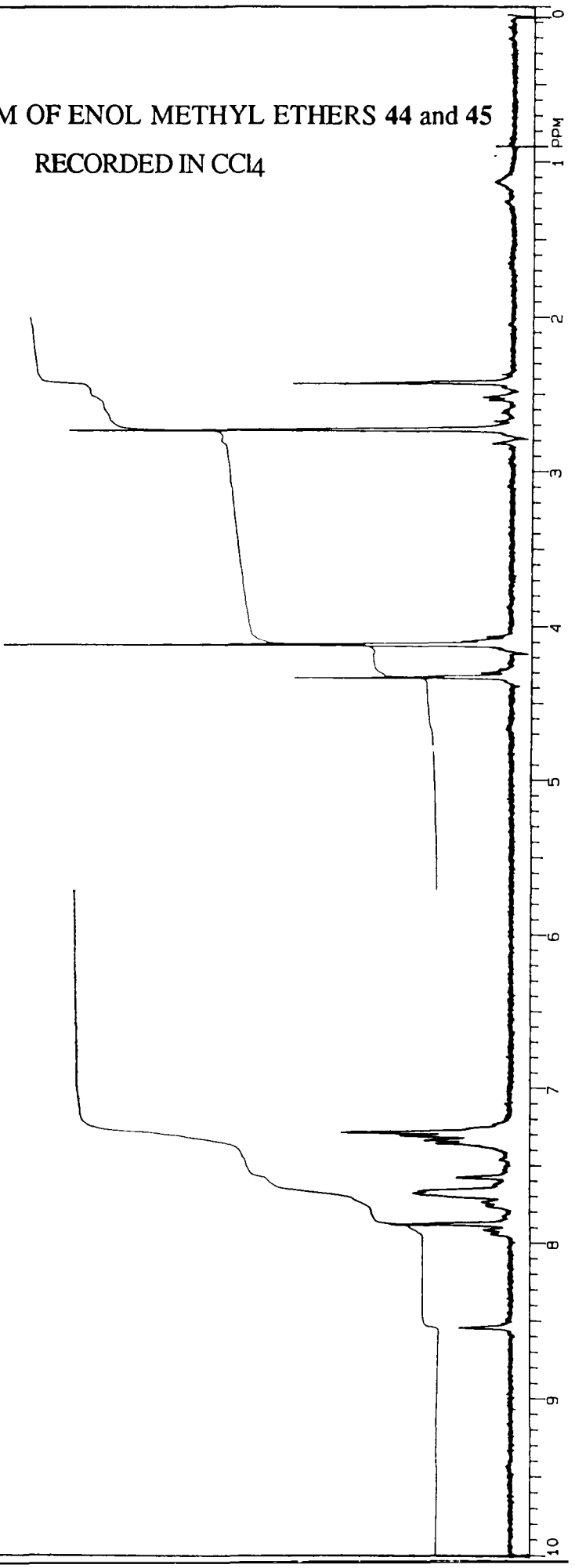


45

+

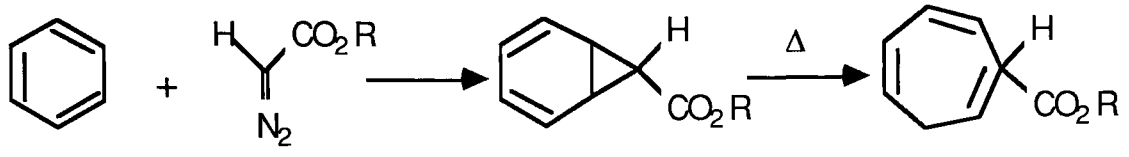


44



Mechanistic Considerations

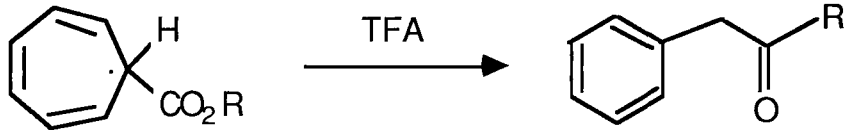
Transition metal carbenoids are known to react with aromatic compounds to give norcaradienes **46** which thermally ring open to give conjugated cycloheptatrienes **47**. Studies using various acetate ligands for rhodium(II) catalysis



46 **47**

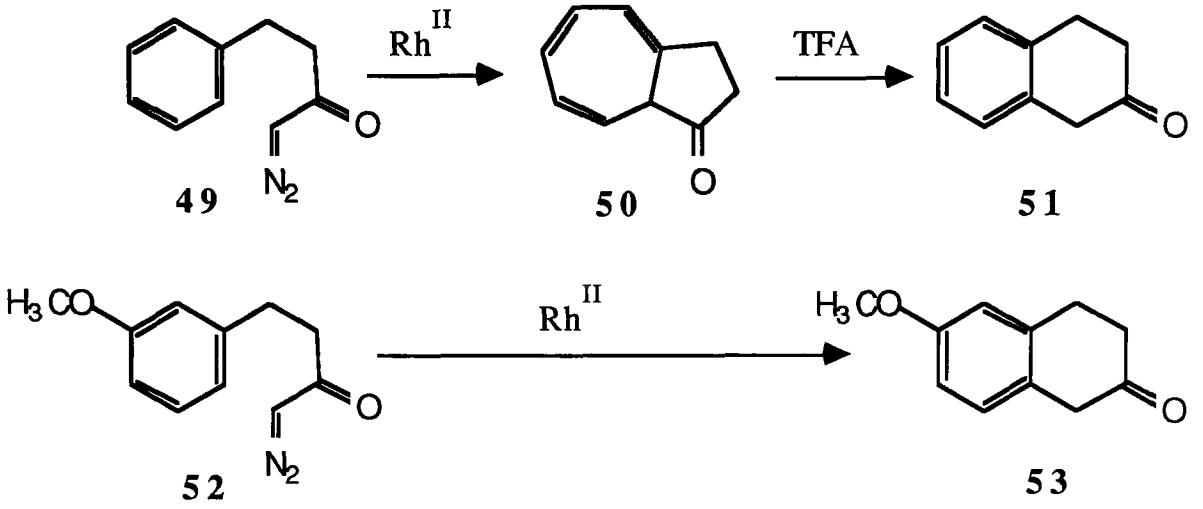
as well as variously substituted benzenes as substrates generally support the assumption that the reaction proceeds vis an electrophilic carbenoid intermediate.[30]

McKervey[31] has demonstrated that the intermolecular reaction of benzene with α-diazoketones catalyzed by rhodium(II) trifluoroacetate gives "essentially quantitative yield(s)" of non-conjugated cycloheptatrienes that are converted directly into benzyl ketones **48** by stirring with TFA;

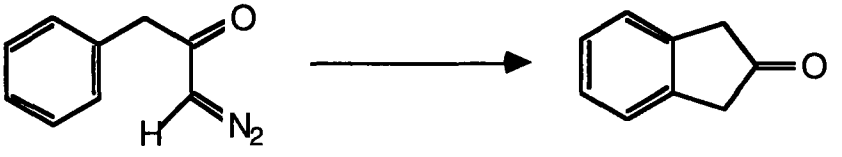


47 **48**

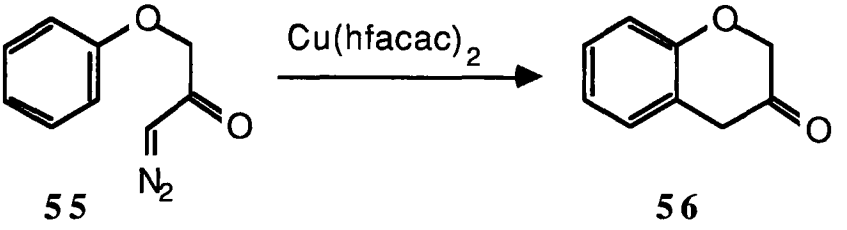
and that α-diazoketones derived from arylpropionic acids **49** give bicyclic cycloheptatrienes **50** which can be converted to 2-tetralones **51** by the action of TFA.[32] However, if a methoxy group was present *meta* to the propionyl side chain (eg. **52**) then the reaction proceeded directly to the insertion product **53**, and no bicyclic compound was observed.



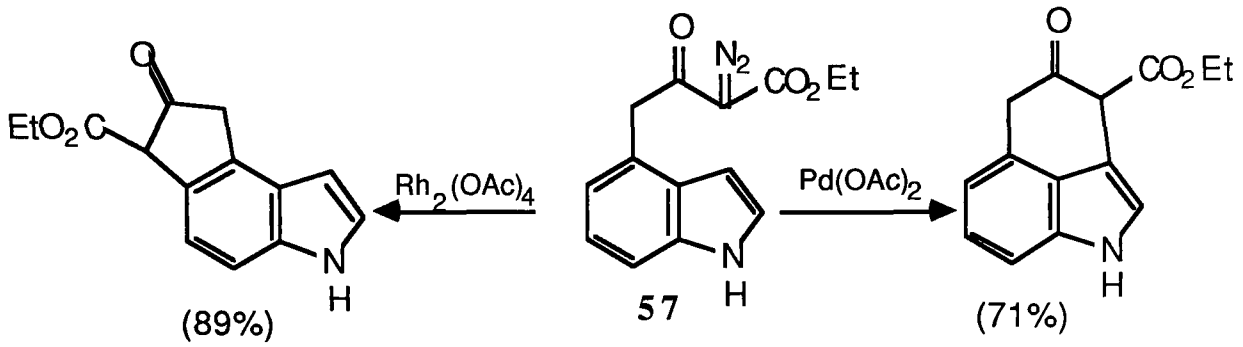
Following publication of our "sulfone" results, Nakatani[10] has prepared 2-indanones **54** via a route similar to McKervey. In these cases no cycloheptatrienes were detected.



Saba[33] has cyclized a series of α-diazoketones **55** to benzopyrans **56** by reaction with copper(II) hexafluoroacetoacetone in methylene chloride. No mention was made about possible cycloheptatriene intermediates. A direct insertion may have occured here, but electrophilic attack by the copper carbenoid on the aromatic ring followed by proton transfer also explains the observed results .



Finally, Matsumoto[34] has found that 4-indolyl diazo ester **57** reacted with rhodium(II) acetate to give insertion into the aromatic C-H bond at C-5, (no cycloheptatrienes were observed) and with palladium(II) acetate to give insertion into the heteroaromatic C-H bond at C-3.



In summary, we have seen that cycloheptatriene intermediates have been observed during: i) intermolecular aromatic C-H insertions promoted by rhodium(II) trifluoroacetate (McKervey, Noels); ii) intramolecular aromatic C-H insertions promoted by rhodium(II) acetate in cases where the isomeric norcaradiene is not excessively strained and acid catalyzed rearrangement results in the formation of 2-tetralones which result in the annulation of a five-membered ring onto an existing aromatic system.

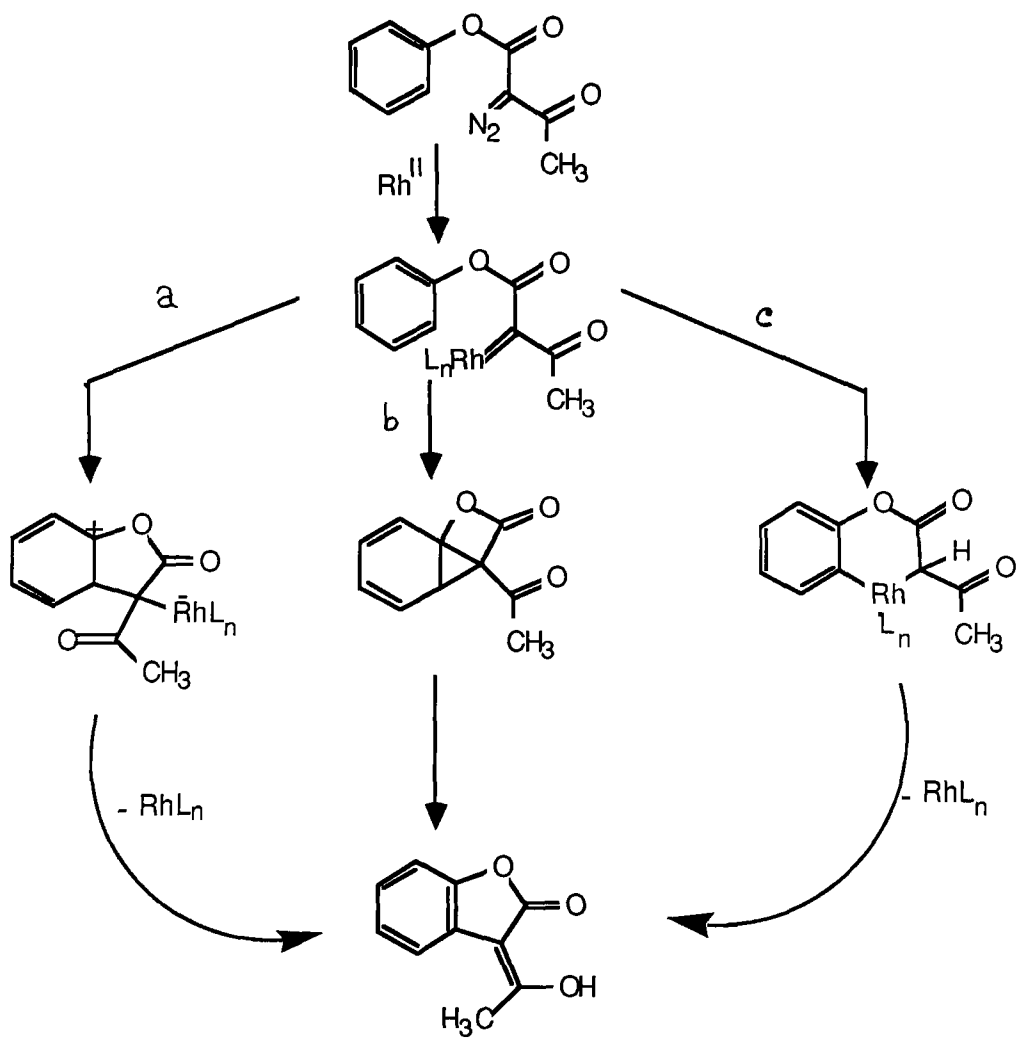
Cycloheptatriene intermediates have <u>not</u> been observed during intermolecular aromatic C-H insertions promoted by rhodium(II) acetate in which a five-membered ring is formed (Hrytsak, Nakatani, Matsumota)

The results described by us and others can be explained by one or a combination of several possible mechanisms. The possibilities are outlined below:

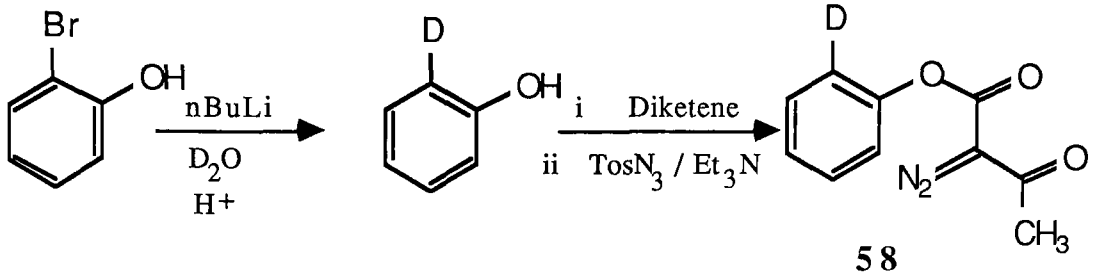
a) electrophilic aromatic substitution followed by proton transfer

b) cyclopropanation (norcaradiene formation) followed by ring opening and rearrangement

c) direct insertion (*ortho*-metallation, oxidative addition-reductive elimination)

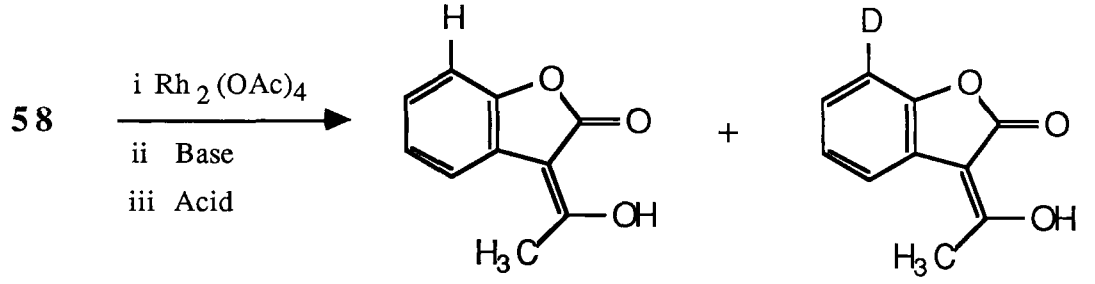


In an effort to distinguish which of these mechanisms was operating in our five-membered ring forming case, we synthesized the deuterated compound **58** by the following route;



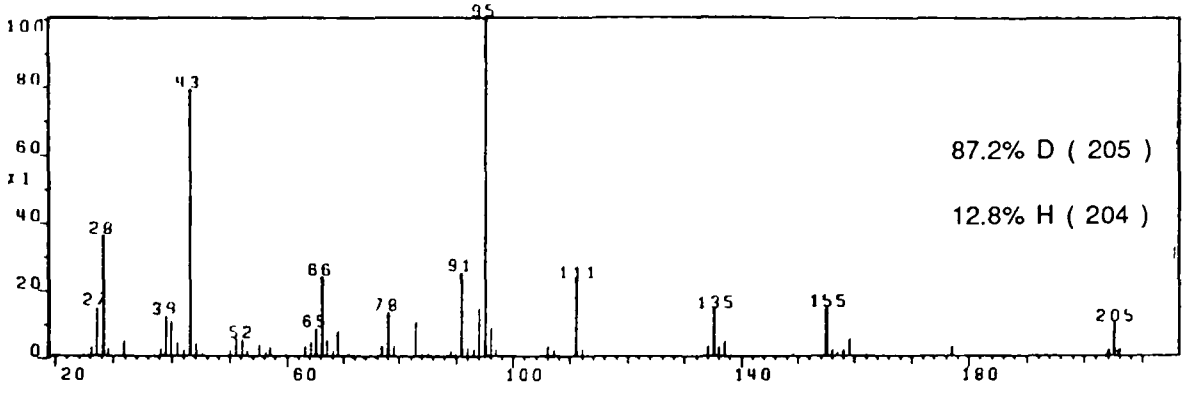
58

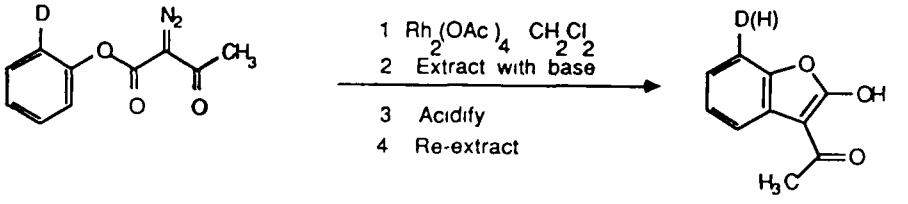
and proceeded to perform the insertion reaction by our usual procedure. The product benzofuranone **59** was washed with aqueous acid then extracted into sodium bicarbonate and was isolated by acidification/ re-extraction into methylene chloride. This would effectively remove any enolic deuterium from **59** that arose from insertion into a C-D bond rather than a C-H bond.

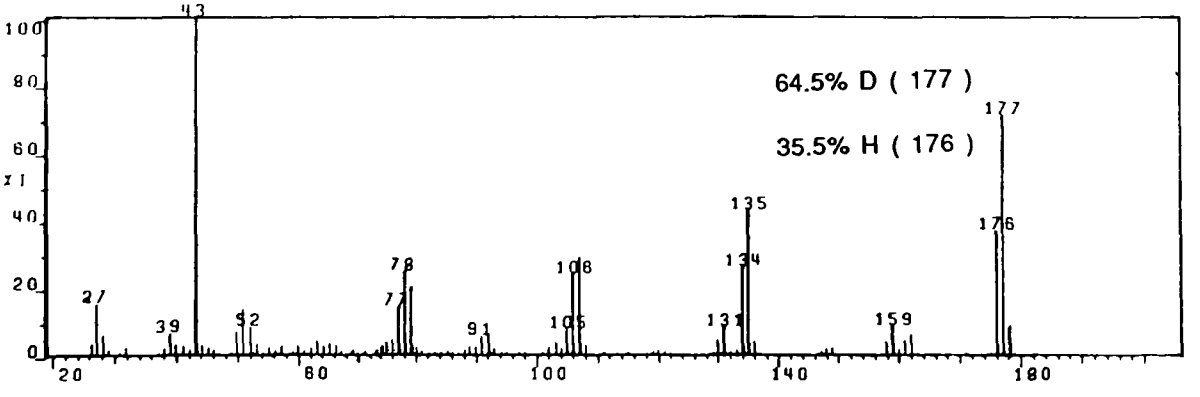


The starting ester was determined to be 87.2% monodeuterated by mass spectral analysis, and the product was shown to be 64.5% (The percentages are adjusted for the $M^+ + 1$ contribution of the non-deutero portion with the M^+ 1 contribution of the deutero being negligible. Detailed calculations appear in the appendix). Therefore the product contained 26% less deuterium than the starting diazoester. This corresponds to a kH/kD= 74/26= 2.85. A similar calculation from the starting phenol (90.85% D) gives a

MASS SPECTRA OF DEUTERO ESTER AND PRODUCT



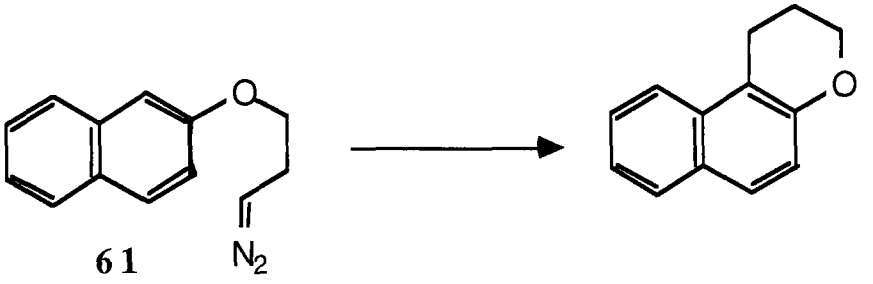




kH/kD= 2.45, so we quote an average kH/kD≈ 2.65(± 0.2). Since no loss of deuterium is expected during the reaction of phenol-2-D with diketene, or during the subsequent diazo transfer reaction, the difference in isotope content of the phenol and the diazo ester must be due to the instrumental limitations. An isotope effect of this magnitude is only compatible with a mechanism in which the C-H bond breaking is occurring to a considerable extent in the transition state of the rate determining step.

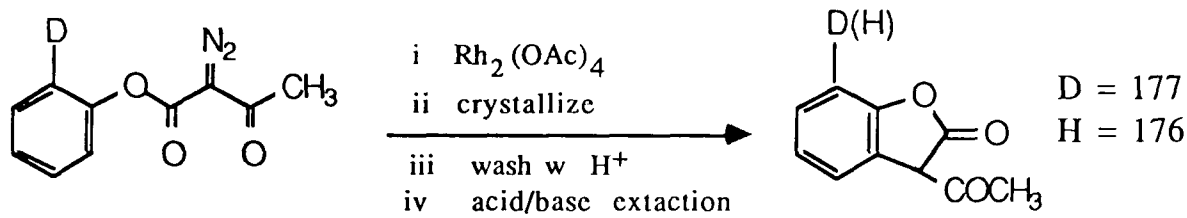
Many examples of the deuterium isotope effect in electrophilic aromatic substitution reactions have been determined.[35] Typically, the kH/ kD is <1.3 in reactions in which the C-H/ C-D bond is not broken in the rate determining step. [Reactions in which the σ-complex is formed reversibly show variable isotope effects ranging from 3-7.[36] Although no data is available we feel that the reversible formation of the σ-complex is unlikely.]

Another piece of evidence mitigating against electrophilic aromatic substitution is the product obtained from the β-naphthyl diazo ester insertion. Recall that we isolated a linear product (insertion into the 3-position) rather than the angular one. Saba noted the following orientation for the six-membered ring forming reaction of a β-naphthyl derivative catalyzed by copper(II).



61

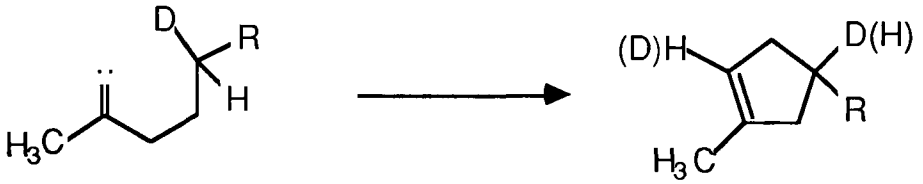
KINETIC ISOTOPE EFFECT - PRODUCT IONS IN THE MASS SPECTRUM



ION	RATIO OF MASS	% OF HIGHER MASS ION BEFORE H^+ WASH	AFTER H^+ WASH	AFTER ACID/BASE
M^+	177/176	79	63	63
M^+ -42	135/134	60	61	62
M^+ -42-28	107/106	55	55	55
M^+ -99	78/77	58	65	63

We also feel that, while not disproven, cyclopropanation to form an intermediate norcaradiene (path b) is less likely to occur in our reactions than for the 2-tetralone formation due to the highly strained structure of the necessary tricyclic intermediate. Furthermore, once formed such an intermediate would not be expected to revert to the initial rhodium carbenoid and thus this mechanism is not consistent with C-H bond breaking in the rate determining step. Recall that no cycloheptatrienes have been observed in the five-membered ring forming reactions.

Gilbert[37] has measured a kH/kD= 3.5 and 2.0 for the intramolecular1,5-insertion of the alkylidene carbenes **59** and **60** respectively;

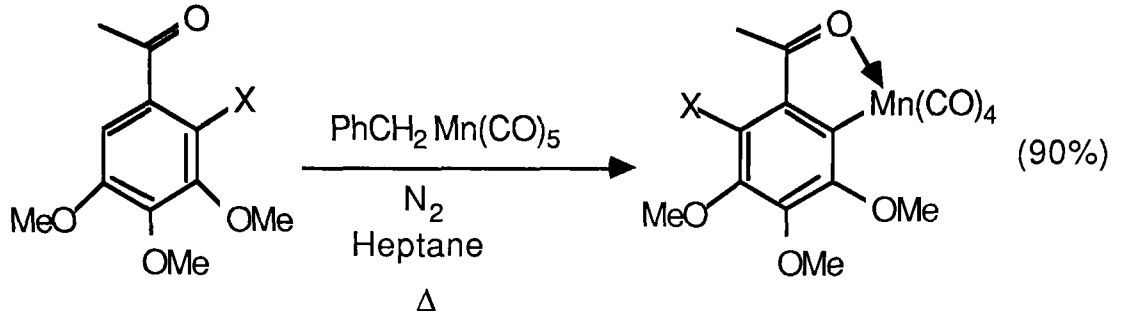


59 R= Ph

60 R=CH_3

and Scaiano[38] has observed a combined primary-secondary isotope effect of kH/kD=2.1 for the intermolecular reaction of 1 naphthylcarbene with cyclohexane:cyclohexane-d_{12}(1:1).

Nicholson[39] has measured a kH/ kD= 3.0 for the *ortho*-metallation of an acetophenone derivative **62a,b** with manganese.



62a X= H
62b X= D

63a X= H
63b X= D

While to our knowledge there have been no published deuterium isotope effects for rhodium carbenoid insertion reactions, we feel that our data is more consistent with a direct insertion (metallocycle) mechanism rather than an electrophilic aromatic substitution mechanism. The metallocycle mechanism requires the participation of a rhodium(I) species to allow for the oxidative addition-reductive elimination sequence.

In conclusion, transition metal carbenoids may "insert" into aromatic C-H bonds by a number of mechanisms depending on the ring substituents, the metal catalyst involved and the ring size being formed. The isotope effect evidence presented here adds a new piece to the puzzle of catalysis mechanisms. More work, especially in the area of isotope effects in the 2-tetralone forming reaction should help clarify the picture.

Experimental

The general comments made regarding instruments and reagents made in the Experimental section of Chapter 2 are applicable here as well.

General Procedures for the Preparation of the Benzylic Sulfides (Table 3)

All of the sulfides were obtained as viscous oils and were of sufficient purity to carry on to the next (oxidation) step in the synthetic scheme.

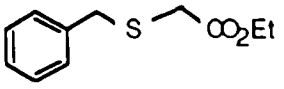
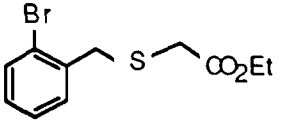
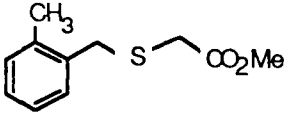
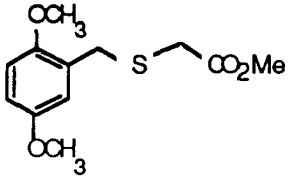
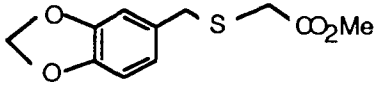
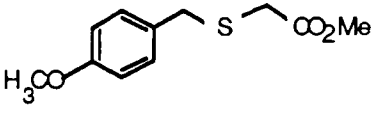
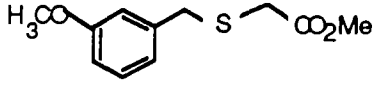
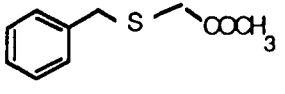
METHOD A: Preparation of Entry 7, Table 3 A solution of 3-bromomethyl anisole (16.85 mmole) in 10 ml of methanol was added to a stirred solution of methyl thioglycolate (16.85 mmole) and potassium hydroxide (17 mmole) in 15 ml of methanol, and the resulting mixture was stirred overnite (≈18h). The mixture was poured into 50 ml of ether layered over saturated sodium chloride solution, and the ether layer was separated, washed with saturated sodium carbonate solution, dried over $MgSO_4$ and was evaporated to give 3.0 g of benzylic sulfide (78%) as a yellow oil.

METHOD B: Preparation of Entry 4, Table 3 A solution of 2,5-dimethoxybenzyl alcohol (14 mmole) in 30 ml of CH_2Cl_2 was stirred under N_2, and methyl thioglycolate (14 mmole) was added with stirring followed by powdered zinc(II) iodide (7 mmole). The mixture was stirred at room temperature for 45 min, then it was washed

with water and the resulting organic phase was dried over $MgSO_4$ and evaporated to give the crude benzylic sulfide. This was eluted through a silica gel column with hexane-EtOAc to give 3.1 g of pure sulfide (86%) as a clear oil.

METHOD C: Preparation of Entry 8, Table 3 Powdered potassium hydroxide (23 mmole) was dissolved in 50 ml of ethanol under N_2, and benzyl mercaptan (21.3 mmole) was added followed by chloroacetone (33 mmole). The reaction mixture was stirred for 30 min at room temperature, then evaporated. The residue was dissolved in CH_2Cl_2 and washed with 10% sodium hydroxide solution, then the organic layer was dried over $MgSO_4$ and evaporated to give 3.75 g of benzylic sulfide (98%) as a yellow oil.

TABLE 3

ENTRY	SULFIDE	METHOD[a]	YIELD(%)	MP(°C)	N.M.R.[b]
1		C	96	oil	3.00 (s,2H), 3.76 (s, 2H), 7.33 (s, 5H)
2		available	—	oil	3.07 (s, 3H), 3.87 (s, 2H) 6.95-7.60 (m, 4H)
3		B	88	oil	2.36 (s, 2H), 3.03 (s, 2H), 3.76 (s, 2H), 7.10 (s, 4H)
4		A	86	oil	3.10 (s, 2H), 3.5-3.8 (s, 11H) 6.5-6.7 (m, 3H)
5		A	98	oil	3.10 (s, 2H), 3.73 (s, 5H), 6.20(s, 2H),6.65-6.75(m,3H)
6		A	98	oil	2.96 (s, 2H), 3.87 (s, 5H), 6.70 (d, 2H), 7.13 (d, 2H)
7		B	78	oil	2.98 (s, 2H), 3.85 (s, 2H), 6.75-7.20 (m, 4H).
8		C	98	oil	2.23 (s, 3H), 3.03 (s, 2H), 3.63 (s, 2H), 7.23 (s, 5H) .

a) METHODS A Benzylic alcohol/ ZnI_2 / Ethyl or Methyl thioglycolate
B Benzylic bromide/ Methyl thioglycolate/ KOH
C Benzyl mercaptan/ chloroacetone

b) The methyl and ethyl ester resonances were typically found at 3.8 ppm and 1.3, 4.2 ppm.

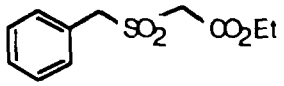
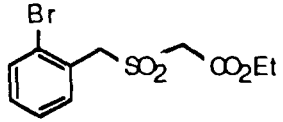
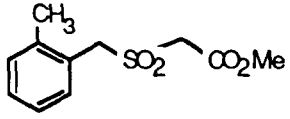
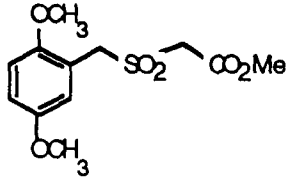
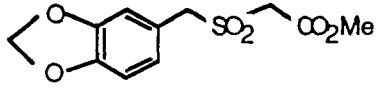
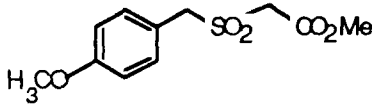
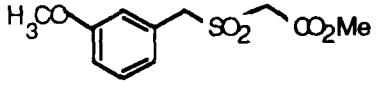
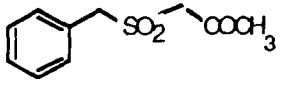
General Procedures for the Preparation of the Benzylic Sulfones (Table 4)

All of the crude sulfones obtained were of sufficient purity to carry on to the next (diazo transfer) step in the synthetic scheme.

METHOD A: Preparation of Entry 8, Table 4 A solution of sulfide (Entry 8, Table 3, 5.55 mmole) in 15 ml of CH_2Cl_2 was cooled in an ice bath, and *meta*-chloroperoxybenzoic acid (11 mmole, 2 eq) was added in small portions. The mixture was stirred at 0 °C for 45 min following the addition of the peracid, whereupon t.l.c. analysis revealed that all of the starting sulfide had been consumed. The mixture was filtered to remove the by-product *meta*-chlorobenzoic acid, and the filtrate was successively washed with 10% Na_2SO_3 then 5% $NaHCO_3$ solutions and then dried over $MgSO_4$ and evaporated to give 1.09 g of sulfone (92%) as a white powder.

METHOD B: Preparation of Entry 5, Table 4 A solution of sulfide (Entry 5, Table 3, 13.9 mmole) in 50 ml of glacial acetic acid was stirred at room temperature, and a solution of 7.4 g of 30% hydrogen peroxide in 50 ml of glacial acetic acid was added in a dropwise fashion. The resulting solution was stirred at room temperature for 48 h, whereupon 100 ml of water was added, and the diluted solution was extracted with CH_2Cl_2 (2 X 50 ml). The organic extracts were washed successively with 10% Na_2SO_3, 5% $NaHCO_3$ and saturated $NaHCO_3$ solutions then were dried over MgSO4 and evaporated to give 2.93 g of sulfone (77%) as a clear oil.

TABLE 4

ENTRY	SULFONE	METHOD[a]	YIELD(%)	MP(° C)	N.M.R.[b]
1		A	59	48-49	3.73 (s, 2H), 4.43 (s, 2H), 7.2-7.4 (m, 5H)
2		A	68	90-91	3.9 (s, 2H), 4.7 (s, 2H), 7.0-7.7 (m, 4H)
3		A	93	67-69	2.40 (s, 3H), 3.83 (s, 2H), 4.50 (s, 2H), 7.0-7.3 (m, 4H)
4		B	77	91-92	3.63 (s, 9H), 3.83 (s, 2H), 4.38 (s, 2H), 6.71 (m, 3H)
5		B	77	74-75	4.33 (s, 2H), 3.86 (s, 2H), 5.93 (s, 2H), 6.6-6.8 (m, 3H)
6		B	72	68-69	3.70 (s, 2H), 3.87 (s, 3H), 4.36 (s, 2H), 6.83 (d, 2H), 7.25 (d, 2H)
7		A	69	oil	3.72 (s, 2H), 3.83 (s, 3H), 4.40 (s, 2H),6.80-7.20(m,4H)
8		A	92	63-64	2.2 (s, 3H), 3.0 (s, 2H), 3.6 (s, 2H), 7.2 (s, 5H).

a) METHODS of OXIDATION A- meta-chloroperoxybenzoic acid B- hydrogen peroxide in acetic acid

b) The methyl and ethyl ester resonances were typically found at 3.8 ppm and 1.3, 4.2 ppm.

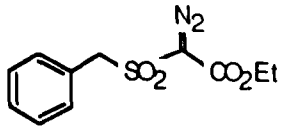
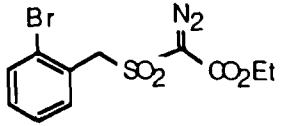
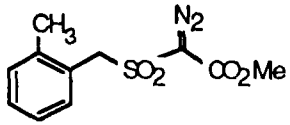
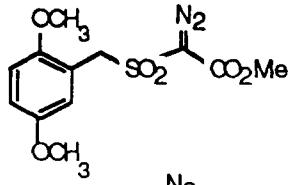
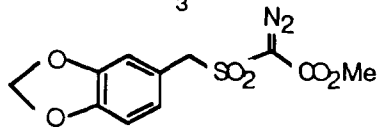
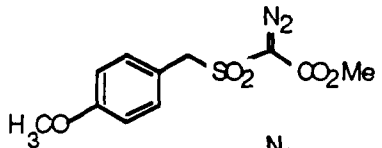
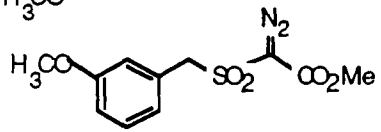
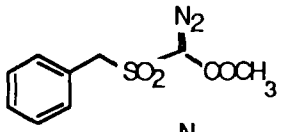
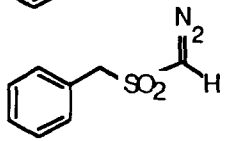
General Procedures for the Preparation of the Benzylic Diazo Sulfones (Table 5)

METHOD A: Preparation of Entry 1, Table 5 A solution of sulfone (Entry1, Table 4, 2 mmole) in 10 ml of dry ethanol was cooled in an ice bath with stirring, and then powdered potassium hydroxide (2.4 mmole) was added in one portion followed by dropwise addition of tosyl azide (2.2 mmole). The ice bath was removed and the mixture was stirred for 40 min at room temperature. The product mixture was evaporated and the residue that remained was dissolved in ether. The ethereal solution was washed with 10% potassium hydroxide solution and was dried over $MgSO_4$ and evaporated to give 305 mg of orange oil. Tis was chromatographed on silica gel with hexane-EtOAc (3:1) to give 214 mg of pure diazo ester (40%).

METHOD B: Preparation of Entry 3, Table 5 A solution of sodium methoxide in methanol (0.413 mmole in 1 ml) was added to an ice cold stirred solution of sulfone (Entry 3, Table 3, 0.413 mmole) and stirring was continued for 5 min whereupon methyl formate (0.413 mmole) was added followed 5 min later by tosyl azide (0.413 mmole). The reaction mixture was stirred at room temperature for 2.5 h, then evaporated. The crude residue was dissolved in CH_2Cl_2, washed with 10% potassium hydroxide solution , dried over $MgSO_4$ and evaporated to give 106 mg of yellow oil. Chromatography on silica gel with hexane-EtOAc (7:3) gave 58 mg of pure diazo ester (52%).

METHOD B: Preparation of Entry 8, Table 5 To a solution of sulfone (Entry 8, Table 4, 11.78 mmole) in CH_2Cl_2 was added triethylamine (11.78 mmole) followed by tosyl azide (11.78 mmole). The mixture was stirred at room temperature for 18 h, then evaporated. The crude red residue was dissolved in EtOAc, washed with 10% potassium hydroxide solution, dried over $MgSO_4$ and evaporated. The crude product was chromatographed by HPLC (silica gel, hexane-EtOAc (7:3)) to give 1.42 g of pure diazo ester (51%).

TABLE 5

ENTRY	DIAZOSULFONE	METHOD [a]	YIELD(%)	MP(°C)	N.M.R. [b]
1		A	40	oil	4.53 (s, 2H), 7.3 (s, 5H)
2		A	15	oil	4.8 (s, 2H),7.1-7.7 (m, 4H)
3		B	52	63-68	2.15 (s, 3H), 4.33 (s, 2H), 6.9-7.0 (s, 4H)
4		A	27	75-78	3.6 (s, 9H), 4.40 (s, 2H), 6.73 (s, 3H).
5		A	18	oil	4.33 (s, 2H), 5.87 (s, 2H), 6.6-6.7 (m, 3H).
6		A	52	oil	4.43 (s, 2H), 3.78 (s, 3H), 6.83 (d, 2H), 7.17 (d, 2H).
7		B	38	oil	3.73 (s, 3H), 4.46 (s, 2H), 6.65-7.15 (m, 4H).
8		C	51	85-86	2.07 (s, 3H), 4.40 (s, 2H), 7.30 (s, 5H).
9		acyl cleavage	80	98-99	4.26 (s,2H), 4.96 (s,1H), 7.33 (s, 5H).

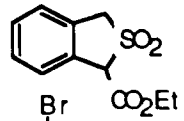
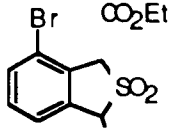
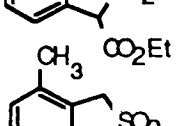
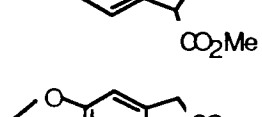
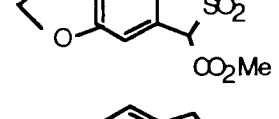
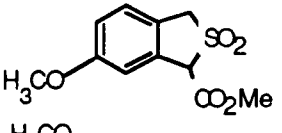
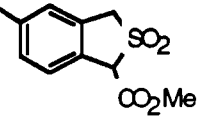
a) METHODS of DIAZO TRANSFER A- KOH/ ROH/ Tosyl azide B- NaOMe/ MeOCHO/ Tosyl azide C- Triethylamine/ Tosyl azide

b) The methyl and ethyl resonances were typically found at 3.8 ppm and 1.3, 4.2 ppm.

General Procedure for the Diazo-sulfone Cyclizations to the 1,3-Dihydrobenzo [c] thiophene-2,2-dioxides (Table 6)

Preparation of Entry 1, Table 6 A solution of diazo-sulfone (Entry 1, Table 5, 0.41 mmole) in 2 ml of dry CH_2Cl_2 was stirred at room temperature. To the above solution was added 9 mg of rhodium(II) acetate (5 mole%) in one portion. Gas evolution occured, and the progress of the reaction was monitored by t.l.c. (silica gel, hexane-EtOAc (2:1)) that showed the reaction was complete after 2 h. The less polar diazo-ester (R_f= 0.47) was replaced by a more polar compound (R_f= 0.33). The reaction mixture was filtered through a cotton plug and evaporated to give 100 mg of green oil. Chromatography of this material on silica gel with hexane-EtOAc (2:1) gave 45 mg of pure bicyclic sulfone (46%) as a pale yellow oil.

TABLE 6

ENTRY	THIOPHENE	YIELD	MP(° C)	ACC. MASS Calcd.	ACC. MASS Found	I.R.(cm^{-1})	N.M.R.[b]
1		46	oil	240.0455	240.0443	1740, 1335	4.43 (2H), 5.00 (s, 1H), 7.33 (s, 4H)
2		48	127-128	317.9559	317.9559	1740, 1340	4.43 (2H), 5.10 (s, 1H), 7.0-7.6 (m, 3H).
3		14[c]	110-112	240.0456	240.0459	1755, 1335	2.33 (s, 3H), 4.42 (2H), 5.16 (s, 1H), 7.25 (m,3H)
4		47	184-185	270.0196	270.0171	1742, 1332	4.39 (2H), 5.02 (s, 1H), 6.04,6.03 (s,1H),6.79, 6.80 (s, 1H).
5		45	oil	256.0403	256.0410	1742, 1332	3.70 (s, 3H), 4.33 (2H), 4.96 (s, 1H), 6.80 (s, 1H), 6.86 (d, 1H), 7.16 (d, 1H).
6		42	147-148	266.0403	256.0422	1740, 1332	3.80 (s, 3H), 4.30 (2H), 4.90 (s, 1H), 6.76 (s, 1H), 6.83 (d, 1H), 7.16 (d, 1H).
7		56[a]	oil	210.0394	210.0372	1720, 1325	4.44 (2H), 5.25 (s, 1H), 7.3-7.5 (m, 4H).

a) using Rhodium(II) trifluoroacetate as catalyst.
b) The methyl and ethyl resonances were typically found at 3.8 ppm and 1.3, 4.2 ppm.
c) Also recovered 41% of the ether formed by insertion of two diazoesters into one water.

General Procedure for the Preparation of the Diazo esters (Table 7)

The starting aryl esters used to make the diazo esters in Table 7 were prepared as per the following representative example. A 20 mmole sample of 3,4-methylenedioxy phenol (sesamol) was dissolved in 5 ml of ether containing 100 µl of triethylamine, and the solution was cooled to -15 °C. To the cooled solution was added 20 mmole of diketene in 2 ml of ether over a 30 min period. The reaction mixture was allowed to come to room temperature, and the crystalline product was filtered off and washed with ether-hexane (9:1) to give 3.4 g of pure β-keto phenylester (77%). An analytical sample was recrystallized from warm ether-hexane to give a white powder of mp 76-77 °C. (Generally these esters were obtained as an oil of sufficient purity to be used in the subsequent diazo transfer reaction).

The diazo esters of Table 7 were prepared by the following method. The arylester was dissolved in dry CH_2Cl_2 and 2 eq of triethylamine was added with stirring followed by 1 eq of tosyl azide. The reaction mixture was stirred at room temperature for 1 h, then concentrated to a yellow residue. This residue was dissolved in ether, washed with 10% potassium hydroxide solution, dried over $MgSO_4$ and evaporated. The crude diazo ester was:

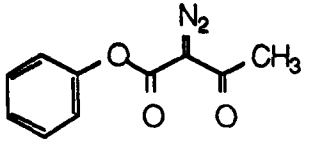
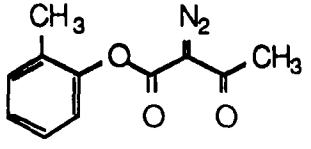
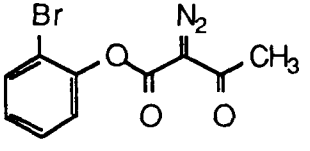
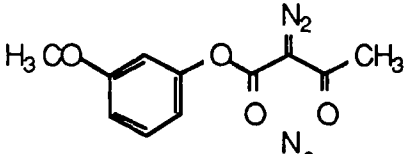
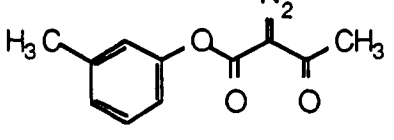
a) purified by column chromatography on silica gel using hexane-EtOAc (7:3) or

b) used as such if the nmr spectrum and t.l.c. analysis indicated that there were no major impurities present or

c) used as such if the diazo ester was a solid free of major impurities; an analytical sample was recrystallized from warm ether.

In cases where the starting arylester contained large amounts of by-products from the phenol-diketene addition, the purity was estimated by nmr and the quantity of tosyl azide used was adjusted accordingly. In these cases the yields reported are based on tosyl azide. All of these α-diazo-β-keto arylesters gave infrared spectra that featured bands at or about 2120, 1730 and 1660 cm^{-1} as well as ci-ms spectra that showed a strong M^++1 ion and a base peak of M^++1-28.

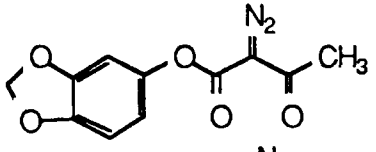
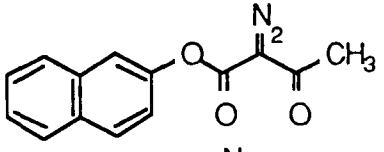
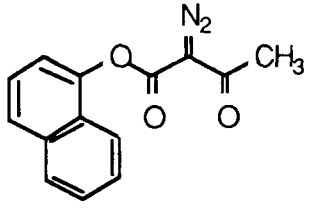
TABLE 7

ENTRY	DIAZOESTER	YIELD	M.P.(°C)	N.M.R.
1		71[b]	oil	2.36 (s, 3H), 6.93-7.40 (m, 5H)
2		94[a]	oil	2.10 (s, 3H), 2.36 (s, 3H), 6.93-7.30(m, 4H)
3		66[a]	oil	2.50 (s, 3H), 6.90-7.70 (m, 4H)
4		65[b]	oil	2.50 (s, 3H), 3.77 (s, 3H), 6.60-7.40 (m, 4H)
5		98[a]	oil	2.33 (s, 3H), 2.46 (s, 3H), 6.60-7.25 (m, 4H)

a) isolated, based on tosyl azide (limiting reagent)

b) isolated

TABLE 7 (continued)

ENTRY	DIAZOESTER	YIELD	M.P.(° C)	N.M.R.
6		98[a]	98-99[c]	2.50 (s, 3H), 5.90 (s, 2H), 6.36-6.80 (m, 3H)
7		94[b]	86-88[c]	2.53 (s, 3H), 7.24-7.89 (m, 7H)
8		94[a]	138-139[c]	2.54 (s, 3H), 7.30-7.91 (m, 7H)

a) isolated, based on tosyl azide (limiting reagent)

b) isolated

c) analytical samples were recrystallized from warm ether

General Procedure for the Preparation of the 3-Acetylbenzofuran-2(3H)-ones and 3-Acetylnaphthofuran-2(3H)-ones (Table 8)

Preparation of Entry 2, Table 8 The diazo ester (Entry 2, Table 8, 1 mmole) was dissolved in 5 ml of dry CH2Cl2 and the solution was stirred at room temperature then 22 mg of rhodium(II) acetate (5 mole%) was added in one portion. Vigorous gas evolution occurred and the solution began to turn green. Some of the catalyst appeared to dissolve. After 1 h t.l.c. analysis showed that the less polar starting diazo ester (R_f= 0.50) was completely and cleanly replaced by a more polar compound of R_f= 0.13. The solution was filtered through a cotton plug and was evaporated to give 189 mg of crude (98%) as a pale green powder. This material was homogeneous by t.l.c. and chromatography on silica gel gave 186 mg of a deep blue compound identical to the crude by t.l.c. and nmr. An analytical sample was recrystallized from ether-hexane containing a trace of methanol to give a white powder of mp . The nmr spectrum of this material was the same as the crude as was its t.l.c. Since the blue coloration problem was preventing chromatographic purification of the crude and since the crude was homogeneous by nmr and t.l.c., the crude yields are reported. The spectral data reported is of the recrystallized material.

TABLE 8

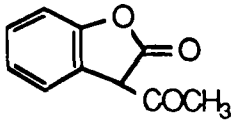
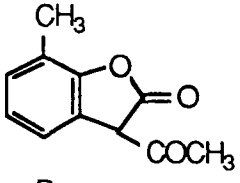
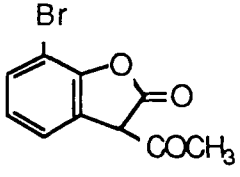
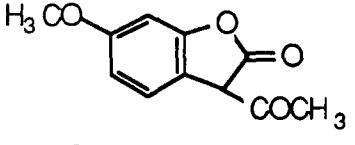
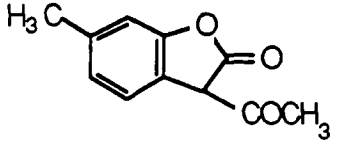
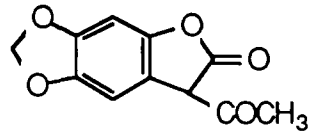
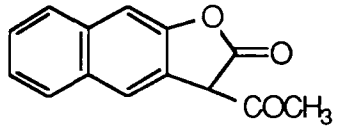
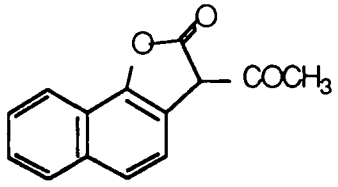
ENTRY	BENZOFURANONE	YIELD	M.P.(° C)	I.R.(cm^{-1})	ACC. MASS Calcd.	ACC. MASS Found	N.M.R.
1		98	133-134	1725,1710, 1637	176.0473	176.0492	(CCl_4) 2.23 (s, 3H), 7.04 - 7.24 (m, 4H), 11.96 (br. s., 1H).
2		98	112-113	1710,1637, 1620	190.0630	190.0640	(acetone d_6) 2.29, 2.35 (s, 3H), 2.54, 2.68 (s, 3H), 7.02 (d, J= 5.7, 1H), 7.14 (d, J= 5.7,1H), 7.37,7.58 (t, 1H).
3		92	164-166	1730-1715, 1628	253.9577	253.9588	(acetone d_6) 2.58 (s, 3H), 7.06 (dd, J= 8.0, 7.2, 1H), 7.35 (d, J= 7.8, 1H), 7.72 (d, J= 7.8,1H)
4		95	142-144	1725,1630	206.0615	206.0574	(acetone d_6) 2.41, 2.53 (s, 3H), 3.81, 4.03 (s, 3H), 6.66-6.82 (m,2H) 7.13-7.21 (m, 1H)
5		93	133-135	1715,1637	190.0630	190.0649	($CDCl_3$) 2.38 (s, 3H), 2.43 (s, 3H), 6.97 (d, J= 8.2, 1H), 6.99 (s,1H) 7.19 (d, J= 8.2, 1H), 11.74 (s, 1H).

TABLE 8 (continued)

ENTRY	BENZOFURANONE	YIELD	M.P.(C)	I.R.(cm^{-1})	ACC. MASS Calcd.	ACC. MASS Found	N.M.R.
6		91	211-212	1720-1710, 1640 (KBr)	220.0372	220.0372	(acetone d $_6$) 2.60,2.47 (s, 3H), 5.96, 6.02 (s, 2H), 6.71, 6.88 (s, 1H), 7.05, 7.21 (s, 1H).
7		94	214-216	1725, 1630, 1640	226.0630	226.0620	(acetone d $_6$) 2.66,2.73 (s, 3H), [7.39-8.21 (m, 6H) including 7.46, 7.66 (s,1H), and 8.03, 8.21 (s, 1H)]
8		90	175-177	1728, 1650	226.0630	226.0633	(CCl_4) 2.53 (s, 3H), 7.39-7.59 (m, 4H), 7.77 (d, J= 8.3, 1H), 8.06 (d, J= 8.3, 1H).

Deuterium Isotope Effect Experiments

Phenol-2-D Was prepared by a literature procedure (2-bromophenol/ n-butyllithium/ D_2O/ H^+) The resulting phenol-2-D was shown to be 90.85% deuterium incorporated by mass spectral analysis. No starting 2-bromophenol was present as determined by g.l.c. analysis.

Deuterated β-Keto phenylester Was prepared by the usual reaction sequence (phenol-2-D/ diketene) in 91% crude yield, used subsequently as such.

Deuterated α-Diazo-β-keto phenylester Was prepared from the crude β-keto phenylester above by the usual procedure (tosyl azide/ triethylamine) in 68% yield after chromatography on silica gel using hexane-EtOAc (4:1) as a yellow oil. This was shown to be 87.2% deuterium incorporated by mass spectral analysis of the molecular ion region.

Insertion Reaction The insertion reaction was performed on the deuterated diazo ester as per the standard procedure, and the resulting 3-acetylbenzofuran-2(3H)-one was analyzed by mass spectrum, and was shown to contain 79% deuteration by inspection of the molecular ion region. This material was dissolved in ether and washed with dilute HCl and the product re-isolated. This time mass spectral analysis indicated a deuterium content of 63% (the ratios of

the other major ions remained similar to the unwashed material). Finally, this material was extracted into 10% $NaHCO_3$, the basic extract was acidified with 10% HCl and the 3-acetylbenzofuran-2(3H)-one was re-extracted with ether. The ether layer was removed in-vacuo to give a product that still contained 63% deuteration. Hence we had arrived at a constant value for the extent of deuterium remaining following the insertion reaction.

Appendix 1

Calculation of kH/ kD

A) Deuterated α-Diazo-β-keto phenylester

Observed Ratio of Mass 205/ 204 = 9.7:1.4

= 100:14.4

Calculated M^++1 of 204 = 11.98%

Corrected for M^++1 of 204 = 100-(14.4 x 0.1198):14.4

= 98.3:14.4

= 87.2% D

B) Phenol-2-D

Observed Ratio of Mass 95/94 = 100:10

Calculated M^++1 of 94 = 6.73%

Corrected for M^++1 of 94 = 100-(10 x 0.673):10

= 99.3:10

= 90.85% D

C) 3-Acetylbenzofuran-2(3H)-one (Constant D-content)

Observed Ratio of Mass 177/ 176 = 100:51.9

Calculated M^++1 of 176= 11.24%

Corrected for M^++1 of 176 = 100-(51.9 x 0.1124):51.9

= 94.3:51.9

= 64.5% D

D) Calculated kH/ kD Effect

1) From diazo ester (87.2%-64.5%)/87.2% = 26% loss of D

So kH/ kD = 74/26

= 2.85

2) From phenol-2-D (90.85%-64.5%)/90.85%= 29% loss of D

So kH/ kD = 71/29

= 2.45

Therefore the average effect is (2.45 + 2.85)/2= 2.65 ±0.2

or 71-74% of D is retained (72.5 ±1.5%).

REFERENCES

[1] This work has appeared in part in the following communications. M. Hrytsak, N. Etkin, T. Durst *Tetrahedron Lett.* 1986, **47**, 5679; M. Hrytsak, T. Durst *J. Chem. Soc. Chem. Commun.* 1987, 1150.

[2] W. Oppolzer *Heterocycles* 1980, **14**, 1615.

[3] M.P. Cava, A.A. Deana *J. Am. Chem. Soc.* 1959, **81**, 4266.

[4] M.P. Cava, M.J. Mitchell, A.A. Deana *J. Org. Chem.* 1960, **25**, 1481.

[5] K.C. Nicolaou, W.E. Barnette, P. Ma *J. Org. Chem.* 1980, **45**, 1463.

[6] W. Oppolzer, D.A. Roberts, T.G.C. Bird *Helv. Chim. Acta*, 1979, **62**, 2017.

[7] W. Oppolzer, D.A. Roberts *Helv. Chim. Acta*, 1980, **63**, 1703.

[8] T. Durst, E.C. Kozma, J.L. Charlton *J. Org. Chem.*, 1985, **50**, 4829.

[9] D.F. Taber, R.E. Ruckle Jr., *Tetrahedron Lett.*, 1985, **26**, 3059.

[10] K. Nakatani *Tetrahedron Lett.* 1987, **28**, 165.

[11] M.C. Pirrung, J.A. Werner, *J. Am. Chem. Soc.*, 1986, **108**, 6060.

[12] J.L. Charlton, T. Durst *Tetrahedron Lett.* 1984, **25**, 2663.

[13] O. Kromatka *Chem. Ber.* 1932, **65**, 123.

[14] E.C. Horning, R.U. Schock *J. Am. Chem. Soc.* 1948, **70**, 2441.

[15] A. Mustafa " Benzofurans "; John Wiley and Sons: New York, 1974, p 251.

[16] J. Santesson *Acta Chem. Scand.* 1970, **24**, 371.

[17] J. Gripenberg, J. Martikkala *Acta Chem. Scand.* 1969, **23**, 2583.

[18] M. Norte, J.J. Fernandez *Tetrahedron Lett.* 1987, **28**, 1693.

[19] A.W Weston *J. Am. Chem. Soc.* 1947, **69**, 980.

[20] T.A. Geissman, A. Armen *J. Am. Chem. Soc.* 1955, **77**,1623.

[21] J.N. Chatterjea *J. Indian Chem. Soc.* 1956, **33**, 175.

[22] J.A. Elix, B.A. Ferguson *Aust. J. Chem.* 1973, **26**, 1079.

[23] R.N. Lacey *J. Chem. Soc.* 1954, 854.

[24] N. Platzer, J.J. Basselier, P. Demerseman *Bull. Soc. Chim. France* 1974, **5**, 905.

[25] J.P. Freeman, R.C. Grabiak *J. Org. Chem.* 1976, **41**, 2531.

[26] J.N. Chatterjea *J. Indian Chem. Soc.* 1957, **34**, 299.

[27] C.J. Pouchert, " The Aldrich Library of NMR Spectra", 2nd ed., Aldrich Chemical Co., Inc., Milwaukee, 1983, p 306D.

[28] R.J. Ponsford, R.J. Southgate *J. Chem. Soc. Chem. Commun.* 1979, 846.

[29] J.N. Chatterjea, S. Lal, U. Jha, D. Rycroft, J. Carnduff *J. Chem. Research* 1979, 4075.

[30] A.J. Anciaux, A. Demonceau, A.F. Noels, A.J. Hubert, R. Warin, P. Teyssié *J. Org. Chem.* 1981, **46**, 873.

[31] M.A. McKervey, D.N. Russell, M.F. Twohig *J. Chem. Soc. Chem. Commun.* 1985, 491.

[32] M.A. McKervey, S.M. Tuladhar, M.F. Twohig *J. Chem. Soc. Chem. Commun.* 1984, 129.

[33] A. Saba *Synthesis* 1984, 268.

[34] M.Matsumoto, N. Watanabe, H. Kobayashi *Heterocycles* 1987, **26**, 1479.

[35] For a general discussion of isotope effects in aromatic electrophilic substitution see J. March, "Advanced Organic Chemistry, Reactions, Mechanisms and Structure" 2nd ed., McGraw-Hill, 1977, p 454.

[36] H. Zollinger *Adv. Phys. Org. Chem.* 1964, **2**, 163.

[37] J.C. Gilbert, D.H. Giamalva, M.E. Baze *J. Org. Chem.* 1985, **50**, 2557.

[38] R.L. Barcus, L.M. Hadel, L.J. Johnston, M.S. Platz, T.G Savino, J.C. Scaiano *J. Am. Chem. Soc.* 1986, **108**, 3923.

---

[39] L.H.P. Gommans, L. Main, B.K. Nicholson *J. Chem. Soc, Chem. Commun.* 1986, 12.

CHAPTER 4

Studies on Various Aspects of Carbapenem Synthesis

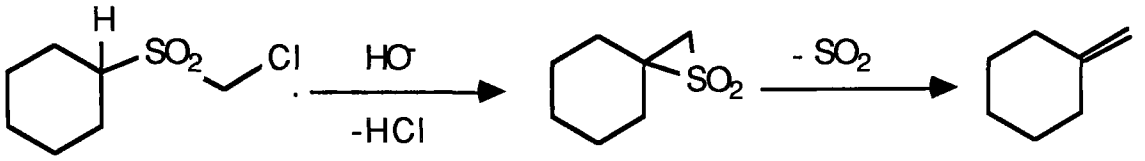
This chapter is a summary of a series of four smaller projects that gave some interesting results that may form the basis for further investigation. The reader is asked to indulge in the inclusion of partial spectral data in the text as structure proof; full data for the compounds in this chapter does appear in the Experimental section. Note that none of the four projects discussed here were carried to their intended conclusions. However, inclusion of the results of these projects is warranted by their value as a starting point for further studies as well as for the detailed preparations of several new and interesting compounds that were characterized.

Carbapenems via a Ramberg-Backlund Approach

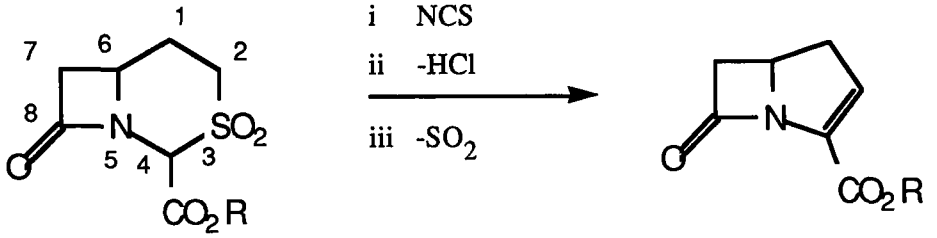
The synthesis of carbapenem antibiotics has generated much interest as evidenced by the number of publications cited in recent review articles.[1,2,3] There are presently many excellent methods for the construction of the carbapenem skeleton **2**, possibly the best of which is the rhodium(II) carboxylate catalyzed N-H insertion reaction discussed in Chapter 1.

We thought that a simple, yet unexplored method of construction of the carbapenem ring system would be to form the fused five membered ring system (penam) by ring contraction of a

fused six membered ring system (cepham). The Ramberg-Backlund reaction[4] is a way of forming a carbon-carbon double bond via base catalyzed extrusion of SO_2 from an α-halosulfone that has been used to form double bonds of predictable location in many types of molecules.

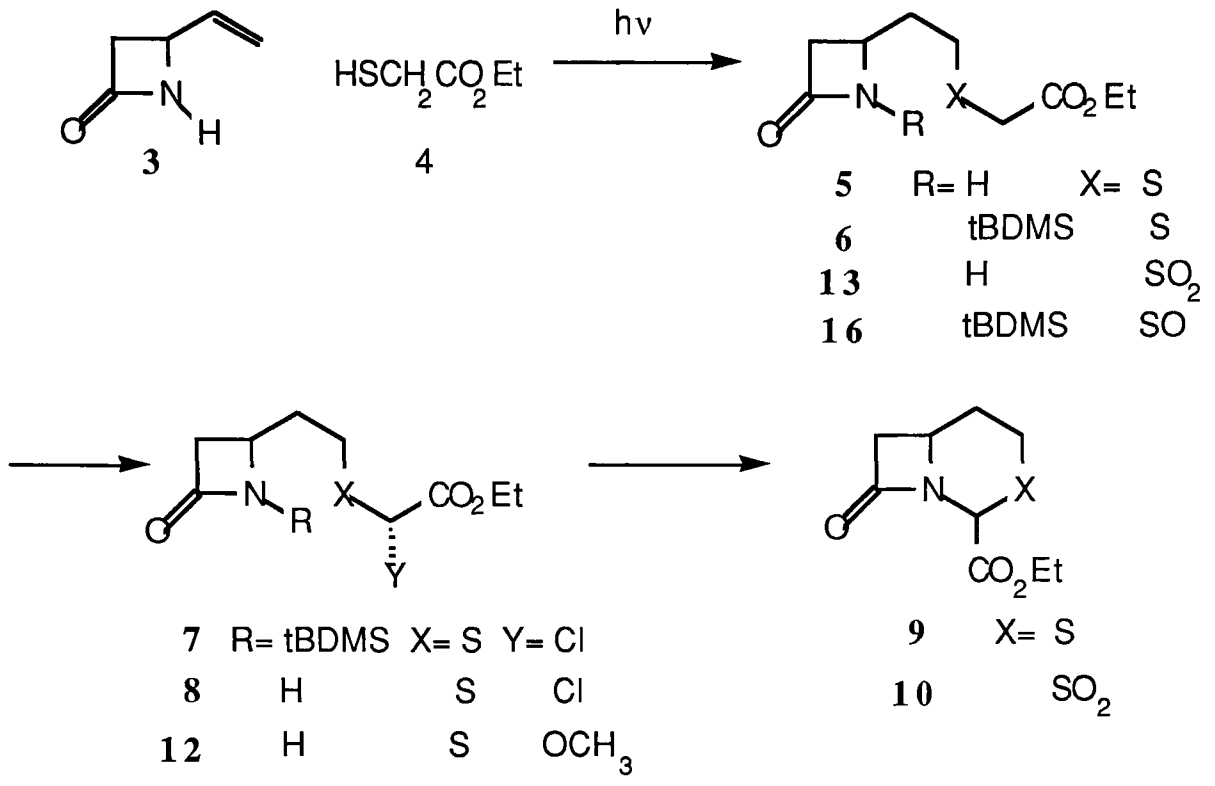


If the Ramberg-Backlund reaction sequence is applied to the 3-isocephem **1**, one should arrive at **2**.



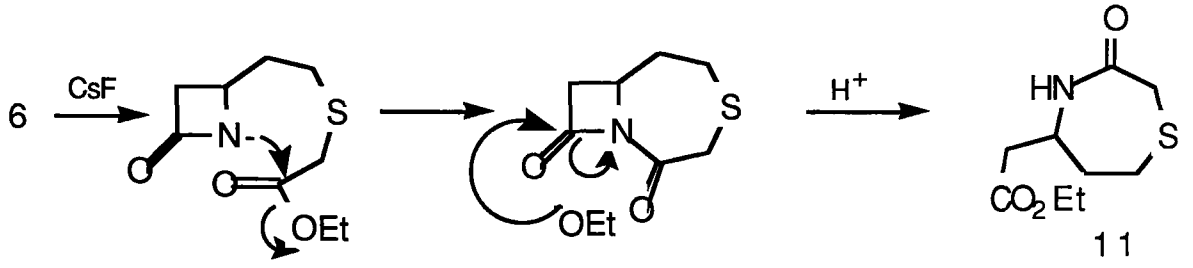
1 **2**

To test our hypothesis, we prepared an example of the 3-sulfonyl cepham **1** according to the following route.



The β-lactam **5** was obtained via the radical addition of ethyl thioglycolate **4** to 4-vinylazetidin-2-one **3**. This reaction was carried out by simply mixing **3** and **4** without solvent, and monitoring the progress of the reaction by following the disappearance of the vinylic signals in the proton nmr spectrum of the mixture (2 weeks). Compound **5** could be obtained in a pure form by silylation of the β-lactam nitrogen to give **6** (in 66% yield), followed by chromatography and desilylation with HCl in methanol in 82% yield. The nmr spectrum of **5** showed the required N-H resonance at δ= 6.6 and the methylene resonance at δ= 3.2. The infrared spectrum of **5** displayed a broad band at 1750-1715 cm^{-1} due to the β-lactam and ester C=O.

When desilylation of **6** was attempted with CsF in acetonitrile, a 61% yield of **11** resulted, presumably by the following pathway. Compound **11** was identified by its 300 MHz ^1H nmr spectrum that featured an AB pair at δ= 3.0 ($COC\underline{H}_2S$), a multiplet at δ= 3.80 ($CH_2C\underline{H}NH$) and a doublet at δ= 2.46 ($C\underline{H}_2CHNH$, J= 6Hz). The infrared spectrum of **11** displayed bands at 1715 and 1660 cm^{-1} for the ester and lactam C=O respectively.

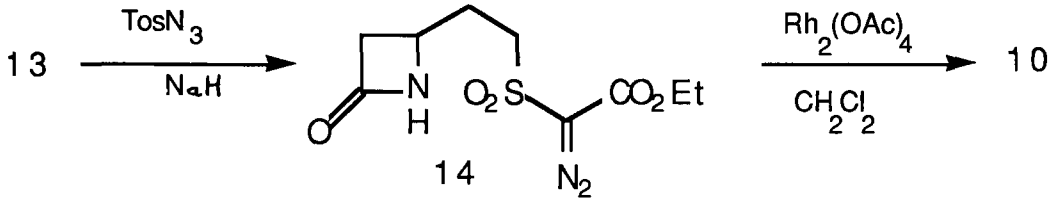


11

Reaction of **6** with N-chlorosuccinimide gave a 53% yield of the fairly unstable chloro compound **7**, accompanied by 5% of dichlorinated material. Removal of the silyl group of **7** with HCl in methanol led to an 86% yield of **12**, formed by the solvent displacement of chlorine. Compound **5** was chlorinated with SO_2Cl_2/ triethylamine to give **8** in 44% yield. Stirring **8** alone in methanol also resulted in solvent displacement of chlorine. Therefore nucleophilic substitution at this center must be a facile process, yet the β-lactam nitrogen was not sufficiently nucleophilic to achieve ring closure by displacement of chlorine. Ring closure of **8** to **1** could not be achieved, even in the presence of triethylamine or silver tetrafluoroborate.

In a final effort to produce the bicyclic sulfonyl cephem **1**, compound **5** was oxidized with two eq. of *meta*-chloroperoxybenzoic

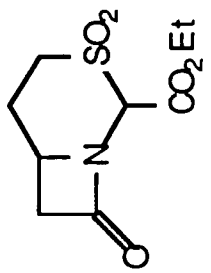
acid to give the sulfone **13** in 60% yield. The ester sulfone **13** was diazotized with tosyl azide/ sodium hydride to afford **14** in 34% yield. The nmr spectrum of **14** lacked the methylene resonance found in **13**, and the resonances present were in agreement with the assigned structure (see the Experimental section). The infrared spectrum of **14** featured bands at 2140, 1765, and 1715 cm^{-1} due to the diazo, β-lactam and ester functions.



Treatment of **14** with rhodium(II) acetate in refluxing CH_2Cl_2 gave the desired sulfonyl β-lactam **10** in 74% yield as a white solid after chromatography. The nmr spectrum of **10** featured a resonance at d= 5.32 assigned to the C-3(H). The rest of the required resonances were also present. The ci-ms of **10** showed a base peak at 248 (M^++1, 100%).

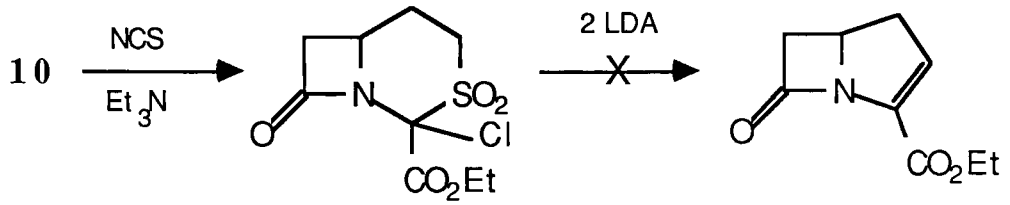
Pinto[5] has prepared a 2-sulfonyl penam (5-membered ring) via a similar route. Ours is the first example of fusion of a six-membered containing a sulfone moiety to a β-lactam via the rhodium carbenoid route.

NMR SPECTRUM OF 10



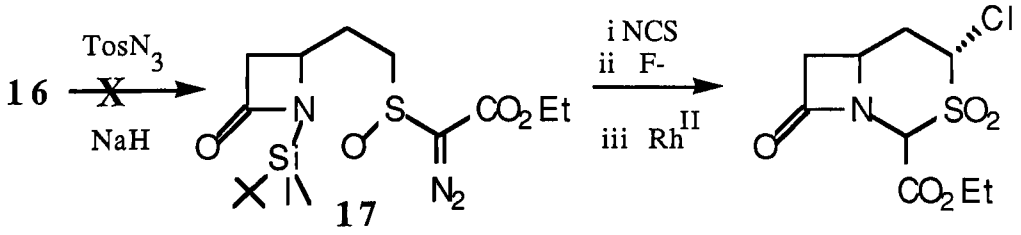
10

We were finally in a position to attempt the Ramberg-Backlund ring contraction. Chlorination of **10** with N-chlorosuccinimide/ triethylamine resulted in a 68% yield of the 4-chloro compound **15**. The chloro-lactam **15** was characterized by nmr, which no longer showed the C-3(H) resonance at δ= 5.32; the ci-ms of **15** showed a peak at m/z 282 (13%) corresponding to the M^++1 ion.



15

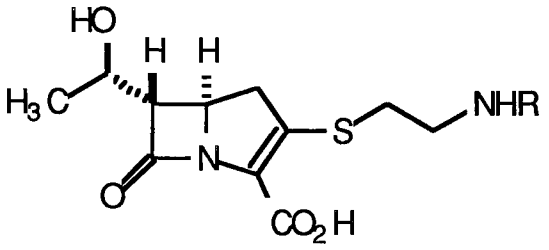
Unfortunately, reaction of **15** with lithium diisopropylamide led to it's destruction and no identifiable products were recovered. Ideally, one would want to have the chlorine present at C-2 of **15** rather than at C-4 so that the anion generation could be facilitated, and the elimination of HCl performed under milder conditions (NaOAc?). Attempts to convert the sulfoxide **16** into **17**, which in principle could be chlorinated α to the sulfoxide and oxidized to the sulfone failed at the diazo transfer stage.



Since preparation of the required bicyclic sulfone proved to be much more difficult than anticipated, the project was abandoned.

2-Methylthioethyl ester as a Carbapenem Protective Group

In the synthesis of carbapenem antibiotics such as thienamycin **18**, a most important step is the final deblocking of the C-3 carboxylic acid group.

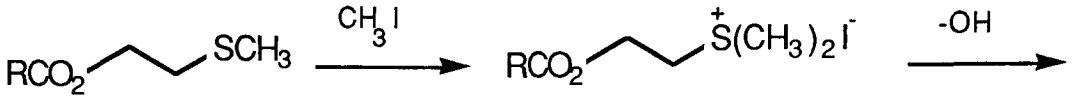


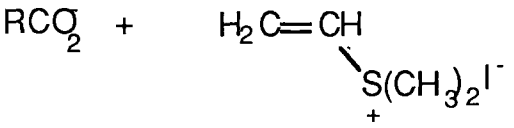
18

Due to the nature of the carbapenem ring system, a suitable protecting group must be removable under mild conditions. Traditional protecting groups used in the cepham series such as *tert*-butyl or benzhydryl are unsuitable due to the acid instability of the carbapenems. Previous syntheses of carbapenems have utilized the *para*-nitrobenzyl,[6] *ortho*-nitrobenzyl,[7] allyl,[8] 2-(trimethylsilyl)ethyl,[9] and *para*-methoxybenzyl esters as protective groups removable with H_2/Pd, hv, $Pd(PPh_3)_4$, fluoride ion and $AlCl_3$/anisole[10] respectively.

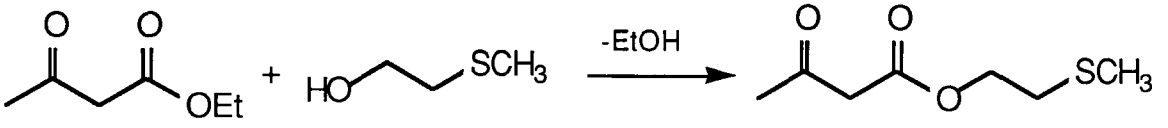
We sought to add a base labile protective group to this repertoire, the 2-methylthioethyl group that is removable by alkylation followed by treatment with base.[11] Thus, the protective group would be stable to base-mediated transformations required during synthetic schemes and would only become labile after alkylation of the sulfur atom. This ester has found use in the area of peptide chemistry where it has been used to protect the carboxyl group of amino acids such as glycine and phenylalanine. An aqueous

solution of base in the range of pH 10-11 was used to effect the deprotection step. We hoped to bring about the same result with an amine base.

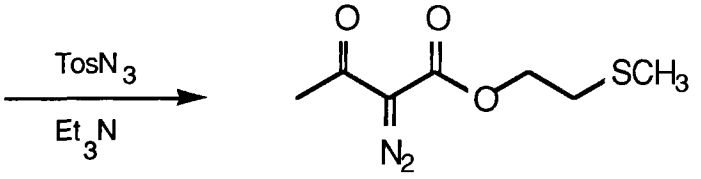




To test our scheme, 2-thiomethylethyl 4-oxobutyrate **19** was prepared by ester exchange reaction of ethyl acetoacetate with 2-thiomethylethanol in toluene. Diazotization of **19** with tosyl azide/ triethylamine gave the diazo ester **20** in 94% yield.

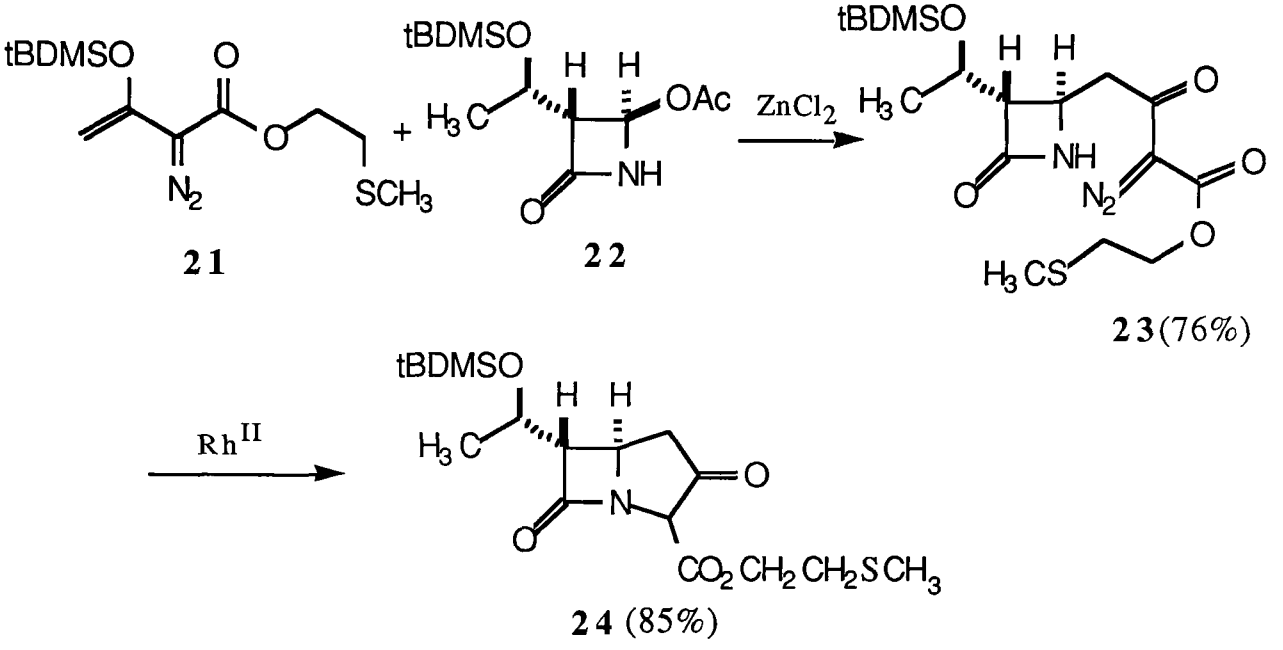


19 (65%)

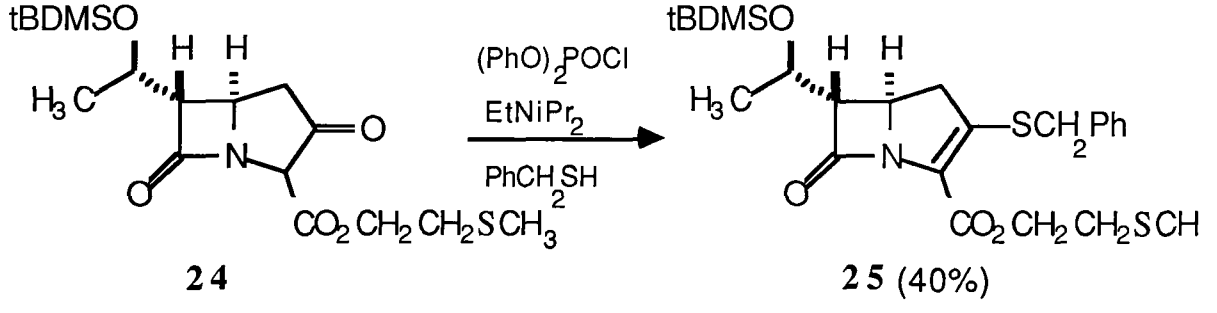


20 (94%)

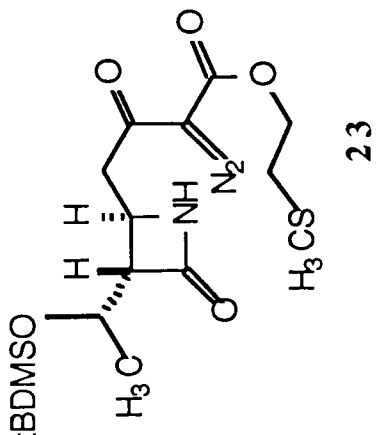
The enol silyl ether **21** was prepared in situ from **20** and *tert*-butyldimethylsilyl triflate/ triethylamine in CCl_4, and was reacted with **22** (a gift from Bristol Laboratories of Canada) under $ZnCl_2$ catalysis in the usual manner[12] to give **23** in 76% yield as a yellow oil. Treatment of **23** with rhodium(II) acetate in refluxing EtOAc furnished **24** as a yellow syrup in 85% yield.



The bicyclic β-lactam **24** was converted into a model thienamycin analogue **25** by the standard method of reacting **24** with $(PhO)_2POCl$/ $EtNiPr_2$ followed by $PhCH_2SH$.

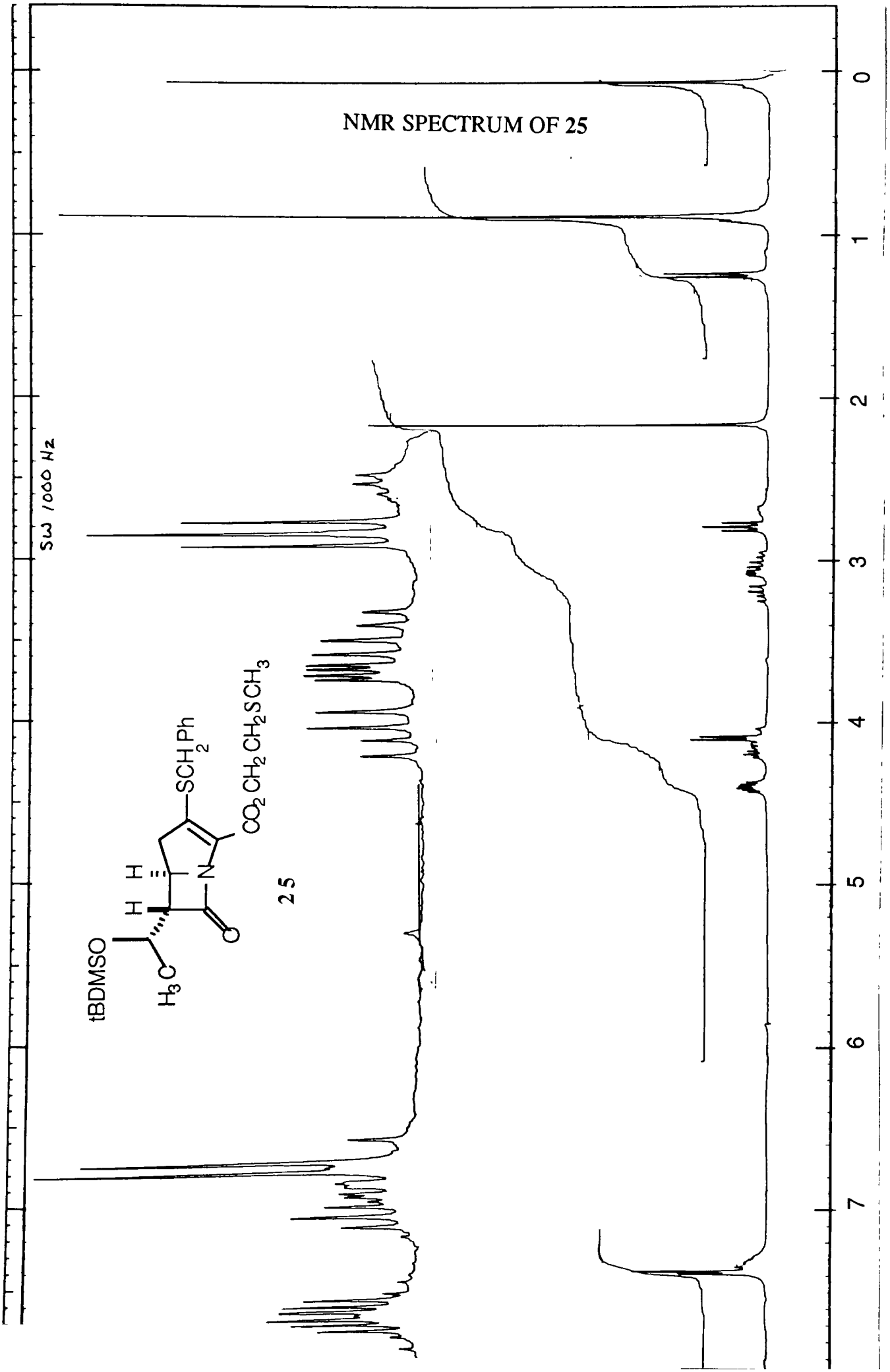


NMR SPECTRUM OF **23**



23

NMR SPECTRUM OF 25



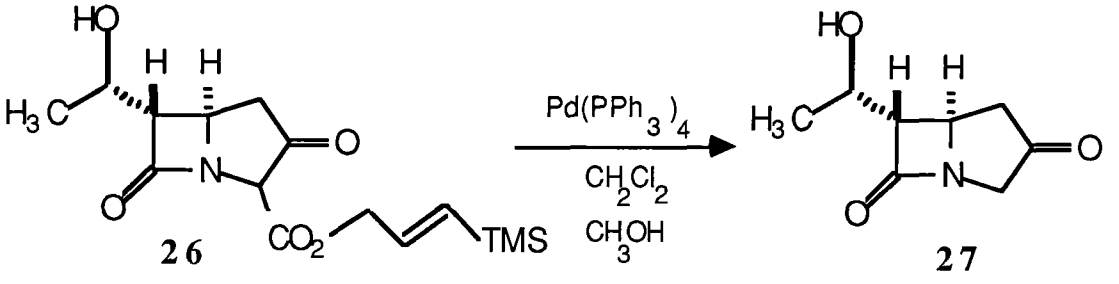
We were now ready to test the deprotection reaction, however we had to determine the mildest reaction conditions that would effect removal of the 2-thiomethylethyl ester. Using the 2-thiomethyl ester of *trans*-cinnamic acid (from cinnamoyl chloride and 2-thiomethylethanol) we found that treatment with methyl triflate at O °C for 30 min would quantitatively give the corresponding sulfonium salt , in contrast to methyl iodide which required reflux in ether. The final deprotection of the triflate salt was carried out under the following conditions regenerating the *trans*-cinnamic acid after acidic workup.

TABLE 1

Base/Solvent	Temperature(°C)	Time(min)	Yield(%)
i $Pr_2NEt/EtOH$	25	15	0
i $Pr_2NEt/EtOH$	60	15	73
KOH/CH_2Cl_2	0	15	74
$NaOCH_3/CH_3OH$	0	15	86

We were dissappointed in the strength of base required for this deprotection, and we felt that the β-lactam may not survive treatment with such a strong base. However, since we had already prepared the compounds for testing, we proceeded to attempt the deprotection of **23**.

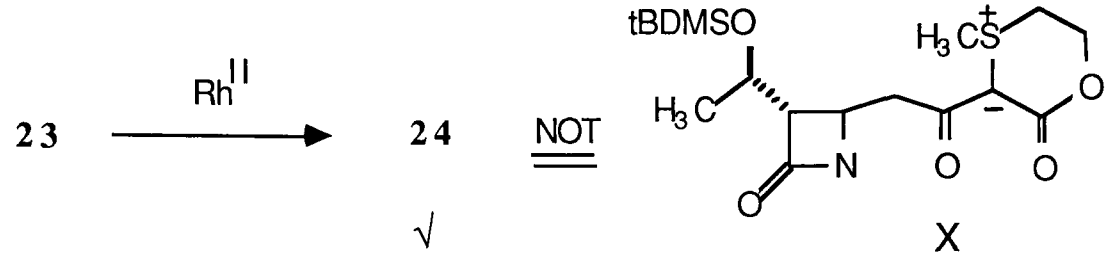
We chose methyl triflate/ sodium methoxide at 0 °C for 15 min as our mildest conditions for efficient removal of the ester. Would the carbapenem survive these conditions? When **23** was treated as per the methyl triflate/ sodium methoxide protocol only a complex mixture of decomposition products resulted, no deprotected β-lactam was recovered. An attempt was made using potassium *tert*-butoxide in place of sodium methoxide with the same result. Mastalerz[13] has demonstrated that the related β-lactam **26** could be converted into **27** in 67% yield by the action of $Pd(PPh_3)_4$ in CH_2Cl_2/ methanol.



Since **24** could not be deprotected, we did not attempt to deprotect the more sensitive thienamycin analogue **25**.

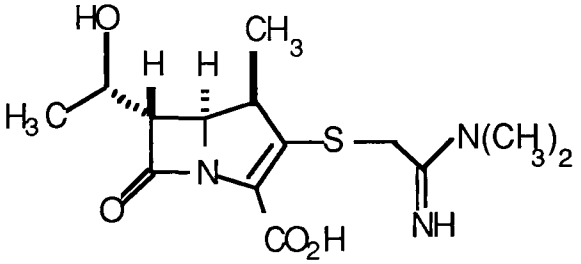
Clearly, the 2-thiomethylethyl ester failed as a protective group for the carbapenem carboxylate group. It is interesting to note however, that in the preparation of **24**, intramolecular N-H insertion (5-membered ring) successfully competes with sulfur ylide formation (6-membered ring) resulting in the carbapenam ring system. This is quite remarkable given the ease in which sulfur ylides are formed by exposure to rhodium carbenoids. This further

demonstrates the propensity for rhodium carbenoids to form 5-membered rings in preference to six-membered rings.



1-β-Methylcarbapenems via Nitroethane

While there have been many natural and synthetic carbapenems reported, none of these has demonstrated both excellent antibacterial activity and stability towards the deactivating renal dipeptidase-I enzyme, with the exception of the 1-β-methylcarbapenem **28**.[14] This compound is

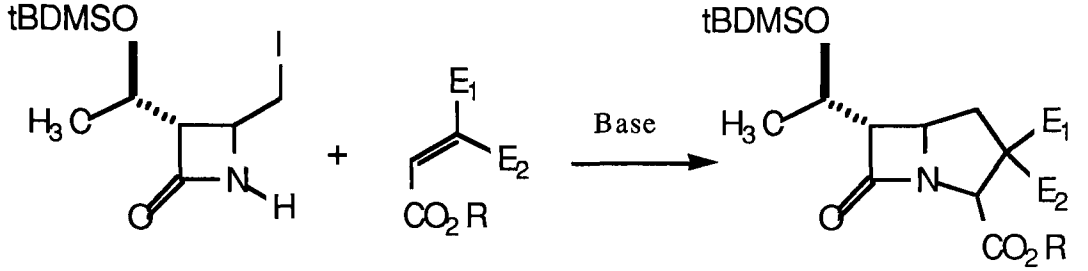


28

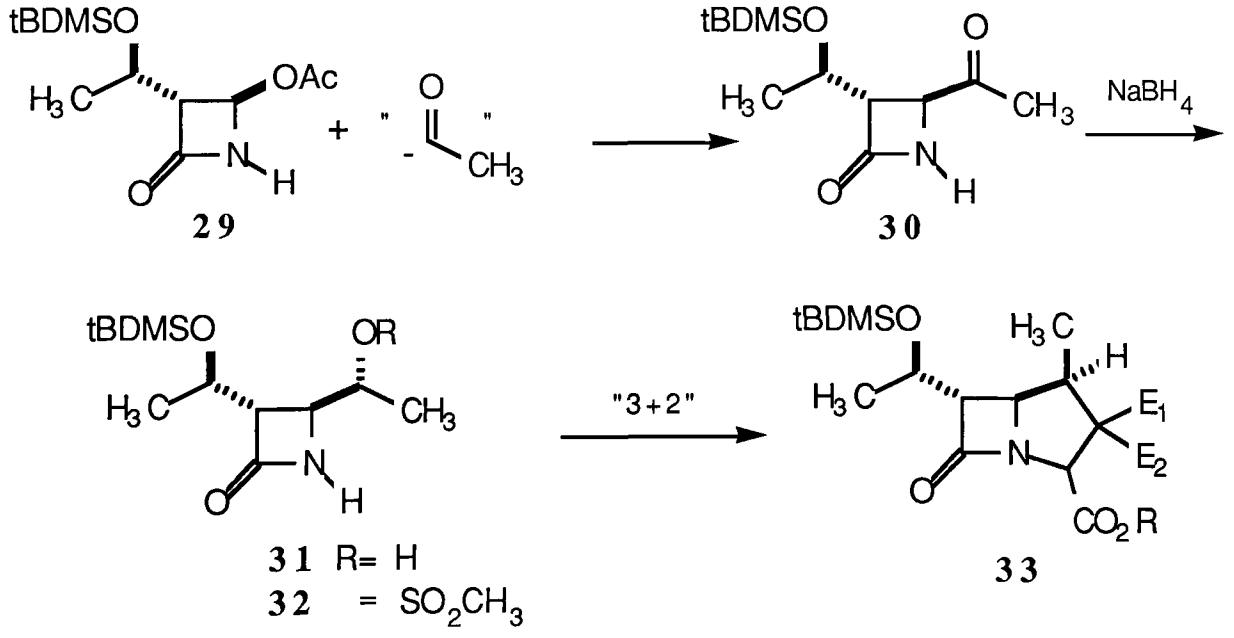
exceptionally stable and very potent against a variety of pathogenic bacteria compared to thienamycin. Compound **28** is prepared by the usual rhodium(II) carboxylate catalyzed cyclization of the appropriately substituted diazo precursor.

An ongoing project in our laboratory is the preparation of carbapenams via a "3+2" cyclization reaction,[15,16] where a pre-formed β-lactam anion adds to an activated alkene in a Michael

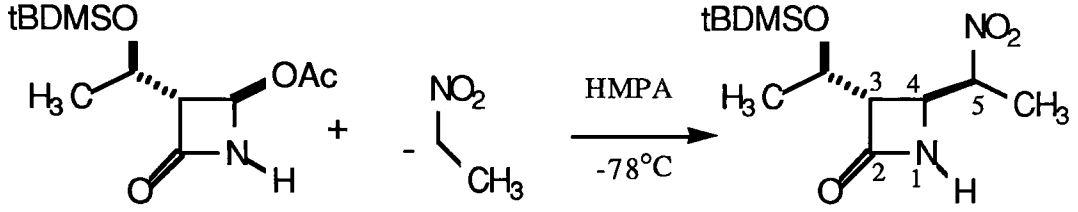
fashion, that in turn displaces a leaving group attached to the C-4(1') of the β-lactam.



We sought to use this methodology to prepare the 1-β-methylcarbapenam system by the following route. We had in our possession the known β-lactam **29**[17] in an optically pure form, and we reasoned that displacement of the 4-acetoxy group by an "acyl anion equivalent" would lead to the 4-acetyl lactam **30**. Reduction of the ketone should give the alcohol **31**. Mesylation of **31** to give **32** followed by the "3+2" cycloaddition should give the 1-β-methylcarbapenam **33**.

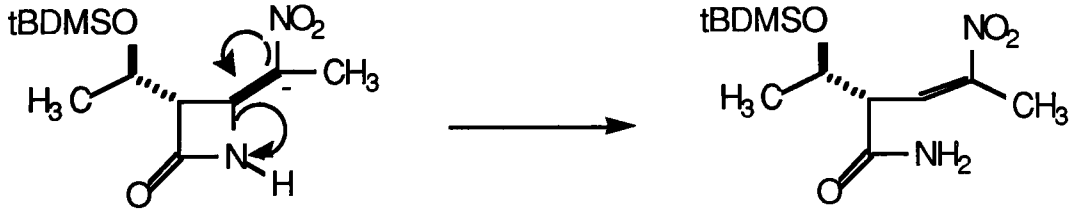


We chose as our acyl anion synthon 1-nitroethane. After displacement of the 4-acetoxy group by the anion of nitroethane, the nitro group should be convertible to a keto group to give **30** by one of several known methods.[18] Thus, reaction of the β-lactam **29** with the lithium nitronate of nitroethane in tetrahydrofuran at -78 °C in the presence of 2 eq of HMPA gave a 67% yield of nitro-lactam **34** (a 2:1 mixture of C-5 epimers) as a white powder after



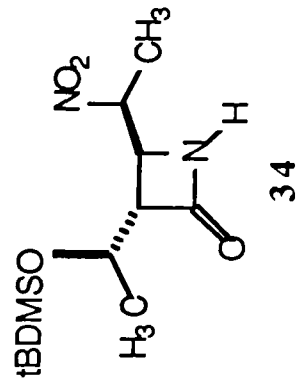
29 **34**

chromatography. Compound **34** was identified by its nmr spectrum that showed a major and minor diastereomer. Selected data include δ= 1.63 (d, $C\underline{H}_3CHNO_2$) and 4.74 (m, $CH_3C\underline{H}NO_2$). The infrared spectrum of **34** featured bands at 1760, 1550 and 1330 cm^{-1} due to the β-lactam and nitro functions respectively. The ci-ms showed a base peak at m/z 303 (M^++1, 100%). The reaction proved to be very capricious, and if left to stir at room temperature substantial amounts of the amide **35** were formed by ring opening of **34**.



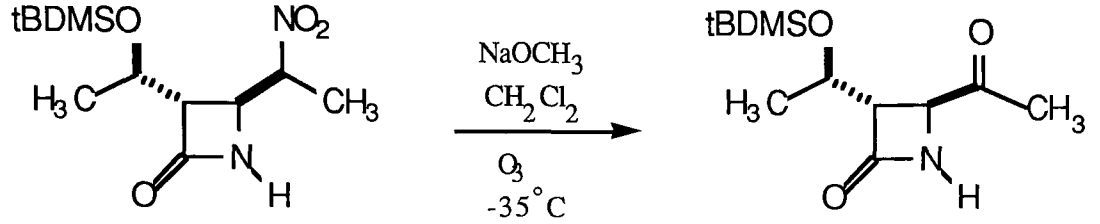
34 **35**

NMR SPECTRUM OF **34**



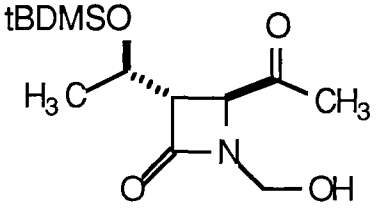
34

The desired β-lactam **34** was converted into the 4-acetyl lactam **30** by ozonolysis of the sodium nitronate of **34** in CH_2Cl_2.[19] Compound **30** was obtained as a clear colourless oil



34 **30**

in 40% yield after chromatography. The ^1H nmr was identical with that previously reported.[20] If the ozonolysis was carried out in methanol, the only product isolated in 59% yield was **36** the result of nucleophilic attack of the β-lactam nitrogen on formaldehyde formed in situ from the oxidation of methanol by ozone.

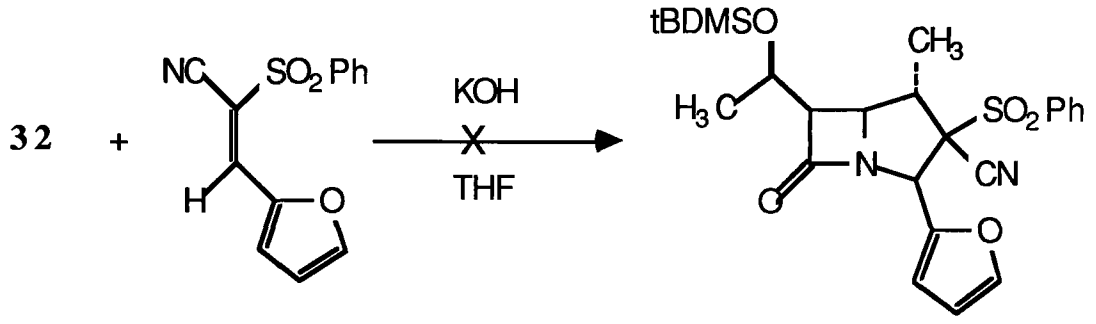


36

The reduction of **30** with sodium borohydride in methanol furnished the alcohol **31** in 95% yield as a clear oil. The stereochemistry at C-5 was not determined, rather we proceeded with our scheme by mesylation of **31** with methanesulfonyl chloride/ triethylamine to give **32** in 60% yield. The mesylate appeared to be an approximate 1:1 mixture of diastereomers as evidenced by two closely spaced singlets for the $OSO_2C\underline{H}_3$ signals (δ= 3.03, 3.07) in the ^1H nmr. The diastereomeric ratio may possibly be improved by use of other reducing agents and or metal salts for

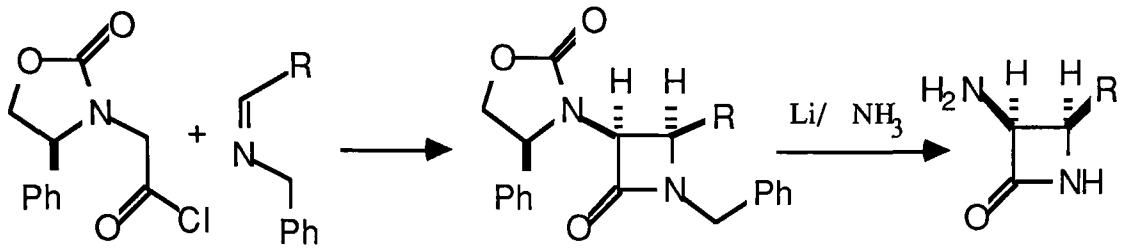
chelation control. We decided to test the "3+2" addition with our diastereomeric mixture rather than explore the reduction.

When the mesylate **32** was reacted with the Michael receptor shown below, no addition or cyclization products were isolated. The project was abandoned at this stage.



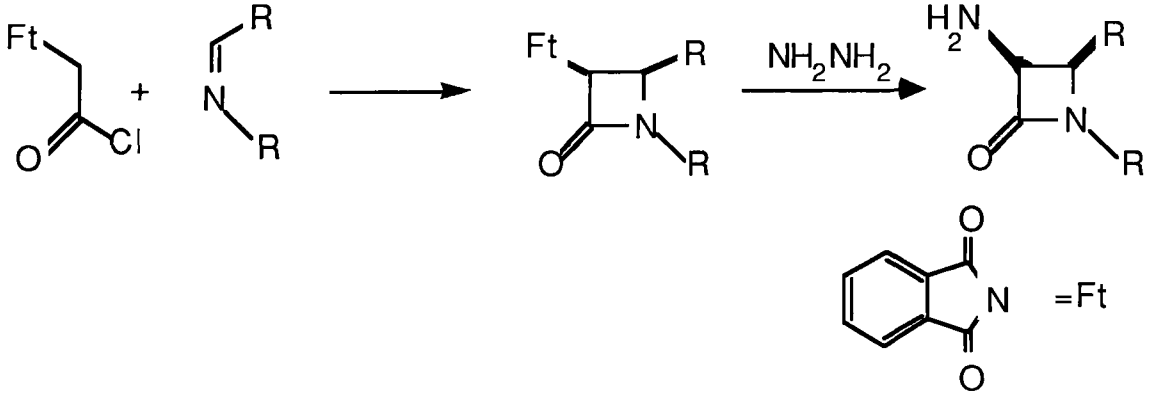
Camphor as a Chiral Auxiliary in the Staudinger Reaction

The preparation of azetidin-2-ones in an enantiospecific fashion has always been an important objective in the chemical synthesis of β-lactam antibiotics. There have been developed many approaches to chiral β-lactams, most have been reviewed recently.[1,2] Conceptually, one of the more interesting chiral syntheses relies on the formation of the β-lactam ring via the ketene-imine cycloaddition approach (Staudinger reaction) using a chiral acetic acid derivative.[21] Thus, reaction of **37** with imines results in excellent yields (80-90%) of *cis* β-lactams of high (84-94%) enantiomeric excess.

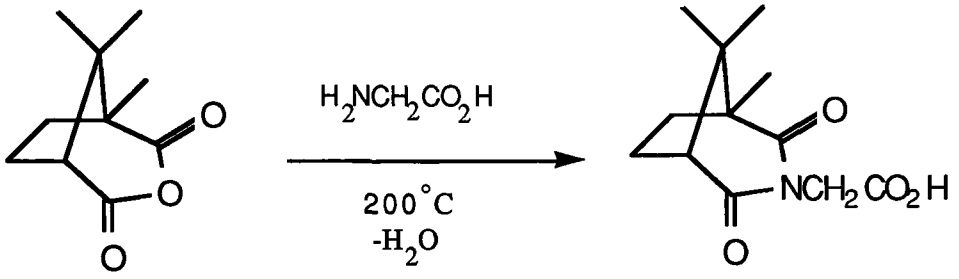


37

The 4-phenyloxazolidone auxiliary (and the N-benzyl group) is removable with lithium in liquid ammonia, providing a relatively easy access to homochiral *cis* fused azetidin-2-ones. A drawback to this synthesis is the destructive removal of the relatively complex chiral auxiliary; we therefore sought to improve upon this method. Our plan was to use a simpler, more readily accessible chiral auxiliary that could possibly be removed in a non-destructive manner. The phthalimido group has been used extensively in the area of β-lactam synthesis as an N-protecting function for the C-3 amide nitrogen. The usual procedure is to form the β-lactam from phthalimidoacetyl chloride and an imine by the Staudinger reaction, the C-3 nitrogen is revealed at the appropriate time by reaction with hydrazine.

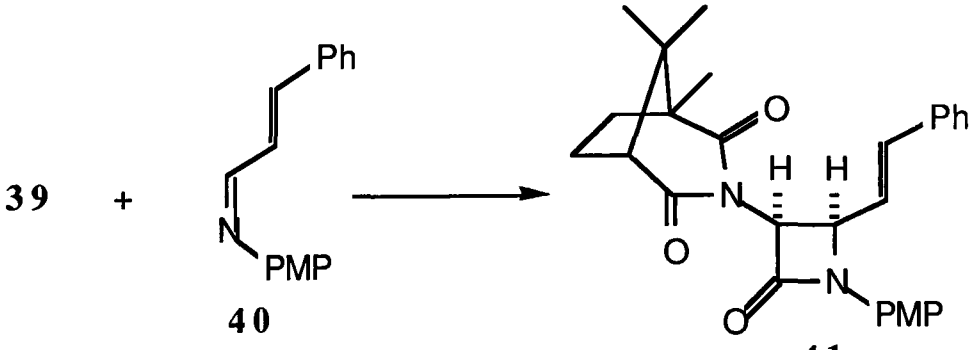


We reasoned that a chiral imide might induce chirality in the β-lactam formation step just as the 4-phenyloxazolidone, with the added feature of ease of removal and possibility of recovery. We therefore prepared **39** from *d*-camphoric anhydride[22] **38** and glycine by melting an intimate mixture in a Kugelrohr apparatus under N_2 followed by extractive isolation. The imido-acid **39** was obtained in 66% yield as white crystals from ether-hexane, mp 169-172 °C(brown), $[\alpha]_D$= +13.3 (c=1, $CHCl_3$).



38 **39**

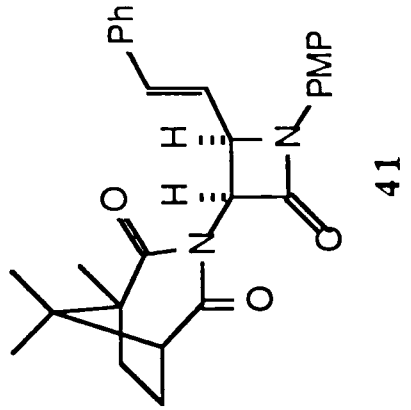
This chiral acid was reacted with oxalyl chloride in benzene to form the corresponding acid chloride in situ, and this was reacted with N-(3-phenyl-2-propenylidene)-4-methoxyaniline **40** to give a 53% yield of *cis* β-lactam **41**, mp 187-197 °C(soft-brown), $[\alpha]_D$= +8.4 (c=1, $CHCl_3$).



40 **41**
(cis-relative)

The 300 MHz ^1H nmr spectrum of **41** was complicated by dynamic effects, however when the spectrum was recorded at 55.4°C some of

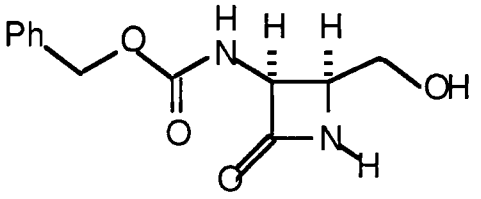
NMR SPECTRUM OF **41**



41

the once broad unresolved peaks were resolved. In particular the resonance attributed to PhC<u>H</u>=CH- went from a broad hump at δ= 6.63 to a clean doublet, J= 15.6 Hz. Unfortunately, the ring protons at C-3 and C-4 were never fully resolved. Most interesting was the resonance corresponding to PhCH=C<u>H</u>- that appeared as a doublet of doublets, J= 15.6, 8.4 Hz, with two sets of signals being present. This could be due to some rotational phenomenon or the presence of a pair of diastereomers.

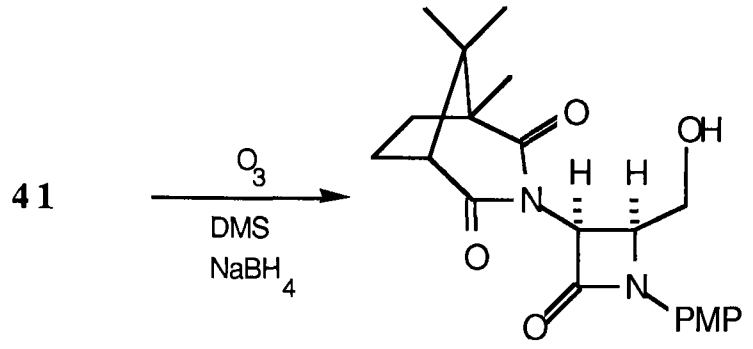
In order to determine if **41** was homochiral or a diastereomeric pair we attempted to convert **41** into the known compound **42**[19] by



42

first removing the camphoryl moiety with hydrazine. Dissappointingly, all attempts to remove this group with hydrazine, butylamine, sodium hydroxide or sodium borohydride met with failure, and the starting β-lactam was recovered in all cases. Compound **41** proved to be extremely stable!

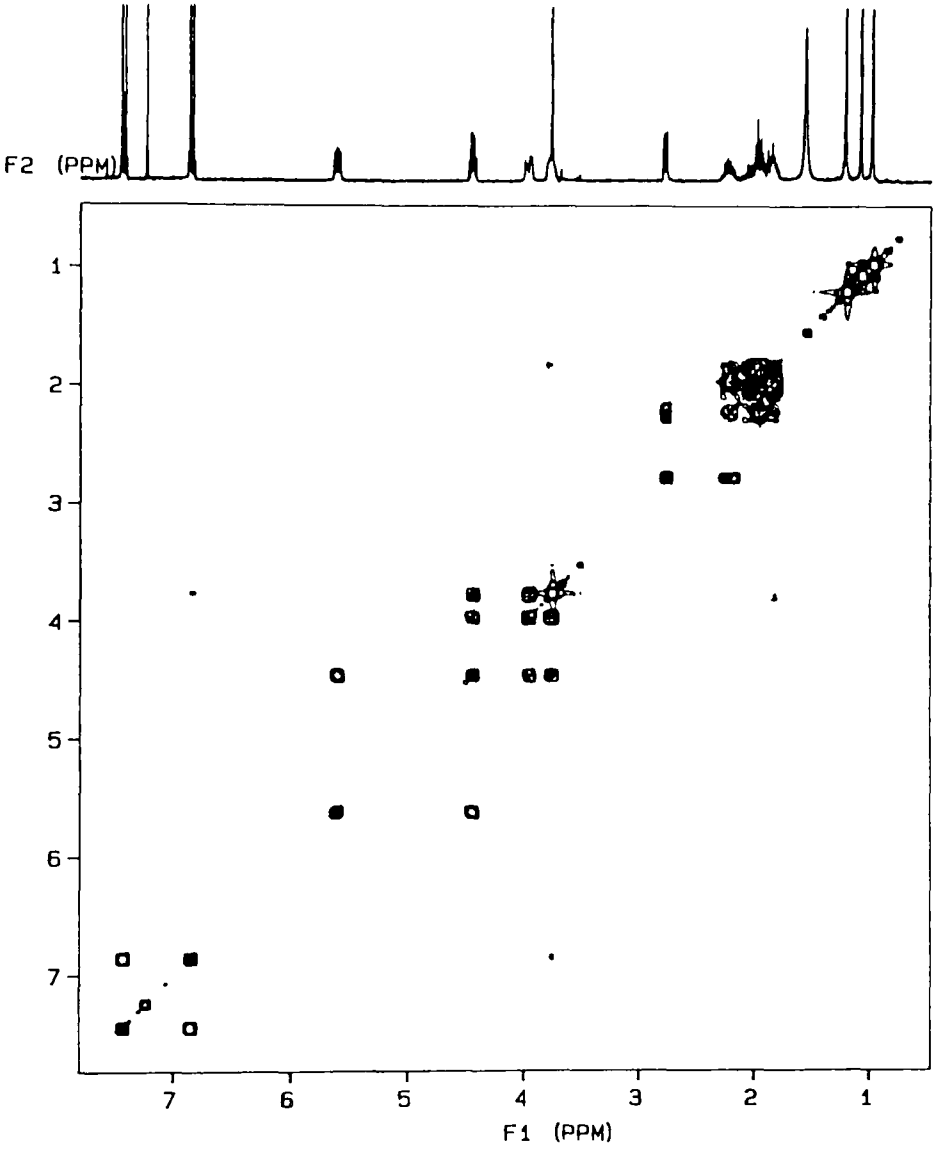
The 4-styryl side chain was converted to a hydroxymethyl group via ozonolysis and reduction in an effort to obtain a simpler nmr spectrum, free of dynamic effects. The ozonolysis and reduction were performed on **41**, and a 63% yield of alcohol **43** was recovered following chromatography.

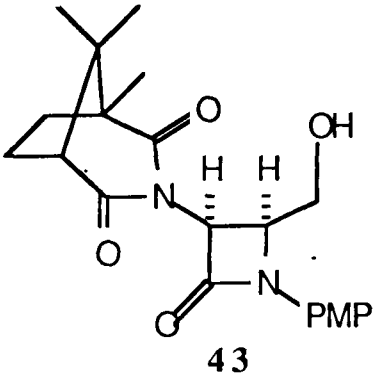


43
(cis-relative)

The 300 MHz ^{1}H nmr spectrum of **43** was much simpler, with all signals well resolved. The C-3 proton at δ= 5.62 appeared as a pair of doublets, each having a 5 Hz coupling constant. A HOMCOR spectrum of **43**, recorded later, was to reveal that the C-3 proton was coupled only to the C-4 proton as expected and the two sets of signals were probably due to diastereomers. The ^{13}C nmr spectrum of **43** showed doubling of almost all of the signals, most probably indicative of the presence of a pair of diastereomers. This observation, though inconclusive, coupled with our inability to convert the β-lactam **41** into a known, chiral compound led us to abandon this approach.

HOMCOR NMR SPECTRUM OF **43**





43

Experimental

The general comments made regarding instruments and reagents made in the Experimental section of Chapter 2 are applicable here as well.

β-Lactam **6** A solution of 2.77 g of *tert*-butyldimethylsilyl chloride (18.4 mmole) in 10 ml of dry CH_2Cl_2 was added dropwise to a stirred solution of 4.0 g of crude β-lactam 5 (≈ 18.4 mmole) in 25 ml of dry CH_2Cl_2 containing 1.86 g of triethylamine (18.4 mmole), and the resulting mixture was stirred for 1 h. The reaction mixture was poured into water, the organic layer was separated and washed with 1% HCl then 5% $NaHCO_3$, dried over $MgSO_4$ and evaporated to give 5.7 g of crude silyl-lactam. Purification by HPLC using hexane-EtOAc (3:1) afforded 4.0 g of pure **6** as a pale yellow oil (66%); ir ($CHCl_3$) 1750 br. cm^{-1}; nmr δ 0.06, 0.08 (s, $SiCH_3$), 0.74 (s, SitBu), 1.14 (t, CH_3, J= 6 Hz), 1.60 (m, 1H, $C\underline{H}_2CH_2S$), 2.10 (m, 1H, $C\underline{H}_2CH_2S$), 2.5 (m, CH_2S), 3.0 (m, 1H, C3-H), 3.06 (s, SCH_2CO_2), 3.46 (m, C4-H), 4.06 (q, $C\underline{H}_2CH_3$, J= 6 Hz).

β-Lactam **7** A 134 mg portion of N-chlorosuccinimide was added to a stirred solution of dry CH_2Cl_2. After 10 min t.l.c analysis revealed that the reaction was complete. The reaction mixture was poured into water, the organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated to give 260 mg of crude chloro-lactam **7**. Column chromatography with hexane-EtOAc (3:1) gave 171 mg of pure **7** as a clear colourless oil (47%); ir ($CHCl_3$) 2930,1750 br. cm^{-1}; nmr (diastereomers) δ 0.10 (s, $SiCH_3$), 0.94 (s, SitBu), 1.32 (t, CH_3, J= 6 Hz), 1.70 (m, 1H, $C\underline{H}_2CH_2S$), 2.20 (m, 1H,

$C\underline{H}_2CH_2S$), 2.65 (dd, C3-H, J=2,15 Hz), 2.7-2.9 (m, CH_2S), 3.16 (dd, C3-H, J= 5,15 Hz), 3.62 (m, C4-H), 4.28 (q, $C\underline{H}_2CH_3$, J= 6 Hz), 5.37, 5.38 (s, CHCl); ei-ms m/z 308 (M^+-57, 31.7%), 266 (308-42, 21.1%), 238 (13.4%), 148 (54.7%), 100 (100%).

β-Lactam **10** A solution of 210 mg of diazo-lactam **14** (0.763 mmole) in 5 ml of dry CH_2Cl_2 was refluxed with 5 mg of $Rh_2(OAc)_4$ for 18 h. The solvent was evaporated, and the remaining residue was eluted through a plug of silica gel. Concentration of the eluate gave 156 mg of pink oil. Chromatography with EtOAc afforded 139 mg of pure **10** (74%) as a clear colourless syrup that solidified on storage at 5 °C; ir ($CHCl_3$) 2950, 1760, 1730, 1325, 1120 cm^{-1}; nmr δ 1.27 (t, CH_3, J= 7 Hz), 2.48 (m, 2H, C1), 2.71 (dd, 1H, C-7, J=2,15 Hz), 3.04 (m, 1H, C2), 3.21 (dd, 1H, C7, J= 5,15 Hz), 3.53 (m, 1H, C-2), 4.22 (m, 1H, C-6), 4.26 (q, $C\underline{H}_2CH_3$, J= 6 Hz), 5.32 (d, 1H, C-3, J= 2 Hz); ci-ms m/z 248 (M^++1, 100%).

β-Lactam **11** A 200 mg portion of dry CsF (1.3 mmole) was added to a solution of 100 mg of **6** (0.3 mmole) in 2 ml of dry acetonitrile. The mixture was stirred at room temperature for 6 h, whereupon t.l.c. analysis with hexane-EtOAc (1:1) revealed the less polar **6** (R_f= 0.58) was replaced by a more polar spot of R_f= 0.19. The mixture was filtered and evaporated to give 50 mg of crude **11**. Preparative layer chromatography afforded 40 mg of pure **11** (61%). ir ($CHCl_3$) 3390, 2990, 1715, 1660 cm^{-1}; nmr δ 1.18 (t, CH_3, J= 6 Hz), 1.68 (m, 1H, CH_2CH_2S), 1.98 (m, 1H, CH_2CH_2S), 2.46 (d, CH_2CO, J= 6 Hz), 2.7-2.94 (m, CH_2S), 3.0 (d, 1H, $COCH_2S$, J= 14 Hz), 3.44 (d, 1H, $COCH_2S$, J= 14 Hz), 3.80 (m, 1H, $C\underline{H}NH$), 4.10 (q, $C\underline{H}_2CH_3$, J= 6 Hz), 5.95 (br.s.,

NH); ei-ms m/z 217 (M^+, 95%), 142 (M^+-75, 100%); ci-ms 218 (M^++1, 100%).

β-Lactam **12** A solution of 450 mg of **7** (1.23 mmole) in 8 ml of CH_3OH was stirred at room temperature while 620 µl of 6N HCl (3.7 mmole, 3 eq) was added in a dropwise fashion. Analysis by t.l.c. showed that the starting β-lactam **7** (R_f= 0.80) was replaced by a more polar material of R_f= 0.24 after 45 min. The reaction mixture was neutralized with 10% K_2CO_3 and concentrated to 50% of it's original volume. The concentrate was saturated with NaCl and extracted with EtOAc. The organic extract was dried over $MgSO_4$ and evaporated to give 261 mg of **12** (86%); ir ($CDCl_3$) 3390,1750 , 1710 cm^{-1}; nmr (diastereomers) δ 1.26 (t, CH_3,), 1.85 (m, 1H, $C\underline{H}_2CH_2S$), 2.62 (m, CH_2S), 3.10 (m, C3-H), 3.34, 3.42 (s, OCH_3), 3.65 (m, C4-H), 4.25 (q, $C\underline{H}_2CH_3$, J= 6 Hz), 4.78, 4.76 (s, $C\underline{H}OCH_3$), 6.0 (br., NH); ei-ms m/z 247 (M^+, 0.6%), 174 (M^+-73,25.7%), 118 (30.4%), 29 (100%).

β-Lactam **13** A solution of 4.34 g of crude **5** (≈ 20 mmole) in 30 ml of CH_2Cl_2 was cooled to 0 °C, and 7.59 g of *meta*-chloroperoxybenzoic acid (≈44 mmole) in 20 ml of dry CH_2Cl_2 was added dropwise with stirring. The reaction mixture was stirred at room temperature for 3 h following addition, then the by-product *meta*-chlorobenzoic acid was filtered off, and the filtrate was washed with 10% Na_2SO_3, dried over $MgSO_4$ and concentrated to a white solid. This material was purified by HPLC with EtOAc to give 3.0 g of pure sulfone **13** (60%); ir ($CDCl_3$) 3390,1740 br., 1310, 1110 cm^{-1}; nmr δ 1.27 (t, CH_3, J= 7 Hz), 2.3 (m, $C\underline{H}_2CH_2S$), 2.5-3.5 (m, CH_2S, C3-H's), 3.9 (m, C4-H), 4.0 (s, $O_2SCH_2CO_2$), 4.20 (q, $C\underline{H}_2CH_3$, J= 7 Hz), 6.6 (br., NH).

β-Lactam **14** A solution of 584 mg of sulfone **13** (2.3 mmole) in 2 ml of dry tetrahydrofuran was added dropwise under N_2 to a stirred slurry of 110 mg of NaH (2.3 mmole, 50% w/w in oil, washed in hexane) in 10 ml of dry tetrahydrofuran at -40 °C. After stirring for 5 min, a solution of 500 mg of tosyl azide (2.5 mmole, 1.1 eq) in 2 ml of dry tetrahydrofuran was added in a dropwise manner. A t.l.c. taken 10 min later showed the presence of reactants only, so the cold bath was removed and the solution allowed to warm to room temperature. The warming was accompanied by a colour change from yellow to deep brown. At this point the reaction mixture was poured into saturated NH_4Cl layered over with ether, the ethereal layer was separated, dried over $MgSO_4$ and concentrated to furnish 593 mg of pink oil. Chromatography with EtOAc afforded 215 mg of pure **14** (34%) as an orange foam; ir ($CDCl_3$) 3420, 2140, 1765,1715, 1345, 1300 cm^{-1}; nmr δ 1.27 (t, CH_3, J= 7 Hz), 2.3 (m, $C\underline{H}_2CH_2S$), 2.5-3.5 (m, CH_2S, C3-H's), 3.9 (m, C4-H), 4.20 (q, $C\underline{H}_2CH_3$, J= 7 Hz), 6.6 (br., NH).

β-Lactam **15** A 126 mg portion of N-chlorosuccinimide (0.95 mmole, 1.1 eq) was added to a solution of 213 mg of bicyclic β-lactam 10 with stirring at room temperature, followed by 96 mg of triethylamine (0.95 mmole). After 2 h the solvent was evaporated, and the resulting oil was taken up in EtOAc and eluted through a plug of silica gel to give 380 mg of red oil. Chromatography with EtOAc-hexane (6:4) gave 135 mg of pure 15 (48%) as a clear colourless oil; ir ($CDCl_3$) 1790, 1760, 1725, 1350, 1155 cm^{-1}; nmr δ 1.40 (t, CH_3, J= 7 Hz), 2.50 (m, 2H, C1), 2.87 (dd, 1H, C-7, J=2,15 Hz),

3.20 (m, 1H, C2), 3.25 (dd, 1H, C7, J= 5,15 Hz), 3.70 (m, 1H, C-2), 4.0 (m, 1H, C-6), 4.47 (q, $C\underline{H_2}CH_3$, J= 6 Hz); ci-ms m/z 282 (M^++1, 13.0%).

β-Lactam **16** A solution of 410 mg of **7** (1.24 mmole) in 12 ml of CH_2Cl_2 was cooled to -78 °C, and 214 mg of *meta*-chloroperoxybenzoic acid (≈1.24 mmole, 1 eq) in 3 ml of dry CH_2Cl_2 was added dropwise, and the mixture was stirred at -78 °C for 3 h. After warming to room temperature, the reaction mixture was washed with 10% Na2SO3, 5% NaHCO3 and water, the organic layer was dried over $MgSO_4$ and evaporated to give 571 mg of crude sulfoxide. Chromatography with EtOAc-CH3OH (95:5) afforded 323 mg of pure sulfoxide **16** (75%) as a pale yellow oil; ir (neat) 2930,1755 br., 1200, 1030 cm^{-1}; nmr δ 0.03 (s,$SiCH_3$), 0.95 (s, SitBu), 1.3 (t, CH_3, J= 6 Hz), 1.8-3.2 (m, $C\underline{H_2}CH_2S$, C3-H's), 3.6 (m, C4-H), 3.7 (s, $OSCH_2CO_2$), 4.17 (q, $C\underline{H_2}CH_3$, J= 6 Hz).

2-(Thiomethyl)ethyl 3-oxobutyrate **19** A solution of 5.2 g of ethyl acetoacetate (40 mmole) and 3.68 g of 2-(methylthio)ethanol (40 mmole) in 60 ml of toluene was heated to reflux, allowing toluene to distill from the reaction mixture. When 10 ml of distillate was collected it was discarded, and replaced by a fresh 10 ml of toluene. After about eight changes of solvent aliquots, the toluene solution was evaporated, and the residual oil was distilled. The main fraction of b.p. 95 °C/ 5mm was collected to afford 4.55 g of pure **19** as a yellow oil; nmr δ 2.10 (s,CH_3), 2.23 (s, SCH_3), 2.70 (t, CH_2S), 3.43 (s, $COCH_2CO_2$), 4.26 (t, CH_2O).

2-(Thiomethyl)ethyl 2-diazo-3-oxobutyrate **20** A 1.97 g aliquot (10 mmole) of tosyl azide was added to a stirred solution of 1.76 g (10 mmole) of 19 in 15 ml of dry acetonitrile containing 1.01 g

(10 mmole) of triethylamine. The resulting solution was stirred at room temperature for 2.5 h, the solvent was removed under vacuum, and the remaining yellow solid was dissolved in ether. The ethereal solution was washed with 5 ml of 10% KOH, 5 ml of 3% KOH, 5 ml of water , dried over $MgSO_4$ and evaporated to give 1.90 g of 20 (94%) as a yellow oil, subsequently used as such; ir ($CHCl_3$) 2890, 2120, 1710, 1650 cm^{-1}; nmr δ 2.13 (s,CH_3), 2.43 (s, SCH_3), 2.73 (t, CH_2S), 4.33 (t, CH_2O); ei-ms m/z 174 (M^+-28, 1.3%), 155 (M^+-SCH_3, 2.4%), 74 ($CH_2CH_2SCH_3^+$, 100%).

β-Lactam **23** A 2.0 g portion of freshly fused $ZnCl_2$ was crushed to a powder in dry CH_2Cl_2 under a stream of N_2. The acetoxy β-lactam **22** (3.82 g, 13.3 mmole) was added and the slurry was stirred at 0 °C. A solution of 4.04 g (20 mmole) of diazoester **20** in 40 ml of dry CCl_4 under N_2 was cooled to 0 °C and 2.43 g of triethylamine was added followed by 5.82 g (22 mmole) of *tert*-butyldimethylsilyl triflate. The reaction mixture was stirred at 0 °C for 40 min at which time a floating layer of triethylammmonium triflate was removed by pipette. The remaining solution was transferred by double ended cannula to a dry dropping funnel fitted to the reaction flask containing the $ZnCl_2$/ β-lactam slurry. The crude enol-silyl ether solution was added dropwise to the stirred slurry, the the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by pouring into water, the organic layer was separated and dried over $MgSO_4$ then evaporated to give 7.42 g of crude **23** as a yellow oil. Purification by HPLC using hexane-EtOAc (2:1) gave 4.32 g of pure **23** (76%) as a yellow oil; ir ($CHCl_3$) 3400, 2920, 2120, 1755, 1710, 1645 cm^{-1}; nmr δ 0.06 (s, $SiCH_3$), 0.80 (s, SitBu), 1.21 (d,

$CHC\underline{H}_3$, J= 6 Hz), 2.22 (s, SCH_3), 2.74 (t, CH_2, J= 6 Hz), 2.82 (dd, C3-H, J= 2,4 Hz), 2.94 (dd, 1H, CH_2CO, J= 18, 10 Hz), 3.36 (dd, 1H, CH_2CO, J= 18, 4 Hz), 4.00 (m, C4-H), 4.22 (m, $C\underline{H}CH_3$), 4.40 (t, CH_2O, J= 6 Hz), 6.0 (br. s., NH).

β-Lactam **24** (Cyclization of **23**) A solution of 2.15 g of **23** (5 mmole) in 25 ml of EtOAc was heated to reflux, and 20 mg of $Rh_2(OAc)_4$ was added. Vigorous gas evolution occured and a burgundy solution resulted. After 1 h 15 min t.l.c. analysis revealed that the starting β-lactam had been completely replaced by a less polar compound. The reaction mixture was cooled to room temperature and evaporated to give 2.04 g of crude 24 as a burgundy oil. This was eluted through a pad of silica gel with hexane-EtOAc to give 1.7 g of cyclized material(85%) as a yellow syrup; ir ($CHCl_3$) 2930, 1760 br. cm^{-1}; nmr δ 0.09 (s, $SiCH_3$), 0.90 (s, SitBu), 1.27 (d, $CHC\underline{H}_3$, J= 6 Hz), 2.16 (s, SCH_3), 2.42 (dd, H1-α, J= 7,18 Hz), 2.74 (t, CH_2S, J= 6 Hz), 2.90 (dd, H1-β, J= 7,18 Hz), 3.12 (dd, C6-H, J= 2, 6 Hz), 4.1-4.4 (m, CH_2O, C7-H, C5-H), 4.68 (s, C3-H).

β-Lactam **25** A solution of 100 mg of **24** (0.25 mmole) in 3 ml of CH3CN was cooled to 0 °C and 74 mg of diphenylphosphochloridate (0.275 mmole, 1.1 eq) was added followed by 10 mg of 4-dimethylaminopyridine and 33 mg (0.25 mmole, 1 eq) of ethyldiisopropylamine. The resulting mixture was stirred at 0 °C for 10 min, and cooled to -15 °C whereupon 31 mg of benzyl mercaptan (0.25 mmole, 1 eq) and 33 mg of ethyldiisopropylamine (0.25 mmole, 1 eq) were added and the reaction mixture was stirred at -10 °C for 1.5 h. The solution was then poured into water, the organic layer was separated and washed with saturated $NaHCO_3$ and saturated NH_4Cl,

dried over $MgSO_4$ and evaporated to give 206 mg of crude. Column chromatography with hexane-EtOAc (5:1) gave 50 mg of pure 25 as a white powder (40%). This compound was quite unstable, and decomposed to a pink oil after storage for one month at 0 °C; ir ($CHCl_3$) 2930, 1770, 1700, 1120 cm^{-1}; nmr δ 0.06 (s, $SiCH_3$), 0.88 (s, SitBu), 1.23 (d, $CHC\underline{H}_3$, J= 6 Hz), 1.37 (s, SCH_3), 2.78 (t, CH_2S, J= 6 Hz), 2.98 (dd, H1-α, J= 7,18 Hz), 3.07 (dd, C6-H, J= 2, 6 Hz), 3.20 (dd, H1-β, J= 7,18 Hz), 4.09 (d, CH_2Ph, J=14 Hz), 4.10-4.45 (m, CH_2O, C5-H,$C\underline{H}CH_3$); ei-ms m/z 507 (M^+, 2.0%), 349 (M^+-158, 3.7%), 91 (100%).

.Nitro β-Lactam **34** A solution of 144 mg of nitroethane (1.91 mmole) in 10 ml of dry tetrahydrofuran containing 685 mg of hexamethyl phosphoric triamide (3.82 mmole) was cooled to -78 °C under N_2, and 0.82 ml of n-butyllithium (2.33 M in hexane) was added dropwise with stirring. A milky solution of the nitronate anion resulted. The anion solution was transferred to a solution of 500 mg of acetoxy β-lactam **29** (1.74 mmole) in 10 ml of dry tetrahydrofuran at -78 °C under N_2 via double ended cannula. The reaction mixture was stirred at -78 °C for 40 min, then was allowed to warm to room temperature over 15 min. The colour of the mixture goes from a milky white to a clear light yellow as warming occurs. The reaction is quenched with saturated NH_4Cl and poured into brine layered over with ether. The ethereal extracts are dried over $MgSO_4$ and evaporated to give 930 mg of crude **34** as a yellow oil. Column chromatography with hexane-EtOAc (7:3) afforded 350 mg of pure **34** as a white powder; mp 123-125 °C; ci-ms m/z 303 (M^++1, 100%), 245 (M^+-57, 82.9%)), 228 (M^++1-75, 72.5%), 184 (89.2%), 159 (62.0%); ir ($CHCl_3$) 3390, 1760, 1550, 1360 cm^{-1}; nmr (major

diastereomer) δ= 0.06 (s, $SiCH_3$), 0.88 (s, SitBu), 1.18 (d, $CHC\underline{H}_3$, J= 6 Hz), 1.63 (d, $CH(NO_2)C\underline{H}_3$, J= 6 Hz), 3.02 (dd, C3-H, J= 2,4 Hz), 4.16 (dd, C4-H, J= 2,4 Hz), 4.24 (m, $OC\underline{H}CH3$), 4.74 (m, $C\underline{H}NO_2$), 6.04 (br., NH); (minor diastereomer) δ= 0.06 (s, $SiCH_3$), 0.88 (s, SitBu), 1.25 (d, $CHC\underline{H}_3$, J= 6 Hz), 1.64 (d, $CH(NO_2)C\underline{H}_3$, J= 6 Hz), 2.85 (ddd, C3-H, J= 1,2,4 Hz), 4.03 (dd, C4-H, J= 2,9 Hz), 4.24 (m, $OC\underline{H}CH3$), 4.54 (m, $C\underline{H}NO_2$), 6.14 (br., NH); Also isolated was 77 mg of **35** (15%) as an orange solid; ir ($CHCl_3$) 3490, 2920, 2850, 1680, 1580, 1520, 1340, 1260 cm^{-1}; ei-ms m/z 259 (M^+-43, 2.1%), 245 (M^+-57, 16.6%), 75 (100%); nmr δ= 0.08, 0.10 (s, $SiCH_3$), 0.90 (s, SitBu), 1.21 (d, $CHC\underline{H}_3$, J= 6 Hz), 2.22 (d, $O_2NCC\underline{H}_3$, J= 1 Hz), 3.22 (dd, $OC\underline{H}$-CH=, J= 4,8 Hz), 4.20 (m, CHOSi), 5.7, 6.4 (br., NH), 7.3 (d, $C\underline{H}$=$C(NO_2)CH_3$).

.4-Acetyl β-Lactam **30** A solution of 104 mg of **34** (0.34 mmole) in 5 ml of CH_2Cl_2 was cooled to -5 °C with stirring, and 0.36 ml of an $NaOCH_3$ solution (0.95 M in CH_3OH, 1 eq) was added. The resulting solution was stirred at -5 °C for 3 min, then cooled to -78 °C and ozonized until a faint blue colour persisted. The excess ozone was purged with N_2, approximately 0.5 ml of dimethyl sulfide was added, the solution warmed to room temperature and was evaporated. The residue was partitioned between EtOAc-brine and the organic layer was dried over $MgSO_4$ and evaporated to give 87 mg of colourless oil. Chromatography with hexane-EtOAc (7:3) afforded 38 mg of pure **30** as a colourless oil; nmr δ= 0.07, 0.08 (s, $SiCH_3$), 0.86 (s, SitBu), 1.28 (d, $CHC\underline{H}_3$, J= 6 Hz), 2.24 (s, $COCH_3$), 3.07 (m, C3-H), 4.26 (m, C4-H, CHOSi), 6.20 (br., NH).

β-Lactam **31** A solution of 97 mg of **30** (0.36 mmole) in 2 ml of CH_3OH was cooled in an ice bath , and 10 mg of $NaBH_4$ was added.

The reduction was complete in 15 min, as indicated by t.l.c. ; the mixture was acidified to pH≈ 5 with Amberlite IR-120 (H^+), then the mixture was filtered and evaporated. The residue was taken up in wet CH_2Cl_2 and filtered through a plug of $MgSO_4$ and the solvent was evaporated to give 93 mg of **31** (95%) as a clear colourless oil; ir ($CHCl_3$) 3400(s), 3500-3200(br), 2920, 1750, 1260, 1140 cm^{-1}; nmr δ= 0.07 (s, $SiCH_3$), 0.90 (s, SitBu), 1.33 (br.d, $CHC\underline{H}_3$,), 3.0-4.3 (br, 5H), 6.6 (br., NH).

Mesylate β-Lactam **32** Alcohol **31** (93 mg, 0.34 mmole) was dissolved in 5 ml of dry CH_2Cl_2 and cooled in an ice bath, then 41.3 mg of triethylamine (0.408 mmole, 1.2 eq) was added followed by dropwise addition of 42.8 mg of methanesulfonyl chloride (0.374 mmole, 1.1 eq). The reaction mixture was stirred at 0 °C for 15 min, then was poured into water. The organic layer was separated and washed successively with 5% HCl, 5% $NaHCO_3$ and brine, then dried over $MgSO_4$ and evaporated to give 107 mg of crude mesylate. Chromatography with hexane-EtOAc (1:2) gave 72 mg of pure mesylate 32 (60%) as a light yellow oil; nmr δ= 0.10 (s, $SiCH_3$), 0.90 (s, SitBu), 1.14 (d, $SiOCHC\underline{H}_3$, J= 6 Hz), 1.43 (d, $O_2SOCHC\underline{H}_3$, J= 6 Hz), 3.03, 3.07 (s, OSO_2CH_3), 3.0-4.5 (m, 4H), 6.45, 6.70 (br., NH).

Preparation of Imido-Acid **39** A finely ground mixture of 3.64 g of *d*-camphoric anhydride (20 mmole) and 2.25 g of glycine (30 mmole) was placed in a 100 ml Kugelrohr bulb and was heated at 200 °C under a stream of N_2 for 1.5 h. The brown tarry mixture that resulted was cooled, dissolved in $CHCl_3$, washed with 10% HCl and the desired acid extracted with 5% $NaHCO_3$. Acidification of the basic extract with 10% HCl followed by extraction with $CHCl_3$, drying of the

organic layer with $MgSO_4$ and evaporation gave 3.14 g of acid **39** as a white powder. A sample was recrystallized from ether-hexane; mp 169-172 °C (brown); $[\alpha]_D=^{+}13.3°$(c=1, $CHCl_3$); ir ($CHCl_3$) 3020, 2980, 1730, 1685 cm^{-1}; nmr δ= 0.94 (s, CH_3), 1.04 (s, CH_3), 1.16 (s, CH_3), 1.8-2.2 (m, 4H), 2.72 (d, bridgehead CH, J= 7 Hz), 4.43 (s, $C\underline{H}_2CO_2H$); ei-ms 239 (M^+, 19.6%), 195 (M^+-CO_2, 85.2%), 109 (84.5%), 95 (100%).

Preparation of β-Lactam **41** A mixture of 956 mg of **39** (4 mmole) and 761 mg of oxalyl chloride (6 mmole, 1.5 eq) in 10 ml of benzene was heated at 60 °C (oil bath temperature) for 1.5 h at which time all materials present were in solution. The solvent benzene was evaporated, and the brown oil remaining was dissolved in 12 ml of dry CH_2Cl_2 and cooled to -78 °C. To this cooled solution of crude acid chloride was added 1.5 eq of triethylamine followed by a solution of 1.04g of imine **40** (1.1 eq) in 8 ml of dry CH_2Cl_2. The -78 °C cooling bath was removed and was replaced by an ice bath and the solution was stirred for 24 h. After stirring, the reaction mixture was washed with 10% HCl and dried over $MgSO_4$. Evaporation of the solvents gave 1.55 g of crude β-lactam **41** as a light brown foam. Recrystallization from ether gave 965 mg of dull brown crystals (53%); mp 187-197 °C (soft, dec.); $[\alpha]_D=^{+}8.4°$(c=1, $CHCl_3$); ir ($CHCl_3$) 2980, 1755, 1740, 1690, 1510, 1250 cm^{-1}; nmr (at 55 °C) δ= 0.88 (s, CH_3),1.16 (s, CH_3, CH_3), 1.81-2.20 (br., 4H), 2.68 (m, bridgehead CH), 3.75 (s, OCH_3), 4.93 (m, C4-H), 5.72 (br., C3-H), 6.22 (dd, C$\underline{H}$=CHPh, J=15.6, 8.4 Hz), 6.68 (d, CH=C$\underline{H}$Ph, J=15.6 Hz), 6.82-7.40 (aromatics); ci-ms 459 (M^++1, 5.4%), 458 (M^+, 16.1%), 336 (8.2%), 309 (O=C=N-PMP^+, 25.6%), 236 (49%), 128 (100%).

Preparation of β-Lactam **43** A solution of 150 mg of **41** (0.33 mmole) was cooled to 78 °C and ozonized until a deep blue colour persisted. The solution was purged with N_2 until the blue colour was no longer evident, 5 ml of CH_3OH was added followed by 30 mg of $NaBH_4$ (2.4 molar eq). The reaction mixture was stirred for 45 min at 0 °C, then was acidified to pH≈5 with 10% HCl and the solvent was evaporated to one half of it's original volume. The concentrate was poured into saturated NaCl and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated to give 153 mg of crude alcohol **43** as a yellow foam. Column chromatography with hexane-EtOAc (55:45) gave 80 mg of pure **43** as a white powder (63%); mp 75-90 °C (subl.); ir ($CHCl_3$) 3480, 2970, 1755, 1732, 1685, 1510, 1240, 1040 cm^{-1}; ^{13}C nmr δ= 178.63, 176.45 (imide CO), 162.10 (lactam CO), 156.20 (4°,PhO), 131.14 (4°,PhN), 118.63, 114.33 (d, aromatic CH), 59.82 (t, OCH_2), 58.59, 56.64, 56.40 (d, CH), 55.41 (q, OCH_3), 44.20, 55.03 (4°, aliphatic), 34.30, 25.39 (t, CH_2), 21.94, 19.48, 13.90 (q, CH_3); ei-ms m/z 386 (M+, 49.5%), 211 (16.4%), 205 (61.6%), 165 (57.8%), 149 (100%); ^1H nmr δ= 0.98 (s, CH_3), 1.07 (s, CH_3),1.21 (s, CH_3), 1.45-2.21 (br., 5H, aliphatics, OH), 2.77 (m, bridgehead CH), 3.98 (dd, C<u>H</u>OH, J= 4.9, 12.3), 3.77 (s, OCH_3), 3.78 (dd, C<u>H</u>OH, J= 5.6, 12.3), 4.45 (m, C4-H), 5.60 (dd, C3-H, J= 5 Hz), 6.8-7.4 (aromatics).

REFERENCES

[1] T. Nagahara, T. Kametani *Heterocycles* 1987, **25**, 729.

[2] T. Kametani *Heterocycles* 1982, **17**, 463.

[3] W. Dürkheimer, J. Blumbach, R. Lattrell, K.H. Scheunemann *Ang. Chem. Int. Ed.* 1985, **24**, 180.

[4] L.A. Paquette " Organic Reactions "; W.G. Dauben Ed.; John Wiley and Sons: New York, Vol. 25, 1977, p 1.

[5] J. Brennan, I.L. Pinto *Tetrahedron Lett.* 1983, **24**, 4731.

[6] T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen, F.A. Bouffard *J. Am. Chem. Soc.* 1980, **102**, 6161.

[7] L.D. Cama, B.G. Christensen *J. Am. Chem. Soc.* 1978, **100**, 8006.

[8] S.W. McCombie, A.K. Ganguly, V.M. Girijavallabhan, P.D. Jeffrey, S. Lin, P. Pinto *Tetrahedron Lett.* 1981, **22**, 3489.

[9] Private communication, H. Masterlerz, Bristol Laboratories (Canada).

[10] M. Ohtani, F. Watanabe, M. Narisada *J. Org. Chem.* 1984, **49**, 5271.

[11] M.J.S.A. Amaral, G.C. Barret, H.N. Rydon, J.E. Willet *J. Chem. Soc.* [C] , 1966, 807.

[12] Private communication, H. Masterlerz, Bristol Laboratories (Canada).

[13] H. Masterlerz *J. Org. Chem.* 1984, **49**, 4092.

[14] D.H. Shih, F. Baker, L. Cama, B.G. Christensen *Heterocycles* 1984, **21**, 29.

[15] M.K. Sharma, H. Schwartz, T. Durst Unpublished results.

[16] K. Fujimoto, Y. Iwano, K. Hirai *Tetrahedron Lett.* 1984, **25**, 1151.

[17] Compound **29** was a gift from Bristol Laboratories (Canada), whose generosity is gratefully acknowledged here.

---

[18] D. Seebach, E.W. Colvin, F. Lehr, T. Weller *Chimia* 1979, **33**, 1.

[19] J.E. McMurry, J. Melton, H. Padgett *J. Org. Chem.* 1974, **39**, 259.

[20] M. Shiozaki, N. Ishida, H. Maruyama, T. Hiroaka *Tetrahedron* 1983, **39**, 2399.

[21] D.A. Evans, E.B. Sjogren *Tetrahedron Lett.* 1985, **26**, 3783.

[22] J.E. Baldwin, M.L. Lusch *J. Org. Chem.* 1979, **44**, 1923.

CLAIMS to ORIGINAL RESEARCH

1. Several O-2-isocephems were prepared via an intermolecular rhodium carbenoid N-H insertion reaction. One of these was tested for antibacterial activity and was found to possess low levels of activity.

2. A conceptually new route to 1,3-dihydrobenzo[c]thiophene-2,2-dioxides was developed, featuring as the key step an intramolecular rhodium carbenoid insertion into an aryl C-H bond. Nine examples were reported.

3. A series of six α-diazo-β-keto arylesters were converted into 3-acetylbenzofuran2(3H)-ones by treatment with rhodium(II) acetate, extending the scope of the aforementioned insertion reaction. Two α-diazo-β-keto naphthylesters were converted into their respective 3-acetylnaphthofuranones.

4. An unusual eight-membered ring di-sulfur ylide was formed by intramolecular reaction of two molecules of a γ-diazo sulfide promoted by rhodium(II) acetate.

5. Two γ-lactones were prepared by a 1,5-rhodium carbenoid insertion into an aliphatic C-H bond a to silicon.

6. The intramolecular deoxygenation of a sulfone to a sulfide by a rhodium carbenoid was briefly investigated.

7. A carbapenem bearing a 2-thiomethylethyl ester protecting group was prepared via an intramolecular rhodium carbenoid insertion reaction.

8. A 3-sulfonyl cepham was prepared via an intramolecular rhodium carbenoid insertion reaction.

9. A 3-camphoryl-imido β-lactam was prepared by the ketene-imine reaction.

10. The mechanism of the benzofuran forming reaction was investigated by kinteic isotope effect.

PUBLICATIONS from this THESIS

"Intramolecular Rhodium Carbenoid Insertions into the N-H Bond of β Lactams. Synthesis of O-2-Isocephems."; M. Hrytsak, T. Durst *Heterocycles* 1987, **26,** 2393.

"Intramolecular Rhodium Carbenoid Insertions into Aromatic C-H Bonds. Preparation of 1-Carboalkoxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxides."; M. Hrytsak, N. Etkin, T. Durst *Tetrahedron Lett.* 1986, **47**, 5679.

"Preparation of 3-Acetylbenzofuran-2(3H)-ones and 3-Acetyl-naphthofuran-2(3H)-ones via Intramolecular Rhodium Carbenoid Insertion."; M. Hrytsak, T. Durst *J. Chem. Soc. Chem. Commun.* 1987, 1150.